International Journal of Advanced Research and Development
www.multidisciplinaryjournal.net
ISSN: 2455-4030
Received: 22-01-2024, Accepted: 14-02-2024, Published: 08-03-2024
Volume 9, Issue 2, 2024, Page No. 17-21

Review on teratogenic agents

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Abstract
Teratogenesis is a process that causes birth defects or malformations in an embryo or foetus the term "teratogen" was first described in Paris, France, in early 1932. "Teratogens" comes from the Greek word terrace, which means "monster" or "miracle" Teratogens are substances that can adversely affect health Embryonic or fetal development when administered under certain conditions related to dosage, route of administration, Gestational age, and genotype. Teratogens are environmental factor such as drugs, viruses, nutritional deficiencies, and physical or chemical agents that comes in contact with the embryo or fetus and can cause congenital anomalies that cause permanent functional or morphological changes in the newborn.

Keywords: Teratogenesis, foetus, abnormalities

Introduction

Teratogenesis is a process that causes birth defects or malformations in an embryo or foetus [1] The term "teratogen" was first described in Paris, France, in early 1932. "Teratogens" comes from the Greek word terrace, which means "monster" or "miracle" [2]. Teratogens are substances that can adversely affect health Embryonic or fetal development when administered under certain conditions related to dosage, route of administration, Gestational age, and genotype [3]. Teratogens are environmental factor such as drugs, viruses, nutritional deficiencies, and physical or chemical agents that comes in contact with the embryo or fetus and can cause congenital anomalies that cause permanent functional or morphological changes in the newborn [4].

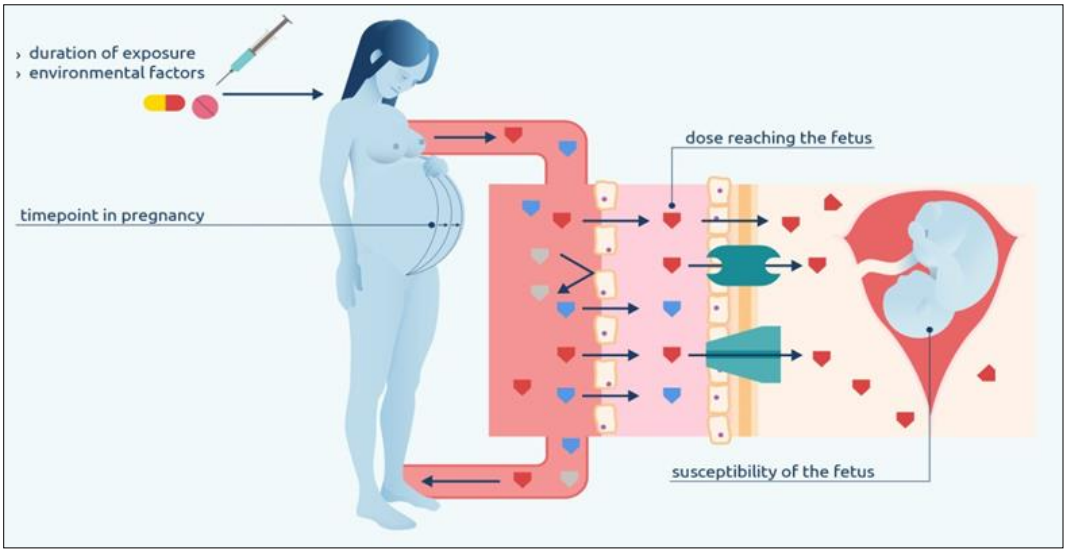

Fig 1

Teratogenicity refers to structural malformations at the onset of fetal development, as Opposed to other types of drug-related fetal harm such as growth retardation, dysplasia (e.g. goiter due to iodine deficiency), or asymmetric reduction of limbs. Exposure to teratogenic chemicals before conception, during prenatal or postnatal development, led to developmental toxicity including the death of the developing organism, structural abnormalities, and changes in growth. It is guessed that around 10-15% of congenital anomalies cause due to bad effects of environmental factors on prenatal development. Factors include chemicals, microorganisms, infections, maternal conditions, and diseases i.e. diabetes and physical factors like radiation.

