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STUDY AND ESSENTIAL REVIEW OF TERATOLOGY AND TO ENHANCE THE QUALITY OF LIFE IN PREGNANCY

C. Mani Sekhar[1*], N. Naveena[2], G. Sindhura[3], Aleem Sarwar[4], K. Bhaskar Reddy[5]

[1]Asst. Professor, Dept of Pharmacy Practice, [2]Asst. Professor, Dept of Pharmacology, [3]M Pharm, Dept of Pharmacology, [4]Asst. Professor, Dept of Pharmacy Practice, [5]Professor & Principal, Sri Venkateswara College of Pharmacy. RVS Nagar, Tirupati Road, Chittoor – 517 127, Andhra Pradesh, India.

ABSTRACT

Background:-Teratology is the science that studies the causes, mechanisms, and patterns of abnormal behavior and metabolic disorder development. Developmental disorders present at birth are called congenital anomalies, birth defect or congenital malformation. Originally Teratology study was conceived as the gross of structural malformations and that birth observable can be associated to some disturbances in the developmental. Teratogenicity, the capacity of an agent to produce birth defects, is governed by certain factors described as Principles of Teratology. Developmental stage at the time of exposure, Dose and duration of exposure, Genotype of the embryo, Mechanisms of action is specific and may involve inhibition of specific biochemical or molecular process; cell death; decreased cell proliferation or other cellular phenomena.

KEY WORDS: Teratology, Pregnancy, Quality of life.

INTRODUCTION

Teratology is the science that studies the causes, mechanisms, and patterns of abnormal behavior and metabolic disorder development. Developmental disorders present at birth are called congenital anomalies, birth defect or congenital malformation. Originally Teratology study was conceived as the gross of structural malformations and that birth observable can be associated to some disturbances in the developmental. Comparison with teratology behavior in infancy originated consideration. In the title of the research article Obstetrical and Gynecological Survey, the first term was used in the publication. Their review purpose was "Teratogenic drugs effects which is susceptible to implicate another system. That is the functional behavior and offspring adaptation of the environment. Attributed causes of variety can be birth defects 65 - 70 percentage classified all unknowing etiology. Cytogenic or chromosomal and defects number three to five of all congenital malformation approximately twenty percentage genetically in nature [1].

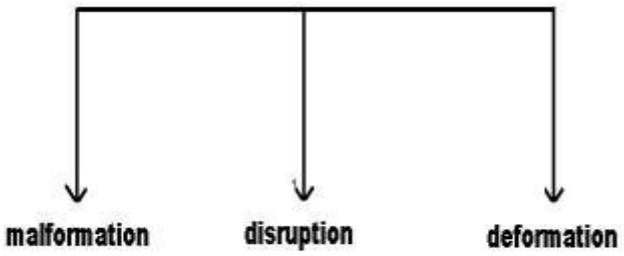
- **Malformation:** is a primary structural defect resulting from a localized error of morphogenesis
- **Disruption:** is specific abnormality that results from disruption of normal developmental processes It depends on time not on agent
- **Deformation:** is an alteration in shape / structure of previously normally formed part
- **Syndrome** : is a recognized pattern of malformations with a given etiology

Teratogenicity, the capacity of an agent to produce birth defects, is governed by certain factors described as Principles of Teratology.

Developmental stage at the time of exposure, Dose and duration of exposure, Genotype of the embryo, Mechanisms of action is specific and may involve inhibition of specific biochemical or molecular process; cell death;

Corresponding Author:- **Mani Sekhar C.** Email:- manisekhar11@gmail.com

decreased cell proliferation or other cellular phenomena. Manifestations of abnormal development are death, malformation, growth retardation and functional disorders [2].



CAUSES OF TERATOGEN:

A teratogen is any agent/factor that can produce a congenital anomaly or raise the incidence of an anomaly in the population. The teratogens have potential to affect the normal development of human embryo following maternal exposure to them.

These agents are usually environmental factors such as drugs, chemicals, radiation, maternal diseases and viruses. The effect varies from death of embryo to any structural, functional, metabolic and behavioral abnormalities.

