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Teratogenic Agents and Related Conditions

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Abstract

The term "Teratogens" was first described in Paris, France in early 1932. "Teratogens" comes from the Greek word τέρας teras, which means "monster" or "marvel". For centuries, the meaning of the term "teratogens' changed and nowadays it refers to many factors, agents or substances that can compromise the normal development of the fetus.

Many factors/agents such as physical, chemical and environmental were found to be harmful when exposure to them occurs during the pregnancy. Exposure to high doses of ionizing radiation, usage of medications, viral and bacterial diseases during the pregnancy can only result in fetus death, congenital malformations and miscarriages.

Introduction

Teratology is a study of the etiology of abnormal development or study of birth defects. Teratogens therefore are agents or substances that cause malformations in the developing fetus. Teratogens may include: substances of abuse, hormones found in contraceptive agents, cigarette components, heavy metals, ionizing radiation as well as agents with viral or bacterial etiology.

History

The word "Teratogens" originates from the Greek word τέρας teras (genitive τέρατος teratos), meaning 'monster' or 'marvel' and was given by a physician from Paris, France in 1932 in order to explain an abnormal human and animal development. For centuries, people developed different theories about the causes for the human abnormalities. In Babylon, people believed, that infants with congenital malformations were constellations in human forms. Aristotle, who lived in Athens, Greece in the fourth century, B.C., believed that birth defects are disturbances in the reproduction, while Hippocrates claimed that a pregnant woman's experiences or emotions, which were called later maternal impressions, can affect the normal development of the fetus (Greece in the fifth century B.C.). This theory of maternal impressions persisted until the early 1900, despite any evidences for the occurrences.

At the beginning of the 19th century, Johann Fredrich Meckhel, an anatomist from Halle, Germany, claimed that deviations from the normal developmental process caused malformations and are most likely caused by agents, called teratogens.

Following Meckel, scientists in the nineteenth century began experimental studies to detect the effect of different teratogens on chicken eggs. Since then, there are many reports of successfully produced abnormalities in chick embryos caused by teratogenic agents.

Nowadays, the meaning of teratogen has been given to a drug or other substance capable of interfering with the development of an embryo fetus that may lead to birth defects or developmental malformations.

The term "teratogens" was popularized in the 1960s by David Smith1, whose name was associated with the discovery of FOAS (fetal Alcohol Syndrom).

Types of teratogenic agents

For the last decades, scientists have tried to classify teratogens based on their nature and etiology. Today, teratogens can be classified in three different categories:

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Physical teratogens
Infectious diseases as teratogens
Chemical teratogens

Environment teratogens is another group of agents that according to some authors can include both physical teratogens as well as infectious agents.

Physical teratogens

Physical teratogens can be ionizing or nonionizing radiation, hypothermia and mechanical forces. Some scientists classify the hypothermia into the maternal conditions group but it can be included as a physical factor as well.

Pregnant women are at risk if exposure to ionizing and non-ionizing radiation occurs. In utero, the exposure to non-ionizing radiation is not associated with significant risk for development of fetus, while the exposure to ionizing radiation can be extremely teratogenic.

X-rays Ionization or ionizing radiation

Ionizing radiation is the energy that moves atoms in a molecule and is able to remove tightly bounded electrons from atoms, creating ions. Usually ionizing radiation are X-rays and gamma rays. X-rays are part of the electromagnetic spectrum and are used to image the inside of objects (medical radiography). This is a type of ionizing radiation that can be harmful to living tissues at highly dosage.

Ionizing radiation is classified as a teratogenic agent because the exposure at high enough levels can cause development risk of the fetus and lead to severe malformations such as mental retardation, impaired brain development, cancer in later life. The eventual adverse effects in fetus depend on the dosage, time of exposure and the gestation age of the fetus. An embryo is most susceptible to the ionizing radiation during the organogenesis especially at first and second trimester of development. High levels of ionizing radiation can injure embryonic cells, resulting in death, retardation of mental development or chromosomal injury.

