

# Medications in Pregnancy and Lactation

## Part 1. Teratology

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One of the least-developed areas of clinical pharmacology and drug research is the use of medication during pregnancy and lactation. This article is the first in a two-part series designed to familiarize physicians with many aspects of the drugs they commonly prescribe for pregnant and breast-feeding women. Almost every pregnant woman is exposed to some type of medication during pregnancy. Although the majority of pregnant and breast-feeding women consume clinically indicated or over-the-counter drug preparation regularly, only few medications have specifically been tested for safety and efficacy during pregnancy. There is scant information on the effect of common pregnancy complications on drug clearance and efficacy. Often, the safety of a drug for mothers, their fetuses, and nursing infants cannot be determined until it has been widely used. Absent this crucial information, many women are either refused medically important agents or experience potentially harmful delays in receiving drug treatment. Conversely, many drugs deemed “safe” are prescribed despite evidence of possible teratogenicity. Novel research and diagnostic applications evolving from the opportunities presented by the advances in genomics and proteomics are now beginning to affect clinical diagnosis, vaccine development, drug discovery, and unique therapies in a modern diagnostic–therapeutic framework—part of the new scientific field of *theranostics*. This review critically explores a number of recently raised issues in regard to the use of several classes of medications during gestation and seeks to provide a general and concise resource on drugs commonly used during pregnancy and lactation. It also seeks to make clinicians more aware of the controversies surrounding some drugs in an effort to encourage safer prescribing practices through consultation with a maternal–fetal medicine specialist and through references and Web sites that list up-to-date information.

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**D**rug therapy is an integral part of the health care system. Almost every pregnant woman is exposed to some type of medication during pregnancy.

When prescribed to pregnant and breast-feeding women, many drugs can exercise a teratogenic effect on fetuses and nursing infants; therefore, rigorous investigation into commonly prescribed drugs is essential. Although the majority of pregnant and breast-feeding women consume clinically indicated or over-the-counter drug preparation regularly, only few medications have specifically been tested for safety and efficacy during pregnancy. Current methods to assess teratogenicity consist mainly of pregnancy registries and case–control surveillance studies; however, these practices have proven insufficient to determine drug safety accurately. This insufficiency is due, in part, to shortcomings in the design of the studies. Physicians are therefore typically dependent on inaccurate or outdated information in prescribing medication. Even the U. S. Food and Drug Adminis-

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tration (FDA) drug classifications suffer from inaccuracies and inconsistencies. Detailed supplemental drug information and new strategies for testing and research, such as those being developed in the new field of theranostics, are critical to safe drug practices. Investigations into how and why current drug information and, in turn, prescribing practices are inadequate are presented here in addition to a summary of the existing evidence—or lack thereof—on many potentially teratogenic drugs commonly prescribed for pregnant and breast-feeding women.

## TERATOGENS

Teratogens are agents that act to irreversibly alter growth, structure, or function of the developing embryo or fetus. Recognized teratogens include viruses (eg, rubella, cytomegalovirus, congenital lymphocytic choriomeningitis virus), environmental factors (eg, hyperthermia, irradiation), chemicals (eg, mercury, alcohol), and therapeutic drugs (eg, inhibitors of the renin-angiotensin system, thalidomide, isotretinoin, warfarin, valproic acid, carbamazepine).<sup>1</sup>

Most drugs reach the fetus by the maternal bloodstream; thus embryonic and fetal exposure depends on several critical factors, such as gestational age, route of administration, absorption of the drug, the dose of the drug medication, maternal serum levels, and the maternal and placental clearance system. Placental passage to the embryo or fetus is necessary for a drug medication to exercise its specific teratogenic effect. In turn, placental transfer depends greatly on maternal metabolism, gestational age, protein binding and storage, charge, liposolubility of the drug, and molecular size.<sup>2</sup> Molecular weight of a substance is an important regulator of its transplacental passage. Previous studies have shown that most substances with mass below 500 Da diffuse rapidly across the placental barrier, whereas agents of higher molecular weight demonstrate more variable transplacental migration rates. Ionization and high fat solubility (eg, in anesthetic gases) assures rapid transfer of these drugs by simple diffusion.<sup>3</sup> Lastly, variations in pH gradients between maternal and conceptual compartments play an important role as well (Fig. 1).

## CRITICAL DEVELOPMENTAL PERIOD

An agent is recognized as a human teratogen if it meets certain criteria. A comprehensive review of the conditions necessary to prove teratogenicity of an agent is in the most recent work of Shepard and Ronald.<sup>4</sup> The criteria include 1) proven exposure at critical times during human development; 2) consistent dysmorphic findings recognized in well-con-



**Fig. 1.** Representative pictures of a fetus with methotrexate embryopathy. **A.** Postmortem examination of the fetus showed craniofacial abnormalities, including a wide anterior fontanelle, low-set and poorly formed ears, absent auditory canals, flat nose, cleft lip, and micrognathia. **B.** Examination of the body showed shortened forearms, hypoplastic thumbs, clinodactyly, brachydactyly of the fifth digit, and pelvic and lower limb abnormalities.

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ducted epidemiologic studies; 3) specific defects or syndromes associated consistently with specific teratogens; 4) rare anatomic defects associated with environmental exposure (eg, facial dysmorphism and nail hypoplasia with carbamazepine); 5) proven teratogenicity in experimental animal models.