Faults in the development of the heart are the most common nowadays and it is around 15% of children have these birth faults. On the other side abnormalities like extra fingers and toes (polydactyly). The four main platforms where the defective gene grows are the intracellular compartment and abnormalities in the structure and function of the cell surface. The third one is an extracellular matrix and fetal environment [5].

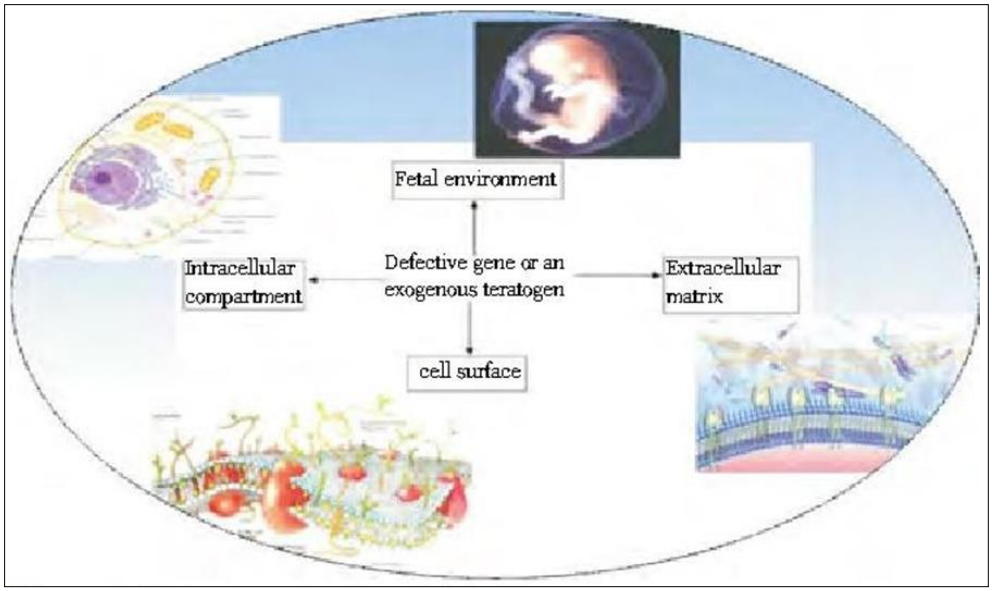

Fig 2: Major sites of action of defective gene or teratogen

History of Teratogenicity

Teratology was first discovered after various experiments on pregnant pigs in the 1930s. In these experiments, pigs were fed a vitamin A-deficient diet. Eventually, these piglets all suffered devastating deformities, especially losing their eyes. Sir Norman Gregg discovered the human rubella virus as the first human teratogen in 1941. Exposure to the virus in utero causes heart defects and congenital cataracts. As science has progressed, the effects of xenobiotic drugs on embryos have been demonstrated through animal studies, possibly with biologically dominant homologs of the molecule, such as the amino acid analog azaserine. In the 1950s, aminopterin was used to terminate pregnancies. Instead, several handicapped newborns were born after drugs failed to terminate pregnancies [6]. About 60 years ago, thalidomide was prescribed to overcome morning sickness in pregnant women. It was the biggest man-made disaster of that time, where 10000 children were born with a high percentage of severe disabilities instead of this the drug is now in a wide range to treat adults' conditions including various types of myeloma and complications of leprosy [7].

The general mode of action of teratogen

Mammalian fetal development passes through three main phases: blastocyst formation, organogenesis, histogenesis, and maturation of purpose. Many teratogens have the capacity to inhibit cell division and kill embryos during cell division, which was implicated in blastocyst formation. Administration of teratogen during the period of organogenesis (Day 17-60) leads to malformations. The type of malformation produced by teratogen involves defects in the eye and brain, skeleton and limbs, heart and major vessels, palate, and genitourinary system.