Nonionizing radiation

Non-ionizing radiation is low energy radiation that is not able to ionize atoms or molecules. It includes sources like power lines, infrared radiation, microwaves and ultrasonography and magnetic resonance imaging. Usually non-ionizing radiation interacts with the tissues through the generation of heat and no substantial risk has been identified 2, 3.

Today, there are no conclusive data that the non-ionizing radiation can be harmful for the developing fetus. Therefore, the ultrasonography is safe to be performed during pregnancy only when it is medically indicated and the lowest possible settings are used.

Mechanical forces

Some of the prescribed medications, taken during the pregnancy, can trigger forceful uterine contractions that can eventually lead to inuring the fetus. Other can compromise the function of the placenta and thus reducing the supply of oxygen and nutrients from mother to the fetus. The movements of the fetus can be restricted by malformations of the uterus and thus to be a reason for congenital dislocations.

Infectious diseases

Many infectious diseases like Varicella Zoster Virus (VZV), Cytomegalovirus (CMV), mumps, toxoplasmosis, rubella during the pregnancy can lead to congenital malformations in fetus. Primary or recurrent CMV infection during the pregnancy can lead to intrauterine growth restrictions, microcephaly, hydrocephaly and delayed psychomotor development. Most common complications of pregnancy when exposure to Herpes virus occur is intrauterine growth restriction, preterm labor and miscarriage4, 5.

One of the most teratogenic viruses is rubella virus. Congenital rubella syndrome (CRS) is characterized by microcephaly, intracranial calcification and neurologic diseases.

Chemical factors/agent

Variety of medications and drugs in abuse are considered to be chemical teratogens. Chemical agents with teratogenic effect can be heavy metals, herbicides and industrial solvents.

Drugs

Majority of pregnant women are exposed to medications during pregnancy. Most of the drugs, taken by a pregnant woman, can cross placenta and thus act directly on the fetus causing damage, abnormal development or death.

According to FDA, there are five categories that can cause birth defects if used during pregnancy (**Figure**.1). Examples for medications, belonging to each group is given in table 1.

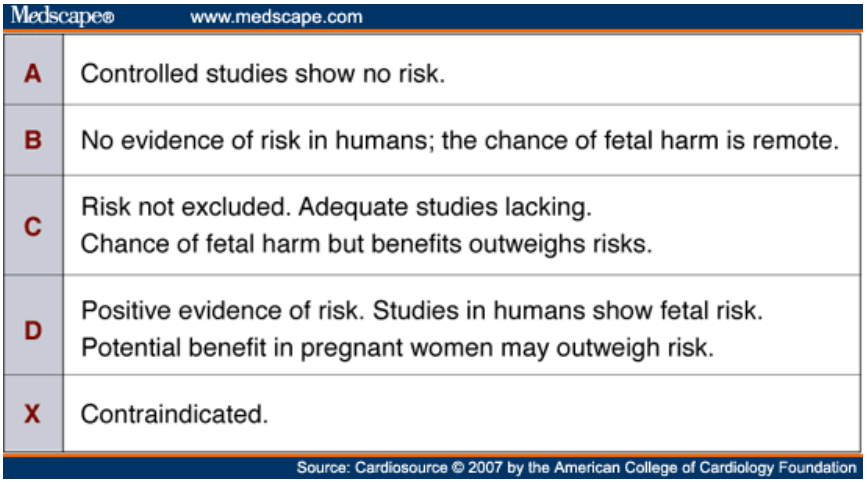

Figure 1. FDA categories of drugs

Figure, borrowed from www.medscape.com6

Table 1. Medications, referred to each drug category

Category	Medication	Effect
A	Folic acid	Important for the proper development of neural tube of the fetus
B	cyclobenzaprine, amoxicillin	Cyclobenzaprine is muscle relaxant used for skeletal muscle spasm and fibromyalgia syndrome; Both are safe to use during pregnancy
C	trazodone, prednisone	Trazodone is antidepressant and there is no data showing that taken during pregnancy causes birth defects. Prednisone is corticosteroid and data shows increased incidence of cleft palate

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D	clonezapam, lorazepam	Anticonvulsant agent can cause congenital malformations. Lorazepam belongs to benzodiazepines which are known with its neurotropic properties. Lorazepam affect the neural crest cells during organogenesis.
X	warfarin, methotrexate	Warfarin, is anticoagulant and taken during pregnancy can cause cerebral hemorrhage, hypoplasia of baby's nose and epiphyses. Methotrexate is folic acid antagonist. Taken during pregnancy it can lead to growth retardation, skull defects, cleft palate.

