Review Article

A Review on Teratogenesis: Current Perspective

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ABSTRACT

Teratogenesis is derived from Greek word "Terato" which means monster. Teratogenesis results in the development of morphologically abnormal individuals. These may include conditions like intellectual disabilities that don't have any visible structural deformities. This defect is mainly produced by teratogens which is genesis of physical and functional defect in human's embryo and fetus. Teratogens have a variety of effects on embryos, including physical deformities, issues with the child's behavioral or emotional development, and a decreased IQ in the child. Teratogens can also have an impact on pregnancies. Physical agents, metabolic circumstances, infections, and finally, medications and chemicals, are the four groups into which teratogens are divided. A few examples of teratogens are prescription medications like thalidomide, environmental poisons like cadmium, and environmental pollutants like pesticides and endocrine disruptors. Viruses, such as the rubella and Zika viruses, physical constriction of the uterus, and a poor diet are additional causes of teratogenesis. This review will examine the drug's history, the scope and kind of the harm it caused, as well as the drug's mechanisms of action, including recent molecular developments and fresh research.

Keywords: Teratology, patents, Embryo deformity, Etiology.

INTRODUCTION

A prenatal toxic condition known as teratogenesis is characterized by structural or functional flaws in the growing embryo or fetus. In this phenomena, birth abnormalities and malformations such intrauterine growth retardation, fetal or embryonic mortality, and transplacental carcinogenesis take place. The word "teratology," which means "study of monsters," is Greek in origin. Teratology is the study of mechanisms that cause anomalies and birth disorders carried by environmental causes other than genetics [1-5]. Teratogens are any substances capable of resulting in a birth abnormality or malformation. Although in several cases, the causes of abnormalities were not revealed clearly. The birth defects might be genetic, chromosomal, or environmental (for example, medications). However, some of the factors promoting teratogenicity are depicted in figure-1 [6-8].

Different types of the teratogens are-

- **Chemical substances,** such as prescription medications like thalidomide and retinoic acid; illicit substances such as alcohol and cocaine; environmental toxins including heavy metals like cadmium; and pollutants like pesticides linked to reproductive and fertility problems, like diethylstilbestrol during pregnancy.
- **Infections** including as rubella and Zika virus.
- **Physical constraint** or in-utero damage, such as clubfoot from oligohydramnios, where the amniotic fluid is lost and the foetus is restricted, can occur. Amniotic band syndrome is one kind of physical harm that occurs to a fetus while it is still inside the mother. In severe situations, the condition can result in death.
- **Hyperthermia**
- **Maternal conditions** like gestational diabetes [9-16].

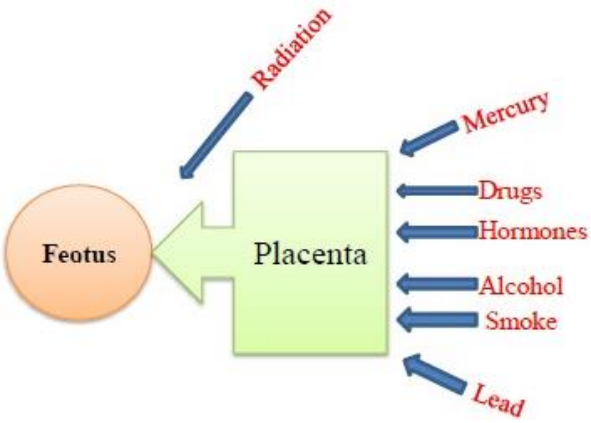

Figure 1: Factors promoting teratogenicity

History of Teratology

Experimental teratology was first described in 1928 in this study exposure to therapeutic radiation during pregnancy it causes microcephaly baby in pregnant women. The 1930s saw the publishing of a series of studies using pregnant pigs fed a diet lacking in vitamin A, which marked the beginning of teratology as a contemporary science [17-28]. The majority of the abnormalities encountered by these piglets, which lacked eyes, were similar. OsefWarkany, a physician, is recognized as the founder of experimental teratology. He was the first to demonstrate, in the 1930s and 1940s of the previous century, that foreign causes can also cause CDDs in mammals [29-32]. Various important events in the history relevant to teratogenesis is shown in table 1.

