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Teratagenecity and Maternogenicity – Myths and Facts

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ABSTRACT

Drug prescription in pregnancy and lactation is a challenge as the benefit provided to the mother has to be balanced with the associated risk to the baby. The obvious solution to fetal and nursing infant risk avoidance is maternal drug abstinence. However, from a practical point of view, that would be impossible to implement. A more pragmatic solution is to disseminate knowledge to all the treating physicians and those involved in the pregnancy and breast feeding processes. About 8% of pregnant women need permanent drug treatment due to various chronic diseases and pregnancy-induced conditions. Many times the pregnant females may consult physicians for simple complaints. Hence it is mandatory for physicians to be aware of the drug use in pregnancy and lactation. This will help to avoid the risk of teratogenicity and maternogenicity and maximize benefits of drugs therapy in pregnant and lactating females. This review tries to shed light on the basic facts and clear the misconception associated with drug use in pregnancy and lactation.
Key words: Teratogenicity, pregnancy, lactation

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INTRODUCTION

Pregnancy and lactation is a unique clinical situation where drug treatment presents a special concern because all the drugs taken by the female have a potential to produce harmful effects in the growing fetus or lactating baby. While in the adult most of the adverse drug effects are reversible, in the embryo these can lead to irreversible abnormalities in the new born. Although, it is overemphasized to avoid all drugs especially during early pregnancy, [1] but this recommendation is unrealistic and may be dangerous. About 8% of pregnant women need permanent drug treatment due to their chronic diseases such as epilepsy, diabetes mellitus, bronchial asthma, hypertension, thyroid disorders, migraine and severe depression [2]. More pregnant women require transient drug treatment because of pregnancy induced complications like pregnancy induced hypertension, gestational diabetes etc. Ingestion of medications by pregnant women is a common occurrence[3]. According to the World Health Organization survey it was observed that 86% of women took medication during pregnancy, receiving on an average 2.9 (range 1-15) prescriptions, 73% were given by obstetrician, 12% by the general practitioner and only 5% by the midwives[4]. Although, maternal drug use during pregnancy is a common phenomena, but drug induced teratogenicity accounts for less than 1% of total congenital abnormalities [5]. One main reason for this could be that, fortunately only few therapeutic agents (approximately 40-50), have possible teratogenic effect in humans. These make up a very short list compared with the numerous drugs and chemicals that women are exposed to during pregnancy. Therefore, the information about these agents is the key element in prevention of drug induced teratogenicity. Whenever prescribing for a pregnant female, complete and accurate information on the risks and benefits of drug use during pregnancy should be given [6]. On the other hand pregnant women using necessary drug treatments may suffer permanent psychological stress due to the anxiety created by the notion, that nearly all drugs cause congenital abnormality. It is therefore, the responsibility of treating clinicians to counsel those women by accurately identifying exposure and risk associated with it. Hence it is essential for the clinicians to be aware of the basic facts regarding the drug use in pregnancy and lactation.

Historical aspects related to teratogenicity

Until the middle of 20th century, it was believed that the uterus served as shield from the external environment and provided a protected environment for the fetus. This belief was questioned in 1930, when a prepartum x-ray was linked to the birth of a malformed human child.[7] Later in 1941, an Australian physician, NM Gregg, observed that women contracting rubella during the first trimester of pregnancy frequently gave birth to infants with specific anatomic defects, mainly in the heart, eyes and ears [7]. This finding forever shattered the concept that the external environment does not affect fetal outcome. However the interest in drug induced teratogenesis remained low until the 1960s. Then 50 years ago, the catastrophic thalidomide disaster occurred, when nearly 10,000 cases of congenital malformation were attributed to this single drug [8]. This misadventure incited the promulgation of the drug regulations of 1962 in the United States, according to which, a drug must be demonstrated to be safe and effective for the conditions of use prescribed in its labeling. It is now mandatory to test for the teratogenicity for any new drug.

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Physiological changes during pregnancy.

The unique physiologic changes of pregnancy, especially during third trimester can affect the pharmacokinetics of medications used by pregnant women [9]. The pregnancy related physiological alterations and their consequences are shown in Table I. These pharmacokinetic changes alter free drug concentration which is a major determinant of a drug transfer across placenta. But, the overall effect on drug disposition is complex and often difficult to predict during pregnancy.

Table I. Major physiological changes and their consequences on drug therapy in pregnant population.

System with physiological change	Consequence
General ↑ Total body fat Relative ↓ in albumin concentration	↑ Vd of lipid soluble drugs requiring higher dose eg. diazepam. ↑ Free drug concentration e.g. anticonvulsants
Cardiovascular ↑ Plasma volume	Subtherapeutic drug levels
Gastrointestinal ↓ Gastric emptying and GI motility Induction of hepatic microsomal enzymes	Slow absorption-Delayed onset of drug effect ↑ drug accumulation or ↓ elimination of some drugs
Renal ↑ GFR ~ 50%	↑ Renal clearance of drugs - subtherapeutic levels achieved
Cardiovascular ↑ Blood pressure in some females	Complications requiring treatment, hospitalization, etc.
Genitourinary Dilatation of ureter	Prone for urinary tract infection due to urinary stasis
Endocrine Impaired Glucose intolerance in some females	Resulting in Diabetes mellitus which needs lifelong treatment.