To cause a birth defect, a teratogen acts during critical periods of embryonic or fetal development; thus, teratogenic drug medications can either induce *embryopathy* or *fetopathy*. From the perspective of *teratogenesis*, human gestation is divided into three peri-



ods: *preimplantation* (fertilization to implantation), *embryonic* (second through ninth week), and *fetal* (ninth week to term). The preimplantation period is traditionally viewed as a gestational window characterized by an “all or nothing” phenomenon: During early mammalian embryo development, injury to a large number of cells will predictably cause an embryonic loss. If only a small number of cells are disrupted, a phenomenon called *compensation* can protect the embryo and facilitate survival without malformation.<sup>5</sup>

A teratogenic agent can cause malformation during *organogenesis* (2 to 8 weeks postconception), when each system has a period of maximum vulnerability (eg, the heart is mostly affected if the teratogen acts between 6.5 weeks to 8 weeks of gestation). However, the fetus can also be affected by alterations in structure and function of the organs that have initially developed normally during embryogenesis. For example, spina bifida, anencephaly, and encephalocele arise due to the failure of closure of the neural tube during the process of neurulation (17th through 30th postfertilization days). Still, neural tube defects (eg, encephaloceles) may also occur postclosure during the fetal period.<sup>6</sup>

Many potent human teratogens act during very specific developmental stages. For instance, it was long believed that angiotensin-converting enzyme (ACE) inhibitors (eg, captopril, enalapril) had no adverse effects during the first trimester and that only a late exposure (second or third trimester) was associated with renal and cardiac malformations.<sup>7</sup> However, a more recent analysis of a large cohort of neonates exposed to ACE inhibitors during gestation disputes the safety of first-trimester exposure to this class of medication, indicating that ACE inhibitors can induce malformations throughout gestation.<sup>8</sup> Likewise, nonsteroidal antiinflammatory drugs (NSAIDs) (eg, indomethacin, ibuprofen) are associated with gastroschisis and other fetal sequelae if the embryo is exposed during early gestation, whereas irreversible closure of the ductus and kidney failure can occur if the fetus is exposed to NSAIDs after 32 weeks.

## ASSESSMENT OF DRUG TERATOGENICITY

Teratology is the study of the biologic mechanisms and causes of abnormal human development and the advancement of preventive strategies.<sup>1</sup> The finding of a birth defect should always raise the question of whether it was the consequence of a genetic defect or if it was the result of prenatal exposure to a teratogen. Recognition of a teratogenic drug after widespread use always causes worry about “failures of the system.”<sup>9</sup> Unfortunately, scientists, physicians, patients, and policy-makers are commonly reassured that the most serious short-term adverse effects of a

drug are identified in premarketing studies. Regrettably, although approval of a drug requires comprehensive animal studies, such models are seriously limited in their ability to predict human teratogenesis because of variations in species-specific effects even between mammalian species.<sup>2</sup> The unfortunate reality is that we learn about virtually all human teratogenic effects only after a drug has received marketing approval by the FDA. Teratogens commonly go undetected in the human trials conducted before FDA approval because most studies are small and routinely exclude pregnant women, particularly if there is any suspicion that a drug might be teratogenic.

## PREGNANCY REGISTRIES AND CASE-CONTROL SURVEILLANCE STUDIES

Pregnancy registries and case-control surveillance studies are currently the two main methods used to identify teratogens.<sup>9</sup> Pregnancy registries are routinely developed to permit identification of drugs that are high-risk teratogens. Because pregnancy registries are typically operated by drug manufacturers and because patients receive multiple drugs or are recruited into multiple, uncoordinated registries, however, concerns have been raised with regard to their accuracy. Inclusion of an adequate number of exposed pregnancies, thorough long-term follow-up, and complete and accurate ascertainment of pregnancy outcome are critical attributes of a well-designed registry.<sup>10</sup> Physicians can access the most up-to-date list of pregnancy exposure registries by consulting the FDA Web site (<http://www.fda.gov/womens/registries/>).

Case-control surveillance studies provide another tool to identify serious illnesses caused by medications used in an outpatient population.<sup>11</sup> By including information on infants with a wide range of birth defects and interviews with mothers focusing on details of their antenatal exposure to all prescription and over-the-counter medications (including herbal products), case-control surveillance studies can provide the required opportunity to examine large numbers of specific defects in relation to the wide range of medications taken by pregnant women.<sup>1</sup>

## BREAST-FEEDING

Breast-feeding is beneficial for the health of mother and child.<sup>12</sup> However, many therapeutic and environmental substances can be transferred into breast milk, commonly causing the risk of breast-feeding to exceed its benefit to the infant, mother, or both.<sup>13</sup> Very few medications are as yet contraindicated for breast-feeding.<sup>14</sup> There is still scant information on the risk of most medications used in human pregnancy and lactation at



the time they receive their FDA approval and are initially marketed.<sup>15</sup> The dose of a drug an infant receives during breast-feeding depends on the amount excreted into the breast milk, the daily volume of milk ingested, and the average plasma concentration of the mother. The milk-to-plasma concentration ratio has large intersubject and intrasubject variability. The transfer of medications across the basal membrane of the mammary gland alveoli depends on lipophilicity and protein binding and on the degree of substance ionization.

Very few studies have investigated drug concentrations in breast milk.<sup>16</sup> To determine exposure of the breast-fed neonate to a specific drug, the weight-corrected percent of the maternal dose ingested by an unsupplemented newborn and the resulting neonatal blood levels is used. Unfortunately, these data are reported for few agents. The milk:maternal plasma ratio conveyed to the clinician can be misleading because it commonly disregards the quantity ingested and its oral bioavailability.

Research into environmentally related chemical contaminants in breast milk is an increasingly important field of research.<sup>17</sup> These pollutants can remain in the human body for decades and thus pose a risk for both mother and her unborn child even in the absence of recent exposure. For example, diet is one major factor influencing breast milk levels of organic pollutants (eg, mercury in fish).<sup>18</sup> Furthermore, the

types of and extent to which medications (eg, mood stabilizers) are used by breast-feeding women have not been thoroughly investigated.<sup>19</sup> Existing literature consists essentially of case reports with few attempts at longitudinal investigation.<sup>20</sup> Findings are often difficult to compare because of discrepant research methodologies or the lack of key pharmacologic or pharmacokinetic information. The most data available are for the tricyclic antidepressants, but reports include fewer than 100 mother–infant pairs even for this group.

Dilemmas about whether to prohibit breast-feeding when the mother is undergoing drug therapy regularly arise. Because the relationship between medication use during pregnancy and lactation has been insufficiently investigated, acute attention should be paid to any drug which is recommended postpartum.<sup>21</sup> Studies designed to quantify the amount of drug passed to the neonate and provide clinically reliable recommendations based on infant clearance, which is itself dependent on the ontogeny of elimination pathways and pharmacogenetics, are critically needed.