Table 1: Various important events in the history of teratogenesis

Year	Event
1905	The first experimentally induced developmental toxicity in mammals. Embryonic lethality induced by X-rays in cats.
1921	The first experimentally induced teratogenicity in mammals. Disorders in limbs in pigs induced by lipid diet.
1928	The first experimentally induced teratogenicity in mammals. Disorders in limbs in pigs induced by lipid diet.
1929	The first description of malformations in humans caused by exogenous factors. Microcephalia caused by X-ray irradiation of the pelvis.
1933	Deficiency of vitamin and the first month before pregnancy and during pregnancy.
1995	Recognition of food deficiency leading to malformations in animals. Eye disorders in pigs due to hypo-vitaminosi

The prevalence of abnormalities is higher in situations like spontaneous abortions than in live-born newborns, which may be a reflection of the fact that many of the most severe issues are insurmountable barriers to survival. The study of teratogenesis is critical for ensuring that medications are secure and/or do not cause birth defects, that is, that they are nonteratogenic. For this reason, teratogenesis research is crucial for ensuring that pharmaceuticals are safe [33-36].

Presently, the molecular mechanism of some of the teratogens is known but for some of the reproductive toxicants and foetotoxicants it is still nameless. Reproductive toxicants can cause disturbances in cell division, enzyme system, water electrolyte balance, membrane characteristics, energy transfer to foetal development and mutation. The factors causing birth defects can vary and their etiology is unknown.

Initially for understanding the situation and providing the drafted information to health professionals and public, the two teratology information centers were established in 1990 [37-39].

1. European Network of Teratology Information Services (ENTIS)
2. Organization of Teratology Information Specialists (OTIS)

TERATOGENESIS ETIOLOGY

The branch of embryology specialized in studying the etiology of abnormal development of embryo is known as "Teratology". There are two etiological groups in which various teratogens participates for inducing congenital anomalies (1) primarily environmental (2) multifactorial origin. The sequence followed in the development of teratogenesis is depicted in figure 2[43-48].

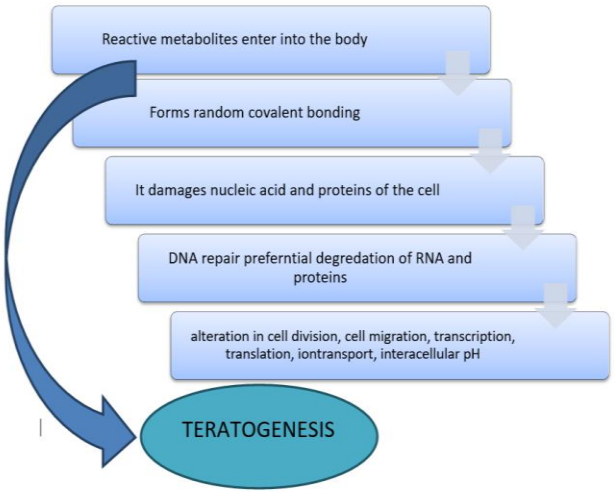

Figure 2: Etiology of teratogenesis

ELEMENTS CAUSING TERATOGENESIS

Most foods or dietary ingredients have teratogenic effects, in addition to medications. Foods that include preservatives typically have a greater teratogenic effect. Therefore, packaged foods are prohibited during pregnancy. Direct or indirect exposure to various harmful chemicals during pregnancy can also leads to teratogenesis in the developing embryo. The major causative agents as like foods, medications, chemical and infections are enlisted in the table no. - 2, 3, 4 and 5 [30-41].