Placenta

The placenta is the organ which mediates the attachment of the embryo to the uterine wall. It is responsible for all the nutritional, secretory and regulatory functions essential for the maintenance of pregnancy. Placental transfer of substances between mother and fetus is established at about the fifth week of fetal life. Any substance administered in sufficient quantity will eventually cross the placenta reach the fetus or embryo. Therefore, the so called concept of placental barrier is a myth and should be discarded [10]

The rate of placental drug transfer largely depends on the physicochemical properties of the drug such as lipid solubility, molecular weight, protein binding and pH difference [11] Other important factors are maternal drug disposition and physiological

activity of the placenta. Small molecular weight and highly lipid soluble drugs diffuse easily across the placental membrane whereas large molecular weight or highly polar drugs tend to cross slowly. Only free unbound drug crosses the placenta and since plasma albumin decrease during pregnancy, the concentration of free drug increases which crosses the placenta to reach the fetus. Fetal pH is slightly more acidic than maternal pH and so weak bases are more likely to cross the placenta [12].

Definition of teratogenicity

The word teratogen is derived from Greek word teras meaning a monster. Traditionally, only gross anatomic malformations were known as teratogenic but nowadays it has a broader meaning. It involves not only congenital malformations present at birth but also any effects (morphological, behavioral, biochemical) induced during embryonic life or fetal life detected at birth or later [13]. In simpler words, teratogenicity not only includes gross anatomical defects but also includes acid base or electrolyte imbalance in fetus, respiratory depression due to use of opioids during labour as well as intrauterine growth retardation. Apart from these, it also includes long term delayed effects of in-utero drug exposure, which are difficult to recognize. Diethyl stilbesterol (DES) serves as an excellent example for this. In 1948, professor O.Smith introduced a synthetic estrogen as a treatment for early pregnancy complications. Twenty three years later (1971) the consequences of this unapproved therapy came into light with the establishment of a relationship between adenocarcinoma of the vagina and in utero exposure to DES [14].

Mechanism of teratogenic drugs

Drugs consumed by the pregnant woman can affect the fetus in several ways. They can either cause indirect damage to the fetus by affecting maternal tissues or placenta or produce direct fetal damage. Physiological changes in mother like changes in maternal serum glucose, electrolytes or acid base balance, deficiency of critical substances like folic acid can have a profound effect on the fetus causing serious problems [15]. Certain drugs like prostaglandins can induce uterine contraction thereby reducing the blood supply or triggering pre-term labor. Alteration in placental function like constricting blood vessels and reducing the blood supply of oxygen and nutrients to the fetus can result in intrauterine growth retardation of the fetus. Direct teratogens can produce adverse effects on the fetus itself. For example thalidomide, interferes with the normal fetal metabolism by acting as a competitive antagonist of glutamine, glutamic acid, and possibly interfere with fetal metabolic pathways [15].

Teratogenic action of teratogen

The mere presence of a teratogen does not necessarily produce congenital malformations. Teratogenicity occurs when the teratogen is present in an appropriate dosage at a very precise moment during the organogenesis of the embryo having genetic susceptibility. However, it is important to note here that Teratogenicity follows a dose effect relationship. All chemicals when taken in extremely large doses can affect the fetus adversely. In general, the dose range which causes Teratogenicity is narrow and the dose effect curve has a steep slope. For example, the risk of major congenital malformations with

valproic acid seems to increase significantly at 600 mg/d, and the largest attributable risk was observed at doses exceeding 1000 mg/d [16]. The action of a teratogenic agent on the conceptus depends mainly on three factors: the developmental stage of intrauterine host, genetic susceptibility of embryo and the pathophysiological status of the mother. We will be discussing each of these factors individually.