## U.S. FOOD AND DRUG ADMINISTRATION DRUG RISK CLASSIFICATION IN PREGNANCY

Physicians routinely rely almost exclusively on FDA classification (A, B, C, D, or X) (Table 1) to make a

**Table 1. U.S. Food and Drug Administration Drug Classification System**

FDA Category*	Pregnancy Category Definition
A	Controlled studies showed no risk to humans Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities
B	No evidence of risk in humans Animal studies have revealed no evidence of harm to the fetus. 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 the fetus
C	Risks cannot be ruled out in humans 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
D	Clear evidence of risk in humans Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk
X	Drugs contraindicated in human pregnancy Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant

FDA, U.S. Food and Drug Administration.

\* Please verify the FDA categorization for each drug.



decision to initiate, continue, discontinue, or replace a medication. This reliance is, unfortunately, misplaced. Although only few drugs are known or strongly suspected to be teratogens, the majority of all drugs marketed in the U.S. are classified Category C—risks cannot be ruled out in humans but the benefits of the medication may outweigh the potential risks—and less than 1% are Category A—no risk to humans. And although major congenital abnormalities complicate 2–3% of all pregnancies, fewer than 10% of these can be associated with a particular drug exposure, possibly due in part to the lack of reliable drug information. Inexplicably, some Category X drugs—clear evidence that the medication causes abnormalities in the fetus—are not absolutely contraindicated during pregnancy, and several Category C or D drugs are either known human teratogens or commonly have serious adverse fetal effects.<sup>14</sup>

Out of 2,150 products searched in the *2002 Physicians' Desk Reference* (Thomson Healthcare, Montvale, NJ), a widely used source of drug information by U.S. clinicians and patients, only 124 drugs were classified as pregnancy Category X.<sup>22</sup> Yet, about one in every five women uses FDA C, D, and X drugs at least once during pregnancy. The most common prescription drugs in pregnancy are antiasthmatics, antibiotics, NSAIDs, anxiolytics, antidepressants, and oral contraceptives.<sup>23</sup> Table 2 shows a list of the most common drugs or drug groups (in alphabetical order) known or strongly suspected to cause developmental defects. Because of the extensiveness of the subject, only the drug medications believed to be most commonly encountered in routine clinical practice are presented.

After review of the label/package insert for each Category X drug to identify risk management strategies for pregnancy prevention, it was concluded that 1) the majority of the labels included only a black box warning and/or a contraindication for use in women who are or may become pregnant; 2) only 13 drugs contained specific pregnancy prevention risk-management strategies in the label to direct the clinician and/or patient (eg, on frequency of pregnancy testing and number and type of contraception methods); 3) only three drugs (isotretinoin, acitretin, and thalidomide) had formal pregnancy prevention risk-management programs. This analysis demonstrates an urgent need both for consistency in the classification of pregnancy Category X products and for the recommendation of pregnancy prevention risk-management strategies included in their classification and labels. Pregnancy risk categories have currently proven suboptimal, outdated, and too superficial to account for the physiology and health care needs of

**Table 2. Commonly Prescribed Teratogenic Drugs\***

Drug	FDA Classification <sup>†</sup>
Agents acting on renin–angiotensin system (captopril, lisinopril, enalapril)	C (first trimester) D (second and third trimesters)
Antidepressants (paroxetine)	D
Antiepileptic drugs (valproic acid, carbamazepine, phenytoin)	D
Anxiolytics (diazepam)	D
Alkylating agents (cyclophosphamide)	D
Androgens (danazol)	X
Antimetabolites (methotrexate)	D, X
Carbimazole	D
Coumarin derivatives (warfarin)	X
Estrogens (diethylstilbestrol)	X
Fluconazole	C
Lithium	D
Misoprostol	X
Oral contraceptives	X
Penicillamine	D
Retinoids (isotretinoin)	X
Radioactive iodine (sodium iodide-128)	X
Thalidomide	X

FDA, U.S. Food and Drug Administration.

Data from Buhimschi CS, Weiner CP. Medications in pregnancy and lactation. In: Queenan JT, Spong CY, Lockwood CJ, editors. *Management of high-risk pregnancy: an evidence-based approach*. 5th ed. Malden (MA): Blackwell Publishing Ltd.; 2007. p. 38–58.

\* Drugs or drug groups known or strongly suspected to cause developmental defects and their pregnancy safety categorization (see Table 1 for an explanation of the safety categories).

<sup>†</sup> Please verify the FDA categorization for each drug.

pregnant and breast-feeding women. They are rarely or too hastily revised as new information becomes available. The common result is confusion among clinicians about whether to prescribe certain drugs.

To ensure that the information included in this summary of teratogenic medication commonly prescribed to pregnant and breast-feeding women is evidence-based, the research strategy included computerized bibliographic searches of MEDLINE (1966–2008), PubMed (1966–2008), and references of published articles. Meta-analysis studies were included only if the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group were appropriately applied. Additionally, the American College of Obstetrics and Gynecology Committee Opinion and Practice Bulletins were used as a reference when relevant. For clinical relevance, trade names for commonly used drugs are also included. See Table 3.