Table 2: Food products causing Teratogenicity

S.no	Chemical constituents	Category	Animal involved in research	Effect
1	Sodium benzoate	Preservative	Long term consumption (mice)	• Carnio facial deformation • Mandibular hyperplasia
2	Potassium benzoate	Preservative	Long term consumption (mice)	• Congenital eye abnormality • Mal formed lenses
3	Asparatame	Artificial sweetener	Long term consumption (chick)	• Retardation of brain • Formation anencephaly
4	Vitamin A	Fortifying agent	-	• Facial nerve paralysis

				• Under developed upper jaws • Malformed ears
5	Taratzine	Colouring agent	-	• Hepatorenal damage • cardiomegaly
6	Carrageenan	Stabilizers	Chick embryo	Prevention of cell activity and morphogenesis as Carrageenan binds to cell
7	Alcohols	Chemical	Chicken and fish	• Mortality eye defects • facial defects

Table 3: Teratogenicity due to medications

S.no	Drugs	Maternal condition	Adverse impact on embryo
1	ACE inhibitors (Benzapril, Ramipril, Qunaipril, Perindopril, Trandopril)	• Hypertension	• Neonatal renal failure • pulmonary • Hypoplasia • death
2	Methimazole	• Hyperthyroidism	• Skull Hypopalasia • psychomotor delay • growth retardation • scalp defects
3	• Amiodarone • Radioiodine	• Thyroid	• Neonatal thyroid dysfunction • Fetal Goitrhypothyroidsm • Goitre
4	Trimethoprim	• Bacterial infection	• Neural tube defects • Oral defects • cardiovascular defect
5	Indomethacin	• Fever • Inflammation • Premature labour hydramnios	• Oligohydramnios • anuria • premature closure of ductus arterious
6	Quinine	• Leg cramps • Malaria	• Deafness • Abortion
7	Misoprostol	• Peptic ulcer disease • Cervical ripening	• Congenital anomalies
8	Penicillamine	• Cystinuria • Rheumatoid arthritis	• Connective tissue abnormalities
9	Thalidomide	• Insomnia • Oesophagus ulcers • Oropharyngeal associated with AIDS	• Limb reduction • Urogenital and gastro intestinal defect • Carnival nerve anomalies
11	Retinoids	• Dermatologic disease	• Organogenesis
12	Cyclophosphamide	• cancer,transplant rejection	• Organogenesis
13	Methylene blue	• Twin pregnancy	• Jejunalartesia

IN VITRO DIAGNOSTIC METHODS

There are several in-vitro diagnostic methods which help in diagnosis of the condition. It can be classified into following classes

(a) Preliminary screen for developmental toxic agents

(b) Estimation of mechanism of normal and abnormal embryogenesis.

The European Centre for the Validation of Alternative Methods (ECVAM) on its 17th meeting endorsed three scientifically validated methods.

1. Embryonic Stem Cell Test (EST) – Two permanent murine cell lines i. e. D3 (Embryonic tissue) and 3T3 fibroblast cell (adult tissue) are used.
2. Micromass Test
3. Whole Embryo Culture Test [41-42]

Table 4: Chemical causing teratogenesis

S.no	Chemicals	Malformation
1	Mercury	Brain development disorder
2	Cadmium	Limb anomalies
3	Poly chlorinated biphenyls	Intra uterine growth retardation

Table 5: Infections causing teratogenesis

Infections	Malformation
Cytomegalovirus	• Brain and sensory anomalies
HIV	• Growth failure • microcephaly • carnio facial defects
Rubella	• Intrauterine growth retardation • Cardiac defects • Deafness and eye defects
Zika virus	• Microcephaly

PREVENTION OF TERATOGENESIS

Teratology has become a big problem today and it is necessary to have new idea and new strategies to stop it. Teratogenesis starts from the womb of the mother and there is no cure for it after the birth of a child, it can be prevented by avoiding teratogen at the different stages of pregnancy. Counselling for pregnancy is the greatest approach to prevent teratogens. Planning for pregnancy enables you to manage long-term medical concerns and make modifications to their lifestyle, such as stop smoking and many more. The preventive measures that must be taken during the pregnancy is shown in the figure 3 [43-51].