Developmental stage of embryo

The development of an embryo into an infant is a complicated, intricate process. The early weeks of pregnancy are implicated in 10 times as many fetal abnormalities as in the second and third trimesters. Conventionally, the first three months of pregnancy are considered as the critical period of most major congenital abnormalities. This hypothesis is unscientific and outdated [17]. The period in which teratogens can affect the development of the human embryo is very short, and lasts from the 29th day to the 70th day of gestation (21th - 56th day post conception). Thus, it is necessary to know that before the first missed menstrual bleeding, teratogens cannot induce congenital malformations and only the second and third months represent the critical period of most major congenital anomalies. Figure 1 shows the effect of a teratogen on various stages of prenatal development. During the preimplantation period when the blastocyst lies freely within the uterus and depends on the uterine secretions for its nutrition, teratogenic agents can kill the embryo, but cannot produce congenital malformations. Slight defects induced by the teratogens can be corrected without obvious harmful consequences on the growing embryo because during this stage, many blastomeres retain their totipotency and thereby replace the damaged cells by new cells. Once implantation has occurred in the human at 7- 8 days after fertilization, the embryo undergoes very rapid and important transformations and organogenesis takes place. It is during this critical period that the vulnerability of the developing embryo is greatest for the occurrence of gross teratogenic malformation. Table II shows the specific time of major organogenesis in the embryo. Drugs produce specific congenital anamolies depending upon the time at which they reach the embryo. Thalidomide is a typical example to illustrate the pattern of pathogenesis of anomalies. The specific abnormalities were produced in the children related to specific days of conception when thalidomide was ingested. Ingestion of thalidomide on day 21-22 lead to absence of external ears and paralysis of cranial nerves; day 24-27 caused maximum phocomelia, day 28-29 produced severe deformities of lower limb and day 34-36 was associated with hypoplastic thumb and anorectal stenosis [18]. Since many organs are developing at the same time, the teratogenetic effect often represents a combination of different anomalies [19]. Although, most of the times the morphological type of anomaly is dependent on the developmental stages at which the teratogenic agent reaches the embryo, few teratogenic drugs show a preferential action upon specific organs. For example, the cytotoxic drug aminopterin mainly produce general growth retardation and central nervous system anomalies, while thalidomide leads to skeletal malformations, normal growth and well developed intelligence [20,21]. After 60 days (end of the eighth week) the fetal period begins, when organogenesis is completed in many systems. Development during this time is primarily maturation and growth. Exposure to teratogenic drugs during this period is not associated with major congenital malformations but they may alter the growth and function of normally formed organs and tissues [22]. Between 60-90 days, the differentiation of external genitalia and central nervous system is continued hence their anamolies can be produced by exposure of

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a teratogen. Various types of behavioral changes or impaired mental development in post natal life can occur due to central nervous system interference [23].

Figure 1. Effect of a teratogen on various stages of prenatal development

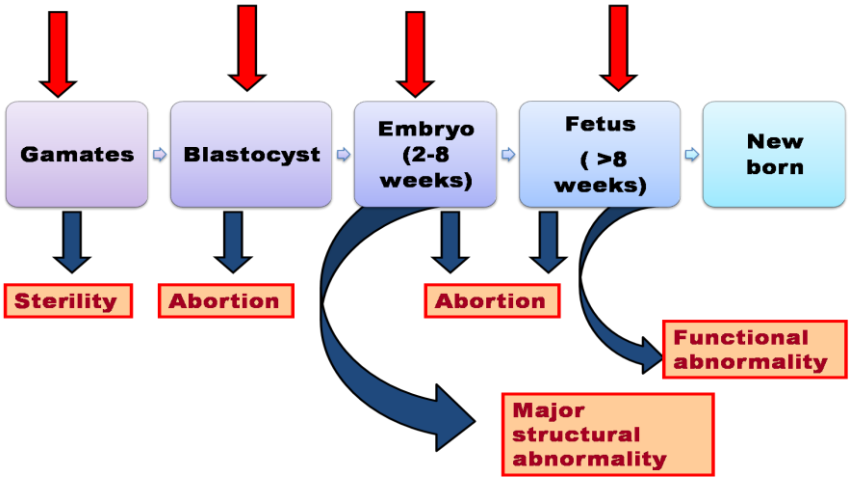

Table II. Specific time of major organogenesis in the embryo.

Days of gestation (Post conception day)	Major organ formation and teratogenic effect
<29 (15)	No differentiation of cells
29-39 (15-25)	CNS differentiation
34-44 (20-30)	Precursor of axial skeleton and musculature occur and limb buds make appearance
38-54 (24-40)	Major differentiation of eyes, heart and lower limbs
74 (60)	Organ differentiation completed in many system
90 (76)	Maturation of organs
>90 (>76)	Little susceptibility of congenital malformation

Genetic susceptibility of embryo.

The reaction of the embryo to the exogenous agents depends upon its genetic constitution. Figure 2 demonstrates the difference in the susceptibility of different embryos based on their genetic makeup. Differences in the reaction to a teratogenic agent between individuals, animal strains and species are ascribed to the genetic susceptibility. High susceptibility of the mouse embryo to corticosteroids induced cleft palate is a typical example. This may be related to the metabolic differences between the mouse and other species in the rate of absorption or degradation of the hormone [24]. Similar individual variations in teratogenic susceptibility have been confirmed in humans. Only less than 25% females who had consumed thalidomide in the critical period of pregnancy had deformed babies, while the remainder escaped the noxious effects of the drug [17]. Children with a genetic susceptibility for hearing impairment are more prone to rubella induced deafness [25]. Similarly all the mothers treated with warfarin during critical period of pregnancy do not give birth to infants with congenital abnormality [26].

