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A Critical Evaluation and Current Problems of Teratogens in Human

Darla R*, Velagapally Spandana, Sambangi Roopa Sri Sai, Jangapally Aishwarya, Neeli Deepika

** Asst professor, Gland institute of Pharmaceutical Sciences, Kothapet, Shivampet (M), Medak, Telangana 502220, India*

Corresponding author: R Darla
Email: rajudarlaofficial@gmail.com

ABSTRACT

Although prescription use is common during pregnancy, the human teratogenic risks are undetermined for quite 90% of drug treatments approved within India during the past decades. A selected birth defect may have its origins through multiple mechanisms and possible exposures, including medications. A specific pathogenic process may end in several outcomes depending upon factors like embryonic age at which a drug is run, duration and dose of exposure and genetic susceptibility. This research focuses on the teratogenic mechanisms with their effects associated with kinds of natural also as synthetic substances. Mechanisms were included only if they are associated with major structural birth defects and medications that are used relatively frequently by women of reproductive age. Identifying teratogenic mechanisms won't only be relevant for etiologic and post marketing research, but also can have implications for drug development and prescribing behavior for girls of reproductive age, especially since combinations of seemingly unrelated prescription and over the counter medications may utilize similar teratogenic mechanisms with a resultant increased risk of birth defects.

Keywords: Teratogens, malformations, disruptions, morphogenesis, environmental exposures

INTRODUCTION

Teratogenesis refers to the assembly of defects within the fetus. A teratogenic agent is responsible for producing such a defect. The term teratogen is cited within the context of causing anatomical defects in an embryo that was previously differentiating normally[1]. Teratogens are substances which can produce physical or functional defects within the human embryo or fetus after the pregnant woman is exposed to the substance. Alcohol and cocaine are samples of such substances. Exposure to the teratogen affects the fetus or embryo during a kind of the way, just like the duration of exposure, the number of teratogenic substance, and thus the stage of development the embryo or fetus is in during the exposure[2]. They affect the embryo or fetus during variety of the way, causing physical malformations, problems within the behavioral or emotional development of the child, and decreased intellectual quotient (IQ) within the kid. Additionally, teratogens also can affect pregnancies and cause complications like preterm labors, spontaneous abortions, or miscarriages. Teratogens are classified into four types: physical agents, metabolic conditions, infection, and eventually, drugs and chemicals [3].

It's estimated that approximately 10-15% of congenital structural anomalies are the results of the adverse effect of environmental factors on prenatal development[4]. This means that approximately 1 in 250 newborn infants have structural defects caused by an environmental exposure and, presumably, a much bigger number of kids have growth retardation or functional abnormalities resulting from nongenetic causes, in other words, from the results of teratogens. A teratogen is defined as any environmental factor which can produce a permanent abnormality in structure or function, restriction of growth, or death of the embryo or fetus. A dose-response relationship should be demonstrated in animals or humans so as that the greater the exposure during pregnancy, the more severe the phenotypic effects on the fetus[5]. Factors comprise medications, drugs, chemicals, and maternal conditions or diseases, including infections. Time of exposure and specificity are shown in Table 1. This manuscript discusses the teratogenic effects of well-documented environmental factors. Brent[4] noted that it's inappropriate to label an agent as teratogenic without characterizing the dose, route of exposure, and stage of

pregnancy when the exposure occurred. This is often actually because, as has long been recognized, the results of an environmental agent on the embryo or fetus depend on the chemical or physical nature of the agent and variety of other factors, like dose, route, and length of exposure; the developmental stage at which the exposure occurs; the genetic susceptibility of the mother and embryo or fetus; and thus the presence and nature of concurrent exposures[6]. Teratogenic exposures during prenatal development cause disruptions regardless of the developmental stage or site of action. Most structural defects caused by teratogenic exposures occur during the embryonic period, which is when critical developmental events are happening and thus the foundations of organ systems are being established[7]. Different organ systems have different periods of susceptibility to exogenous agents.

Drugs administered to the mother can affect the fetus by preventing implantation or by causing resorption of the embryo, abortion or intrauterine death. It is a sobering thought that the first of these mechanisms is dignified by the name 'contraception' which the remainder have far less medicolegal and economic significance than the survival of a defective fetus after a less drastic chemical or physical insult[8]. the general principles of teratogenesis in humans have recently been reviewed by Lewis[9]. The majority of drugs is of relative molecular mass below 1000 and passes the placenta into the fetus. Their rate of transfer is enhanced by small relative molecular mass, lipophilic properties, and a high concentration of nonionized drug, unsure to protein, within the maternal circulation. Drugs that detoxication mechanisms, metabolic degradation or urinary excretion are deficient within the fetus are more likely to accumulate.

The extent and nature of a teratogenic effect depend on length of gestation. Generally, agents administered before implantation either destroy the embryo or damage cells within the blastocyst which can get replaced by undifferentiated cells which retain totipotency. Maximum susceptibility in man is during organogenesis, from the first week after fertilization until the ninth week, that is, from three to 11 weeks after the last menstrual period. the same stimulus may produce a special anomaly at different stages of gestation, relying on which organs are during a critical stage of development. Some agents show a predilection for causing abnormalities especially organ systems; sometimes this may be related to a high local tissue concentration or specific influence on a selected metabolic pathway but in other instances the mechanism is unknown. The genotype of the embryo features a serious influence on its response, and species differences are the primary hindrance to the screening of agents in animals for teratogenic potential and thus the interpretation of the relevance of the results to humans. Even in man, racial and familial predisposition to particular anomalies may influence the character of a teratogenic response.

Recognition of a Teratogenic Effect

The likelihood that some drugs will cause fetal abnormality is often predicted from knowledge of their mode of action, their pharmacological and toxic actions, and their chemical similarity to known teratogens. Primary testing of most new compounds which may be utilized in human therapeutics takes place in animals. Chick embryos and pregnant mice, rats and rabbits are widely used, employing parenteral administration of maximum tolerated doses. Some teratogens will only be detected by the response of 1 species; others will cause species specific anomalies. Agents known to be innocuous in man, by virtue of the various years of wide therapeutic use in pregnant women, sometimes have a teratogenic effect when given in massive overdose during a specific animal test. On the other hand, whilst the animal tests are likely to detect a significant teratogen, this is often by no means certain. It's therefore desirable that every one drugs intended for widespread use within the pregnant female be tested in primates then introduced into human therapeutics with extreme caution and shut monitoring. There are some situations which are unequivocally life threatening to the mother where a replacement drug are often reasonably employed, sort of a replacement antibiotic during a significant infection which proves resistant to available medicaments. The other methods by which adverse effects on fetal development are often detected are epidemiological. When the incidence of a given abnormality is noted to be high or increasing during a community, careful retrospective analysis may reveal the cause. It had been by this means that Lenz[10] found the connection between phocomelia and thalidomide.