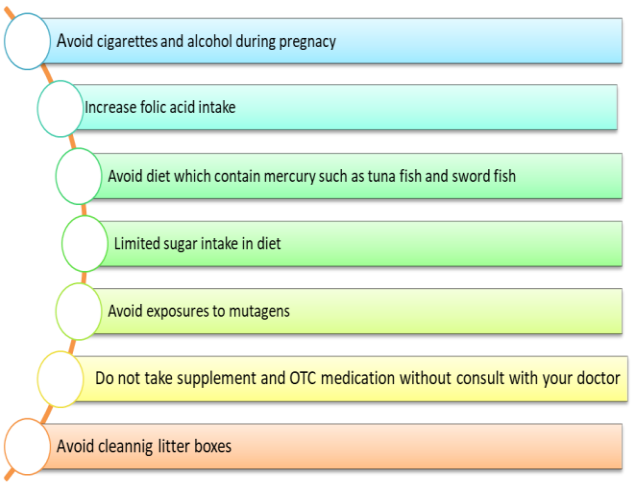

Figure 3: Preventive measures for teratogenesis

RECENT ADVANCEMENT IN TERATOGENESIS

As research is a continuous process, various patents have been published and granted in the field of efficient and fast diagnosis and treatment of teratogenesis. Some of the work published in recent years is cumulated in the below given table 6.

Table 6: Patents related to teratogenesis

S.No.	Title	Patent No.	Published Work	Inventor	Date of Publication	Reference
1	Evaluation of teratogenis cause by Chinese patent drug by using zebra fish embryo	CN107228925A	This strategy effectively examined the possible teratogenesis of Chinese patent drugs, frequently carried out toxicity analyses by using zebra fish embryo	YaoMeicun, ChenJiefeng, ChenZuanguang, Liao Min, LiuTong, Liu Mengping, Huang Danping	2017-10-03	52
2	The procedure for finding Teratogenesis-causing compounds in tobacco chemical fertilizer and their use	CN1069706772A	The present invention extracts teratogen in tobacco compound fertilizer using the method of science.	Chen Zepeng Wan Shuqing Lin Xianfeng	2017-05-24	53
3	Molecular genetic marker related to pig sperm teratogenesis rate and application thereof	CN110714085A	They summarized a report regarding swine sperm teratocarcinoma related molecular genetic marker.	Li Zhili Yuan Sheng Zhang Nan Chi Shihong Yu Weiwei Kwong Wai Kin Wang Meihong	2020-01-21	54

4	Blocking the effect of teratogens on a fetus	EP0616534A1	They described about the agents which can block the effects of teratogens on fetus as well as host.	William F. Geber	1994-09-28	55
5	Method of determining teratogenic risk	WO2013131841A1	They described about the method for determining the risk of drug induced teratogenesis. They utilized pluripotent stem cells.	Eric Chiao, Sei KAMEOKA, Kyle L. Kolaja	2015-05-18	56

CONCLUSION

Teratogenesis is a process that results in deformities or birth abnormalities in an embryo or fetus. Teratogens are the agents that affect the prenatal development in many ways and cause various abnormalities. There are a number of teratogens of food, drug, chemical, and infectious origin. This review describes about the history, etiology, teratogens, in- vitro diagnostic methods and prevention methods for teratogenesis. It causes severe problems and some efficient methods should be discovered to cure this.

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CONFLICT OF INTEREST

There was not any potential conflict of interest between the authors.

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ETHICS STATEMENT

No animal study was performed during the above stated study.

DATA AND MATERIALS

The data supporting the findings of the article is available within the article.

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