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
ACE inhibitors Enalapril (Vasotec) Captopril (Capoten, Lopurin) Lisinopril (Prinivil, Zestril)	<ul style="list-style-type: none"> <li>• Contraindicated in pregnancy.</li> <li>• No adequate reports or well-controlled studies of these drugs in pregnant women.</li> <li>• May be indicated for the control of severe hypertension in extremely rare cases when the patient is refractory to other medications.<sup>24,25</sup></li> <li>• If mothers must take these drugs, close consultation with a cardiologist or a nephrologist and serial monitoring of amniotic fluid and fetal well-being is recommended.<sup>26</sup></li> <li>• Should be discontinued immediately if oligohydramnios is detected, unless lifesaving for the mother.</li> </ul>	<ul style="list-style-type: none"> <li>• Recent information reveals a teratogenic risk for these agents.<sup>27</sup></li> <li>• Crosses human placenta.<sup>28,29,30</sup></li> <li>• Formerly believed that exposure in the first trimester was safe; exposure in the 2nd and 3rd trimesters was associated with oligohydramnios, hypocalvaria, anuria, renal failure, patent ductus arteriosus, aortic arch obstructive malformations, and death.<sup>31,32,33</sup></li> <li>• More recent studies show that even in the first trimester, the fetus has an increased risk for malformations of the cardiovascular (atrial septal defect, pulmonic stenosis, atrial and ventricular defect) and the CNS (microcephaly, eye anomaly, spina bifida, coloboma) systems.</li> <li>• Accuracy of recent studies is limited by the relatively small number of fetuses included in the final analysis and their retrospective design.</li> <li>• Extreme caution and avoidance of ACE inhibitors in the first trimester, if possible, is recommended.</li> <li>• Antenatal surveillance should be initiated if inadvertent exposure occurs.</li> <li>• Oligohydramnios may not appear until after irreversible renal injury.</li> <li>• Neonates exposed <i>in utero</i> should be observed closely for hypotension, oliguria, and hyperkalemia.</li> </ul>	<ul style="list-style-type: none"> <li>• Considered compatible with breast-feeding.</li> <li>• Enalapril and captopril found in breast milk, although the kinetics remain to be clarified.<sup>34,35</sup></li> <li>• Still unknown if lisinopril enters breast milk so infants should be monitored for possible adverse effects, the lowest effective dose should be recommended to the mother, and breast-feeding avoided at times of peak maternal drug levels.</li> </ul>
Antidepressants Whole category (fluoxetine, sertraline, paroxetine)	<ul style="list-style-type: none"> <li>• Because depression is prevalent and commonly unrecognized, universal screening is recommended at the time of first prenatal visit, each trimester, and postpartum.<sup>36,37</sup></li> </ul>	<ul style="list-style-type: none"> <li>• SSRIs cross the human placenta.<sup>40,41,42,43</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Not contraindicated.<sup>49</sup></li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Whole category (fluoxetine, sertraline, paroxetine) (continued)	<ul style="list-style-type: none"> <li>• Pregnancy is not necessarily a reason to discontinue psychotropic drugs.<sup>38</sup></li> <li>• Discontinuation of medication exchanges the risks of embryopathy or fetopathy for the risks of untreated illness: preterm birth, IUGR, and STDs due to potential for engagement in high-risk sexual behavior.</li> <li>• In general, women taking SSRIs during pregnancy require an increased dose to maintain euthymia.<sup>39</sup></li> <li>• Team comprising psychiatrist and obstetrician should decide on necessity of continuing treatment and discuss all risks with mother.<sup>36,37</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Evidence of teratogenicity<sup>40,41,42,43</sup>; appraisal of risk is not unanimous.<sup>44</sup></li> <li>• Not considered major teratogens.</li> <li>• Exposure to SSRIs during early pregnancy is likely associated with an increased risk of cardiac defects (especially after paroxetine exposure).</li> <li>• The absolute risk is small and generally not greater than 2/1,000 births but caution should be used, especially with paroxetine.</li> <li>• Possible association between SSRIs use during gestation and newborn persistent pulmonary hypertension.<sup>45</sup></li> <li>• Late exposure is linked with transient neonatal complications including jitteriness, mild respiratory distress, transient tachypnea of the newborn, weak cry, poor tone, and neonatal intensive care unit admission.<sup>46,47,48</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Infant should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breast-feeding avoided at times of peak drug levels.</li> <li>• Most psychotropic medications are transferred to breast milk in varying amounts, and thus potentially passed on to the nursing infant.</li> <li>• Discarding breast milk obtained at the time of peak drug concentration could allow the mother to reduce the infant's exposure to her medication; however, this is often impractical to do.<sup>49</sup></li> </ul>
Fluoxetine (Prozac, Sarafem)	<ul style="list-style-type: none"> <li>• Effective for postpartum depression.<sup>50</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Fluoxetine crosses the human placenta.</li> <li>• Not considered a teratogen.</li> </ul>	<ul style="list-style-type: none"> <li>• Maternal serum and peak breast milk concentrations predict nursing infant serum concentrations.</li> </ul>
Sertraline (Zoloft, Lustral)	<ul style="list-style-type: none"> <li>• Lacks adequate reports or well-controlled studies of pregnant women.</li> <li>• There is growing experience with its use for the treatment of postpartum depression.<sup>50</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Associated with omphalocele and atrial and ventricular septum defects.<sup>51</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Present in the human milk.</li> <li>• The neonate should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breast-feeding avoided at times of peak drug levels.</li> </ul>
Paroxetine (Paxil)	<ul style="list-style-type: none"> <li>• Recent investigations suggest an increased risk of congenital malformations after exposure in the first trimester:<sup>52</sup> <ol style="list-style-type: none"> <li>1) Number of subjects was small and the conclusions derived subsequent to a large number of statistical analyses.</li> <li>2) Manufacturer changed FDA classification from C to D (see Table 1).</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>• 1.5-fold to twofold increased risk of congenital cardiac malformations (atrial and ventricular septal defects) after first trimester exposure.<sup>40,41,42,43</sup></li> <li>• Associated with right ventricular outflow defects.<sup>51</sup></li> <li>• Associated with anencephaly, craniosynostosis, and omphalocele.<sup>44</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Limited data suggest that paroxetine is not detectable in the neonates who are exclusively breast-fed.<sup>53</sup></li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Paroxetine (Paxil) (continued)	<ul style="list-style-type: none"> <li>Should be avoided during gestation and in women planning pregnancy.<sup>37</sup></li> </ul>		
