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A Brief Review on Teratogenicity

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ABSTRACT

Teratogenicity has increasingly been recognized as a most important part of overall toxicology. Each compound has its own toxicological mechanism of teratogenicity. The present view-point was to explore and review the common teratogenic effects of teratogenic compounds, biological agents and physical agents. Every year millions of different chemicals are produced and used in the world which contaminate environment and these are exposed to human. Many of these chemicals have ability to penetrate into human tissue and developing foetus, negatively impacting the reproductive health of human. Many of the teratogenic effects occur because of biological and physical factors like infection and radiation respectively.

Keywords : Teratogen, Toxicology , foetus , Biological and physical factors.

1. INTRODUCTION

The term "Teratogens" was first described in Paris, France in early 1932. "Teratogens" comes from the Greek word teras, which means "monster" or "marvel"[1].Teratogens are environmental agents such as drugs, viruses, lack of nutrients, and physical or chemical elements that upon contact with embryo/fetus can cause congenital anomalies, generating permanent functional or morphological changes in the newborn [2].

FIGURE NO .1

Congenital anomalies are the leading cause of infant mortality in high-income countries and the second most common cause in many middle-income countries. Such conditions emerge during fetal development and can be inherited or influenced by environmental factors, such as medication exposure [3]. Teratogenesis signifies the structural malformations during fetal development, in distinction from other kinds of drug induced fetal damage such as growth retardation, dysplasia(e.g. Iodine-deficiency-related goitre), or the asymmetrical limb reduction. The exposure of teratogenic chemical priorto conception, during prenatal or postnatal development leads to manifestations of developmental toxicity including the death of the developing organism, structural abnormality, altered growth, and functional deficiency[4]. A recent review of the available data concluded that exposure to trace amounts of nitrous oxide is not associated with impaired fertility or an increased risk of developing cancer; however, recent studies seem to suggest a correlation between nitrous oxide anesthesia and hyperhomocysteinemia, an independent risk factor for coronary artery disease. Long-term exposure to high concentrations of nitrous oxide may cause megaloblastic bone-marrow depression and neurological symptoms.[5]

2. HISTORY OF TERATOGENICITY

Teratology is the science that studies the causes, mechanisms, and patterns of abnormal development. Teratology as a modern science was born in the 1930s with the publication of a set of experiments in which pregnant pigs were fed a diet deficient in vitamin A. All of these piglets suffered a variety of malformations, predominantly a lack of eyes [6].

Figure no .2

The first human teratogen identified in 1941 by an ophthalmologist, Norman Gregg, was maternal rubella infection in pregnancy, which produced a triad of defects (cataracts, heart malformations, and deafness) in the infants.[7]. Nearly 60 years ago thalidomide was prescribed to treat morning sickness in pregnant women. What followed was the biggest man-made medical disaster ever, where over 10,000 children were born with a range of severe and debilitating malformations. Despite this, the drug is now used successfully to treat a range of adult conditions, including multiple myeloma and complications of leprosy [8].

Table no. 1 Historical events in modern teratology [9].

Year	**Historical event**
1905	The first experimentally induced developmental toxicity in mammals. Embryonic lethality induced by X-rays in cats (Tousey)
1921	The first experimentally induced teratogenicity in mammals. Disorders in limbs in pigs induced by lipid diet (Zilva et al.).
1929	The first description of malformations in humans caused by exogenous factors. Microcephalia caused by X-ray irradiation of the pelvis (Goldstein and Murphy).
1935	Recognition of food deficiency leading to malformations in animals. Eye disorders in pigs due to hypovitaminosis A (Hale).
1937	Hormones causing alterations in sexual differentiation in animals. Masculinisation of female foetuses in mice due to theaction of androgens (Raynaud)
1941	Report on virus-induced human malformations. Rose-rash induced eye disorders (Gregg).
1944	The first evidence of postnatal effect following prenatal administration of a chemical substance. Decreased learning ability inrats caused by the administration of sodium bromide (Hamiltonand Harned).
1948	General recognition of chemically induced teratogenicity. Experiments with alkylating agents (Haskin) and trypan blue(Gillman et al.).
1952	The first report on malformations caused by drugs in humans.Multiple malformations in foetuses caused by aminopterin(Thiersch).
1959	The first report on human malformations induced by environmental pollutants. Disorders of the central nervous system anddentition caused by methyl mercury (Kitamura et al.).
1961	Thalidomide-induced embryopathy

