

# TERATOGENIC RISK OF DRUGS USED IN EARLY PREGNANCY

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Running Title: TERATOGENIC RISK OF DRUGS USED IN EARLY PREGNANCY

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**Abstract:** Treatment of common illnesses in early pregnancy is complicated because of the risk of teratogenic effects of drugs on the fetus. The period of greatest risk is between the first and eighth week of pregnancy. Since much of this period occurs before a diagnosis of pregnancy is made, care must be used in treatment of common illnesses in all women susceptible to becoming pregnant. Few, if any, drugs have been tested for teratogenicity in controlled clinical trials. Risk must therefore be based on epidemiological studies, individual case reporting and extrapolation from animal studies. Sufficient information is available on commonly used drugs to establish such risks. It is important that drugs of least known risk but adequate efficacy be used in treating intercurrent illness in the first trimester.

**Keywords:** Teratogenesis, Malformation, Anti epileptic drugs, Risk factors

## INTRODUCTION:

The term “teratogen” is used to describe an agent that can produce structural or functional abnormalities in a developing embryo. teratogenicity is a property of the exposure taken as not only the physical and chemical nature of the agent, but also the dose, route of administration, and gestation, exposure to other agents and susceptibility of the mother and embryo biologically.

During conception and for about 2 weeks thereafter, most cells of the conceptus are not yet committed, One damaged cell can be replaced by another, and normal development will usually occur, the embryo will not survive if too many cells are damaged or killed. This is called the “all-or-nothing” period.[1]. The subsequent period of organogenesis, from 18 to 60 days after conception (about 4.5–11 weeks after the start of the last normal menstrual period) is the time of greatest sensitivity to most teratogenic exposures. Fetal exposure later in gestation usually does not produce gross structural abnormalities, although there are exceptions. Adverse exposures during the fetal period more often result in growth restriction or functional disorders of the central nervous system, kidneys, or other organs.

Dose is a critical feature of any teratogenic exposure. Teratogenic effects occur only when the dose of an agent exceeds a certain threshold [2]. Medications that are generally considered safe during pregnancy can have adverse effects on the embryo or fetus if the mother takes them in doses that are so high that they cause maternal toxicity. Chronic exposure is usually of more concern than a single exposure, if the doses are similar. The route of exposure is also important. For example, risk is unlikely from the use of dermal agents that lack substantial systemic absorption. The teratogenicity of an exposure is also influenced by both the maternal and fetal genotypes, which can result in differences in cell sensitivity, placental transport, metabolism, receptor binding, or drug distribution. Some medications are metabolized extensively by the mother; their teratogenicity depends upon whether a toxic form reaches the embryo or fetus in sufficient quantities to produce adverse effects.

The safety and efficacy of antiemetic drugs used in the treatment of nausea and vomiting during pregnancy are reviewed. Confirmation of the teratogenicity of drugs in humans is difficult; the risk can be estimated from results of cohort studies and case-control studies. The possible teratogenicity of Bendectin (doxylamine succinate and pyridoxine hydrochloride) was studied thoroughly; although the risk was minimal, the drug was withdrawn from the U.S. market. Whether phenothiazines are teratogenic

has still not been conclusively determined. A large number of epidemiological studies have not shown meclizine to be teratogenic in humans. More information about metoclopramide is necessary before it can be safely recommended for use during pregnancy. The risks of using dimenhydrinate and diphenhydramine appear to be low. Pyridoxine is considered safe for use during pregnancy, but its efficacy in treating nausea and vomiting has not been determined. The relative efficacy of these agents has not been determined. The available data suggest that meclizine and dimenhydrinate are the antiemetics that present the lowest risk of teratogenicity; meclizine is the drug of first choice. Phenothiazines should be reserved for treating persistent vomiting that threatens the maternal nutritional status.

For female patients with rheumatoid arthritis (RA), the availability of a host of new disease modifying antirheumatic drugs (DMARDs) has raised important questions about fetal safety if a woman becomes pregnant while she is being treated. In addition, there is limited safety information regarding many of the older medications commonly used to treat RA in women of reproductive age.