Such analyses are not immune from error-the coincident onset of another source of fetal abnormality such as a virus epidemic apparently causing only trivial symptoms can be misleading. In addition it is always possible that it is the disease which the drug is used to treat, or an associated condition, that is the real predisposing factor. Retrospective surveys of the antecedents of a fetal condition of known and consistent incidence are even more susceptible to such errors. They depend on the demonstration of correlations which may not have any causal basis. Only when a relevant mode of action of the suspected teratogen in producing the abnormality in susceptible individuals has been demonstrated can the case be regarded as proven as far as those individuals are concerned. Retrospective surveys are nearly always biased by the enhanced recall of mothers who have produced an abnormal baby. Even prospective surveys are open to the problem that it may be the disease and not the drug used to treat it that is the adverse factor. Only many years of extremely large-scale studies of carefully matched and analyzed cases will serve to determine the true magnitude of the effect of drug therapy during pregnancy in relation to congenital abnormality.

Major Teratogens in Man

These include thalidomide which characteristically causes phocomelia; actinomycin, folic acid antimetabolites such as methotrexate, and alkylating antimitotic drugs, which cause fetal death or a variety of anomalies if the fetus survives; tetracycline which discolors and causes enamel hypoplasia in deciduous teeth; and radioactive 131I which causes fetal goitre. There are very few circumstances in which there is no alternative to the use of these agents in pregnancy. If any of these agents, except tetracycline, is vital to the survival of the mother then the pregnancy should be terminated. Similar considerations apply to the use of irradiation of the pelvis or whole body to treat cancer or related conditions and to open-heart surgery with the use of a bypass circulation which will cause prolonged fetal anoxia. In the last case, it must be remembered that the teratogenic effects of anoxia in early

pregnancy, should the fetus survive, are well established experimentally.

Table 1. Time specificity of action of some human teratogens[11].

Teratogen	Fertilization Age (days)	Malformation
Rubella virus	0-60	Cataract or heart diseases more likely
	0->129	Deafness
Thalidomide	21-40	Reduction defects of extremities
Hyperthermia	18-30	Anencephaly
Male hormones (androgens)	<90	Clitoral hypertrophy and labial fusion
	>90	Clitoral hypertrophy
Warfarin (coumadin)	<100	Hypoplasia of nose and stippling of epiphyses
Diethylstilbestrol	>100	Possible mental retardation
	>14	50% vaginal adenosis
	>98	30% vaginal adenosis
	>126	10% vaginal adenosis
Radioiodine therapy	>65-70	Fetal thyroidectomy
Goitrogens and iodides	>180	Fetal goiter
Tetracycline	>120	Dental enamel staining of primary teeth
	>150	Staining of crowns of permanent teeth

Behavioral teratogens

Teratogens that tend to harm the prenatal brain, affecting the longer term child's intellectual andemotional functioning[12]. Although all teratogens increase the danger of harm to the developing child, none always cause damage; the last word impact depends on the complex interplay of the many factors.

Principles of Teratology

Teratology is that the study of environmentally induced congenital anomalies. A teratogen is an agent, which by working on the developing embryo or foetus can cause a structural anomaly. To date, only a few drugs are proven teratogens. However, malformations induced by drugs are important because they're potentially preventable[13]. Teratogens act with specificity therein they produce specific abnormalities at specific times during gestation. For instance, thalidomide produces limbphocomelia, while Depokene and carbamazepine produce ectoderm defects. Other teratogens are related to recognizable patterns of malformations, for instance, phenytoin with foetal hydantoin syndrome and coumarin anticoagulants with foetal warfarin syndrome. Teratogenic specificity also applies to species, for instance, aspirin and corticosteroids are found to be teratogenic in mice and rats but appear to be safe in humans. Thalidomide, on the opposite hand, wasn't shown to be teratogenic in rats, a tragic incontrovertible fact that resulted in significant human morbidity[14].

Teratogens may demonstrate a dose-effect relationship. At lowdoses there are often no effects, at intermediate doses the characteristic pattern of malformations will result, and at high dose the embryo are going to be killed. A dose-response may be considered essential in establishing teratogenicity in animals, but is uncommonly demonstrated in sufficient data among humans. A threshold dose is that the dosage below which the incidence of adverse effects isn't statistically greater than that of controls. With most agents, a dose threshold for teratogenic effects has not been determined; however they're usually well below levels required to cause toxicity in adults[15]. Teratogens must reach the developing conceptus insufficient amounts to cause their effects. Large molecules with molecular weights greater than 1,000 don't easily cross the placenta into the embryonic-foetal bloodstream to exert potential teratogenic effect. Other factors influencing the rate and extent of placental transfer of xenobiotics include polarity, lipid solubility and therefore the existence of a selected protein carrier[16].

Causes

Causes of teratogenesis can broadly be classified as

- Toxic substances, such as, for humans, drugs in pregnancy and environmental toxins in pregnancy.
- Vertically transmitted infection Lack of nutrients. For instance, lack of vitamin B c in the nutrition in pregnancy for humans may result in spinabifida[16].
- Physical restraint. An example is Potter syndrome dueto oligohydramnios in humans.
- Genetic disorders[16].

Factors influencing the effect of teratogens

•**Timing:** the effect of a teratogen on the developing organism depends on what period within the pregnancy (in development) the kid is exposed to the teratogen.

•some teratogens cause damage only during specific days or weeks in early pregnancy

•other teratogens are harmful at any time during the pregnancy---for example, for behavioral teratogens, there is no safe period---the brain and systema nervosum can be harmed throughout the pregnancy[17].

•**critical period:** in prenatal development, the time when a particular organ or other part is most susceptible to teratogenic damage

.•**Exposure:** the effect of a teratogen on the developing organism also depends on the dose and/or frequency of exposure of/to the teratogen

.•**Threshold effect**: the phenomenon during which a particular teratogen is comparatively harmless in small doses but becomes harmful when exposure reaches a particular level (the threshold).

•**Interaction effect**: the phenomenon during which a particular teratogen's potential for causing harm increases

when it is combined with another teratogen or another risk factor.

Genetic variability: another factor that determines whether a specific teratogen are going to be harmful is that the genetic make-up of the developing organism[18].

•possessing and not possessing certain genes may make the developing child more vulnerable to the effect of a teratogen.

Cellular Action of a Teratogen

A teratogen may potentially affect embryogenesis by causing gene mutation, chromosome breakage or non disjunction, depletion or inhibition of precursors or substrates, depletion of energy sources, inhibition of enzymes, or changes in intracellular milieu secondary to changes in membrane integrity[19]. These cause necrobiosis, reduced cell division, and failure of expected interaction between cells, disruption of cell migration, or mechanical disruption. Regardless of the initial mechanism or the intermediary effect, the ultimate result usually is an organ with too few cells. The critical mass necessary for induction or continuation of differentiation is lacking; thus, the actual organ system fails to develop[20]. Of course, a few anomalies (e.g., polydactyly or labioscrotal fusion) could result either from increased cell proliferation or from failure of localized cell degeneration.