How Drugs Affect The Fetus

Drugs that a pregnant woman takes can affect the fetus in several ways. They can act directly on the fetus causing damage or abnormal development leading to birth defects or death. They can also alter the function of the placenta usually by constricting blood vessels and reducing the blood supply of oxygen and nutrients to the fetus from the mother and thus resulting in a baby that is underweight and underdeveloped. Moreover they can cause the muscles of the uterus to contract forcefully; indirectly injuring the fetus by reducing the blood supply or triggering pre-term labor and delivery[10].

3. TERATOGENIC FACTORS AND THEIR RISKS

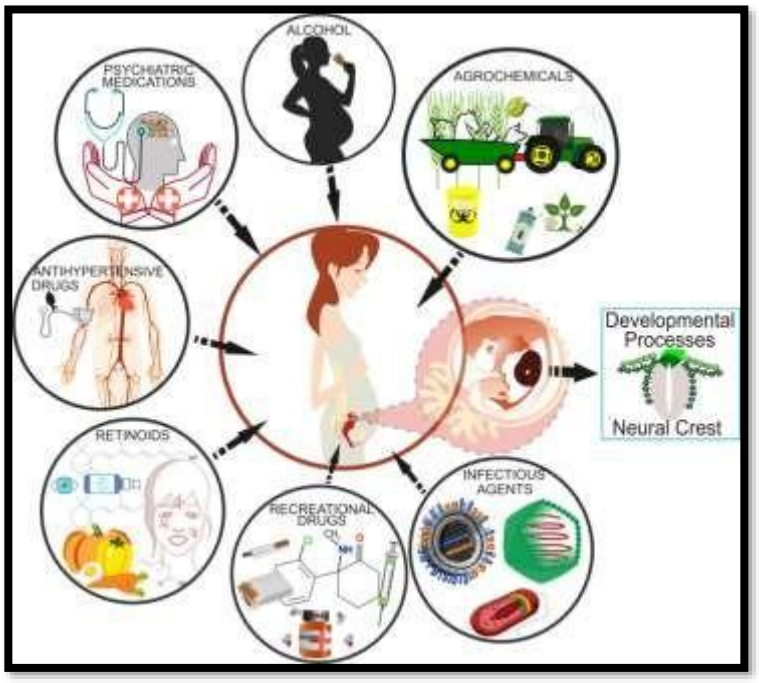

Figure no . 3 [11]

Infectious agents

Some infections during pregnancy are teratogenic like viral infections (e.g. rubella, herpes simplex and cytomegalovirus), spirochetal infections (e.g. syphilis), and protozoal infestations (e.g.toxoplasmosis). First trimester maternal influenza exposure is reported to be associated with raised risk of a number of non-chromosomal congenital anomalies including neural tube defects, hydrocephalus, congenital heart anomalies, cleft lip, digestive system abnormalities, and limb defects [12].