Anticonvulsants Whole category (valproic acid, carbamazepine, phenytoin, lamotrigine)	<ul style="list-style-type: none"> <li>Approximately 500,000 U.S. women require psychiatric care, commonly involving these drugs.<sup>37</sup></li> <li>Recommended to switch to 30–35 micrograms estrogen oral contraception if taking anticonvulsants and wish to avoid pregnancy.<sup>37</sup></li> <li>Negatively affect reliability of oral contraceptives, especially carbamazepine and phenytoin<sup>54</sup> but with possible exception of valproic acid.<sup>55</sup></li> <li>Patients planning pregnancy should be counseled on the risks and the importance of periconceptual folate supplementation (4 mg/d).<sup>56</sup></li> <li>Goal to avoid generalized tonic-clonic seizures with minimized risk to fetus.</li> <li>Monotherapy (at a higher dose if necessary) is preferable to multidrug regimen.<sup>37</sup></li> </ul>	<ul style="list-style-type: none"> <li>Results indicate that the risk of congenital abnormalities in children exposed <i>in utero</i> is reduced but not eliminated by folic acid supplementation at 5–12 wk from the last menstrual period.<sup>57</sup></li> </ul>	<ul style="list-style-type: none"> <li>Breast-feeding infants should be monitored for possible adverse effects and the drug given at the lowest effective dose.</li> <li>Breast-feeding should be avoided at times of peak drug levels.</li> </ul>
Valproic acid (Depakene)	<ul style="list-style-type: none"> <li>No adequate or well-controlled studies.</li> </ul>	<ul style="list-style-type: none"> <li>Known human teratogen.<sup>58,59</sup></li> <li>Rapidly transported across human placenta reaching a fetal:maternal ratio greater than double.<sup>60</sup></li> <li>Risk to fetus is dose-dependent and compounded by low serum folate.<sup>57</sup></li> <li>“Valproate syndrome” includes distinct craniofacial appearance, limb abnormalities, heart defects, a cluster of minor and major anomalies, and CNS dysfunction.<sup>61,62</sup></li> <li>Impairments may be diagnosed <i>in utero</i> with an increased nuchal translucency measurement.<sup>63</sup></li> <li>After delivery, 10% die in infancy; 1/4 has developmental deficits or mental retardation.</li> </ul>	<ul style="list-style-type: none"> <li>Enters breast milk.</li> <li>Neonatal serum concentration levels reach less than 10% of maternal levels.<sup>64</sup></li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Carbamazepine (Tegretol, Atretol, Convuline, Eptol)	<ul style="list-style-type: none"> <li>Used for epilepsy and bipolar disorders.</li> </ul>	<ul style="list-style-type: none"> <li>Well-known teratogen.<sup>65</sup></li> <li>Crosses human placenta.</li> <li>“Carbamazepine syndrome” includes facial dysmorphism, developmental delay, spina bifida, and distal phalange and fingernail hypoplasia.<sup>66,67</sup></li> </ul>	<ul style="list-style-type: none"> <li>Excreted in breast milk.</li> <li>Limited data suggests that breast-feeding while taking this drug is generally safe.</li> <li>Rarely, neonatal cholestatic hepatitis has been reported.<sup>68</sup></li> </ul>
Phenytoin (Dilantin, Aladdin, Dantoin)	<ul style="list-style-type: none"> <li>Stable serum levels achievable during pregnancy<sup>69</sup>:                             <ol style="list-style-type: none"> <li>Low levels could be due to patient noncompliance or to hypermetabolism.</li> <li>High levels can result from hepatic disease, congenital enzyme deficiency, or other drugs that interfere with its metabolism.</li> <li>To reduce the risk of seizure, dose adjustments should be based on clinical symptoms rather than on serum drug concentrations.</li> </ol> </li> <li>May impair effect of corticosteroids, coumarin, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, and vitamin D.<sup>70</sup></li> </ul>	<ul style="list-style-type: none"> <li>Specifically associated with congenital heart defects and cleft palate.<sup>71</sup></li> <li>Monotherapy and the lowest effective quantity given in divided doses to lower the peaks can theoretically minimize the risks.<sup>72</sup></li> </ul>	<ul style="list-style-type: none"> <li>Transfer to breast milk is low.</li> <li>Considered safe for breast-feeding.<sup>73</sup></li> </ul>
Lamotrigine (Lamictal)	<ul style="list-style-type: none"> <li>No adequate or well-controlled studies.</li> <li>Used for epilepsy and bipolar disorders.<sup>74</sup></li> <li>May experience increased risk of seizures in absence of level monitoring.<sup>75,76</sup></li> </ul>	<ul style="list-style-type: none"> <li>Crosses human placenta.</li> <li>Fetal exposure has not been documented to increase the risk of major anomalies.<sup>77</sup></li> </ul>	<ul style="list-style-type: none"> <li>Transfer to breast milk is low.</li> <li>Considered safe for breast-feeding.<sup>73</sup></li> </ul>
Anxiolytics (benzodiazepines) Diazepam (Valium)	<ul style="list-style-type: none"> <li>No adequate or well-controlled studies.</li> <li>Drug prescribed for anxiety disorders including a variety of psychiatric conditions: panic disorders, generalized anxiety disorders, posttraumatic stress disorder, social anxiety, and phobias: Collectively, anxiety disorders comprise the most common psychiatric conditions with a prevalence of approximately 18% in the U.S.<sup>78</sup></li> </ul>	<ul style="list-style-type: none"> <li>No evidence of <i>significant</i> risk of teratogenicity.</li> <li>Rapidly crosses human placenta.<sup>85</sup></li> <li>Overall results are reassuring, revealing no adverse effects on neurodevelopment.</li> <li>Some studies show increased risk of oral clefts with first trimester exposure.<sup>†</sup></li> </ul>	<ul style="list-style-type: none"> <li>Excreted in breast milk.</li> <li>Maximum neonatal exposure is estimated at only 3% of maternal dose.<sup>87</sup></li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Anxiolytics (benzodiazepines) Diazepam (Valium) (continued)	<ul style="list-style-type: none"> <li>• May be beneficial adjunct to IV fluids and vitamins for treating hyperemesis gravidarum.<sup>79</sup></li> <li>• Useful anxiolytic for women undergoing fetal therapy procedures because it causes decreased fetal movement.</li> <li>• Used for prophylaxis and treatment of eclamptic convulsions.</li> <li>• Clinical efficacy was proven less than that of magnesium sulfate, and thus it is not currently recommended as first line therapy.<sup>80,81,82</sup></li> <li>• Initial findings have not been confirmed by long-term follow-up studies.<sup>83,84</sup></li> <li>• Shortest course and lowest dose should be used when indicated.</li> </ul>	<ul style="list-style-type: none"> <li>• Prolonged CNS depression can occur, with symptoms including mild sedation, hypotonia, reluctance to suck, apneic spells, cyanosis, impaired metabolic responses to stress, “floppy infant” syndrome, and marked neonatal withdrawal that can persist for hours to months after birth.<sup>86</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Special attention should be paid to the premature neonate or if the maternal dose is particularly high.</li> </ul>