Variables Affecting Teratogenesis

Specificity of Agent

Some agents are more teratogenic than others. Less obvious is that the axiom that an agent may be teratogenic in just certain species. For example, thalidomide produces phocomelia in primates but not in rodents. Within a given species, however, a given teratogen may affect many organ systems. Some organ systems are preferentially affected, but the pattern of anomalies also reflects the organ systems differentiating at the time the agent was administered. For instance, administering thalidomide between days 35 and 37 causes ear malformations; administering the agent between days 41 and 44 causes ameliaor phocomelia[21].

Dosage

Although high doses of a proven teratogen usually are more deleterious than low doses, this is often not always true. At any given time, an embryo can answer a teratogen in one among three ways: (1) at a coffee dose, there's no effect; (2) at an intermediate dose, a pattern of organ-specific malformations

Can result; and(3) at a high dose, the embryo could also be killed, causing the organ specific teratogenic action to travel unrecognized. In animals, teratogens exert their action within a comparatively narrow dose range, usually one-fourth to one-half the typical dose that would kill the mother[22]. The effect also depends on the developmental stage during which the drugs administered. That is, an agent could also be teratogenic only at higher or lower dose at a special stage. Similarly, at one dose level an agent could be lethal yet not teratogenic, whereas at another level it might be either lethal or teratogenic.

Stage of Embryonic Development

The time during embryogenesis when the fetus is exposed to a potential teratogen is crucial. Three stages of susceptibility may be identified, with these times varying from one organ system to another: (1) the embryo is comparatively immune to teratogenic insults during the primary few weeks of life, perhaps 2 weeks after conception in humans[23]. An outsized insult might kill the embryo, but surviving embryos usually manifest no organ-specific anomalies. Presumably, the reason is that early embryonic cells haven't differentiated irrevocably. If one cell is destroyed, a surviving cell could also be ready to assume its function; (2) organogenesis, the method of organ differentiation, occurs in most human organ systems between embryonic weeks3 to eight (menstrual weeks 5–10); however, differentiating occurs later within the brain and gonads. During organogenesis, susceptibility to teratogens is maximal. Teratogens act in an organ-specific fashion; a teratogen may affect one organ system at one stage of development but another system at another stage. Development of the brain and gonadal tissues continues in the second and third trimesters of pregnancy. Therefore, drug use at this time in pregnancy may be a concern, although the consequences may not be recognized until later in life. A number of the uterine anomalies resulting from diethylstilbestrol occurred with exposure as late as 20 weeks but weren't recognized until after puberty. The brain continues to develop throughout pregnancy and the time of life[24].

Genotype: The genotype of the mother and therefore the fetus influences the efficacy of a teratogen. For instance, genotype determines the prevalence of birth defect in inbred strains of mice whose mothers are administered cortisol during pregnancy[25]. Daily administration of 10-mg cortisol during days11 through 14 produced birth defect in 100% of offspring of A/Jax parents, in 68% of offspring of C3H parents, and in only12% of offspring of CBA parents. Differences in frequencies of anomalies between various strains presumably are genetic. In humans, only 18% of women had clitoral hypertrophy after administration of norethindrone to their mothers during a specific time and at a selected dose[26]. Another example in humans involves a lady who received diphenyl hydantoin during a pregnancy during which she carried dizygotic twins sired by different men[27]. The infant sired by a white man showed the hydantoin embryopathy; the infant sired by the black man was normal. Because the environment was identical for the co-twins, any differences in teratogenic effects must reflect genetic differences in susceptibility

Drug Interactions

Simultaneous administration of two teratogens may produce a special effect from that existing when the 2 are administered separately. For instance, folic acid reduces the frequency of cortisol-induced teratogenesis inmice[28], possibly due to induction of enzyme systems that catabolize the teratogen or compete forbidding sites. Conversely, one agent may enhance the teratogenic potential of another. For instance, the food preservative carboxylic acid enhances aspirin teratogenicity in rats[29]. Possible mechanisms include enzyme inhibition, destruction of enzyme-producing cells, and saturation of binding sites on carrier proteins that, if

available, would decrease levels of the unbound active teratogen.

Other Factors

Variability in teratogenic response sometimes is related to other environmental or morphologic factors: maternal or fetal weight, in utero position of the fetus, proximity to other affected litter mates, uterine vasculature, and diet. However, further investigation usually reveals that these factors are correlated with other factors already cited. For example, the inverse correlation between maternal weight and susceptibility of the fetus to cortisol-induced birth defect is related to not weight intrinsically but to dose per unit mass[30].

Timing of Embryonic and Foetal Development

The effect produced by a teratogenic agent depends upon the developmental stage during which the foetus is exposed to the agent. Several important phases in human development are recognized: The time from conception until implantation known because the "all or none" period, when insults to the embryo are likely to end in death of the concept us and miscarriage (or resorption), or in intact survival. At this stage, the embryo is undifferentiated and repair and recovery are possible through multiplication of the still tot potential cells to exchange those which are lost. Exposure of embryos to teratogens during the

Table 2. Characteristics of the fetal alcohol syndrome[31]

Affected System	Frequent Anomalies	Occasional Anomalies
Growth Deficiency		
Prenatal	<2 SD for length and weight	
Postnatal	<2 SD for length and weight	
	Disproportionately diminished adipose tissue†	
CNS Dysfunction		
Intellectual	Mild to moderate mental retardation	
Neurologic	Microcephaly*	
Behavioral	Poor coordination, hypoptonia	
	Irritability in infancy*	
	Hyperactivity in childhood†	
Dermatoglyphics		
	Prominent thenar crease	
	Nearly absent proximal transverse crease	
	Abrupt turning of distal transverse crease	
	into second interdigital space	
	Fourth interdigital loop	
Facial Characteristics		
Eyes	Short palpebral fissures*	
Nose	Short, upturned†	
	Hypoplastic philtrum*	
Maxilla	Hypoplastic†	
Mouth	Thin upper cermilion*	
	Retrognathia in infancy	
	Micrognathia or prognathia in adolescence†	
Associated Anomalies		
Eyes	Ptosis, strabismus, epicanthal folds	Myopia, clinical microphthalmia, blepharophimosis
Ears	Posterior rotation	Poorly formed concha
Mouth	Prominent lateral palatine ridges	Cleft lip or cleft palate,
	Small teeth with faulty enamel	
Cardiac system	Murmurs, especially in early	Ventricular septal defects,
	childhood, often atrial septal defect	Great vessels anomalies, tetralogy of Fallot
Urogenital system	Labial hypoplasia	Hypospadias, small rotated kidneys, hydronephrosis
Cutaneous system	Hemangiomas, nail hypoplasia	Hirsutism in infancy
Skeletal system	Aberrant palmar crease, pectus excavatum	Limited joint movements (eg, fingers and elbows),
	Synostosis, pectus carinatum, bifid xiphoid	Klippel-Feil anomaly, scoliosis
Muscular system		Hernias of diaphragm, umbilicus, or groin
		Diastasis recti
Central nervous system	Errors in neuronal migration	Cortical nuclear white matter dysplasia
		Rudimentary cerebellum,
		Dysplastic brainstem, hydrophobia, lissencephaly

*Reported in 26%-50% of patients; †Reported in 1%-25% of patients; SD, standard deviation

Pre implantation stage usually doesn't cause congenital malformations, unless the agent persists within the body beyond this era[32]. The embryonic period, from 18 to 54-60 days after conception is that the period when the essential steps in organogenesis occur. This is often the period of maximum sensitivity to teratogenicity since not only are tissues differentiating rapidly but damage to them becomes irreparable. Exposure to teratogenic agents during this period has the best likelihood of causing a structural anomaly. Since teratogens are capable of affecting many organ systems, the pattern of anomalies produced depends upon which systems are differentiating at the time of teratogenic exposure[33].