Although pre-marketing clinical trials and post-marketing safety studies can address questions regarding safety in most segments of the population, pregnant women constitute one special group for whom ethical concerns prohibit the establishment of human drug safety information as part of the drug development and approval process. However, once a new drug is marketed or an existing drug is used for a new indication, if women of reproductive age are prescribed the drug, pregnancy exposures will inevitably occur. This is due to the fact that about half of pregnancies in the US are unplanned [3], and overall fewer than 50% of women recognize they are pregnant by the fourth week in gestation [4], leading to the common occurrence of inadvertent exposure to a medication of unknown safety during a critical period in embryonic development.

Thus, the rheumatologist and the pregnant patient are frequently faced with the dilemma of assessing the potential risk of an exposure to a medication or combination of medications that has already occurred early in pregnancy, or of making the decision to continue or discontinue a medication regimen during a planned pregnancy or breastfeeding.

In the US, the resource that clinicians and patients rely on most heavily in evaluating individual risk is the US Food and Drug Administration's (FDA) Pregnancy Category: A, B, C, D, X [5]. Pregnancy safety cannot be ethically evaluated in pre-marketing human clinical trials. In the post-marketing setting, isolated case reports of adverse pregnancy outcomes are difficult to interpret without a known denominator of exposed women, and post-marketing controlled observational studies are not systematically conducted. Therefore, there are insufficient human pregnancy safety data available for more than 80% of drugs currently available on the US market [6].

Thus, as shown in Table 1, the pregnancy category is a designation that is almost exclusively derived from preclinical animal reproductive and developmental toxicity studies. This is despite the fact that animal studies are not always predictive of human pregnancy risk. Drugs that have been identified as teratogenic in selected animal species may have been tested at doses that far exceed the normal human therapeutic range. Furthermore, even at comparable doses, medications shown to be teratogenic in one or more animal species may not produce the same results in humans or any adverse effects at all. Conversely, drugs that have demonstrated no adverse effects in selected animal species may in fact be human teratogens [7]. Therefore, until adequate human pregnancy safety data are available, the pregnancy category designation has limited value in predicting safety or risk.

Table 1: FDA Pregnancy Category

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risk involved in use of the drug in pregnant women clearly outweighs potential benefits

The purpose of this paper is two-fold. First, we present current summary pregnancy risk information for selected medications or classes of medications used to treat RA. This information is intended to describe both the substantial gaps in current knowledge as well as the frequent discordance between the FDA Pregnancy Category and currently available data. Secondly, we compare the strengths and weaknesses of post-marketing strategies for developing new pregnancy safety information, with a specific focus on pregnancy registries using the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project design for illustration.

## ANTIINFLAMMATORY AGENTS:

### CORTICOSTEROIDS:

An association between prenatal exposure to corticosteroids, such as prednisone, and intrauterine growth restriction in humans has long been recognized. The risk appears to be dose related, suggesting that this concern can be minimized with lower doses [8,9,10]. Although cortisone is known to cause cleft palate in rats and mice, until recently no such association has been suspected in humans [11]. However, among four recent case-control studies and a meta-analysis, three studies and the meta-analysis conclude that systemic corticosteroid use in the period surrounding the time of conception appears to be associated with a three- to six-fold increased risk for cleft lip with or without cleft palate and possibly cleft palate alone. That unclear to what extent this association is explained by the various underlying maternal diseases involved in these studies or other unmeasured confounders [12,13,14,15]. To put these relative risks into perspective, in that the population birth prevalence of all oral clefts combined is approximately 1 per 1,000 live births, systemic corticosteroid use is associated with a risk of either cleft lip with or without cleft palate or cleft palate alone of approximately 1.3 to 3.3 for every 1,000 pregnancies exposed during the critical period for lip/palate closure. Based on these data, it is suggested that the risk associated with prenatal exposure to these medications is minimal.