Alkylating agents Cyclophosphamide (Cytoxan)	<ul style="list-style-type: none"> <li>• Integral part of the multi-agent regimens used to treat cancer of the ovary, breast, blood and lymph systems.</li> <li>• Transient sterility and secondary malignancy are the most common complications of treatment.</li> <li>• Case reports suggest that this drug can be used with good pregnancy outcome.<sup>88,89</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Crosses human placenta.</li> <li>• Neonatal hematologic suppression and secondary malignancies have been reported.<sup>90,91</sup></li> <li>• <i>In utero</i> exposure findings include growth deficiency, high-arched palate, microcephaly, flat nasal bridge, syndactyly, and finger hypoplasia.<sup>92,93</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Not compatible with breast-feeding.</li> <li>• Enters breast milk in high concentrations.</li> <li>• Commonly causes neonatal neutropenia.<sup>94,95</sup></li> </ul>
Hormones/androgens Whole category (methyltestosterone, medroxyprogesterone acetate, danazol)	<ul style="list-style-type: none"> <li>• Insufficient data to quantify risk in humans; however, some reports reveal that synthetic progestins cause mild virilization of female external genitalia.<sup>96,97</sup></li> </ul>	<ul style="list-style-type: none"> <li>• First trimester exposure is an indication for a detailed anatomic ultrasound between 18–22 wk of gestation.</li> </ul>	–
Methyltestosterone (Adoral, Testred)	<ul style="list-style-type: none"> <li>• Recommended for endometriosis and palliation with inoperable breast cancer.</li> </ul>	<ul style="list-style-type: none"> <li>• Unknown if crosses human placenta.</li> <li>• In animal studies, pseudohermaphroditism results in female fetuses; in males, an increased risk of hypospadias.<sup>99,‡</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Unknown if enters breast milk.</li> <li>• Excreted in breast milk in small amounts.</li> </ul>
Medroxyprogesterone acetate (Depo-Provera, Med-Pro, Provera)	<ul style="list-style-type: none"> <li>• Some recommend in combination with estrogens for libido enhancement.<sup>98</sup></li> </ul>	<ul style="list-style-type: none"> <li>• No evidence of <i>significant</i> risk of teratogenicity.</li> </ul>	<ul style="list-style-type: none"> <li>• Does not suppress lactation or adversely affect neonate.<sup>100,101</sup></li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Medroxyprogesterone acetate (Depo-Provera, Med-Pro, Provera) (continued)	<ul style="list-style-type: none"> <li>• Prescribed to prevent first trimester spontaneous abortion:               <ol style="list-style-type: none"> <li>1) No well-conducted studies to substantiate this claim.</li> <li>2) No demonstrable increase in ectopic pregnancy after treatment.</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>• In utero exposure of male fetuses to progestational agents apparently doubles the risk of hypospadias.</li> </ul>	<ul style="list-style-type: none"> <li>• Typically given for contraception 3 d after delivery since progesterone withdrawal may be one stimulus for the initiation of lactogenesis.</li> </ul>
Danazol (Danocrine, Danatrol)	<ul style="list-style-type: none"> <li>• Considered effective for endometriosis.<sup>102</sup></li> <li>• Not an effective contraceptive and should be discontinued immediately if patient becomes pregnant.</li> <li>• No indications during pregnancy.</li> </ul>	<ul style="list-style-type: none"> <li>• Unknown if crosses human placenta.</li> <li>• <i>Classified as Category X.</i></li> <li>• Not always necessary to terminate an exposed fetus.</li> <li>• Can have androgenic effect on female fetuses, including vaginal atresia, clitoral hypertrophy, labial fusion, and ambiguous genitalia.<sup>103,104</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Unknown if enters breast milk.</li> <li>• Contraindicated during breast-feeding.</li> </ul>
Antimetabolites Methotrexate (Folex, Mexate, Rheumatrex, Tremetex)	<ul style="list-style-type: none"> <li>• Commonly recommended to treat ectopic pregnancy, neoplastic disease, autoimmune disorders, and inflammatory conditions (Crohn's disease, rheumatoid arthritis).<sup>105</sup></li> <li>• Considered an efficient medical abortifacient of intrauterine pregnancy when combined with misoprostol.<sup>106,107</sup></li> <li>• Ectopic pregnancy: After administration, women must be clinically tested until there is complete normalization of their serum <math>\beta</math>-hCG titers.<sup>108,109</sup></li> <li>• Women with rheumatoid arthritis commonly experience a disease flare within 3 mo of delivery and drug treatment is required.</li> </ul>	<ul style="list-style-type: none"> <li>• First trimester exposure results in an increased risk of fetal malformations, including craniofacial, axial skeletal, cardio-pulmonary, and gastrointestinal abnormalities (Fig. 1) and developmental delay.<sup>110,111</sup></li> <li>• <i>Most</i> pregnancies exposed to low doses are not adversely affected.<sup>110,111</sup></li> <li>• Even single doses used in medical termination of pregnancy are associated with multiple congenital anomalies.<sup>112</sup></li> <li>• Exposure later in pregnancy seems to be safe.<sup>94</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Unknown if enters breast milk.</li> <li>• Views vary on safety but the drug is generally contraindicated in nursing mothers.<sup>113</sup></li> </ul>
Antithyroids Whole category (propylthiouracil, methimazole)	<ul style="list-style-type: none"> <li>• During gestation, women with hyperthyroidism should have their thyroid function checked every 3–4 wk.</li> <li>• Graves' disease represents the most common cause of maternal hyperthyroidism during pregnancy.</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal reaction is often unpredictable and different than the maternal response.</li> </ul>	<ul style="list-style-type: none"> <li>• No deleterious effects on neonatal thyroid function or on physical and intellectual development of breast-fed infants have been described.<sup>118,119</sup></li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Antithyroids Whole category (propylthiouracil, methimazole) (continued)	<ul style="list-style-type: none"> <li>• There is general consensus among clinicians that the lowest dose needed to keep T3 and T4 within the upper normal range for these women should be used.<sup>114,115</sup></li> <li>• Because women previously ablated with either radioactive iodine or thyroidectomy may still be producing thyroid-stimulating antibodies (even though they are themselves euthyroid), the fetus remains at risk and should be monitored with serial ultrasonography for growth and early detection of goiter.<sup>116,117</sup></li> </ul>		