The foetal phase, from the top of the embryonic stage to term, is the period when growth and functional maturation of organs and systems already formed occurs. Teratogen exposure in this period will affect foetal growth (e.g., intrauterine growth retardation), the dimensions of a selected organ, or the function of the organ, instead of cause gross structural anomalies. The term foetal toxicity is usually wont to describe such an impact. Of particular interest is that the potential effect of psychoactive agents(e.g., antidepressants, anti epileptics, alcohol and other drugs of abuse) on the developing central systema nervosum, which has led to a replacement field of behavioral teratology[34].

Evaluation of medicine for Potential Teratogenicity in Humans

All new drug applications filed with the us Food and Drug Administration (FDA) include data from animal developmental and reproductive-toxicologic studies. Although major new teratogenic drugs in humans are predicted from animal studies, there are problems in extrapolating animal data to humans. Animals have a special "gestational clock" to humans, there's marked interspecies variability in susceptibility to teratogens and no experimental animal is metabolically and physiologically just like humans[35]. Animal studies are important because, in some instances, they need shed light on mechanisms of teratogenicity and since when an agent causes similar patterns of anomalies in several species, human teratogenesis should even be suspected. For obvious ethical considerations no studies of teratogenicity are conducted during embryogenesis in humans. The studies are, therefore, either retrospective in nature (case reports, case-series and case control studies), or prospective cohort studies, where a specific maternal exposure in question is ascertained during pregnancy and the pregnancy outcome is evaluated and compared to a control group. Retrospective case-control studies are less costly and easier to conduct but they need other weaknesses such as the inaccuracy of knowledge collected from medical records and recallbias[36]. For the rare malformation/rare exposure, the case report method is usually wont to suggest association, but case reports are unable to prove or disprove teratogenicity, nor can they provide estimation of teratogenic risk. Human teratogenicity is supported by:

- A recognizable pattern of anomalies
- .A statistically higher prevalence of a specific anomaly inpatients exposed to an agent than in appropriate controls
- .Presence of the agent during the stage of organogenesis of the affected organ system.
- Decreased incidence of the anomaly within the population prior to the introduction of the agent[37].
- Production of the anomaly in experimental animals by administering the agent within the critical period of organogenesis.

Proof of Teratogenicity

Teratogens usually are first identified by alert clinicians. Unfortunately, many agents are falsely implicated, requiring case reports to be assessed critically. Retrospective case-control designs thus are commonly used. Such an experimental design is efficient in identifying teratogens but susceptible to false positive conclusions, because recall biases and memory biases render control and subject (mothers of affected infants) unequal in incentive. That is, normal controls have less incentive to remember events than women having anomalous infants (an "anomaly control," a woman having an abnormal outcome, but not that being tested, can be wont to minimize this problem) [38].However, definitive cohort (prospective) studies are expensive and complex. Thus, there's no ideal way of assessing teratogens. A spread of approaches is often used, usually leading to a scientific consensus eventually. Confounding any study is knowledge that similar congenital anomalies occur in women not exposed to teratogens. Given these caveats, it's not surprising that proof of teratogenicity is difficult. Observations such because the following can implicate a specific agent: (1) the agent was associated more often with subjects having a particular anomaly than with suitable controls; (2) an anomaly or pattern of anomalies is consistently related to the suspected teratogen; (3) the agent was presented during the stage of organogenesis when the anomaly would have been likely to occur; (4) the anomaly was less common before the time the potential teratogen was available (e.g., phocomelia was almost unreported before the time thalidomide was introduced);and (5) the anomaly are often produced in experimental animals by administration of the agent during a stage of organogenesis comparable there upon believed to be involved in causing the anomaly in humans[39]. Epidemiological pitfalls in assessing human involved in causing the anomaly in humans[39] Epidemiological pitfalls in assessing human teratogens are myriad, and a number of other different surveillance methods are used. No single method or design is universally reliable[40, 41].

Harmful Teratogens

Ionizing Radiation

High dose of radiation over a short period of your time results in abnormal brain development, mental retardation, and leukemia in children. This information has come from studies of consequences the atom bomb explosions over Hiroshima and Nagasaki. However, medical diagnostic x ray procedures have much smaller dose of radiation and appear to be safe even with several performed procedures during pregnancy. there's a special situation with a computer tomography (CT) diagnostic technique[42].Even one computer tomography scan (CT-scan) creates a radiation exposure

dose that equals to tens of x-rays and should be avoid during pregnancy.

Chemicals

Organic mercury (methyl mercury) compounds can be extremely dangerous for the developing fetus during a small dose that wouldn't bring any symptoms to an adult human. Pregnant women shouldn't eat some sort of fish with possible high methyl mercury levels as this mercury compound would be easily delivered to the baby's body[43]. Organic mercury exposure can cause damage of neural system, mental retardation, behavioral and cognitive problems, and blindness in a baby. Lead exposure, received through some leaded glass products and pottery that have contact with food, are often a culprit of spontaneous abortions, delayed fetal development, increased risk of sudden infant death syndrome, or abnormal mental or physical development of the kid. Large doses of potassium iodine, found in anti-cough syrups or medical cocktails for x-ray diagnostic, are often a explanation for abnormal thyroid development and function during a fetus. This effect will cause retardation or cretinism during a child[44]. Polychlorinated biphenyls(PCBs) were linked to delayed fetal growth, abnormal neural system development, and impaired behavioral and cognitive functions during a child.
Products containing PCBs were banned within the late 1970s. Since that time level of PCBs within the environment is gradually declining. Pregnant women should avoid PCBs exposure by not consuming some sorts of fish, washing and possibly peeling fruits and vegetables before eating them, and not handling

Table 3. Manifestations in isotretinoin embryopathy[45].