Dugs in abuse

Alcohol

It is well known that an exposure of pregnant woman to some drugs can interfere with normal development of the fetus. It depends not only on the susceptibility of the mother and the fetus, but also the chemical and pharmacological nature of the agent, its dose, the time of gestation age at which the exposure occurs and the time of exposure. Drugs in abuse can be alcohol, tobacco, marijuana, cocaine, methadone, etc.

Alcohol is a CNS depressant and consumption of it during pregnancy can lead to congenital anomalies called fetal alcohol syndrome (FAS). Characteristic features of fetal alcohol syndrome fetal alcohol syndrome occurs in 30-40% of women who drinking heavily during pregnancy. The alcohol freely cross placenta and thus impact negatively the nervous system of the fetus. This can result in functional, neurological and structural abnormalities in the developing fetus.

Tobacco

Many studies show, that smoking during pregnancy can increase from up to 80% the risk of congenital malformations of the fetus. Usually, low birth weight is associated with smoking during pregnancy7.

Marijuana, cocaine, amphetamines

All three groups are well known drugs of abuse. The possible adverse effect of them on the developing fetus can be associated with cardiovascular malformations8, behaviors disturbances, low weight and growth retardation.

Lead, mercury

Lead and mercury exposure in pregnancy can result in neurological delays, miscarriages and encephalopathy. Sometimes consumption of freshwater fish, containing enough mercury can harm the development of the nervous system of the embryo or fetus.

Air pollution

Many compounds such as nitrogen dioxide and carbon monoxide can negatively affect pregnancy and cause growth restrictions, low birth weight and heart and lung problems9.

Figure 2 shows some of the environmental teratogens and their adverse effect.

Some Potentially or Positively Teratogenic Drugs

Category	*Example*	*Drug Use*	*Teratogenic Effect*
Alcohol (ethanol)	Wine, whiskey	Social use	Fetal alcohol syndrome
Analgesics	Acetylsalicylic acid (aspirin)	Minor pain relief	Prolonged pregnancy; maternal bleeding
	Nonsteroidal anti-inflammatory drugs (NSAIDs)		Patent ductus arteriosus
Antineoplastics	Methotrexate	Chemotherapy	Multiple anomalies
	Cyclophosphamide (Cytoxan)	Chemotherapy	Multiple anomalies
Androgens	Danazol	Endometriosis	Masculinization of female fetus
Anticonvulsants	Phenytoin (Dilantin)	Seizures	Fetal hydantoin syndrome
	Valproic acid		Neural tube defects
	Carbamazepine		Neural tube defects
	Lamotrigine		Possibly fetal anomalies
Anticoagulants	Warfarin (Coumarin)	Anticoagulation	Fetal bleeding or anomalies
Antidepressants	Imipramine (Tofranil)	Elevate mood	Cardiovascular anomalies
Antidiabetic agents	Chlorpropamide	Lower blood glucose	Neonatal hypoglycemia
Antischizophrenic	Lithium	Schizophrenia	Hydramnios
Antithyroid	Methimazole	Hypothyroidism	Hypothyroidism in fetus
Antibiotics	Ribavirin	Respiratory infection	Multiple anomalies
	Sulfonamides	Infection	Hyperbilirubinemia in newborn
	Tetracycline	Infection	Teeth and bone deformities
Antihelmintics	Lindane	Eradication of lice	Manufacturer recommends limiting exposure to 2 doses
Angiotensin-converting enzyme inhibitors	Enalapril (Vasotec) Captopril (Capoten)	Reduce hypertension	Oligohydramnios
Caffeine	Coffee, soft drinks, chocolate	Social use	Low birth weight
Hypoglycemics	Tolbutamide (Orinase)	Type 2 diabetes	Profound hypoglycemia in newborn
Nicotine	Cigarette smoke	Relaxation	Growth restriction
Radiopharmaceuticals	Iodide-131	Diagnostic studies	May destroy thyroid of fetus
Narcotics	Cocaine	Social pleasure	Dysmorphic and CNS anomalies
	Heroin		Growth restriction; narcotic withdrawal in newborn
Tranquilizers	Benzodiazepine (diazepam)	Reduce anxiety	Growth restriction; CNS dysfunction
			Hypotonia, respiratory depression
Vaccines (live)	Rubella	Provide immunity	Possible infection in fetus
Vitamin A derivatives	Isotretinoin (Accutane)	Acne	Craniofacial, cardiac, CNS anomalies
	Etretinate (Tegison)	Psoriasis	Craniofacial, cardiac, CNS anomalies