Anomalies caused by genetic factors:

Chromosomal aberrations are common and are present in 6 to 7% of zygotes – (result =abort). Numerical chromosomal abnormalities – usually non-disjunction- error in cell division Down syndrom (21) Edwards (18) Patau (13) Turner (X0), Klinenfelter (XXY). Structural chromosomal abnormalities – chromosome breaks = translocation, deletion (cri du chat syndrome), duplication, inversion. Mutant genes – achondroplasia, fragile-X syndrome

Anomalies caused by environmental factors:

Teratogens are exogeneous agents that may cause developmental defects:

Drugs (warfarin, valproic acid, phenytoin, vitamin A, thalidomide, cytostatic drugs – cyclophosphamide, lithium carbonate), Chemicals (PCBs, methyl mercury, alcohols), Infections (rubella, cytomegalovirus, herpes, toxoplasma, syphilis), Ionizingg radiation (RTG), Maternal factors (diabetes mellitus, hyperthermia, phenylketonuria, hyper-/hypo-thyreosiss.

STAGES OF DEVELOPMENTAL AND EFFECTS OF TERATOGENS:

Trimester: In obstetrics, one of the three divisions of three months each during pregnancy, in which different phases of fetal development take place. The first trimester is a time of basic cell differentiation. The second trimester is a period of rapid growth and maturation of body systems. A second-trimester fetus that is born prematurely may be viable, given the best hospital care possible. The third trimester marks the final stage of fetal growth, in which systems are completed; fat accumulates under the soon-to-be-born baby's skin, and the fetus at last moves into position for birth. This trimester ends with birth.

First trimester:

The uterus as it changes in size over the duration of the trimesters

Minute ventilation is increased by 40% in the first trimester. The womb will grow to the size of a lemon by eight weeks. Many symptoms and discomforts of pregnancy like nausea and tender breasts appear in the first trimester [3].

Pre-embryonic period:

This is the first two weeks after fertilization. During this period, the zygote divides; implantation occurs; amnion, chorionic sac and yolk sac are formed and the embryo becomes bilaminar.

Effect of teratogens:

Teratogens acting during this period either kill the embryo (leading to spontaneous abortion which goes unnoticed as the woman may not realize that she is pregnant) or their disruptive effects are compensated for by powerful regulatory properties of early embryo (so unlikely to produce congenital anomalies).

Second trimester:

By the end of the second trimester, the expanding uterus has created a visible "baby bump". Although the breasts have been developing internally since the beginning of the pregnancy, most of the visible changes appear after this point. Weeks 13 to 28 of the pregnancy are called the second trimester. Most women feel more energized in this period, and begin to put on weight as the symptoms of morning sickness subside and eventually fade away. The uterus, the muscular organ that holds the developing fetus, can expand up to 20 times its normal size during pregnancy. Although the fetus begins to move and takes a recognizable human shape during the first trimester, it is not until the second trimester that movement of the fetus, often referred to as "quickening", can be felt. This typically happens in the fourth month, more specifically in the 20th to 21st week, or by the 19th week if the woman has been pregnant before. It is common for some women not to feel the fetus move until much later. During the second trimester, most women begin to wear maternity clothes. Embryonic period or period of embryogenesis or organogenesis. This is the period from third to eight weeks of gestation, when organ systems are being established. Effect of teratogens is the most sensitive period for inducing major birth defects [4].

Third trimester:

The uterus expands making up a larger and larger portion of the woman's abdomen. At left anterior view with months labeled, at right lateral view labeling the last 4 weeks. During the final stages of gestation before childbirth the fetus and uterus will drop to a lower position. Final weight gain takes place, which is the most weight gain throughout the pregnancy. The woman's abdomen will transform in shape as it drops due to the fetus turning in a downward position ready for birth. During the second trimester, the woman's abdomen would have been very upright, whereas in the third trimester it will drop down quite low, and the woman will be able to lift her abdomen up and down. The fetus begins to move regularly, and is felt by the woman. Fetal movement can become quite strong and be disruptive to the woman. The woman's navel will sometimes become convex, "popping" out, due to her expanding abdomen.