Teratogens and teratogenic effects may generate mutagenic effects such as vitamin A

derivatives (retinoids) which are occupied in morphogenesis and are potent teratogens. Drugs like methotrexate and phenytoin do not react directly with DNA but influence folate

metabolism. The development of the fetus depends on adequate nutrition nutrients in the final stage of tissue formation and functional maturity, and development is regulated by a variety of hormones. Severe structural malformation is not the result of mutagenic exposure at this stage, but teratogenicity interferes with the supply of nutrients or the hormonal environment can have an adverse effect on its development and development. Exposure of female fetuses to Rogen can lead to masculinization. Stilbestrol is commonly used for pregnant women with a history of recurrent miscarriage in the 1950s (for unhealthy reasons) and caused dysplasia of the infant's vagina and increased morbidity Vaginal carcinoma in teenage and twenties girls. Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin receptor antagonists cause oligohydramnios and renal failure if used in late pregnancy because selective inhibition of angiotensin II plays a role an important role in the final stages of fetal development and renal function in the fetus [5]

Teratogenic Factors

Teratogens are mainly classified into four types

Table 1: Teratogens factors

Sr.No.	Factors	Medication
A.	Drugs	ACE inhibitors (captopril, enalapril) NSAID (diclofenac), Thalidomide, Androgen Hormone(oestrogen), Antineoplastic agent (methotrexate) Warfarin, Valproic acid, Retinoic acid
B.	Chemicals	Alcohol, Cocaine, Methyl Mercury Lead acetate
C.	Maternal Factors	Diabetes Mellitus, Epilepsy
D.	Physical Agents	Cigarette, Smoking, Ionizing Radiation

A. Drugs

1. ACE inhibitors: (Captopril and Enalapril)

Angiotensin-converting enzyme inhibitors (ACEIs) are the mainly indicated medications in the treatment of cardiovascular and renal disease, with heart failure, acute coronary syndrome, nephrotic syndrome, diabetes, and hypertension.

2. Non-steroidal anti-inflammatory agents: Diclofenac
Diclofenac is a non-steroidal anti-inflammatory drug and is commonly used by women of childbearing age to treat different conditions. Due to its low molecular weight, diclofenac can easily pass through the human placenta in the first trimester.

3. Thalidomide
Thalidomide is used as a sedative to treat morning sickness in pregnant women. Thalidomide is effective against leprosy the patients. Thalidomide can inhibit tumor necrosis factor-α (TNF-α) production in stimulated human monocytes. In addition, thalidomide and its

4. Androgen hormone: estrogen
Androgens are a group of sex hormones. Natural androgens are steroidal hormones produced by glands and adrenal glands. They help begin puberty and play a role in reproductive fitness and body development. Testosterone is the generally common androgen [10]. Increased level of androgenic hormones during pregnancy causes masculinization of a female fetus. Masculinization means to cause male characteristics in females and pseudo-hermaphroditism in pregnant mothers. The androgenic progestin administered to the mother is changed to estrogen which does not protect the fetus from the masculinization effect and causes cornification of the vagina. Testicular testosterone produced during a critical prenatal period is thought to masculinize and defeminize the male brain from the inherent feminization program. These actions of testosterone show to be exerted not through its androgenic activity, but rather throughout its conversion by brain aromatase into estrogen, with the ensuing activation of estrogen receptor-mediated signaling [11].

5. Antineoplastic Agents
Anticancer drugs are drugs used to treat cancer. Another name for anticancer drugs is anticancer drugs, chemotherapy, and cytotoxic drugs. The use of anticancer agents in pregnant women poses notable risks for the patient and the developing fetus, especially during organ formation. Possible birth defects occur only in about 20% of cases if chemotherapy using cytotoxic anticancer drugs is administered in the first three months. If the patient becomes pregnant during chemotherapy, termination of the pregnancy is an option because there is an increased risk of drug-induced fetal malformations. Pre-menopausal patients are more susceptible to breast cancer hormones and can miss the chance of getting pregnant, as the use of tamoxifen after surgery can be extended the duration [12].

6. Anticoagulant Agents: Warfarin
The competitive inhibitor of vitamin K is warfarin. The bloodstream of the fetus can easily be reached by warfarin after it crosses the placental barrier. It causes fetal warfarin syndrome in children because of its decreased molecular weight. Crosses with warfarin in the placenta and is associated with higher fetal loss rates. Intake of warfarin during the second and third Anomalies in the central nervous system occurs during the trimester. Taking warfarin at dosages more than 5 milligrams can instantly cause fetal death on a daily basis. By not providing warfarin medicine to women who are trying to conceive, warfarin syndrome can be avoided. Avert it five days before conception [13].

