No. 199, November 2007

Principles of Human Teratology: Drug, Chemical, and Infectious Exposure

This consensus has been reviewed by the Genetics Committee and the Maternal Fetal Medicine Committee and approved by the Executive of the Society of Obstetricians and Gynaecologists of Canada.

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Key Words: Teratogens, pregnancy, birth defects, disruption, medications, drugs, viral infections, risk

Abstract

Objective: To provide a teratology update for prescription and non-prescription drugs and infections during pregnancy.

Options: Limited to teratology principles and possible common exposures during pregnancy.

Evidence: A search of Medline and textbooks was conducted for information published to June 2006 on teratology exposure risks. This document represents an abstraction of the information.

Benefits, Harms, and Costs: This consensus provides practitioners with a summary of information regarding teratology risks for drug, chemical, and infection exposures during pregnancy.

J Obstet Gynaecol Can 2007;29(11):911–917

INTRODUCTION

Teratology is the study of anomalous fetal development. The categories of teratogenic exposures during pregnancy include drug and chemical agents, infectious agents, physical agents (e.g., ionizing radiation, mechanical factors, and heat), and maternal or metabolic factors (e.g., diabetes and phenylketonuria). This consensus summarizes fetal and maternal factors relating to common drug/chemical (Table 1) and infectious agent (Table 2) exposure during pregnancy; it is not designed to be exhaustive, but it aims to be a rapid resource for clinical use and education.

Approximately 50% of all pregnancies in North America are unplanned,[1] and women whose pregnancies are unintended and unexpected are more likely to be exposed to a wide range of potential teratogens.[2,3] A recent survey of pregnant women showed that unintended pregnancies are associated with a higher risk for teratogenic exposures during pregnancy than planned pregnancies (alcohol RR 1.9; 95% CI 1.5–2.5; medications RR 3.0; 95% CI 2.0–4.5; cigarette smoking RR 1.5; 95% CI 1.0–2.3; X-rays 2.9; 95% CI 1.1–7.2; any exposure RR 2.0; 95% CI 1.6–2.4).[4]

Rubella, rubeola, and mumps susceptibility in pregnant women was shown to be 9.4%, 16.5%, and 16.3%,

respectively. Susceptibility to at least one virus was 32.6%, but only 1.7% were at risk for all three viruses.[5] The background risk of major fetal anomalies identified at birth is estimated at 3%. At five years of age, the risk of major anomalies increases to 4.5%. The etiology of these birth defects is unknown in greater than 50% of anomalous cases. It is not uncommon for a pregnancy to be exposed to multiple teratogenic risk agents, and therefore precise risk advice becomes complicated. This consensus focuses on fetal structural effects/anomalies and does not consider the complications of infectious etiologies or obstetrical outcomes such as premature rupture of membranes and preterm labour or delivery.

PRINCIPLES OF HUMAN TERATOLOGY

1. Characterization of teratogenic exposures involves the specific agent, the dose of the agent, the gestational age, and other factors such as genetic susceptibility (Table 3).[6]
2. Characterization of teratogenic effects includes general effects such as alterations of morphogenesis or CNS function, death, prenatal onset growth deficiency, specific effects like carcinogenesis and recognizable syndromes, magnitude of risk (absolute, relative), and prenatal diagnosis (invasive and non-invasive techniques) (Table 4).[6]
3. Five categories of maternal benefit to fetal risk with respect to drug exposures have been developed by the USFDA. (A, B, C, D, X).[7] The manufacturer's literature for some drugs in all categories contains warnings with respect to fetal exposure; this is indicated by "m" in Table 1.
   - **Category A:** Controlled studies in women failed to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm appeared remote.
   - **Category B:** Either animal reproductive studies have not demonstrated fetal risks but no controlled studies in pregnant women have been reported, or animal reproductive studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester.
   - **Category C:** Either studies in animals have revealed adverse effects in the fetus but no controlled studies have been reported, or studies in women and animals are not available. Drugs should be given only if potential benefit justifies the potential risk to the fetus.
   - **Category D:** Positive evidence of human fetal risk exists but the benefits for use in pregnant women may be acceptable despite the risk.
   - **Category X:** Contraindicated in pregnancies: studies in animals or human beings have demonstrated fetal anomalies or evidence exists of fetal risks based on human experience or both, and the fetal risk clearly outweighs any possible benefit.
4. Any drug or chemical given to the mother will cross the placenta to some extent unless it is destroyed or altered during placental passage or its molecular size or lipid solubility limits transplacental transfer. The onset of this placental transfer starts at the fifth embryonic week or seventh gestational week. For drugs or chemicals with low molecular weight, the transmission from placenta to fetus is based on the concentration gradient.[8]
5. Fetal anatomical anomalies may represent malformations or disruptions when obvious physical changes are identified, but functional or behavioural changes in the fetus, newborn, or child will be more difficult to link to the teratogenic risks.[6]
6. Recreational, non-prescription, and prescription drug use in pregnancy is common. A WHO survey found that 86% of women took medications during their pregnancy, with an average of 2.9 (range 1–15) prescriptions.[9] Andrade et al.[10] found that 64% of pregnant women received a drug prescription, not including vitamins or minerals, within 270 days of delivery. Approximately 50% of these prescriptions were in the risk categories C, D, or X. (A: 2.4%, B: 50%, C: 37.8%, D: 4.8%, X: 4.6%) Over-the-counter medications commonly used in pregnancy include acetaminophen (65%), ibuprofen (10%), and pseudoephedrine (15%).[11]

ABBREVIATIONS

CHD	congenital heart disease
CI	confidence interval
CL±CP	cleft lip plus/minus cleft palate
CMV	cytomegalovirus
CNS	central nervous system
DES	diethylstilbestrol
FAES	fetal alcohol effect spectrum
GI	gastrointestinal
GU	genitourinary
IUGR	Intrauterine growth restriction (birth weight <5th percentile)
MR	mental retardation
NTD	neural tube defect
PCB	polychlorinated biphenyls
RR	relative risk
SSRI	selective serotonin reuptake inhibitor
TORCH	toxoplasmosis, rubella, cytomegalovirus, herpes simplex
USFDA	United States Food and Drug Administration
WHO	World Health Organization