Head engagement, where the fetal head descends into cephalic presentation, relieves pressure on the upper abdomen with renewed ease in breathing. It also severely reduces bladder capacity, and increases pressure on the pelvic floor and the rectum. It is also during the third trimester that maternal activity and sleep positions may affect fetal development due to restricted blood flow. For instance, the enlarged uterus may impede blood flow by compressing the lower pressured vena cava, with the left lateral positions appearing to providing better oxygenation to the infant [5].

Fetal period:

This is the period from 9th week till birth. This period is characterized by rapid growth and differentiation of the organ system.

Effect of teratogens:

Fetal damage is unlikely to produce malformations but can cause death, growth retardation, disruptions or functional deficits.

US FDA Pregnancy Category:

Category A - Adequate, well-controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first (second, third, or all) trimester(s), and the possibility of fetal harm appears remote.

Category B - Animal studies do not indicate a risk to the fetus; however, there are no adequate, well-controlled studies in pregnant women. Animal studies have shown an adverse effect on the fetus but adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Despite the animal findings, the possibility of fetal harm appears remote, if used during pregnancy.

Category C - Animal studies have shown that the drug exerts teratogenic or embryocidal effects, and there are no adequate, well-controlled studies in pregnant women, OR No studies are available in either animals or pregnant women.

Category D – Positive evidence of human fetal risk exists, but benefits in certain situations (eg, life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks**.**

Category X - Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant [6].

Folate antagonist:

Folate, the generic term for a water-soluble B vitamin, occurs in high concentrations in certain natural foods (fruits, leafy green vegetables, beans and liver) as polyglutamate. The synthetic form, folic acid (a monoglutamic acid), is used in food fortification and vitamin preparations. Folic acid has a higher bioavailability than food folate. Folate is converted through two reduction reactions by dihydrofolate reductase (DHFR) to the naturally bioactive form tetrahydrofolate (THF), which is converted into 5-methyltetrahydrofolate (5-MTHF) monoglutamate. 5-MTHF is the main form of folate in the blood circulation and is transported into cells by three routes: by membrane-associated receptors, by a carrier-mediated system, the reduced folate carrier, and by passive diffusion. folate requirements increase during pregnancy. In addition, DNA methylation is known to be involved in the epigenetic control of gene expression during development. Several drugs disturb the folate metabolism and may have a teratogenic effect through inhibition of the folate methylation cycle. Two general groups of drugs act as folate antagonists. The first group consists of competitive inhibitors of DHFR and includes methotrexate, sulfasalazine, triamterene and trimethoprim, which 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 disease, rheumatoid arthritis, hypertension and urinary tract infections [7].

Anti-epileptic:

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.

Neural Crest Cell Disruption:

The neural crest is an important, pluripotent cell population that originates in the neural folds. The neural crest cells 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 rise to 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 [8].

Vascular Disruption:

Vascular disruption defects are structural birth defects resulting from interference with or extrinsic breakdown of an originally normal prenatal development of the arteries, veins and capillaries. Vascular disruption refers to disturbances in the blood circulation in the uterine-placental unit, the placental-fetal unit or the fetus itself. These disturbances include hyperperfusion, hypoperfusion, hypoxia and obstruction. They may be caused by acute or chronic decreases 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.

Enzyme-mediated teratogenesis:

Angiotensin-converting enzyme and angiotensin II receptors

Two types of commonly used antihypertensive drugs, the angiotensin-converting enzyme (ACE) inhibitors and the AT II receptor antagonists, may disrupt the fetal renin–angiotensin system and thereby impair fetal development. In contrast to other antihypertensive drugs, ACE inhibitors and AT II receptor antagonists also influence renal function.

Cyclooxygenase-1

Non-steroidal anti-inflammatory drugs (NSAIDs) are used for their analgesic, antipyretic and anti-inflammatory effects induced by acting as an inhibitor of cyclooxygenases (COXs), which catalyze the conversion of arachidonic acid to prostaglandins. Two distinct isoforms have been identified, COX-1 and COX-2. Initially, first trimester exposure to NSAIDs did not seem to be associated with birth defects in humans, but recent epidemiologic studies indicate an increased risk of orofacial clefts and cardiovascular defects, especially cardiac septal defects.