Propylthiouracil	<ul style="list-style-type: none"> <li>• First-line treatment for Graves' disease in pregnancy due to lower risks than methimazole.<sup>120,121,122</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Crosses the human placenta.</li> <li>• Associated with fetal hypothyroidism and, rarely, aplasia cutis.</li> <li>• Cordocentesis sometimes recommended to test fetal thyroid function.</li> </ul>	<ul style="list-style-type: none"> <li>• Does not readily cross membranes.</li> <li>• Milk concentrations are quite low.</li> </ul>
Methimazole (Thiamazole, Mercazole, Tapazole)	Second-line treatment for Graves' disease.	<ul style="list-style-type: none"> <li>• Crosses the human placenta.</li> <li>• Can induce fetal goiter and even cretinism in a dose-dependent fashion.</li> <li>• Also commonly associated with fetal anomalies such as aplasia cutis, esophageal atresia, and choanal atresia.<sup>120,121,122</sup></li> <li>• Long-term follow-up studies of exposed children reveal no deleterious effects on either thyroid function or physical and intellectual development with doses up to 20 mg/d.<sup>123</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Excreted in breast milk.</li> </ul>
Coumarin derivatives Warfarin (Coumadin)	<ul style="list-style-type: none"> <li>• Contraindicated in pregnancy.</li> <li>• No adequate reports or well-controlled studies.</li> <li>• Because the risk of a bleeding complication during pregnancy approximates 18%, special attention should be paid when used during pregnancy.</li> <li>• Despite significant preventive effort, thromboembolic disease remains one of the major causes of maternal morbidity and mortality during pregnancy.</li> </ul>	<ul style="list-style-type: none"> <li>• Recognized teratogen.</li> <li>• Exposure from 6–10 wk of gestation is associated with an embryopathy (possibly secondarily from vitamin K deficiency), and subsequent exposure with a fetopathy (possibly secondarily from microhemorrhages).</li> <li>• "Warfarin syndrome" includes nasal hypoplasia, microphthalmia, hypoplasia of the extremities, IUGR, heart disease, scoliosis, deafness, and mental retardation.<sup>130</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Compatible with breast-feeding because it does not enter human breast milk.<sup>132,133</sup></li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Coumarin derivatives Warfarin (Coumadin) (continued)	<ul style="list-style-type: none"> <li>• A dose higher than 5 mg/d is reported to be associated with a greater risk of an adverse outcome.</li> <li>• In women with mechanical heart valves, an INR of 2.3–3.0 is recommended for either prophylaxis or treatment of venous thromboembolism:               <ol style="list-style-type: none"> <li>1) Believed that this INR level minimizes the risk of hemorrhage which is frequently associated with higher doses.<sup>124</sup></li> <li>2) Safe approach: women receiving therapeutic dose anticoagulation with the drug before pregnancy for a hereditary or acquired condition should be transitioned to therapeutic doses of unfractionated heparin or low molecular weight heparin before or within 6 wk of gestation.<sup>125</sup></li> </ol> </li> <li>• Previous studies advise that the maternal morbidity is higher in women with bioprosthetic valves:               <ol style="list-style-type: none"> <li>1) Coumarin derivatives were safe and effective and did not lead to embryopathy.<sup>126</sup></li> <li>2) In such cases therapeutic heparin may not be effective prophylaxis; it may be safest to continue warfarin, although in most instances physicians recommend replacement with heparin or low molecular weight heparin between 6–12 wk.<sup>127</sup></li> </ol> </li> <li>• If the mother's condition requires anticoagulation with warfarin, it should be substituted with heparin at 36 wk to decrease the risk of epidural/spinal anesthesia (subdural hematoma) and warfarin treatment should be resumed postpartum.<sup>128, 129</sup></li> </ul>	<ul style="list-style-type: none"> <li>• In a large series of women treated the duration of pregnancy for a prosthetic valve, the incidence of fetal “warfarin syndrome” was 5.6%, the pregnancy loss rate was 32%, and the stillbirth rate 10% of pregnancies achieving at least 20 wk.<sup>131</sup></li> <li>• Agenesis of the corpus callosum, Dandy-Walker malformation, and optic atrophy are the most common CNS malformations.<sup>131</sup></li> <li>• Long-term follow-up studies reported that school-age children exposed <i>in utero</i> have an increased incidence of mild neurologic dysfunction and an IQ &lt; 80.<sup>131</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Compatible with breast-feeding because it does not enter human breast milk.<sup>132,133</sup></li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Lithium Lithium (Calith, Lithocarb, Lithonate)	<ul style="list-style-type: none"> <li>• Used for the treatment of psychiatric disorders (prevention of recurrent mania and bipolar depression and in reducing risk of suicidal behavior); typically not used for the rapid control of acute mania.<sup>134</sup></li> <li>• The decision to discontinue drug therapy in pregnancy because of fetal risks should be balanced against the maternal risks of exacerbation of illness.<sup>37</sup></li> <li>• Physicians should be aware that pregnancy and especially the puerperium are high-risk times for recurrence of bipolar disease and likewise that sudden discontinuation of the drug can be associated with a high rate of disease relapse.<sup>135</sup></li> <li>• ACOG recommendations (2008):             <ol style="list-style-type: none"> <li>1) In women who experience mild and infrequent episodes of illness, treatment should be gradually tapered before conception.</li> <li>2) In women who have more severe episodes but are only at moderate risk for relapse, treatment should be tapered before conception but reinstated after organogenesis.</li> <li>3) In women who have especially severe and frequent episodes of illness, treatment should be continued throughout gestation and the patient counseled regarding the risks.<sup>37,136</sup></li> </ol> </li> <li>• A special concern is the use of lithium prior to delivery:             <ol style="list-style-type: none"> <li>1) Many recommend that the drug be tapered gradually over the month prior to delivery, maintaining serum levels between 0.5–1.2 mEq/L.<sup>137</sup></li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>• Crosses the placenta and may be a weak human teratogen (small increase in congenital cardiac malformations reported).<sup>138</sup></li> <li>• Associated with fetal and neonatal cardiac arrhythmias, hypoglycemia, nephrogenic diabetes insipidus, polyhydramnios, changes in thyroid function, premature delivery, LGA infant, and “floppy infant” syndrome.