Abnormality	Manifestations
Brain	Hydrocephalus, leptomeningeal, heterotopias, vermis hypoplasia, Dandy-Walker, corticospinal tract malformations
Brain (occasional)	Gyral defects including grade 3 lissencephaly, regional pachygyria, subcortical heterotopias
Brain function	Severe or profound mental retardation, hypotonia, diminished deep tendon reflexes (absent or abnormal)
Craniofacial	Low-set, small or atretic, malformed ears; small or atretic external auditory meatus; microphthalmia; telecanthus;
	epicanthal folds; low nasal bridge; small jaw, sometimes with U-shaped cleft palate (Robin sequence)
Heart	Ventricular septal defect, truncus arteriosus, double-outlet right ventricle; interrupted aortic arch; patent ductus arteriosus

Old fluorescent lumps or old mechanisms with hydraulic or heat transfer fluids[46].Toxoplasma-Toxoplasma may be a single-celled protozoa—"pre-animal"—that can be an infection of other animals. Cats are known hosts of toxoplasma and a person's could be infected after handling the infected cat's feces and not washing hands properly after that action. Toxoplasma can also be contracted by eating undercooked meats, trying raw minced meat while cooking, ornot washing hands or utensils properly after meat handling. If a pregnant woman was never exposed to toxoplasma before pregnancy and had not developed the immunity, the obtaining of toxoplasma infection during pregnancy are often extremely dangerous to the baby[47]. It can lead to spontaneous abortion or delivery of the dead infant; or the baby might have underdevelopment of the brain, brain calcifications, blindness, and seizures.

Syphilis Bacteria

Syphilis may be a sexually transmitted disease caused by very small, corkscrew shaped bacteria—Treponemes. If left untreated, this disease progresses through three clinical stages, causing severe damage to a person's health. If a pregnant woman has syphilis and isn't treated quickly, these tiny bacteria travel together with her blood to the baby's body. Syphilis infection is often a explanation for fetal death and miscarriage, or may result within the delivery of the dead baby, or the baby can die within several days of life. If the baby survives, there's a high risk that this baby will have copious nasal discharge(snuffles) full of treponemes and severe inflammatory reaction as a consequence, destroying nasal cartilages and bones[48]. The baby will likely suffer from liver and spleen enlargement and dysfunction, meningitis or meningo encephalitis, and inflammatory skin rash—all of these are symptoms of early congenital syphilis. Some babies will not develop signs of early congenital syphilis, but around eight years aged or older they're going to demonstrate symptoms of late congenital syphilis: their vision will become deteriorated due to inflammatory changes in eyes, a number of their central permanent teeth will have unusual conic shape and notching, and that they may become deaf with complaining of vertigo and ringing in the ears. Their bones are going to be deformed, leading to the design of "saddle" nose and "saber" shins[49].

Viruses

Viruses are incredibly small live particles composed of RNA or DNA that can't produce their own energy for multiplication. In fact, they're parasites that survive certain cells of other creatures, called viral hosts. An epidemic penetrates the host's cell and uses the host's cellular mechanism for its own multiplication by many viral copies inside the cell. Finally, many new viruses will leave the cell either killing it or creating certain damage[50]. These new millions of viruses will target other cells of the viral host, one virus per one cell, to supply more viral copies and make more damage on the host's cells. Most of the time, the host's immune system will defeat these invaders. However, loss of certain cells or their damage during a growing fetus is often catastrophic. Certain types of viruses are well-known to make birth defects. Rubella or German measles virus exposure to the fetus are often a culprit of congenital heart defects, deafness, and blindness.
Rubella virus also can be a explanation for abnormal brain development and other internal organs, and creates characteristic bluish-red skin lesions referred to as "blue

berry muffin spots."[52] Fortunately, if the mother had rubella within the past or was vaccinated against the rubella virus before pregnancy, her system will eliminate the rubella virus before it can reach the fetus. Cytomegalovirus(CMV) is that the commonest sort of fetal infection because of the ubiquitous nature of this virus. Fortunately, 90% of the babies born with CMV exposure haven't any symptoms. However, in some babies, CMV are often a explanation for underdevelopment o the brain, calcifications inside the brain, blindness, deafness, dysfunction of the liver and spleen, jaundice or lesions on the skin referred to as "blueberry muffin spots." [52-54]. Herpes virus infection, in about 5% of cases, can infect a baby in the uterus. The results are catastrophic—from fetal death to permanent problems like underdevelopment and/or calcification of the brain, blindness, or abnormal limb formation. If the herpes virus was acquired by the baby during or simply after the delivery, the baby will get herpetic pneumonia or meningoencephalitis [55]. Varicella zoster virus is a cause of chickenpox (mostly in children), and herpes zoster or shingles (mostly in seniors). If a pregnant woman would contract varicella zoster virus for the primary time during the pregnancy, there's a 25-40% risk that the fetus will have underdeveloped limbs, brain or eye malformations, and specific zig-zag skin scarring[56]. If varicella zoster virus was transmitted to the baby just before the delivery, an infant can suffer from severe varicella zoster pneumonia. Like with rubella virus, if the mother had chickenpox in the past or was vaccinated against the rubella virus in her childhood or before pregnancy, her system will eliminate the rubella virus before it can reach the baby[56]. Congenital cytomegalovirus infection is that the most common virus infection of the fetus. Infection of the early embryo during the primary trimester most ordinarily results in spontaneous termination. Exposure later within the pregnancy results in intrauterine growth retardation, micromelia, chorioretinitis, blindness, microcephaly, cerebral calcifications, mental retardation, and hepatosplenomegaly[57].

Thermo disruptions

Hyperthermia is defined as a blood heat of at least 38.9°C and is an antimitotic teratogen after exposure between weeks 4 and 14[58-60]. During a retrospective study, Smith et al[61] presented 21 patients who had been exposed during pregnancy to hyperthermia caused by infections or by sauna bathing. Severe moronity, seizures in infancy, microphthalmia, midface hypoplasia, and mild distal limb abnormalities were related to hyperthermia[62]. Infants exposed to maternal hyperthermia at 7 to 16 wkof gestation have hypotonia, neurogenic arthrogryposis, or CNS dysgenesis[63]. Shiota[64] studied100 embryos with CNS defects and located that 18% of mothers of anencephalic infants had experienced hyperthermia at the critical embryonic stage[65]. Occipitalencephalocele has also been associated with hyperther. Embryonic studies in guinea pigs and rats have highlighted the sensitivity of brain growth to elevated temperatures.Hypothermia is defined as a core blood heat of less than35°C. Cardiopulmonary bypass during a pregnant patient is associated with a fetal death rate of 16% to 33%. One infant with multiple congenital defects has been described. Another infant had severe disruptive defects of the brain and distal spinal cord, suggesting hypo perfusion injuries associated with hypothermia[66]. Toxic distal spinal cord, suggesting hypo perfusion injuries associated with hypothermia.

Toxic Metals

Lead

A lady who has had plumbism can pass lead on other fetus if she becomes pregnant, albeit she not is exposed to steer. This happens because quite 90% of the lead could also be stored in bone and released into the bloodstream years later. Blood Pb levels of ≥10 µg/dl are considered to be elevated but not dangerously high. The term "leads poisoning "refers to blood Pb levels ≥50 µg/dl. Deleterious effects of lead exposure haven't been convincingly shown to occur at blood Pb levels ≤20 µg/dl. Lead crosses the placenta as early as the12th to 14th weeks of gestation and accumulates in fetal tissue. The adverse effects of lead include miscarriage and stillbirth. a little but significant increase in minor malformations, including hemangiomas, lymphangiomas, hydroceles, skin tags, skinpapillae, and undescended testes, was seen in infants with high lead levels within the umbilical. The VACTERL (vertebral, anal, cardiac, tracheoesophageal fistula, renal and limb abnormalities) association has been reported with prenatal exposure to high lead levels, almost like animal models of leadteratogenicity[67].