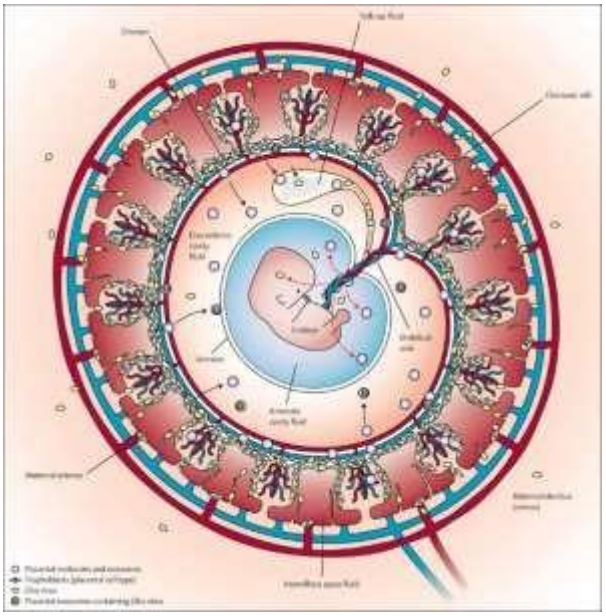

Figure no.4 The gestational sac in the first trimester before the onset of maternal placental blood flow [13]

Alcohol

During the primary four weeks of pregnancy, the baby develops the foremost crucial organs and organ systems in their body, such as the heart, central nervous system, eyes, arms, and legs. The baby's brain starts developing around the third week of its intrauterine life and steadily matures together with the pregnancy. Whenever the mother consumes alcohol, it can easily bypass through the placenta, giving rise to irrevocable changes. Alcohol breakdown within the baby's body is way slower than the fully mature adult body. Thus, causing irreparable changes in fetal development. One can barricade these changes by avoiding alcohol consumption during pregnancy and protecting the baby from fetal alcohol spectrum disorder [14].

CHEMICAL AGENTS

Medical prescription and over-the-counter drug use are common and necessary for many pregnant women nowadays. The principal challenge of prescribing physicians is "Will these drugs induce teratogenic effects?" Such a drug-phobia arose after the eruption of thalidomide teratogenicity disaster in 1960s; when the drug was used to relieve morning sickness associated with pregnancy.6 Most of medication exposures during pregnancy do not carry an increased risk of congenital malformations. health literacy and perception of teratogenic risk, beliefs about medications, and adherence or nonadherence to prescribed medicines during pregnancy. It was found that health literacy was significantly associated with maternal health behaviors regarding medication non-adherence. Clinicians should devote some time to inquire into their patients' ability to understand health information, perception and beliefs, in order to promote drug adherence during pregnancy.[15]

- Osteoporosis, osteomalacia , osteosclerosis, hyperostosis, and osteonecrosis may be related to drug effects.
- Methotrexate osteopathy is characterized by bone pain, osteoporosis, and insufficiency fractures.
- Antiepileptic drugs may cause rickets, osteomalacia, osteoporosis ,and increased risk for fracture, and phenytoin can cause calvarial thickening.
- Retinoids may produce birth defects, hyperostosis, ligament calcification, or ligament ossification.
- Fluorosis results in characteristic skeletal changes, including osteosclerosis and calcification or ossification of tendons and ligaments.
- Fluoroquinolones may produce tendinopathy or tendon tears, especially in patients with other predisposing conditions.
- Infection may complicate immunosuppressive or anti-TNF alpha drugs [16].

MATERNAL CONDITIONS

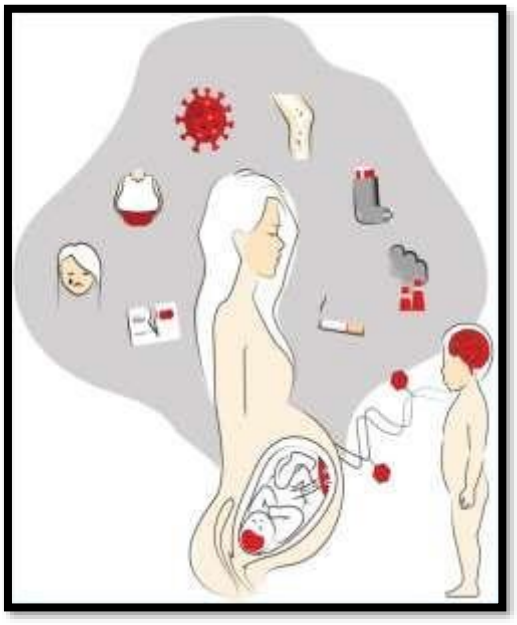

FIGURE NO .5[17]