Figure 2. Teratogenic agents and their adverse effects.

Table, borrowed from http://tr-i-life.tumblr.com/post/31097290784/pharm-for-ob-teratogenic-effect

Maternal medical condition

Increase incidence of developing heart diseases, central nervous system defects and congenital malformations usually is observed on babies of mothers with diabetes mellitus. A strict glycemic control in first trimester of pregnancy is critical.

Table 2 shows all teratogenic factors that influence the development of the fetus and its adverse effects

Table 2. Teratogens and adverse effects.

Agent	Example	Structural anomaly
Drugs	Alcohol	Microcephaly, heart defect
	Cocaine	Vascular disruption
	Valproate	mandibular/ear abnormalities
	Vitamin A	Spina bifida
Infection	Rubella	Microcephaly, heart defect
	Toxoplasma	Hydrocephalus
	Varicella	Limb defects
Maternal factors	Diabetes	Heart defects, neural tube defects
	Phenylketonuria	Microcephaly, heart defect

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Physical agents	V-ray	Neural tube defects, CNS abnormalities
	Hyperthermia	Microcephaly, heart defect

Factors influencing the effect of teratogens

The pathogenic effect of teratogens is associated with the nature of the agents, their mechanism of action, gestation age at which the exposure occurs as well as the dosage and duration of that exposure.

Nature of teratogenic agent and the ability to cross placenta

Not all teratogens can pass directly through the tissue (radiation and ultrasound). Most of the teratogenic agents access the embryo through fluids (blood) after formation of the placenta. Now it is known that the "placenta barrier" does not protect the fetus from readily passing pharmacologic substances through it. Teratogenicity of agents depends on their ability to cross placenta. The nature of teratogens is strongly related to that ability. Teratogens with high molecular weight of 500Da (and less) and low ionic charge can pass placenta by simple diffusion. Some chemical compound with greater molecular weight (above 600Da) cannot pass through placenta readily, therefore heparin (with molecular weight of 20 000Da) as a coagulant can be given instead of warfarin-like compounds during pregnancy10. Placenta transfer depends strongly not only on the chemical structure of teratogens, but also on the placenta proteins, related to the binding with the agents, crossing placenta. Since the placenta is buildup of membranes with lipid structure, the transfer of lipid-soluble agents is more facilitated. Or in other word, the more lipid soluble, the easier the drug crosses placenta. Also, the transport depends on the size of the compound and its charge. The less charged and the smaller the molecule is, the more easily it crosses placenta9. For example, retinoids are considered to be teratogens and should not be taken during the pregnancy due to their ability to easily cross placenta. Taking Vitamin A supplements above RDA of 2,700 IU can result in hydrocephalus, heart defects and defects in cardiovascular system.

Mechanism of action

There are several mechanism of action of teratogens described. Folic acid inhibitors, drugs that can change the metabolism of hormones, redox-cycling agents and neural crest inhibitors are four types of teratogens that have different mechanism of action. They have their unique way to inhibit/change the metabolism of the fetus and thus to lead to variety of congenital malformations.

