Obstetric Toxicology: Teratogens

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KEYWORDS

• Antibiotic • Anticoagulant • Antihypertensive • Antiarrhythmic • Anticonvulsant • Pregnancy • Teratogen • Teratogenicity

KEY POINTS

- The pregnancy risk classification developed by the US Food and Drug Administration is an imperfect source of information and should not be relied on to determine treatment or guide counseling of pregnant patients.
- An accurate, up-to-date, readily available source of information to guide clinicians in determining the teratogenic risks of medications is needed.
- Proper education and counseling of pregnant patients are paramount. Clinicians are encouraged to seek expert advice from teratologists when data regarding an agent's safety are limited or conflicting.

INTRODUCTION

Annually, more than 6.4 million pregnancies occur in the United States, with a resulting 4.14 million live births.[1] Many of the women carrying these pregnancies are treated in US emergency departments (ED). Although the exact prevalence of pregnancy among ED patients is not known, by some estimates nearly 10% of all women seeking care in an ED are pregnant.[2] Consequently, emergency physicians need to be familiar with which drugs should be avoided in pregnancy and which drugs are deemed safe.

An important historical event changed our understanding of pharmaceutical teratogens. In 1956, thalidomide was used for the treatment of influenza.[3] Shortly thereafter, it was used as a sedative and ultimately as an antiemetic during pregnancy. It was marketed under 37 names worldwide, but it never received approval from the US Food and Drug Administration (FDA) because of concerns about its safety.[4,5] When administered to pregnant women, many of their offspring developed a pattern of malformations consisting of phocomelia, thumb aplasia, congenital heart and ear defects,

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duodenal atresia, and triphalangism.[4,5] The drug was withdrawn worldwide in the early 1960s after its teratogenic effects were confirmed. Fewer than 30 pharmaceutical agents are proven human teratogens when administered at clinically relevant doses.[6] Of the known teratogens, only a few remain in clinical use (**Table 1**).

Following this important historical event, awareness of the potential teratogenic effects increased, as did regulation. Pharmaceutical manufacturers are required by law to label their products regarding use in pregnancy according to standards established by the FDA. The FDA categorizes prescription drugs according to their risk of causing fetal harm (**Table 2**). This classification is based on the strength of evidence available at the time a drug is approved. Category C is the default category, and most drugs fall into this group. Because the risk is unknown, the drug might be capable of teratogenic effects or it might be perfectly safe. This classification system has many limitations and many teratologists find it misleading. It is often criticized for being overly conservative, it is rarely updated or revised, and medicolegal or liability issues may drive an agent's classification. Consequently, clinicians cannot rely on this categorization as a reliable, updated source of information to guide their practice. And, as in the nonpregnant population, prescription drug use among pregnant women is common. In one Canadian population-based study, 63.5% of pregnant women consumed a prescription medication during their pregnancy, with nearly 8% of these being category D or X medications.[7] In a similar study in the United States involving more than 150 000 births identified through 8 health maintenance organizations, 64% of the women received a prescription medication during their pregnancy and 9.4% of them received a category D or X medication.[8]

Many pharmaceutical agents known to be human teratogens have either been removed from the market or are not likely to be prescribed by emergency physicians (eg, thalidomide, diethylstilbestrol, systemic isotretinoin). Environmental exposures or drugs of abuse (eg, radiation, methylmercury, ethanol) are beyond the scope of this article. Thus, this review focuses on those drugs likely to be prescribed by emergency physicians during their routine practice and care of pregnant patients. In addition, this

Table 1
Drugs with known teratogenic effects in humans

Drug	Clinical Effects
Methotrexate	CNS and limb malformations
ACE inhibitors	Renal failure, renal dysgenesis, skull malformations
Antithyroid drugs (PTU, methimazole)	Fetal goiter, hypothyroidism
Carbamazepine	Neural tube defects
Lithium	Ebstein anomaly
Misoprostol	Moebius syndrome
Phenytoin	CNS deficits, growth retardation
Retinoids	CNS, craniofacial, CV, and other defects
Tetracycline	Anomalies of the teeth and bone
Thalidomide	Phocomelia
Valproic acid	Neural tube defects
Warfarin	Skeletal and CNS defects, Dandy-Walker syndrome

Abbreviations: ACE, angiotensin-converting enzyme; CNS, central nervous system; CV, cardiovascular; PTU, propylthiouracil.

This table represents known teratogens still clinically available and potentially encountered by emergency physicians. It does not represent an all-encompassing list.

Data from Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998;338:1128–37.