DIABETIS

Maternal pregestational diabetes (type 1 or type 2) poses an increased risk for a broad spectrum of birth defects. To our knowledge, this problem first came to the attention of the Teratology Society at the 14th Annual Meeting in Vancouver, B.C. in 1974, with a presentation by Lewis Holmes, "Etiologic heterogeneity of neural tube defects". Although advances in the control of diabetes in the decades since the discovery of insulin in the 1920's have reduced the risk for birth defects during diabetic pregnancy, the increasing incidence of diabetes among women of childbearing years indicates that this cause of

birth defects is a growing public health concern. Major advances in understanding how a disease of maternal fuel metabolism can interfere with embryogenesis of multiple organ systems have been made in recent years[18].

HYPERTENSION

Hypertensive disorders of pregnancy, an umbrella term that includes preexisting and gestational hypertension, preeclampsia, and eclampsia, complicate up to 10% of pregnancies and represent a significant cause of maternal and perinatal morbidity and mortality. Despite the differences in guidelines, there appears to be consensus that severe hypertension and non-severe hypertension with evidence of end-organ damage need to be controlled; yet the ideal target ranges below 160/110 mmHg remain a source of debate [19]. The prevalence of hypertension in reproductive-aged women is estimated to be 7.7%[20].Hypertensive disorders of pregnancy, an umbrella term that includes preexisting and gestational hypertension, preeclampsia, and eclampsia, complicate up to 10% of pregnancies and represent a significant cause of maternal and perinatal morbidity and mortality[21].

4. 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

- **Whole Embryo Culture Test**
- **Micromass Teratogenic Test**
- **Emryonic Stem Cells Test**
- **Dictyostelium Discoideum Based Assay[23]**

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[24]. 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 [24]. 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. If it is, risk of these abnormalities is increased. Alternatively, a blood test (called cell-free fetal nucleic acid [cfDNA] testing) may be done. For this test, small fragments of the fetus's DNA, which are present in the pregnant woman's blood in tiny amounts, are analyzed. This test can accurately determine the risk of Down syndrome and some other chromosomal abnormalities in couples with a high risk of having a fetus with a chromosomal abnormality. The test can be done as early as 10 weeks of pregnancy but can also be done later. Many doctors offer this test to all pregnant women[24,25]

- **WHOLE EMBRYO CULTURE TEST**

FIGURE NO .6

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 em-bryos, 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 . Regrettably, at present no general agreement exists on the extent of correlation between many of these events and terato-genicity. So, the three endpoints generally used are mortality, malformation and growth inhibition . Whole embryo culture fulfills most of the requirements of Wilson`s ideal teratogenicity screen. However, teratogen test systems employing embryo culture are unlikely to be adopted as sole predictors of teratogenic potential in humans. The validity of data derived remains un-certain. In particular, variations due to techni-cian biases in terms of judging malformation and in selecting test concentrations narrow the significance of gained results [26]. Despite these limitations, the potential of whole embryo culture systems to mimic human teratogen metabolism, coupled with their assessment of developmentally relevant endpoints may secure their place in a battery of teratogen screens[27].