7. Valproic Acid
For those with epilepsy and bipolar illnesses, valproic acid (VPA) is a regularly recommended medication. When used by pregnant women, VPA has a well-known teratogenic potential, which increases the risk of birth problems like neural tube defects (NTDs) and other congenital deformities. Valproic acid causes valproic syndrome. Developmental issues are becoming more prevalent and are frequently accompanied by communication issues in people with autism spectrum disorder (ASD), which are evidenced by verbal intelligence decline [14].

8. Retinoic Acid
Vitamin A, or retinol compounds, are called retinoids. Vitamin A, also known as retinol, is a necessary nutrient that aids in controlling the cellular development of epithelial tissue. Vitamin A overdose can affect embryonic development and cause teratogenesis in an embryo in the process of development. The fetal skull, face, limbs, eyes, and central nervous system are the concerned organs as a result of an excess of retinoids. Retinoids should be avoided in excess during pregnancy to ensure that the baby is born a whole human being with no deformities [15].

B. Chemical Factors
a. Unnecessary chemical
1. Alcohol
The baby's body develops its organ systems during the first four weeks of pregnancy, including the heart, central nervous system, eyes, arms, and legs. The brain of the unborn child begins to grow about the third week of the fetus' intrauterine life and gradually matures throughout the pregnancy. Alcohol diffuses through the placenta and distributes fast into the fetal compartment, accumulating in the amniotic fluid, and can have direct toxic and teratogenic effects on a developing fetus.

C. Maternal Factors
1. Diabetes Mellitus
Diabetes mellitus is an assembly of physiological dysfunctions categorized by hyperglycaemia resulting directly from insulin resistance, insufficient insulin secretion, or extreme glucagon secretion. Insulin is a hormone in the body of human. Insulin helps to obtain enough glucose into the body cells to be used as fuel whenever there is no exterior food source.

D. Physical agents
1. Cigarette smoking
Cigarette smoking by the mother is one of major reasons of general developmental abnormalities. Reduced growth in fetus is observed. The array of chemicals like nicotine, carbon monoxide and cyanide released during tobacco smoking interfere with the transport of amino acids across the placenta. Several mechanisms have been proposed like placental necrosis, inhibition of placental exchange and activation of metabolic enzyme based toxic reactive metabolites that produce teratogenic effect, but exact mechanism responsible for teratogenic effects in human is unclear. Carbon monoxide produced during smoking crosses placenta and increases carboxyhemoglobin levels in blood which has longer half-life in fetal blood than in maternal

blood. Nicotine released during cigarette smoking has vasoconstriction effect that results in uterine vascular constriction and intrauterine growth retardation because of decreased perfusion of fetal tissues. It also increases the risk of perinatal mortality and morbidity [3]. The perinatal mortality is attributed to abruption placentae, placenta previa, spontaneous abortion, prematurity and intrauterine growth retardation, preterm delivery, perinatal mortality, subfertility, abnormal placentation, childhood morbidity and mortality, congenital malformations, gastroschisis, cardiac defects, chromosomal anomalies and central nervous system defects [5].

Teratogenic Defects in Infants

1. Spina bifida

Spina bifida is a birth defect in which a developing baby's spinal cord fails to develop appropriately. It's a form of neural tube defect. Spina bifida is a congenital malformation in which the spinal column is split as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization. In its commonest and most severe form, myelomeningocele (MMC) the spinal cord is open dorsally, forming a placode on the back of the fetus or newborn baby that normally rests on a meningeal sac. Individuals with MMC often reveal motor and sensory neurological shortage. This may result in lower limb weakness or paralysis that prevents walking, and lack of sensation. Urinary and fecal incontinence occur commonly.

Pathophysiology and mechanisms

The primary disorder in the pathogenesis of MMC is failed neural tube closure in the embryonic spinal region, which leads to prolonged exposure of the open neural tube to the amniotic fluid environment. The bifid neuroepithelium initially undergoes relatively normal neuronal differentiation, with development of spinal motor and sensory function even below the lesion level. As gestation progresses, however, the uncovered spinal cord becomes haemorrhagic and neurons expire as a effect of toxicity of the amniotic fluid. Axonal connections are interrupted, and function is lost Hence, neurological disability in MMC is often measured a _two-hit‘ process: failed neural tube closure followed by neurodegene ration in utero [18].