Mercury

Organic sorts of mercury are more toxic than the inorganic forms. Methyl mercury, the foremost toxic organic form, causes severe brain damage, as in Minamata disease, which occurred in epidemic proportions on the japanese island of Minamata after maternal ingestion (by both humans and cats) of methlymercury-contaminated shellfish[68]. an identical exposure occurred in Iraq after the ingestion of bread prepared from wheat treated with methyl mercury that was used as a fungicide[69].The blood Hg assay measures exposure to all or any sorts of mercury, but because mercury remains within the bloodstream for less than a few days after exposure, the test should be done soon after exposure. Most non-exposed people have blood Hg levels of 0 to 2 µg/dl. Levels >2.8 µg/dl are required to be reported to the state health department. The assay is often influenced by eating fish that contain mercury. Early effects of mercury toxicity have been found when the blood Hg level exceeds 3µg/dl[70]. Methyl mercury poisoning produces atrophy of the granular layer of the cerebellum and spongiose softening in the visual cortex and other cortical areas of the brain[71]; polyneuritis also can occur.

Lithium

it's utilized in the treatment of manic depression. If possible lithium should be withheld during the primary trimester of pregnancy and ladies taking lithium shouldn't breast feed their infants. The ratio of lithium concentrations in umbilical cord blood to maternal blood is uniform (mean 1.05 ± 0.13).Infants with high lithium concentrations (>0.64 mmol/L) at delivery have significantly lower Apgar scores. High lithium concentrations at delivery are associated with perinatal complications, and lithium concentrations can be reduced by brief suspension of therapy proximate to delivery. Cardiovascular malformations, especially Ebstein

anomaly and tricuspid atresia, are associated with lithium exposure. Infants exposed in utero to lithium may experience transient lethargy, hypotonia, cyanosis, poor feeding, and poor respiratory efforts during the first time of life. Other defects that are noted in infants exposed to lithium ion utero include malformations of the CNS, ear, andureter, altered thyroid and cardiac function, and congenital goiter. Some abnormalities (mainly heart defects such as Ebstein malformation) within the newborn occur in 6% to10% of pregnancies involving trimester exposure to lithium[72, 73].

Maternal Conditions

ObesityDuring pregnancy, obesity is related to adverse outcomes that include macrosomia, hypertension, preeclampsia, gestational DM (GDM), and fetal death[74]. additionally, many investigators have reported an increased risk of birth defects.

Diabetes mellitus: Although hyperglycemia could also be key in the pathogenesis of diabetic embryopathy, other factors contained in diabetic serum can also contribute to the embryopathy .Hyperglycemia results in inhibition of the myoinositol uptake that is important for embryonic development during gastrulation and neurulation stages of embryogenesis[75, 76]. Deficiency of myoinositol appears to cause perturbations within the phosphoinositide system that lead to abnormalities within the arachidonic acid-prostaglandin pathway. The gastrulation and neurulation stages of development are particularly sensitive to hypoglycemia and end in growth retardation also as cranial and caudal ectoderm defects(NTDs). Obesity that happens with variety of metabolic abnormalities, including abnormal glucose metabolism, is associated with a better risk of malformations. A possible role of free oxygen radicals in diabetic teratogenicity has been suggested. The pathogenesis of diabetic embryopathy is heterogeneous maintenance of glucose homeostasis is vital for the prevention of diabetic embryopathy.

Hypothyroidism: in infants occurs when the fetal thyroid glandh as been suppressed by antithyroid drugs (propylthiouracil, carbimazole, iodides), radioactive iodine (Bunn et al., 1976) or possibly maternal antibodies (Dunn et al., 1979). Transfer of maternal thyroxin to the fetus is negligible during early pregnancy. During the ultimate weeks of pregnancy, thyroid binding globulin (TBG) may compete for thyroxin. Triiodothyronine isles bound by TBG and may more freely cross the placenta.

Hyperthyroidism: during pregnancy is typically thanks to Graves disease. The presence of thyroid stimulating globulins may result in thyrotoxicity within the fetus and newborn no matter the treatment of maternal disease. Neonatal thyrotoxicosis is usually a transient phenomenon lasting several months. Affected infants have goiter, exophthalmos, restlessness, tachycardia, periorbital edema, ravenous appetite, hyperthermia, cardiomegaly, cardiac failure, and hepatosplenomegaly[77].

Hyperparathyroidism: Infants of mothers with untreated hypoparathyroidism may have transient hyper parathyroidism during the fetal and neonatal periods[78]. The fetal parathyroid hyperplasia that happens in response to low maternal and fetal serum calcium concentration is mediated by the maternal parathyroid dysfunction. Bone demineralization and subperiosteal reabsorption occurs within the long bones. IUGR, pulmonary artery stenosis, VSD, and muscle hypotonia also occur.

Cretinism and iodine deficiency: Iodine deficiency is the cause of endemic goiter and cretinism thanks to deficiency or of insufficient availability of thyroxine at the feto-placental level. There is a task of maternal T4 in neurological embryogenesis, before the onset of fetal thyroid function and, therefore, its protective role in fetal thyroid failure. In early pregnancy, iodine deficiency induces a critical decrease of T4 levels with consequent TSH increase liable for hypothyroidism in about 50% of iodine-deficient pregnant women [78].

Myotonic dystrophy: The myotonic muscular dystrophy gene contains a segment of CTG repeats that tends to amplify in eachgeneration[79]. Infants born of girls with myotonic dystrophy may show fetal hypokinesia and generalized weakness, and should experience difficulty in respiration and feeding. The facies characteristically shows tenting of the upper lip, ptosis, absence of movement, and anterior cupping of the pinnas. Clubfoot is usually present and postnatal growth is slow.

Phenylketonuria: Maternal phenylketonuria (PKU) leads to defects that include intrauterine and postnatal growth retardation, cardiovascular defects, dislocated hips, and other anomalies[80]. Infants of mothers with PKU are heterozygous, and since phenylketonuric heterozygotesare generally normal, the defect within the fetus must be attributed to the maternal metabolic disturbance. These effects are directly related to the maternal phenylalalnine level. When the level exceeds 20 mg/ml, 92% of infants have mental retardation;73%, microcephaly; 40%, IUGR; and 12%, cardiac malformations. One fourth of pregnancies abort spontaneously.

Mechanical forces: also can act as teratogens. Malformations of the uterus may restrict fetal movements and be associated with congenital dislocation of the hip and clubfoot. Oligohydramnios can have similar results and mechanically induce abnormalities of the fetal limbs. These abnormalities would be classified as deformations or abnormal forms, shapes, or positions of body parts caused by physical constraints. Amniotic bands are fibrous rings and cause intrauterine amputations or malformations of the limbs also. These abnormalities would be classified as disruptions or defects from interference with a normally developing organ system usually occurring later in gestation.