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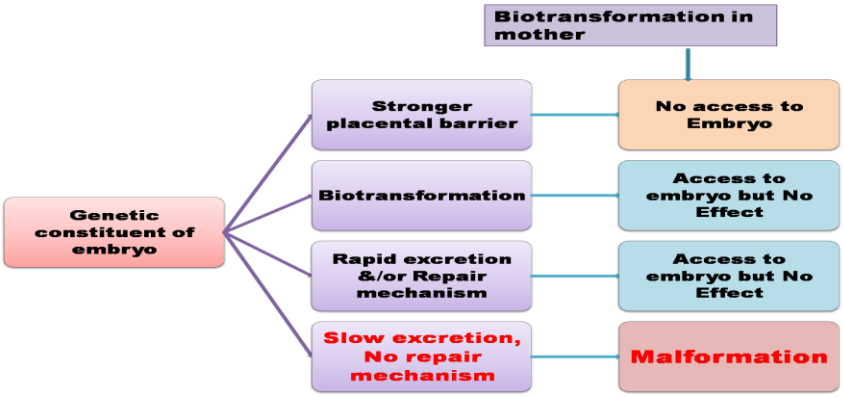
Figure 2. Susceptibility of different embryos to a teratogen based on their genetic makeup.



Pathophysiological status of the mother

The teratogenic action of the drug also depends upon physiological and pathological status of the mother. Physiological factors like age, nutrition, local uterine conditions and hormonal imbalance are of great importance. The risks of malformations are higher in mothers of extreme of age [27]. Deficiency and excess of certain nutrients can affect the expression of genes and may enhance the harmful effect of drugs [28]. Deficiency of folic acid is associated with neural tube defects and similarly Vitamin C deficienty can also lead to fetal abnormalities [29]. Therefore prophylactic folic acid should be prescribed to all female with early pregnancy. Although vitamins are routinely taken during pregnancy, but their excess can also cause toxicity. Excessive vitamin A is been known to cause increase intracranial pressure and other symptoms of hypervitaminosis A in the fetus [30]. Hypervitaminosis D is been associated with hypercalcemia, supravalvular aortic syndrome and mental retardation [31]. Excessive maternal doses of vitamin C can induce scurvy shortly after birth [32]. Large doses of vitamin K analogues given to mothers shortly before delivery can produce kernicterus [33]. Certain chronic and metabolic diseases such as diabetes mellitus, hypertension and systemic lupus erythematosus can enhance the toxic action of drugs and increase the frequency of fetal damage [34]. The higher susceptibility to teratogens of pregnant women who have a metabolic disease may be attributed to the altered drug disposition between the fetal and maternal compartments [27].

Preclinical testing

There is no direct relationship between the chemical structure, pharmacological activity, or the toxicity of a drug in the adult and its specific action on the embryo. Therefore test for Teratogenicity of drugs must be conducted in animals before prescribing during human pregnancy, even though animals are not the ideal model. Animals have a different genetic makeup, reproductive processes, metabolic pathways and sensitivities than humans. Therefore the results of animal studies do not have one to one relationship with humans. Despite the numerous teratogens discovered in animals, only a few have a proof of their noxious effects in the human embryo [28]. Another handicap of animal studies is the difference in the reactions of different species for a given teratogen [28]. This difficulty has been partially overcomed by using several animal species in teratogenic screening procedures.

The best example is of thalidomide which produces obvious malformation in certain strain in rabbit, but is apparently safer in the rat. Cortisone, a potent teratogenic agent in the rabbit and mouse does not produce malformations in the rat [28]. Lastly, the type of malformations produced by a specific teratogen can be different in each species. For example, carbutamide produces eye anamolies in the rat and mouse, while leads to facial and visceral malformations in rabbits [28]. Despite these limitations, animal studies constitute the only approach available to evaluate the teratogenic potential of the drugs.

Fetal risk categories

Most drugs are not studied during pregnancy before being marketed and animal studies are also not available for all the agents. Hence experts in many countries have developed a fetal risk classification system that determines the teratogenic risk of drugs by considering the quality of data from animal and human studies. The examples of fetal risk classification systems are those given by US Food and Drug Administration (FDA), the Australian Drug Evaluation Committee (ADEC) and the Swedish Catalogue of Approved Drugs (FASS). For obvious ethical reasons, clinical trials are not routinely performed to evaluate the drug safety and efficacy in pregnancy. Studies of aspirin in the prevention of pre-eclampsia and trials of antihypertensive agents in pregnancy are among the few exceptions to this rule [35,36]. Current methods of assessing Teratogenicity in humans include mainly pregnancy registries and case– control surveillance studies; [37] however, these practices are insufficient to determine drug safety accurately. This insufficiency is due, in part, to serious methodological weakness in design of these studies, which are based on retrospective maternal information with obvious recall bias exaggerating the teratogenic risk [38]. Physicians are therefore typically dependent on inaccurate or outdated information in prescribing medication. Moreover there are inconsistencies regarding the interpretation of fetal risk. One study compared the drugs included in the fetal risk classification systems from the US- FDA, ADEC and FASS, on basis of the risk factor category to which they had been assigned. Only 61 (26%) of the 236 drugs common to all 3 systems were placed in the same fetal risk factor category.39 Differences in category allocation for the same drug may limit the usefulness and reliability of fetal risk classification systems. Moreover pregnancy category is not available for all the drugs. Only 40% of drugs in physician desk reference (PDR), a widely used source of drug information by U.S. clinicians and patients, have their pregnancy category listed.