Evidence from controlled trials has demonstrated the safety and efficacy of the following drugs for the treatment of varying degrees of NVP: doxylamine/pyridoxine±dicycloverine (dicyclomine), antihistamine H<sub>1</sub> receptor antagonists, and phenothiazines (as a group). However, pooled data for doxylamine/ pyridoxine±dicycloverine, H<sub>1</sub> antagonists and phenothiazines were not homogeneous. Other therapies, such as pyridoxine alone, metoclopramide, ondansetron and the corticosteroids may be beneficial in managing NVP. However, limited efficacy studies and the paucity of well-controlled safety studies may limit the use of some of these agents among patients not responsive to first-line agents. Well-controlled safety and effectiveness trials in patients with NVP are lacking for nonpharmacological treatments (e.g. acupressure).

## CURRENT STATE OF KNOWLEDGE ABOUT THE EFFECTS OF MEDICATION USE DURING PREGNANCY:

### Maternal effects:

Many women begin pregnancy with medical conditions that require ongoing or episodic treatment. Examples include asthma, epilepsy, and hypertension. In addition, other medical problems, such as migraine headache or auto-immune disorders, may be exacerbated by pregnancy. When planning for the management of maternal conditions during pregnancy, it is important to distinguish conditions for which withholding treatment could be harmful to the mother, embryo, or fetus, from those for which cessation of treatment is unlikely to pose significant risk. For example, women with major depression who discontinue antidepressant medication before conception are at high risk of relapse and consequent self-injurious or even suicidal behavior [16]. In contrast, cessation of treatment for moderate hypercholesterolemia with a statin drug while a woman is pregnant is unlikely to increase her cardiovascular morbidity or mortality significantly.

Physiologic changes occur during pregnancy that can alter the effective dose of medications a woman is taking. Some changes occur abruptly, while others evolve slowly. Most begin during the first trimester and peak during the second trimester of pregnancy [17]. It may be necessary to adjust the dose and/or frequency of medication use repeatedly during pregnancy. Physiologic changes that can affect the pharmacokinetics and/or pharmacodynamics of medications during pregnancy include:

- Changes in total body weight and body fat composition.
- Delayed gastric emptying, prolonged gastrointestinal transit time, and decreased gastric acid secretion, all of which can affect the bioavailability of drugs [18,19,20].
- Expanded plasma volume and significantly increased extracellular fluid space and total body water content. These vary with the patient's weight and can affect the volume of distribution of drugs [21].
- Increased cardiac output, stroke volume, heart rate, and blood flow to the uterus, kidneys, skin, and mammary glands. The percentage of cardiac output attributed to hepatic blood flow is lower during pregnancy [22].
- Decreased concentration of plasma albumin, which can reduce the protein binding of some drugs [23].
- Increased glomerular filtration rate early in pregnancy, with a continued rise throughout pregnancy [24]
- Changes in the activity of hepatic enzymes, including the cytochrome P450 enzymes, xanthine oxidase, and N-acetyltransferase [25, 26].

Unfortunately, there are relatively few studies of drug pharmacokinetics during pregnancy. The dose of medications usually prescribed during pregnancy is the same used in nonpregnant adults, but this may result in substantial under- or over-dosage during pregnancy. When blood or serum concentrations of medications can be measured and the most effective level is known, they should be monitored throughout pregnancy and appropriate dosage adjustments made as needed. Further well-designed and well-conducted pharmacokinetic and pharmacodynamic studies of medications during pregnancy are needed.

Fetal effects:

Maternal treatment with conventional doses of some medications during a susceptible period of pregnancy is known to be harmful to the developing embryo. Thalidomide and isotretinoin are the most notable examples, but there are others [27]. In contrast, taking some other medications or dietary supplements such as folic acid helps to prevent adverse pregnancy outcomes [28]. Because pregnant women are traditionally excluded from clinical trials for ethical reasons and because premarketing animal studies do not necessarily predict the effects of treatment in human pregnancy, little information about the teratogenic risks or safety of most drugs is available at the time they are marketed. Animal teratology studies are not routinely conducted for non-prescription drugs, vitamins, and dietary and herbal supplements, although these substances may produce pharmacological or toxic effects in the fetus. Moreover, there is no standard requirement for studies of adverse effects among children of women who took a drug during pregnancy after it has been approved by the FDA. In a review conducted in 2001, researchers found that there was not enough information to assess the teratogenic risk or safety during human pregnancy of more than 90% of prescription medications approved by the FDA in the previous 20 years [29].