Folic acid antagonists

Folic acid is essential for normal development of neural tube of the fetus. Some drugs, taken during pregnancy, can inhibit the synthesis of folic acid. Many anti-folic agents targeting fast-dividing cells and thus result in adverse effects on the skin, hair, bone marrow. Trimethoprim, for example, is prescribed for treatment of urinary infections and there is data showing that taken during first trimester can lead to increased risk of neural tube defects as well as oral clefts, urinary-tract defects and cardiovascular defects.

Antibiotics as folic acid inhibitors, such as tetracycline's, can easily cross placenta and inhibit the bone growth of the fetus. The usage of aminoglycosides during first trimester of pregnancy can lead to congenital deafness.

Hormones as disruptors of endocrine system

The metabolism of endogenous hormones may be disrupted by many synthetic estrogens, given during pregnancy. One of the mechanisms of synthetic estrogens is disruption of the signaling pathway of androgen that can lead to reproductive disorders in offspring. Androgenic hormones such as synthetic progesterone, which were used in treatment of breast cancer, can lead to spontaneous abortions. Using them to control the bleeding during pregnancy can result in masculinization of female fetuses11. Hormone disruptors may either block the binding of a hormone to its receptor or block their synthesis.

Oxidative stress

Many drugs that are widely used for treatment of cardiac diseases and epilepsy are known as redox cycling agents. Their mechanism of action involves formation of various radicals such as superoxide that can lead to oxidative stress and thus inactivate many enzymes and cell death12. Current antiepileptic drug targets are voltage-gated sodium and potassium channels, responsible for depolarization of the nerve cell membrane. Blocking the membranes, they lead to generation of radicals that are harmful for the organogenesis.

Exposure to sodium valproate as an antiepileptic drug has high risk of major congenital malformations13, while treatment with carbamazepine has lower risk of birth defects.

Neural crest disruptors

This group includes drugs that cause interference in migration, proliferation and differentiation of neural crest cells. Some of teratogenic drugs within this group are bosentan, isotretinoin and ketoconazole14. Since the neural crest is important pluripotent cell population for cranial and cardiovascular region, the treatment with neural crest inhibitors during pregnancy leads to cardiovascular and craniofacial malformations.

Timing of exposure

An important factor for the normal development of the fetus is the time (gestational age) when the exposure to teratogens occurs. All embryo organs passes through different periods of development during each it can be or cannot be susceptible to teratogens.

Each organ has its critical period of development which corresponds to the time when the organ develops most rapidly. During this critical period, exposure to teratogens can cause morphological changes to the fetus. **Figure** 3 shows the stages of development of the fetus and its sensitivity to teratogens.