US FDA Fetal risk category

The widely accepted system for teratogenic potential, was introduced by the US Food and Drug Administration (FDA) in 1979, using the letters A, B, C, D and X for five categories [40]. The description of this categories is given in table III. According to this system category A drugs are the safest drugs to be used in pregnancy and any fetal risk is unlikely in category B .There is no appropriate data for drugs in category C. Category D include those agents which even though have evidence of human fetal risk, but they have to be given to mother in a life-threatening situation. Finally, drugs with classification X are absolutely contraindicated in pregnancy. Table IV gives the list of some of the agent having definitive teratogenic risk in humans.

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Table III. FDA fetal risk category

Category	Description	Example
A	Adequate well controlled studies in pregnant females have not shown an increased risk of fetal abnormalities.	Folic acid, thyroxine
B	Animal studies have revealed no evidence of harm to the foetus ;however , there are no adequate and well controlled studies in pregnant women OR Animal studies have shown an adverse effect ,but adequate and well controlled studies in pregnant women have failed to demonstrate a risk to foetus.	Amoxicillin, metformin
C	Animal studies have shown an adverse effect and there are no adequate and well controlled studies in pregnant women. OR No animal studies have been conducted and there are no adequate and well controlled studies in pregnant women.	Morphine, steroid
D	Studies, adequate well controlled or observational, in pregnant women have demonstrated a risk to the foetus. However the benefit of the therapy outweighs the potential risk.	Antiepileptics, antimalarials, anti-tubercular
X	Studies, adequate well controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contradicted in women who are or may become pregnant.	Retinoids, ergometrine

Table IV. Drugs with Significant Teratogenic effects on the Foetus.

Drug	First-trimester fetal effects	Second- and third-trimester fetal effects
Antibiotics		
Chloramphenicol	None known	Gray baby syndrome
Aminoglycosides	Otoxicity	Not known
Tetracycline	None known	Staining of teeth, and increased susceptibility to cavities in the baby
Anticoagulants		
Warfarin	Fetal warfarin syndrome-Nasal hypoplasia and depressed nasal bridge	CNS malformation/Risk of bleeding.
Anticonvulsants		
Carbamazepine,	Neural tube defects	Neurocognitive effects
Phenytoin	Fetal hydantoin syndrome	Neurocognitive effects
Trimethadione	Multiple congenital anomalies	Neurocognitive effects
Valproate	Neural tube defects, cardiac and limb malformations	Neurocognitive effects
Antihypertensives		
Angiotensin-converting enzyme (ACE)	Cardiac/CNS malformations	Oligohydramnios, IUGR, renal failure
Beta-blockers		Foetus bradycardia and growth restriction.

Thiazide diuretics		Hypoglycaemia, hyponatremia, hypokalemia and thrombocytopenia
Antidepressants Tricyclic Selective Serotonin Reuptake Inhibitors	Not known Not known	Neonatal withdrawal symptoms Neonatal withdrawal symptoms
Anticancer drugs Busulfan Chlorambucil Cyclophosphamide Mercaptopurine Methotrexate	Multiple Birth defects , abortion	Hypoplastic gonads, IUGR
Mood stabilizing agents Lithium	Ebstein anamoly	Not known
Nonsteroidal anti-inflammatory drugs (NSAIDs) Aspirin Ibuprofen Naproxen	Cardiac, gastroschisis, miscarriage	Premature closing of ductus arteriosus,
Oral antihyperglycemic drugs Chlorpropamide Tolbutamide		Prolonged symptomatic neonatal hypoglycemia
Sex hormones Danazol Diethylstilbestrol (DES) Androgens		 Masculinization of a female foetus's genitals Vaginal adenosis, clear cell vaginal adenocarcinoma Masculinization of female foetus
Skin treatment Retinoids	Extremely high risk of defects, such as cardiac anamolies, small ears, and hydrocephalus	Stillbirth, mental retardation
Antithyroid drugs Methimazole Propylthiouracil Radioactive iodine	Fetal thyroid development	Hypothyroidism Congenital goiter CNS development
Miscellaneous Thalidomide	Phocomelia, internal malformations	