Even when available, studies addressing fetal effects of maternal medication use during pregnancy may provide conflicting results or insufficient information to assess all potential outcomes or levels of risk. The concept of safety implies the absence of risk, which is impossible to demonstrate conclusively with any kind of study. Thus, it can be difficult for women and health care providers to decide whether to use a medication during pregnancy. The balance of risk, benefit, and efficacy of treatment for both mother and fetus is not always clear and must be individualized for different women under different circumstances.

#### **BASIC COMPONENTS OF PRECONCEPTION CARE THAT CAN MINIMIZE THE RISK OF BIRTH DEFECTS:**

Serious congenital anomalies, including chromosome abnormalities and Mendelian disorders, can be identified in about 2% of infants at birth. However, some anomalies do not become apparent until later in life [30]. While most birth defects are not preventable, some can be avoided through appropriate planning and medical interventions. The following components of preconception care can help minimize the risk of birth defects:

- Optimize health before conception occurs. This includes counseling women to avoid smoking, use of excessive alcohol and illicit drugs, and exposure to potentially toxic environmental or occupational hazards before they are pregnant.
- Establish effective treatment for chronic conditions before conception occurs.
- Carefully manage all chronic conditions and intercurrent illnesses throughout pregnancy.
- Counsel women to avoid the use of nonessential medications, including prescription and over-the-counter medications and dietary or herbal supplements.
- Avoid the use of medications with high teratogenic risk when equally effective treatments with lower risks are available.
- Limit the use of essential medications to the smallest number of drugs possible that will effectively treat maternal disease without compromising the health of the woman or her fetus.
- Limit each essential medication to the smallest dose that can be used to effectively treat maternal disease without compromising the health of the woman or her fetus.
- Recommend that all women who are capable of becoming pregnant take a vitamin supplement or eat fortified foods to assure consumption of 0.4 mg (400 micrograms) of folic acid per day.

Effective pregnancy management in women with chronic conditions requires careful planning, close medical supervision before and during pregnancy, and continuous communication between the pregnant woman and her health care providers.

Avoiding teratogenic treatments for non life-threatening maternal conditions—isotretinoin

Isotretinoin is indicated for the treatment of severe nodular cystic acne unresponsive to other therapy but is also used to treat non-nodular, but scarring, acne. A single course of therapy typically lasts 15–20 weeks and can result in complete and prolonged remission of the acne in many patients. However, isotretinoin treatment in the first trimester of pregnancy is teratogenic. Exposed infants can have craniofacial, cardiac, thymic, and central nervous system malformations [31]. Research has also shown a high incidence of developmental delay in children whose mothers used isotretinoin early in the first trimester, regardless of whether the children had structural malformations [32].

Isotretinoin is indicated for use only in men and nonpregnant women. It should never be used during pregnancy. However, because approximately half of pregnancies in the United States are unintended, some women use isotretinoin in the early weeks

of gestation before realizing they are pregnant [33]. Teratogenic outcomes have been reported after only one dose of isotretinoin during pregnancy [34]. The half-life of isotretinoin is approximately 24 h, but about 2 weeks are required to eliminate 99% of the drug from the body after cessation of use.

Several risk management strategies have been implemented to prevent the use of isotretinoin during pregnancy, but pregnancy exposures continue to occur [35]. An enhanced risk management program called iPLEDGE became fully operational in March 2006 [36, 37]. iPLEDGE is a single, mandatory program for all marketed isotretinoin products. It requires that wholesalers, pharmacies, doctors, and patients register with the program in order to obtain the drug.

## CONCLUSION:

Although it is always better to avoid unnecessary medical treatment during pregnancy, some women with chronic conditions may not be able to become pregnant without appropriate therapy. In many other cases, proper treatment of a chronic condition during pregnancy may be safer for both the woman and her baby than stopping this treatment. It is important that women who are planning a pregnancy talk with their health care provider before beginning a new medication or making changes in current medications for the management of acute or chronic conditions. Continuous communication between a pregnant woman and her health care providers, careful preconceptional planning, effective management of conditions prior to pregnancy, and close medical supervision during pregnancy can help assure the best possible outcome for every woman and baby.

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