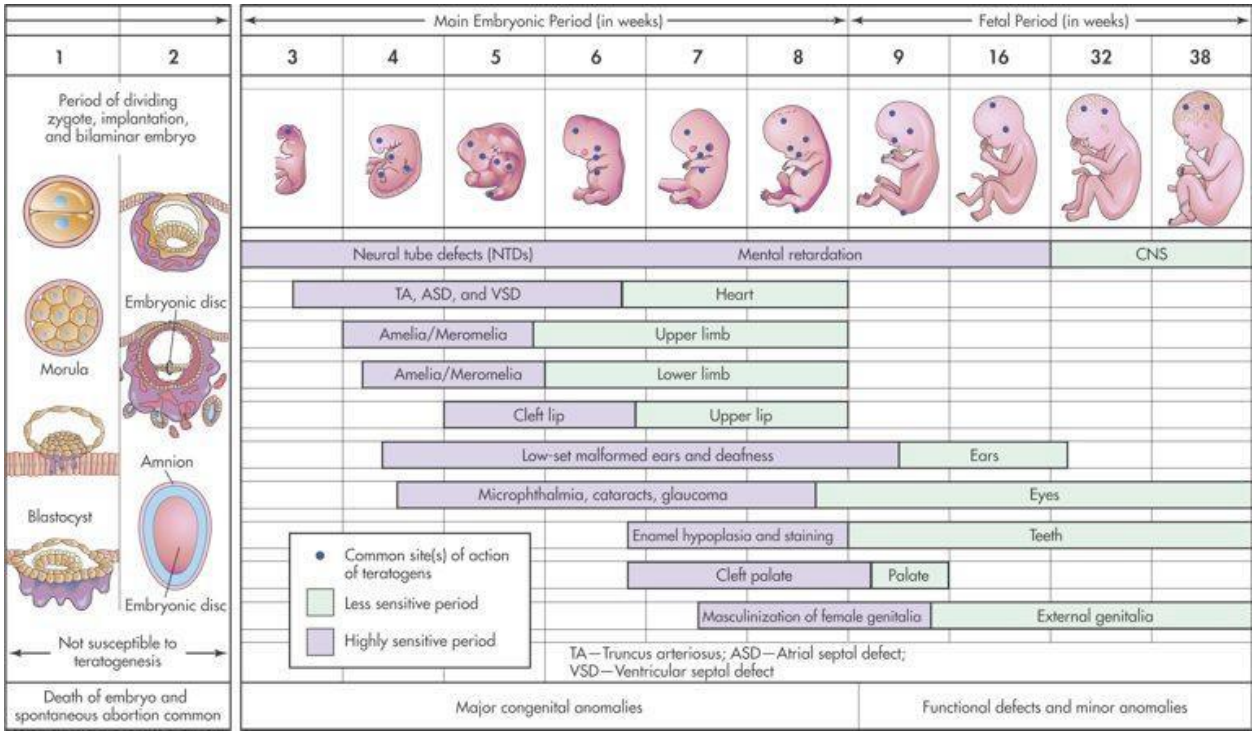

Figure 3. Stages of fetus development and sensitivity to teratogens

Figure15, borrowed from https://sara1hays.wordpress.com/2008/02/12/antepartal-care-teratology/

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As shown in **Figure**.1, each organ has limited period of susceptibility to teratogens. There are periods to where the particular organ has less or higher sensitivity to the agents. Usually the first eight weeks of early development are essential and the development of the fetus can be compromised by teratogens. Drugs, prescribed for nausea and vomiting in pregnancy like Antihistamines (H1 blockers) have been used for treatment of morning sickness. Some of them have been associated with fetal malformations when they were used in first weeks of pregnancy. Thalidomide (for leprosy and cancer treatment) was widely used as an anti-nausea agent and in 1960s and one of the birth defects observed was shortened limbs.

Usually, first trimester exposure to variety of teratogens is a risk factor for major congenital malformations. For example, many epileptic drugs, taken during first trimester of cause congenital malformations like cleft palate, cardiovascular defect and growth retardation.

Exposure to teratogens during second and third trimester also has risk to the fetus and unlikely result in physical birth defects. The critical period for brain growth is from 3 to 16 week, so exposure to teratogens during the period can result in mental retardations during both embryonic and fetal period. The stage of exposure is a critical parameter for the normal development of the embryo/fetus (table 3)

Table 3. Stage of exposure and related outcome.

Stage of exposure	Outcomes
Pre-implantation	Embryonic lethality
Implantation to time of organogenesis	Morphological defects
Fetal-neonatal stage	Functional disorders, growth retardation

Variety of analgesics (aspirin), anticonvulsants, anticoagulants, Vitamin A, aminoglycoside can affect the fetus if taken in first trimester of pregnancy. The possible adverse effects are shown in table 4.

Table 4. Adverse effect of some of teratogens during first, second and third trimester of pregnancy.

Trimester	Teratogen	Adverse Effects
First trimester	analgetics (aspirin)	Gastroschisis; during pregnancy can lead to bleeding because aspirin decrease platelet aggregation
	anticonvulsants	Fetal hydantoin syndrome; congenital heart disease, short limb formation
	anticoagulant (Wafarin)	Fetal wafarin syndrome; respiratorry distress syndrome
	Antidepresant	cleft palate; cardiovascular defect
	Vitamin A	Cranio-facial dysmorphism
	aminoglycosides	Ototoxicity, congenital deafness
Second trimester	ACE inhibitors (Diazepam)	death, fetal hypotension, cleft palate
Third trimester	Antibiotics (Tetraciclines)	maternal hepatotoxicity; dental discoloration in children

	ACE inhibitors (Diazepam)	death, fetal hypotension, cleft palate
	Aminoglycosides	vestibulary nerve damage
	Sylfamethoxazole trimethoprim	neonatal haemolysis

Pattern of exposure

The duration of the stimulus and the dose of exposure to teratogens are related to the type of abnormalities. Usually the dose of the teratogenic agent is critical and it influences the degree of harm of the fetus. In order to control the level of exposure to teratogens, the dose-response function is important to be known for each particular component. The range of doses can be devided into three categories - subthreshold, teratogenic and lethal category.