Limitations of US FDA fetal risk category

Though US FDA is most widely cited system several limitations have been observed when this system is applied to practical medicine. First of all, there are very few drugs in category A and category X. In fact, 70% of drugs are category C, but not all category C drugs have the same level of risk. This category itself is ambiguous and fails to provide any guidance in making an informed decision. Secondly, pregnancy categories are rarely or too

hastily revised as new information becomes available resulting in confusion among clinicians regarding the prescription certain drugs. Several drugs have been labeled "D or X" despite extensive opposite human safety data (eg. Progesterone,corticosteroids). Thirdly, current labelling does not discriminate between potential adverse effects on the basis of severity, incidence, or type of effect or on the basis of dose, duration, frequency, route, and gestational timing of exposure. Agents cannot be classified as teratogens or non-teratogens without consideration of the dose, route, duration, and gestational timing of the exposure. For a drug which produces major anatomical defect like ventricular septal defect, consumption of drug after the critical period will not cause any malformation and therefore stopping a useful drug at this point is illogical and may even be harmful if the disease being treated worsens. Similarly, if a teratogen is still in the body during organogenesis, even though the course of treatment was completed before conception (eg. Retinoids) then there is the potential for harm. And finally, the current label inadequately addresses inadvertent exposures, focusing instead on planned prescribing during pregnancy. A more common scenario is that woman had accidently consumed a drug during her first trimester without the knowledge of her pregnancy. For example, tetracycline can be commonly prescribed for acne inadvertently for a brief time early in the first trimester. But, such an occurrence would not ordinarily justify termination of the pregnancy on medical grounds.

Because of these limitations, the FDA made an announcement in May 2008, stating that it is revamping the current pregnancy labeling system with a new system that would have more details about a particular drug [41]. The new system will improve the data collection process to address the safety of medications in the pregnant population. The new labelling system will be separated into three separate sections: (1) Clinical management statement, (2) summary risk assessment, and (3) discussion of data. The risk summary section will incorporate human and animal data and clinical consideration section will address risk assessment and how to handle inadvertent fetal drug exposure. The third section will be summarizing the evidence discussed in the other two sections along with therapeutic alternatives [41]. Although, the new system looks good on paper, it will be important to determine whether or not it results in effective risk communication and appropriate clinical decision-making. However, to date, the pregnancy risk categories are still in effect and are still being used by physicians.

Is it safe to avoid drugs in pregnancy?

Avoiding drug use in pregnancy has its own set of risks. The teratogenic risk of medicinal drugs is often over exaggerated and can lead to serious consequences [38]. Many pregnant females don't receive necessary drug treatment resulting in serious consequences for both the mother and the fetus. High fever in early pregnancy is in itself a cause of teratogenesis unless treated appropriately [42]. Similarly many pregnant females suffering from sexually transmitted disease (STD) remain untreated during pregnancy leading to preterm birth or serious intrauterine infection of the fetus [43]. Some studies have also pointed out that inappropriately treated asthmatic pregnant females have a higher risk of intrauterine growth retardation [44].

Misconception that all drugs are teratogenic can cause significant psychological stress in females using drug therapy during pregnancy [45]. Moreover exaggerated risk of

drug induced Teratogenicity may cause unnecessary anxiety in pregnant females exposed to drugs during early pregnancy leading to termination of otherwise planned pregnancy [1].

Why is drug induced teratogenic risk exaggerated?

Unrealistically high teratogenic risk assigned to drugs use can be attributed to two main reasons: misinformation and misperception.

Misinformation

One study revealed that different popular magazines and books dealing with pregnancy, friends and relatives were a more likely source of information about drugs during pregnancy than doctors or midwives [46]. These sources usually stress risks and very rarely address the safety of specific drugs. Moreover they tend to assign risk to drugs not proven to be risky and increase a tendency to alarm readers without justification [47]. Another source of misinformation are physicians. Many times women are advised to terminate pregnancy despite non Teratogenicity by their physicians. This may be attributed either to a defensive approach in the current litigious atmosphere, or the possibility that physicians themselves are misinformed. One study indicated that many women advised medical abortion by the physicians did not have more accurate information of risk involved [47]. An important example of physician misinformation is with the use of cocaine. Cocaine (FDA category C), has no evidence to suggest that it increases teratogenic risk when used in early pregnancy. However, a survey revealed that the majority of participating physicians felt that malformations were associated with cocaine use and wish to terminate a pregnancy where exposure to cocaine occurred during the first 8 weeks of gestation [48]. This is alarming, as physicians' erroneous perceptions may lead them to offer women unjustified terminations of pregnancy. Possible sources of misinformation among physicians can be reference sources which includes warnings on exposures during pregnancy that are no longer correct. New information about the effects of medication use and the optimal management of maternal conditions during pregnancy continually becomes available. Many sources of information about potential teratogens are available as publications, though they are less frequently updated [49,50]. Table V lists references of regularly updated computerized databases of such information. ''Reprotox'' is most useful site as it is especially developed to provide summary information to health care providers on the effects of various chemicals and physical agents on pregnancy and lactation.