Proven Teratogenic Drugs in Humans

Thalidomide: quite the other event, the thalidomide tragedy alerted the planet to the teratogenic potential of medicine. Thalidomide was marketed in 1956 and was available for four years before its teratogenicity was recognized. Thalidomide produced malformations limited to tissues of mesodermal origin, primarily limbs, ears,

circulatory system, and gutmusculature. The types of malformations might be associated with the developmental stage of the embryo at the time of ingestion. Malformations resulted from repeated use also as from single ingestions during the critical period from the 27th day to the40th day of gestation[81]. In women, a single dose of but 1 milligram per kilogram has produced the syndrome. Abnormal development of long bones produced a variety of limb reduction defects. Typically the upper limbs were more severely involved than the lower limbs. However, any of the bones might be defective or, in severe cases, totally absent. Phocomelia, polydactyly, syndactyly, oligodactyly were all reported. Lower extremities might be similarly affected, although less frequently and fewer severely.

Alcohol: The foetal alcohol syndrome may be a clinical pattern of anomalies characterized by intrauterine growth retardation which commonly continues postnatally[82]. These include: microcephaly, developmental delay, and dysmorphicfacies consisting of low nasal bridge, midface hypoplasia, long featureless philtrum, small palpebral fissures and thin upper lip. Cleft palate and cardiac anomalies can also occur. Full expression of this syndrome occurs with chronic daily ingestion of a minimum of 2 grams alcohol per kilogram (eight drinks per day).The full syndrome is present in about one third of those mothers and partial effects occur in approximately three quarters ofoffspring[82].

Table 4. Abnormalities in thalidomide embryopathy[83]

Skeletal defects	
Absent radii	
Hand	Limited extension, club hand, hypoplastic or fused phalanges, finger syndactyly, carpal hypoplasia or fusion, radial deviation
Ulna	Short and malformed, unilaterally or bilaterally absent
Humerus	Hypoplastic, absent
Shoulder girdle	Abnormally formed with absent glenoid, fossa and acromion process, hypoplastic scapula and clavicle
Hips	Unilaterally or bilaterally dislocated
Legs	Coxa valga, femoral torsion, tibial torsion, bilateral or unilateral stiff knee, abnormal tibiofibular joint, dislocated patella(e)
Feet	Overriding fifth toe, calcaneovalgus deformity
Ribs	Asymmetric first rib, cervical rib
Spine	Cervical spina bifida, fused cervical spine
Mandibular hypoplasia	
Maxillary hypoplasia	
Cardiac anomalies	Tetratology of Fallot, atrial septal defect, patent foramen ovale, dextrocardia, congestive heart failure leading to death Systolic murmur, cardiomegaly Suspected congenital heart disease
Other abnormalities	Apparently low-set ears, malformations extending to microtia
	Urogenital anomalies
	Micrognathia
	Meckel diverticulum
	Uterine anomalies

Angiotensin converting enzyme inhibitors (ACEI) (captopril, enalapril, lisinopril)

ACEI are potent antihypertensive drugs. Their use in latepregnancy has been related to foetal toxicity including intrauterine insufficiency. Reports of neonatal hypotension, oliguria with kidney failure, and hyperkalemia have been reported with ACEI use in pregnancy. Complications of oligohydramnios (i.e., foetal limb contractures, lung hypoplasia, and craniofacial anomalies), prematurity, intrauterine growth retardation, and foetal death have also been reported with the use of those agents late in pregnancy[84]. The adverse effects are associated with the haemodynamic effects of ACEI on the foetus, teratogenic risk with first trimester exposure to those agents appears to be low.

Carbamazepine: Exposure to carbamazepine in utero carries a1% risk of ectoderm defects (10 times their baseline risk). A pattern of malformations almost like those described with the foetal hydantoin syndrome has also been associated with carbamazepine exposure in pregnancy[84].

Cocaine: Cocaine use during pregnancy has been associated with disorder, prematurity, foetal loss, decreased birth weight, microcephaly, limb defects, urinary tract malformations, and poorer neuro developmental performance. The contribution of cocaine to the incidence of congenital malformations is difficult to assess due to methodological problems, which make the results difficult to interpret. Cocaine abuse is usually related to poly-drug abuse, alcohol consumption, smoking, malnutrition, and poor prenatal care[85]. Experimental animal studies and human epidemiology indicate that the danger of major

malformation from cocaine is perhaps low, but the anomalies may be severe.

Coumarin anticoagulants: trimester exposure tocoumarin derivatives are related to a characteristic pattern of malformations termed the foetal warfarin syndrome. Clinical features contain nasal hypoplasia and calcific stippling of the epiphyses. Intrauterine growth retardation and developmental delay to central system a nervosum damage, eye defects, and hearing loss have also been described. The critical period of exposure for the foetal warfarin syndrome appears to be between 6 and 9 weeks of gestation. A prospective study found evidence of warfarin embryopathy in about one third of the cases where a coumarin derivative was given throughout pregnancy[86]. Oral anticoagulants are also associated with a high rate of miscarriage. Exposure to oral anticoagulants after the primary trimester presents a risk of central nervous system damage to haemorrhage. Unlike heparin, oral anticoagulants readily cross the placental barrier.

Diethylstilbestrol: Diethylstilbestrol was utilized in the 1950s and1960s for the diagnosis of recurrent miscarriage. Clear cellad enocarcinoma of the vagina was found to be associated with diethylstilbestrol treatment of the patient's mother during the first trimester of pregnancy. Over 90% of the cancers occurred after 14 years aged[86]. Clear cell carcinoma has not occurred in women exposed in utero after the 18th week of gestation. A high incidence of benign adenosis of the vagina was found in women prenatally exposed to this nonsteroidal estrogen analogue. during a prospective study, exposure starting at 4 weeks was related to adenosis in56% of the offspring, decreasing later to 30% at 16 weeks and10% at 20 weeks. Miscarriage rate and preterm delivery were significantly more common in women exposed in utero to diethylstilbestrol compared to matched controls. In 134 males exposed in utero to the agent no signs of malignancy were found but 27% had genital lesions (epididymal cysts, hypotrophic testes, or capsular induration of the testes). In 29%,pathologic changes were found in spermatozoa[86].

Folic acid antagonists: **Aminopterin and methotrexate**

Aminopterin has been known since 1950 to end in foetal death, which led to its use as a person's abortifacient. The foetalaminopterin syndrome was described supported anomalies observed in aborted foetuses and infants born following unsuccessful abortions. Malformations include central nervous system defects (hydrocephalus, meningomyelocele), facialanomalies (cleft palate, high arched palate, micrognathia, ocularhypertelorism, outer ear anomalies), abnormal cranial ossification, abnormalities in first gill arch derivatives, intrauterine growth retardation and retardation[87]. Infants are born with features of the aminopterin syndrome after pregnancy exposure to methotrexate (methylaminopterin). it had been suggested that the maternal dose necessary to induce defects is above 10 mg per week with a critical period of 6 to eight weeks post conception being postulated

.**Hydantoins (phenytoin and trimethadione):**Hydantoins have been related to a recognizable pattern of malformation termed the foetal hydantoin syndrome. The clinical features include craniofacial dysmorphology (wide anterior fontanelle, ocular hypertelorism, metopic ridge, broad depressed nasal bridge, short anteverted nose, bowed upper lip, cleft lip, cleft palate), also as variable degrees of hypoplasia of the distal phalanges, nail hypoplasia and low arch dermal ridge patterning[88]. Growth retardation, moronity and cardiac defects are additional features of the syndrome.