In general, there is a range of doses below which no effect occurs (low teratogenicity, no effect on the fetus). The exposure dose in this case is referred to as threshold dose (**Figure**.4). Usually an increase of intensity or duration of treatment reflects to an increase in frequency and severity of the defect.

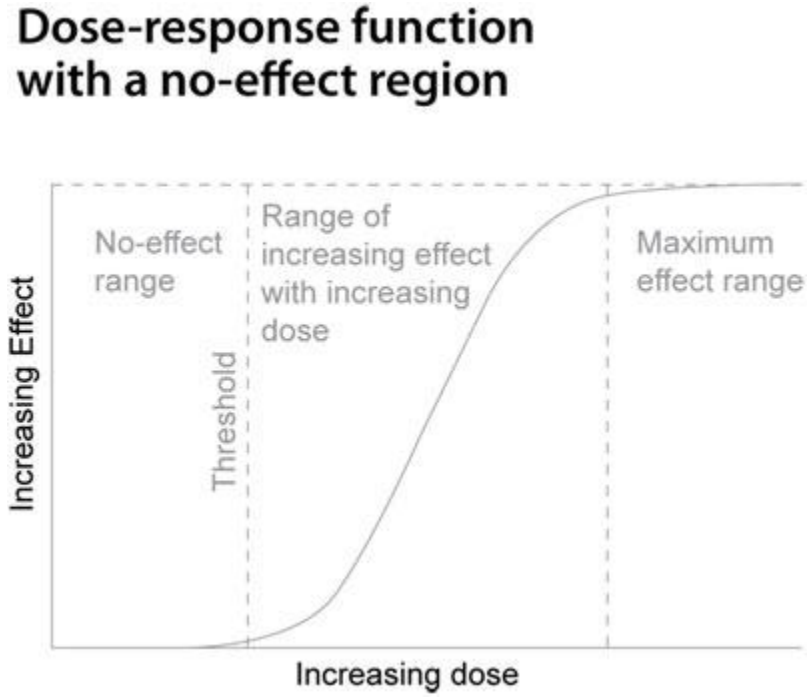

Figure 4. Dose-response effect of teratogens

Table was borrowed from http://www.mackinac.org/media/images/2010/MS2010-01-graph1LRG.jpg

The teratogenicity depends on the route of administration of the agent as well. An example of dose-response relationship is Accutane taken by mouth and Rein A, applied topically for treatment of acne of pregnant women. Accutane causes major malformations and high rate of mental retardations while the Retin-A has no effect on the development of the fetus. Another example is the dose-relationship between Valproic acid given in different dosages. When the dose, to which the fetus was exposed, is around 75mg/l, the most common adverse effect is spine bifida. In contrast, exposed fetuses to dose of 44mg/l there are no any birth defects observed17.

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Genetic factors

The susceptibility to environmental agents varies extremely from one individual to another, even after an identical exposure to teratogens occurs. Both maternal and fetus genotypes can affect the teratogenicity of variety environmental agents.

There is evidence, that compromised embryo glucose control for example predispose embryo to developmental anomalies. Other metabolite syndromes and diseases such as diabetes create a compromise environment for the developing embryo.

The genetic factor is very important for the susceptibility to certain teratogens and the outcome of the teratogenicity.

There are evidences that the intrauterine exposure to valproate show that not all fetuses were born with birth defects. This confirms the fact that there is multifactorial factor in which other components were involved, mostly likely genetic predisposition19.

Risk factors

Teratogens any agents from the environment, that can cause variety of birth defects and congenital malformations of the developing fetus. They can cause damage only if the exposure occurs during sensitive periods of the development.