Table V. Resources of computerised databases on teratogenic information

Organisation	Website
National Library of Medicine	www.nlm.nih.gov
Organization of Teratogen Information Services	www.otis.pregnancy.org
Pharmaceutical companies	www.pharmacy.org/company.html
Pregnancy exposure registries	www.fda.gov/womens/registries/default.htm
Reproductive toxicology center	http://reprotox.org
Physician's Desk Reference	http://www.pdr.net/login/Login.aspx

Misperception

During pregnancy there is an increased sensitivity to this issue, leading to a distorted perception of risk [47]. Appropriate counselling significantly affects the perception of women exposed to nonteratogenic agents in terms of estimating the risk as well as in the tendency to continue the pregnancy. Therefore it is the responsibility of treating physician to assess the risk associated with particular drug and assess the need of continuing drug therapy and counsel the patient appropriately. The key to this however lies in the fact that the physician himself is well versed with the recent facts.

Rationalized drug use in pregnancy

Pregnant females may require medication at any point of pregnancy. The appropriate drug use in pregnancy not only improves the maternal health but is also advantageous for the fetus as well. Appropriate management of diabetes can prevent diabetic embryopathy, [34] treatment of STDs like syphilis can prevent birth defects and preterm labour [51]. Most importantly periconceptional folic acid supplementation can prevent most neural tube defects and also minimize other anamolies [52, 53]. It is clear that we can't avoid drug use in pregnancy. The decision to use the drug in pregnancy is typically guided by the principle that "The benefit of the drug outweighs its risks." However, accurately weighing benefit against risk requires a thorough understanding of those benefits and risks. Principles of drug therapy for chronic ailments in pregnancy are same as in the nonpregnant state. For example in case of epilepsy, the safest drug is the one that controls the epilepsy and therefore the early part of pregnancy is not the best time to start trying different treatments, particularly if the existing treatment is working. Knowledge about one or two medications for each disorder is recommended. Table VI gives a list of first line, second line and contraindicated agents in pregnancy for some common conditions [54]. Since Teratogenicity has a dose –effect relationship, so whenever possible lowest effective dose of the medications should be used. For most drugs, typical doses are not anticipated to increase the risk of congenital anomalies.

Issues related to therapeutic failure in pregnancy

Drugs may not have their expected therapeutic effect during pregnancy. They may be less effective because of pharmacokinetic changes such as increased metabolism (eg. phenytoin) or excretion (eg. amoxycillin).These drugs may need to be prescribed either in a higher dose or more frequently to obtain therapeutic concentrations during pregnancy [55,56]. Another important and under recognised reason is the poor compliance of pregnant women. One study found that 50% of pregnant women do not take drug treatment as prescribed by their doctor [46]. Fear of harming the fetus is the main concern for mothers, and it is important that these women should be counselled appropriately, explaining the benefits and risks of treatment and of stopping treatment in a balanced manner. It has been seen that, appropriate counselling can empower the majority of women who discontinued their drugs to resume their use [57]. Because of the combined effects of poor compliance and possible changes in clearance, monitoring the therapeutic concentration of drugs during pregnancy may be helpful, especially in conditions such as epilepsy.

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Table VI. List of some first line, second line and contraindicated agents for some common ailments in pregnancy.

Common medical conditions	I[st] line	II[nd] line	Contraindicated
Nausea & vomiting	Pyridoxine Doxylamine Meclizine Cyclizine	Promethazine Metoclopramide Ondansetron	
Heartburn	Non-systemic antacids	Ranitidine Lansoprazole Pantoprazole	
Constipation	Dietary fiber Excessive fluid Bulk purgatives	Osmotic purgatives	
Antihypertensives	Methyldopa Labetalol Nifedipine	Propranolol Atenolol Diuretics Hydralazine	ACE inhibitors
Anticonvulsants	Lamotrigine Gabapentin Folic acid supplement	Carbamazepine Phenytoin Valproate	
Antidiabetic therapy	Insulin Glyburide	Metformin	
Antidepressants	Selective serotonin reuptake inhibitors Tricyclic antidepressants	Bupoprion Duloxetine Benzodiazepines	
Antiasthmatics	Beta 2 agonist Oral corticosterioids	Inhaled corticosterioids Anticholinergic agents Methylxanthines Leukotriene modifiers	
Antithyroid agent	Propylthiouracil	Methimazole	Radioactive iodine
Antipyretic & NSAIDs	Paracetamol	Opioids	NSAIDs >48 hours
Antibiotics	Penicillin Cephalosporins Macrolides Choroquine	Sulfonamide Trimethoprim Nitrofuratoin Metronidazole Gentamycin Clindamycin	Tetracycline Doxycycline Quinolones
Antitubercular	Isoniazid	Rifampin Ethambutol Pyrazinamide	Streptomycin
Anticoagulant	Heparin		Warfarin

Therapeutic drug actions in fetus

There is other side of the coin also. The effect of maternally ingested drug to the fetus can be exploited pharmacologically for the fetal benefit. Fetal therapeutics is an emerging area in perinatal pharmacology. It involves drug administration to the pregnant woman with the fetus as the target of the drug therapy. At present, corticosteroids are used to stimulate fetal lung maturation when preterm birth is expected [58]. Before

phototherapy was available phenobarbital was used for neonatal indirect hyperbilirubinemia to induce fetal hepatic enzymes responsible for the glucuronidation of bilirubin. Maternal use of zidovudine decreases the transmission of HIV from the mother to the fetus by two thirds. Medical management of fetal tachyarrhythmia is also a well know entity where the antiarrythmic drugs are administered maternally [59].