Isotretinoin (13-cis-retinoic acid): Isotretinoin may be a synthetic vitamin A derivative, prescribed for severe cystic acne that has been proven to be a potent human teratogen also as a behavioral teratogen when given systemically. A pattern of anomalies termed retinoic acid embryopathy has been associated with isotretinoin (and other retinoic acid derivatives such as etretinate and megadoses of vitamin A) exposure in pregnancy[89]. The clinical features include craniofacial anomalies (microtia or anotia, access oryparietal sutures, narrow sloping forehead, micrognathia, flatnasal bridge, harelip and palate, and ocular hypertelorism),cardiac defects (primarily conotruncal malformations),abnormalities in thymic development, and alterations in central nervous system development. the danger for associated miscarriage was 40%.

Misoprostol: Misoprostol may be a synthetic prostaglandin E1analogue, prescribed for duodenal and gastric ulceration, also used as an a bortifacient by women in Brazil. A Brazilian case series suggested an association between trimester exposure to misoprostol and limb defects with or without Moebius' sequence. The association was further supported by a case control study comparing the frequency of misoprostol use during the primary trimester by mothers of 96 infants with Moebius' syndrome and mothers of infants with neural tube defects. Among the mothers of infants with Moebius 'syndrome, 49% had used misoprostol, as compared with 3% of the mothers of infants with ectoderm defects (odds ratio,29.7; 95% confidence interval 11.6 to 76.0)[89] Despite the strong association between misoprostol exposure during the primary trimester and Moebius 'syndrome, its absolute teratogenic risk is perhaps not high.

Tetracyclines: Yellow-brown discolouration of teeth may occur thanks to deposition of the antibiotic in calcifying teeth with tetracycline use in late pregnancy. the danger is clear only after 17 weeks of gestation when the deciduous teeth begin to calcify. Generally, only the deciduous teeth are involved ,although with administration of the drug on the brink of term the crowns of the permanent teeth could also be stained[90]. Oxytetracycline and doxycycline are related to a lower incidence of enamel staining.

Possible Teratogenic Drugs in Humans

D-penicillamine: supported several case reports, high dose treatment of the pregnant woman with D-penicillamine has been related to animal tissue disorders (cutis laxa).Methimazole: Methimazole treatment during pregnancy has been related to scalp defects (aplasia cutis congenita)based on case reports and on an epidemiological study in which methimazole had been added to animal feeds as a weight enhancer, and in those areas a better incidence of cutis a plasiacongenita was found (Birth Defects, 2014).

Diazepam: trimester exposure to diazepam has been associated in small studies with a little increase in the incidence of harelip and palate. Larger studies didn't confirm the association (Birth Defects, 2014).

Teratogenic Counseling

In counseling the pregnant patient exposed to a potential lhuman teratogen, it's important to stress the significance of exposure to the patient. Ascertaining the clinical facts regarding the character of the exposure: the length, dosage, and timing of exposure during pregnancy, also as other exposures of concern about which the patient might not ask (e.g., alcohol, cigarette smoking). All available current data regarding the agent are then collected, and conclusions regarding the risks of exposures are drawn. Counseling should include the background human baseline risk for major malformations ,whether the foetus is at increased risk, which anomaly has been associated with the agent in question, a risk assessment, methods of prenatal detection, when available, limitations in our knowledge, and limitations of prenatal diagnostic capabilities[91]. Additional aspects include the potential risk of the medical condition that a drug is prescribed, known interactions (in both directions) between the disease state and therefore the pregnancy and preventive measures, when applicable (e.g., vitamin Bc supplementation within the case of carbamazepine exposure). Because quite 50% of pregnancies in North America are unplanned, teratogenic risk assessment should be started before pregnancy.

Some Recent Findings

Dispensing of probably teratogenic drugs before conception and during pregnancy: a population-based study[92]. "To study the dispensing of probably teratogenic drugs in the 12-month period before also as during pregnancy in the Netherlands. Drug-dispensing information was identified from the PHARMO Database Network for the 12-month period before conception and through pregnancy. Drugs with either a Swedish FASS 'D' classification, an Australian ADEC or American FDA 'D' or 'X' classification were considered potentially teratogenic (n = 202). ...Five percent of the pregnancies received a potentially teratogenic drug during pregnancy and 0.66% received a drug from the danger category X. It may be possible to scale back these proportions when reasons for prescription are explored."

Teratogen Screening Using Transcriptome Profiling of Differentiating Human Embryonic Stem Cells."Teratogens are substances which will cause defects in normal embryonic development while not necessarily being toxic in a dults. Identification of possible teratogenic compounds has been historically beset by the species-specific nature of the teratogen response. to look at teratogenic effects on early human development we performed non-biased expression profiling of differentiating human embryonic and induced pluripotentstem cells treated with several drugs; ethanol, lithium, retinoic acid, caffeine and thalidomide, which is known to be highly species specific. Our results point to the potency of specific teratogens and their affected tissues and pathways. Specifically, we could show that ethanol caused dramatic increase in endodermal differentiation, retinoic acid caused misregulation of neural development, and thalidomide affected both these processes. We thus propose this method as a valuable addition to currently available animal screening approaches." Maternal exposure to multi-wall carbon nanotubes does not induce embryo-fetal developmental toxicity in rats[93]. "

The results show that repeated oral doses of multi-wall CNTs(MWCNTs) during pregnancy induce minimal maternal toxicity and no embryo-fetal toxicity at 1,000 mg/kg/day in rats. The no-observed-adverse effect level of MWCNTs is considered to be 200 mg/kg/day for dams and 1,000 mg/kg/day for embryo fetal development. during this study, the dosing formulation wasn't analyzed to work out the degree of reaggregation (or not), nor were blood levels of CNT's measured within the dosed animals to verify or characterize absorption."

CONCLUSIONS

The practitioner who restricts his prescribing for pregnant women to circumstances where medication is really indicated, and employs medicines which have been widely used in pregnancy for many years without apparent harm is unlikely to contribute significantly to the incidence of congenital malformations Drugs which will cause birth defects are said to be ‘teratogenic drugs’. life science cannot always predict how exposure to a teratogenic drug will affect a developing fetus. It can be dangerous for a pregnant woman to prevent taking prescription drugs if she features a medical condition or become ill. Without treatment, the health and welfare of both the mother and her unborn baby might be in danger. Today, the FDA monitors teratogen exposures to pregnant women with a number of regulations and risk management programs.

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