***N*-methyl-d-aspartate receptors:**

N-methyl-d-aspartate (NMDA) receptors appear to play an important role in neuronal migration and in the formation and elimination of synapses. It may be concluded that exposure to NMDA receptor antagonists, such as amantadine, dextromethorphan and ketamine, could result in minor malformations of the brain [9].

5-Hydroxytryptamine receptors and transporters:

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter, which is derived from the maternal circulation and transported to the embryo. It is involved in a wide range of processes during development, including morphogenesis of craniofacial structures, cranial neural crest migration and cell proliferation.

γ-Aminobutyric acid receptors:

γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter, which binds to specific transmembrane GABA receptors. Extraneuronal GABA-ergic systems are thought to be present in other tissues as well, including the testis, oviduct and ovary and pancreas. These drugs are commonly used during pregnancy and neonatal complications such as the 'floppy infant syndrome' and the 'withdrawal syndrome' have frequently been observed data on the teratogenicity of benzodiazepines are scarce and inconsistent.

Carbonic anhydrase:

Carbonic anhydrases are metalloenzymes that catalyze the reversible hydration of CO_2 into the bicarbonate ion and protons. This reaction is involved in many biological processes, including pH homeostasis, respiration, biosynthetic reactions and bone resorption. A reduction in embryonic intracellular pH is thought to be the teratogenic mechanism of carbonic anhydrase inhibitors. Intracellular pH has been shown to control or to be associated with various cellular functions, including protein synthesis, proliferation and glycolysis. Interference with these processes may result in abnormal development, but evidence of the existence of this mechanism in humans is lacking [10].

Special precautions for the pregnant women:

The first three months of pregnancy is the most crucial stage in your babies development as all organs are forming throughout your pregnancy but especially during the first three months be very careful about using alcohol, during and medication. Indicating that blockade of 5-HT uptake might produce cardiovascular malformations.

Fish and seafood:

Fish and seafood are excellent low — fat sources of many nutrients and an important part of healthy diet however there is a concern about eating fish and seafood during pregnancy, since some type may contain high level of mercury to be safe choose wisely among type of fish.

Precautions:

Eat no more than 12 ounces of cooked fish a week, Do not eat shark, swordfish king mackerel (or) tilefish. It you eat fish caught by family and friends form local waters, check local advisories about the safety of fish. Fish sticks and fast food sandwiches are commonly made from fish low in mercury.

Alcohol:

The danger of alcohol use during pregnancy is that it may cause foetal alcohol syndrome (FAS).

Babies born with (FAS) may grow more slowly, have learning problems, have abnormal facial features

Precautions:

Because there is no known safe level of alcohol taken during pregnancy, the National institute of alcohol abuse and alcoholism and the March of dimes caution pregnant women to follow the safest course by completely avoiding alcoholic beverages while pregnant [11].

Caffeine:

Caffeine is stimulant that affects people differently. Caffeine can cause nervousness, irritability, anxiety, irregular heartbeats and problems sleeping. How Caffeine affects an unborn baby is still under investigation. Some scientists believe Caffeine can cause premature or smaller than normal babies (or) possible birth defects.

Precautions:

Cut down or eliminate food and drinks that contains Caffeine such as Coffee, tea, colas and other soft drinks like cocoa and chocolate. Caffeine is an ingredient in many non-prescription medicines such as headache, cold, allergy, and pills made to combat drowsiness. If you have been consuming Caffeine in large quantity gradually decrease your intake. Stopping all at once can cause severe headaches, nausea, fatigue and other symptoms.

Cigarettes:

Cigarette smoking may lead to serious health problems. Women who smoke during pregnancy usually give birth to babies that weigh less than those of women who don't smoke. Low birth weight babies are more likely to have health problems, such as: Infections, Trouble keeping warm, Feeding problems, Breathing problems, Sudden infant death syndrome [SIDS]. New research shows that exposure second hand smoke is also linked to SIDS and can cause major health problems to your baby.