2. Cleft lip and palate

Cleft lip and cleft palate are birth defects that arise when a baby‘s lip or mouth do not appears properly during pregnancy. These birth defects togetherly called as ―orofacial clefts‖ Cleft lip and cleft palate are caused by a grouping of genes and other factors, such as things the mother get in touch with environment, or what the mother eats or drinks, or sure medications she uses during pregnancy

Cleft Lip: The lip forms among the fourth and seventh weeks of pregnancy. As a baby develops throughout pregnancy, body tissue and special cells from each side of the head grow toward the center of the face and join mutually to make the face. This joining of tissue forms the facial features, like the lips and mouth. A cleft lip happens if the tissue that makes up the lip does not join entirely before birth. This results in a gap in the upper lip. The opening in the lip can be small or large. A cleft lip may be one or both sides or in the middle of the lip. Children having a cleft lip may also form a cleft palate.

How are Teratogen Related Birth Defects Diagnosed?

Due to the number of new substances coming into use every year and the increasing amounts of chemicals, which are introduced into the environment, there is a high demand for a rapid, reliable and cost-effective method for detection of developmental toxicity. To meet this challenge various *in vitro* techniques have been established additional to *in vivo* animal testing [22].

During pregnancy: Prenatal testing

Screening Tests

- Screening tests Whole Embryo Culture Test
- Micromass Teratogenic Test
- Emryonic Stem Cells Test
- Dictyostelium Discoideum Based Assay

A screening test is a procedure or test that 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. Less often, a screening test result can be normal and miss a problem that does exist. During pregnancy, women are usually offered these screening tests to check for birth defects or other problems for the woman or her baby. Talk to your doctor about any concerns you have about prenatal testing. First trimester screening is a combination of tests completed between weeks 11 and 13 of pregnancy. It is used to look for certain birth defects related to the baby‘s heart or chromosomal disorders, such as Down syndrome. This screen includes a maternal blood test and an ultrasound. Screening during the first trimester usually consists of- Blood tests to measure levels of pregnancy-associated placental protein A (produced by the placenta) and beta-human chorionic gonadotropin in the pregnant woman‘s blood. Ultrasonography to measure a fluid-filled space near the back of the fetus‘s neck (called fetal nuchal translucency). Ultrasonography can help estimate the risk of Down syndrome and certain other chromosomal abnormalities. It can show whether the space at the back of the fetus's neck is enlarged [4].

- **Whole Embryo Culture Test**

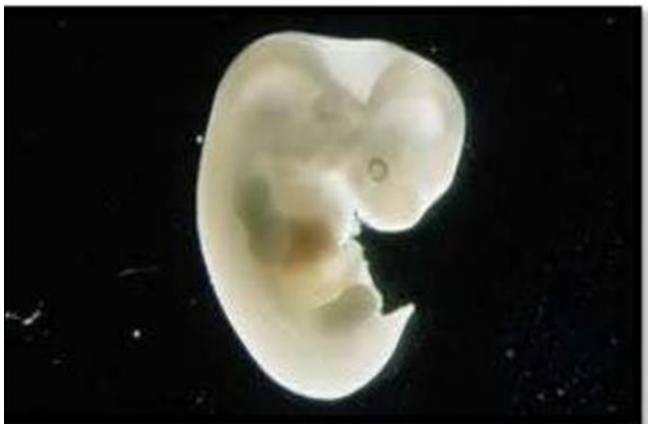

Fig 3

Culturing of whole embryos at an early stage of organogenesis, and exposing of these to a potential teratogen, allows for the valu-ation of a relative index of teratogenicity of the test substance. Both mammalian embryos, namely from the rat or the mouse (rodent embryo culture), and embryos of the South African clawed frog Xenopus laevis (frog embryo teratogenesis assay-Xenopus, FETAX) are in use in teratogen screening. The tests are able to evaluate single compounds or their joint action as well as environmental mixtures. However, the question as to what minimal change in a de-velopmental parameter would display the presence of a potential teratogen is still challenging. There are numerous parameters which may indicate a deviation from normal. Micromass Teratogenic Test

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