MICROMASS TERATOGENIC TEST

The in vitro micromass 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 compounds such as pharmaceuticals, agricultural and 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 embryotoxicity (Flint,1993)[28]. The Micromass culture technique, devised by Umansky (1966), reported that when cells from the undifferentiated mesenchyme of early chick embryo limbs cultured in small volumes at high density, they formed numerous small foci of differentiating chondrocytes within a background of apparently undifferentiated cells. It has been well documented by now that the characteristics such as cell proliferation, adhesion, movement, division, differentiation and cell to cell extracellular matrix interactions all occur in micromass cultures (Flint, 1983; Umansky, 1966). The test involves exposing the rat embryo limb cells or cells of central nervous system (CNS) to various test agents for different time intervals and estimating the inhibition of cell differentiation in these cultures (Flint, 1984; Tsuchiya et al., 1991). In principle,the micromass teratogen test is based on detecting the ability of a particular chemical to inhibit the formation of foci. Thus the positive chemicals will reduce the number of foci or number of cells within foci. Any interference with these basic cell developmental functions may provide primordial endpoints for detecting teratogenecity in vitro. The technique has subsequently been modified for use with 96 well microtitre plates (Flint, 1993). Flint (1983) also introduced the use of central nervous system cell culture[28].

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 unspecialized but can be triggered to become specific cell type of the body such as heart, nerve, or skin 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 caused by mutations and teratogens affecting early human development could also be studied on this basis. Moreover, 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 cell-based developmental assays for pharmacological and toxicological screening[29].

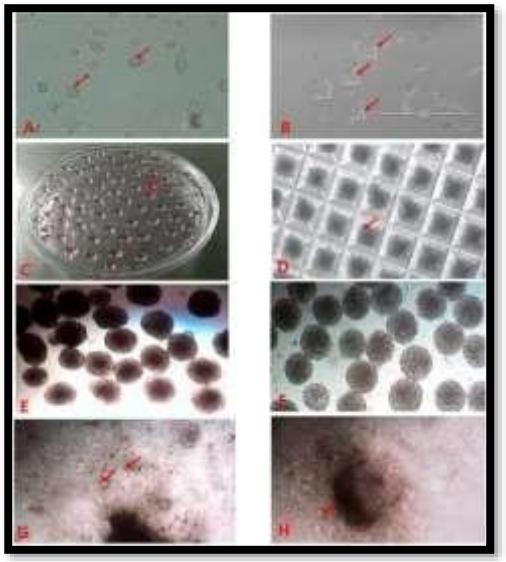

FIGURE NO .7 [30].

FDA CATEGORIES FOR DRUG USE IN PREGNANCY

In 1979, the Food and Drug Administration developed a system determining the teratogenic risk of drugs by considering the quality of data from animal and human studies. It provides therapeutic guidance for the clinician. Category A is considered the safest category but some drugs from categories B, C and D are also used during pregnancy .Category X is the only rating that denotes a drug is absolutely contraindicated for use during pregnancy [31,32].

Table no .2 FDA categorization of drugs for use in pregnancy[31,32].

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. Or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to thefetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

TABLE NO.3 PRESCRIBING IN PREGNANCY [33].

PRINCIPLES OF PRESCRIBING DURING PREGNANCY
➢ **Where possible use nondrug therapy.**
➢ **Prescribe drugs only when definitely needed.**
➢ **Choose the drug having the best safety record over time.**
➢ **Avoid newer drugs, unless safety is clearly established.**
➢ **Over-the-counter drugs cannot be assumed to be safe.**
➢ **As far as possible, avoid medication in the initial 10 weeks of gestation.**
➢ **Use the lowest effective dose.**
➢ **Use drugs for the shortest period necessary.**
➢ **If possible, give drugs intermittently.**

CONCLUSION

A large proportion of pregnancies are unintended. Most pregnancies are not diagnosed until after the early period of organogenesis. Environmental exposures, illnesses, and teratogens can have adverse effects on the fetus very early in pregnancy. Chronic disease management and modification of lifestyle behaviors can be adjusted prior to conception. Preconception care could protect from these adverse effects by informing, screening and managing couples. Keeping the fetus safe from teratogens during pregnancy can help prevent congenital disabilities. The first step is to be aware that certain harmful substances can reach the fetus in the womb and negatively affect their development. Avoiding teratogens helps support a healthy pregnancy and gives your baby a great start in life. Next, be open with your healthcare provider about medications you take, as well as alcohol consumption and workplace or living conditions. They can help answer your questions about what substances may cause birth abnormalities and ensure you and the fetus are safe.

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