Maternogenicity

Maternogenicity is defined as drug excretion in breast milk [60]. After delivery, drugs gain access to the infant through the breast milk. The infant may be exposed to a wide variety of medications by breast feeding. Unless contrary information exists, it can be assumed that any orally administered to the mother will be excreted in her milk. For a majority of drugs the concentration achieved in the milk is insufficient to elicit any effect in the infants. However, some drugs like anticoagulants, tetracyclines are excreted in sufficient quantities to cause serious effects in the infants. It is extremely important for the breast feeding mother and the physician to be aware of and avoid those medications. The excretion of drugs in breast milk is dependent on the following physiochemical characteristics - pH gradient between plasma & milk, degree of ionization, lipid- water solubility concentration gradient [61]. In general basic drugs are excreted in high concentration in milk, whereas acidic drugs are less concentrated in milk. Highly ionized drugs like heparin, insulin or protamine diffuse extremely poorly across cell membrane. Drug with high lipid solubility will diffuse very poorly in breast milk but will attain a high level of concentration in fat depots. Diffusion against the concentration gradient with the help of drug transporters like P glycoprotein also plays a role in drug excretion in breast milk. Pharmacokinetic alterations which increase the serum drug concentration can increase the concentration of otherwise minimally excreted drug in the breast milk. In general, unless the mother ingest high doses of drug the suckling infant is unlikely to encounter adverse effect with few exceptions.

Table VII. Some drugs contraindicated in lactation

Drug	Possible adverse effect on infant
Amiodarone	Risk of hypothyrodism
Anticancer drugs	Anemia, immunosuppression
Chloramphenical	Diarrhoea, bone marrow depression
Ciprofloxacin	Theoretical risk of arthropathy
Ergotamine	Ergotism, Suppression of lactation
Indomethacin	CNS effects, Convulsions
Lithium carbonate	Cardiac arrhythmias
Tetracyclines	Growth retardation, candidiasis, tooth discoloration

Table VII enlists some of the drugs which should be avoided during lactation. Practically, if a breast feeding mother is taking any medication she must consume the drug about 15 min after nursing or 3-4 hours before the next feeding. This allows enough time for most drugs medications to clear maternal serum and achieve a relatively low milk concentration. Conversely, medications taken 30-60 minutes prior to a feeding usually achieve a peak serum and milk concentrations during nursing. If a mother has to consume a new or untested medication, breast feeding should be temporarily stopped. Fortunately,

very few mothers have to discontinue breast feeding because of the consumption of medications.

Future of drug use in pregnancy and lactation

Clinical trials are not routinely performed in pregnant and lactating females because of ethical reasons. Thus, certainty is a rare commodity when trying to provide information on drug treatment during pregnancy. Novel approaches in the field of theranostics can possibly address this research shortfall. Theranostics is the term used to describe the proposed process of diagnostic therapy for individual patients - to test them for possible reaction to taking a new medication and to tailor a treatment for them based on the test results [62]. Theranostics can provide insight into the details of drug response during pregnancy. Since, genetic susceptibility of the embryo is one of the major determinants of Teratogenicity, theranostic strategy can be utilized to develop rapid genotyping assays for pregnant women that are predictive of phenotype expression in the mother and fetus [63]. In future more genotypic variations will be identified and correlated with biological and clinical presentations. Rapid genotyping may soon become a clinical reality for the targeted treatment of maternal and fetal disease once their pharmacologic and pharmacokinetic relationships are established.

CONCLUSION

Drugs use in pregnancy and lactation requires maintenance of fine balance, so that no harm must come to mother-baby because a disease is being inadequately treated & at the same time no harm should be allowed to befall the baby because of the drug. Prescription during pregnancy and lactation must be decided based upon consideration of many factors, including, but not limited to, gestational age of the embryo or fetus, pharmacokinetic properties of the drug, the necessary effective dose of the drug, whether monotherapy is sufficient or multiple drugs are required and in future even the mother's genotype. The fetal risk classifications can be useful to summarise general information on drug use during pregnancy, but this approach alone can be misleading. The data upon which these categories are based is varied, incomplete, and often not uniformly applied. Due to the lacunae in the current pregnancy risk category system, the FDA has proposed revisions to the longstanding system of pregnancy category labelling for all medications, but it will take a while for it implementation. Meanwhile, before prescribing, physicians should look more critically at a drug's classification and the available data of Teratogenicity including both animals and human studies. The correct assessment of teratogenic risk is important, and both underestimation and overestimation must be avoided.

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