There are some risk factors that are essential and the normal development of the fetus depends strictly on them:

Maternal health status (existing maternal conditions such as hypertension, diabetus mellitus).

Nutrition - pregnant women should be advised to take vitamin supplements, eat folacin rich food and should take 400ug folic acid daily.

Stress - prolonged stress can put a fetus at risk for lower birth weight and children with emotional problems and behavior disorders.

Working environment - pregnant women should avoid working in environment with hazardous compounds

Prevention

Variety of birth defects and congenital malformations are caused by many environment factors. Prevention is important part for the normal development of fetus.

One of the prevention factors is the modification of the prenatal environment. This can be achieved when pregnant women consume 400mg of folic acid daily so normal development of neural tube can occur. The intake of folic acid supplements show prevention of 50% to 70% of neural tube defects in fetus.

Limiting exposure to teratogens such as smoking, alcohol consumption, medications, hazardous materials and industrial chemicals.

Reducing sugar intake. The right nutrient balance is an important factor in the development of a healthy child. The control of gestational diabetes by limiting sugar intake and exercising is extremely important for the normal outcome.

Detection and early treatment of birth defects - ultrasonography and maternal serum screening to detect serious fetal anomalies, neural tube defects and chromosomal disorders.

The awareness of the effects of various teratogen factors could reduce the probability of some birth defects.

Risk assessment

It is important to fully understand and evaluate the potential risk to pregnant women’s health from exposure to variety of teratogen agents including chemicals, drugs, medications, environmental factors. The exposure too many chemicals, hazardous materials, pharmaceutical drugs can compromise the normal development of the embryo.

In order to assess the risk of all environmental factors that can influence the development of the fetus, four steps were followed:

1. Identification of drugs, medications, hazardous material - important to determine whether the medication that was prescribed or the chemical component that the mother was exposed to during the pregnancy is related to particular health effects.
2. Dose-response - it is very important to determine the relationship between the dose of the environmental factor and the probability of occurrence of health effects.
3. Type of exposure - it includes the source of exposure and the pathways of exposure.
4. Teratogen risk counseling - counseling to possible teratogenic risks should be provided by physician or other health care professionals. When estimating the potential teratogenic risk, the maternal health and the gestational age should be taken as a consideration.
5. Risk characterization - to describe the possibility of the risk, including all sources of uncertainty.

Work-related aspects

Approximately 10% of all birth defects are caused by environmental contaminants such as chemicals, industrial products, and air pollution. According to statistic, there are about 4 million chemicals presented in home and work environments. Many hazardous compounds are found to be teratogenic and are harmful for pregnant women. The control on the working environment is strictly regulated by three instances. The Occupational Safety and Health Administration (OSHA) is a federal agency responsible for setting standards for working with hazardous materials. Protection Agency (PA) is responsible for controlling the maximum levels of hazardous substances in the air and water. Finally, Food and Drug Administration 9FDA) regulates the presence of hazardous compounds in food, drugs, cosmetic products. While all of these agencies work to protect the health of the public, it is still possible for a pregnant woman to be exposed to these harmful chemicals. Knowing which to avoid during pregnancy is crucial to protecting the health of the mother and her child.

Hazardous compounds such as toluene, xylene, organic solvents, methyl ethyl ketone, chlorine, ethers are all teratogens that can compromise the development of the fetus. Pregnant women, working with hazardous material should avoid contact with them in order to minimize the risk of birth defects.

Conclusion

Prevention and risk assessment of teratogens is essential for the normal development of the fetus. The exposure to variety environmental factors such as chemical, physical, viral/bacterial diseases can lead to many congenital malformations or birth defects.

Very recently, FDA provided key messages for the management of teratogens in order to mitigate teratogenicity risk. The risk management strategies are divided into two groups.

Label + Med Guide - includes boxed warning, contraindication, warning and precaution and pregnancy category.

REMS - includes pharmacy certification, health care setting limits, and patient access to drugs, patient monitoring and patient registry.

Endpoint measure, measures of risk and compliance assessment could potentially provide determination of effectiveness and management of exposure to teratogens and to limit the adverse effects19.

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