Precautions:

Stop smoking or cut down your smoking when pregnant there are many community programs available to assist you call the American cancer society for information on smoke-stopper programs in your area

Food additives:

Whenever possible, try minimizing your use of: Processed food items such as hot dogs. Food containing sodium nitrate such as cured meats like ham (or) bacon. These substances may be carcinogenic (cancer causing). Be sure to wash fruits and vegetables and peel carrots to avoid eating pesticides used to farms to kill insects.

Food handling concerns:

Eating raw fish, meats (or) poultry may increase your risk of infection or parasitic disease. Cooking food destroys bacteria and parasites milk. That is not pasteurized may also cause illness.

Precautions:

Avoid eating raw fish, such as sushi and ceviche, meats (or) eggs, Only drink pasturized milk, Cook your fish, meat, poultry and eggs thoroughly, Always wash cutting boards after slicing any raw fish, meats, or poultry [12].

Medications and herbs:

Some medications and herbs may harm your baby. Before taking any medication (or) medicinal herbs during your pregnancy. Fetal solvent syndrome - risk for major birth defects exposure to chemicals may cause birth defects. Talk to your health care provider if you are concerned about exposure to chemicals in your environment.

Preeclampsia:

Preeclampsia is also called pregnancy induced Hypertension (PIH) or to toxemia. The cause of preeclampsia is unknown. It occurs in about of 5% pregnancies and is most common in: First pregnancies, Twin or other multiple pregnancies, Women with high blood pressure before 20 weeks of pregnancy, Women with diabetes symptoms of preeclampsia include a rise in blood pressure, protein in your urine and rapid weight gain due to fluid retention. If left untreated, preeclampsia can cause many. problems that could be life threatening to you and your baby. Early preeclampsia can be diagnosed during a routine visit early. If you experience blurred vision, headache, upper abdominal pain, rapid weight gain (or) increased swelling.

Gestational diabetes:

Gestational diabetes only occurs during pregnancy. The changes in your body during pregnancy can cause your blood sugar (glucose) levels to be high, which can cause problems for you and your baby will receive a specific education on how to care for yourself if you develop gestational diabetes. It is very important to follow the diet, the exercise and blood sugar monitoring [13].

Baby:

Premature birth, Low blood sugar, Stillborn (although this is rare.

Mother:

High blood pressure, Bladder or kidney infection, Shortness of breath, Harder Birth and longer recovery time, increased chance of cesarean delivery.

Informational hotlines — chemical use and precautions:

Pregnant women are concerned about the possible effects of different products on their developing baby. These may include household cleaners, insecticides, hair dyes, finger nail polish electrolysis, paint fumes, microwares and tanning beds.

Teratology Information Services:

Teratology Information Services (TIS) provide information on the possible risks of exposure to drugs and other exogenous agents during pregnancy and lactation. Teratology Information Services are consulted by the medical profession and other health care professionals, some of them counsel lay people as well. Answers provided are specifically oriented towards individual patients. Detailed knowledge of dose, time of exposure, adverse effects on the mother related to the exposure, diseases, previous pregnancies, family history of the patient and the pharmacological and toxicological properties of the agents have to be taken into account to make a specific risk assessment.

Picture-1. Developmental progression and susceptibility to teratogens and fetal loss.

