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The *Hospital Physician Obstetrics and Gynecology Board Review Manual* is a peer-reviewed study guide for residents and practicing physicians preparing for board examinations in obstetrics and gynecology. Each quarterly manual reviews a topic essential to the current practice of obstetrics and gynecology.

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Teratology

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Teratology

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INTRODUCTION

Many pregnant women express concern about the potential impact of medications, environmental exposures, drugs, and other physical agents on fetal development. Patient fears may be related, at least in part, to the legacy of thalidomide.¹ Although a common topic of discussion during prenatal evaluations, expert consensus on the safety of many fetal exposures does not exist.²

Patients should understand that all birth defects occur at a background rate expected for the given population. For example, approximately 1 in every 1000 babies born has a cleft lip³ and at least 8 of every 1000 infants born has a heart defect.⁴ Regardless of exposure history, prenatal history, family history, and parental health, approximately 3% of all babies born have a major structural anomaly that requires medical intervention.² If inclusive of all pregnancies (ie, liveborns, stillborns, intrauterine fetal demises, miscarriages, and children diagnosed with an anomaly such as hydrocephaly as they grow), the observed rate of anomalies actually is significantly greater than 3%.^{2,5}

An etiology is determined for less than 50% of these birth defects.² Less than 1% of birth defects are specifically attributable to prescription medications,^{6,7} and only up to 10% of congenital anomalies are known to be the result of prenatal environmental exposures.^{7,8} Even after exposures to clear teratogens, the birth of a normal, healthy baby is the most likely outcome. Unfortunately, incomplete and inaccurate information can lead to the elective abortion of wanted pregnancies and the avoidance of needed therapy.^{1,9}

WHAT CONSTITUTES A TERATOGEN?

Teratology is the study of abnormal embryonic development. When determining whether a substance is teratogenic, its risk must always be viewed in relation to the 3% background risk. Therefore, a teratogen is any agent or factor that can produce a specific congenital anomaly or raise the incidence of that anomaly in the population. In addition to congenital anomalies, other potential adverse effects include fetal death, fetal growth restriction, and functional deficits.¹

The number of proven teratogens is quite small.¹⁰ Of the more than 2500 agents listed in the *Catalog of Teratogenic Agents*,¹¹ only about 40 are known to cause birth defects in humans. Proving that a substance is teratogenic or safe in humans can be complicated because congenital anomalies occur spontaneously, without teratogenic exposure. For a substance to be proven teratogenic, human studies must be performed and the sample size must be adequate. Human subjects are necessary because different species have varying susceptibility to prenatal exposures. For this reason, the effects observed in small mammals given greater than human therapeutic doses of a particular substance cannot establish a medication as teratogenic in human pregnancy.¹⁰ Such information should not be interpreted as conclusive and should be used cautiously, if discussed with patients at all. Similarly, discussing single case reports of poor outcomes often can unnecessarily alarm patients.

Another problem with studies attempting to prove teratogenicity relates to the accuracy of the information supplied regarding the exposure. For example, retrospective studies rely on a patient's recall of important information such as dose, timing, and duration of exposure, which may become biased given a positive or negative outcome at the time of delivery.⁹ Individuals with adverse outcomes may be more likely to contact the drug manufacturer than are individuals with uneventful pregnancies, subsequently skewing the information obtained. Therefore, prospective studies are preferred. However, ethical concerns have prevented large prospective human trials that could provide more accurate risk assessments of potential teratogenic exposures. To combat these difficulties, pregnancy registries for some medications have been established by manufacturers and university hospitals as an approach for compiling and assessing information with regard to potential fetal risks.

FACTORS AFFECTING TERATOGENICITY OF AN EXPOSURE

Timing of Exposure

One of the most important issues in considering the teratogenic potential of an agent is the timing of the exposure during pregnancy. Embryonic exposures to any potential teratogen during the first 2 weeks after conception or 4 weeks gestation from the last menstrual period