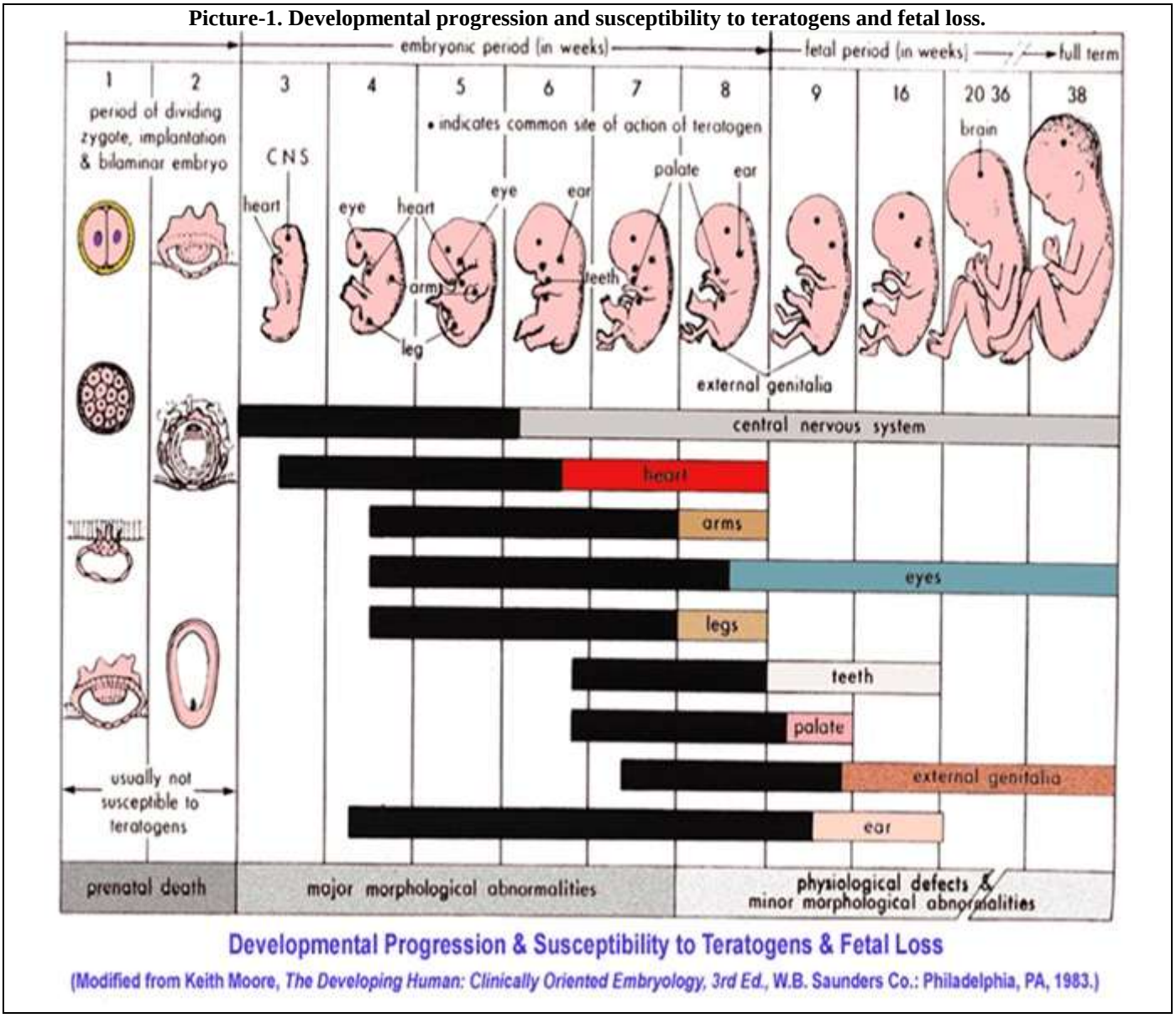


Table 1. US FDA Category drugs and their effects in trimester

Known Teratogens and Their Effects*

Drug (FDA Category)	Common Effect	Trimester Of Greatest Danger
Androgens (X)	Masculinization of female fetus	First 12 weeks
ACE inhibitors (D)	Renal tubular dysplasia, skull hypoplasia oligohydramnios, pulmonary hypoplasia	2nd & 3rd trimester
Antineoplastics (D) alkylating agents	Growth retardation, cleft palate, microphthalmia, cloudy cornea, agenesis of kidney, cardiac defects	1st–3rd trimester
Antimetabolite agents	Growth retardation, malformation of ear, eye, nose, cleft palate, malformation of extremities, fingers, brain, skul	
Carbamazepine (C)	Craniofacial abnormalities, growth retardation, neural tube defects, fingernail hypoplasia	1st trimester
Cocaine (C)	Premature birth, abruptio placentae, SIDS, perinatal morbidity, growth retardation, in utero stroke, bowel atresias, defects of genitourinary system, heart, limbs, face	
Coumarin Derivatives (D)	Fetal warfarin syndrome	Weeks 7–12
	Optic atrophy, cataracts, mental retardation, microcephaly, microphthalmia, fetal and maternal hemorrhage	2nd & 3rd trimester
Ethanol (high dose)	Fetal alcohol syndrome	1st trimester
Iodides, PTU, (D)	Goiter, fetal hypothyroidism	3rd trimester
Methimazole (D)	Aplasia cutis	1st trimester
Lithium (D)	Ebstein's anomaly, other cardiac defects	1st trimester
Phenytoin (D)	Fetal hydantoin syndrome** including heart defect, low nasal bridge, growth retardation, nail hypoplasia, mental retardation	1st trimester
Retinoids (X) (isotretinoin, etretinate)	Heart defect, spontaneous abortion, microtia, microcephalus, hydrocephalus, deformity of ears, face, limbs, liver, cognitive defects, thymic hypoplasia	1st trimester
Tetracyclines (D)	Weakened fetal bone and tooth enamel dysplasia, permanent tooth discoloration	2nd & 3rd trimester
Thalidomide (X)	Anomalies of ears, teeth, eyes, intestine, limbs, heart, kidney, deafness	Days 34–50
Valproic acid (D)	Spina bifida, facial anomalies, slow development, microcephaly, CNS and cardiac defects	1st trimester

CONCLUSION:

During whole period of pregnancy the first three months of pregnancy is the most crucial stage in fetal development as all organs are forming so, it is very important for mother to follow special precautions, and it is also very important to continue these precautions during lactation period for maintenance of good health of mother and as well as baby [14].

REFERENCES

1. Roger's developmental toxicology "casarette & Doulls toxicology: the basic science of poisons, 1996, 301 - 331.
2. Walmod PS, Gravemann U, Nau H, Berezin V, Bock E. Discriminative power of an assay for automated in vitro screening of teratogens. *An International Journal Published in Association With BIBRA*. 18(4), 2004, 511–525.
3. Rasmussen SA, Erickson JD, Reef SE, Ross DS. Teratology: From science to birth defects prevention. *Birth defects* res a clin mol teratol. 85, 2009, 82–92.

4. Anis NA, Berry SC "Stages of Developmental and effects of teratogen *Br J Pharmacol*. 79, 1983, 565 – 575.
5. D.C. Dutta "Trimesters" perinatology and contraception. *American journal of* perinatology, 64, 2006, 642 – 645.
6. Jelínek R. The contribution of new findings and ideas to the old principes of teratology. *Reproductive Toxicology*. 20, 2005, 295–300.
7. Tillner J, Winckler T, Dingermann T. Developmentally regulated promoters from Dictyostelium discoideum as molecular markers for testing potential teratogens. *Pharmazie*. 51(11), 1996, 902–906.
8. Danielsson and B.R. et al. Australian categorisation system for prescribing medicines in pregnancy. *British National formulary*, 2008, 434 – 464.
9. Amy Holmes P. Evaluating Medication Use in Pregnancy and Lactation. *J Pediatr Pharmacol Ther*. 18(3), 2013, 247–258.
10. Hannah M.E. and Hannah W.J "Teratology information services. *Br. J. Pharmacol.* 1993, 525 – 528.
11. Tillner J, Nau H, Winckler T, Dingermann T. Evaluation of the teratogenic potential of valproic acid analogues in transgenic dictyostelium. *Toxicol in vitro*. 12(4), 1998, 463–469.
12. Tandon S. and Jyoti S. Embryonic stem cells: An alternative approach to developmental toxicity testing. *J Pharm Bioallied, Sci*. 4(2), 2012, 96–100
13. Jelínek R. The contribution of new findings and ideas to the old principles of teratology. *Reprod Toxicol.* 20, 2005, 295–300.
14. Bushnell PJ, Kavlock RJ, Crofton KM, Weiss B, Rice DC. *Neurotoxicol Teratol*. 32, 2010, 313–328.