<sup>37,139</sup></li> <li>• Several studies noted an increased prevalence of Ebstein’s anomaly, although this finding was not confirmed in a prospective, multicenter study.<sup>140</sup></li> <li>• The risk ratio for cardiac malformations is approximately 1.2–7.7 and the risk ratio for overall congenital malformations is 1.5–3.<sup>141</sup></li> <li>• Fetal echocardiography is recommended in women exposed during the first trimester.<sup>142</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Excreted in breast milk and detectable levels can be measured in the nursing newborn.<sup>143</sup></li> <li>• Whether nursing mothers should continue drug therapy while breast-feeding is subject of controversy.<sup>144</sup></li> <li>• Neonatal clearance rate is slower than in the adult; thus, in the neonate the level of circulating drug might be much higher than expected.</li> <li>• If lithium must be continued during breast-feeding, its levels should be measured in the neonatal blood to note any adverse effects.</li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Lithium Lithium (Calith, Lithocarb, Lithonate) (continued)	2) Levels should be monitored weekly after 35 wk of gestation, and therapy either discontinued or decreased by one quarter 2–3 d before delivery.		
Misoprostol Misoprostol (Cytotec)	<ul style="list-style-type: none"> <li>• Not FDA-approved for any indications in pregnancy.</li> <li>• Currently, FDA-approved only for the treatment and prevention of intestinal ulcer disease resulting from NSAID use.</li> <li>• Well-studied and extensively used for both cervical ripening and induction of labor during the second and third trimesters.<sup>145,146</sup></li> <li>• Combined with mifepristone, the drug is safe and effective for medical termination of early pregnancy.<sup>147</sup></li> <li>• In 2000, the manufacturer (Pfizer) issued a warning letter to U.S. health care providers, cautioning against the use of misoprostol in pregnant women secondary to the lack of safety data for its use in obstetric practice.</li> <li>• In 2002, ACOG concluded that the risk of uterine rupture during vaginal birth after cesarean delivery is substantially increased by the use of the drugs as well as other prostaglandin cervical ripening agents.<sup>148</sup></li> <li>• ACOG recommendations (2003):               <ol style="list-style-type: none"> <li>1) If used for cervical ripening or labor induction in the third trimester, 25 micrograms should be considered for the first dose.</li> <li>2) Higher doses (50 micrograms every 6 h) can be used in some situations.</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>• Associated with a higher rate of fetal variable decelerations, and, as a result, a higher prevalence of meconium.<sup>149</sup></li> <li>• Although such complications occur more frequently with the use of this drug compared to oxytocin, there is no increase in the incidence of cesarean delivery for fetal distress or umbilical acidemia.</li> <li>• Congenital defects after unsuccessful first trimester medical abortions have been reported, including skull defects, cranial nerve palsies, facial malformations, and limb defects.<sup>150</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Excreted in breast milk.</li> <li>• Milk levels rise and decline rapidly (essentially undetectable in 5 h), significantly lowering infant exposure.<sup>151</sup></li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Misoprostol Misoprostol (Cytotec) (continued)	<ol style="list-style-type: none"> <li>3) Uterine hyperstimulation, and meconium staining of amniotic fluid are recognized complications.</li> <li>4) The drug should not be administered more frequently than every 3–6 h.</li> <li>5) Oxytocin should not be administered less than 4 h after the last misoprostol dose.</li> <li>6) When used for labor induction, fetal heart rate and uterine activity monitoring should be initiated in a hospital setting.</li> <li>7) Contraindicated in women with prior uterine scar.<sup>148</sup></li> </ol>		
Oral contraceptives Oral contraceptives	<ul style="list-style-type: none"> <li>• Numerous studies have addressed the safety and effectiveness of hormonal contraceptive use in healthy women: <ol style="list-style-type: none"> <li>1) Data are far less complete for women with underlying medical problems.<sup>152</sup></li> <li>2) Decisions regarding contraception, especially for women with medical problems may be complicated.</li> <li>3) Age, smoking, hypertension, diabetes, dyslipidemia, and migraines are important risk factors to be considered prior to recommending any form of hormonal contraception.</li> <li>4) In some cases, medications taken for certain chronic conditions may alter the effectiveness of hormonal contraception.</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>• Risk for major congenital malformations probably related to the drugs used to control a particular medical condition and not to the oral contraceptive (see Anticonvulsants).</li> <li>• About 1% of pregnant women use oral contraceptives during the first part of their pregnancy and thereby expose their fetuses to estrogens; however, exposure to specific estrogens or progestogens <i>seems to be</i> unrelated to the occurrence of malformations.</li> <li>• Causal relationship between a syndrome of multiple congenital anomalies (vertebral, anal, cardiac, tracheoesophageal, renal, and limb) and maternal progesterone/estrogen exposure has <i>possibly</i> been established.<sup>154</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Postpartum women remain in a hypercoagulable state for weeks after childbirth.</li> <li>• Product labeling for combination oral contraceptives recommends their use only after 4 wk postpartum in non-breast-feeding women.</li> <li>• Because progestin-only oral contraceptives and depot medroxyprogesterone acetate do not contain estrogen, these methods may be safely initiated immediately postpartum.</li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Oral contraceptives Oral contraceptives (continued)	<p>5) Pregnancy in these cases may pose substantial risks to the mother and her fetus.</p> <ul style="list-style-type: none"> <li>• For more information, refer to the most recent ACOG Practice Bulletin (2006) on which this topic is extensively covered.<sup>152</sup></li> <li>• Contraceptive failure with concomitant antibiotics reported; however, evidence exists only for rifampin.<sup>153</sup></li> <li>• Studies have demonstrated reduced serum levels of oral contraceptives in women taking anticonvulsants; however, ovulation and accidental pregnancy were not observed.</li> <li>• Higher risk of contraceptive failure in obese women; however, use should not necessarily be discontinued.</li> </ul>	<ul style="list-style-type: none"> <li>• A study providing evidence between oral contraceptives and birth defects (limb anomalies) found only males affected; however, this link remains weak and it was suggested that if oral contraceptives are teratogenic, it is with people who are predisposed.</li> <li>• Apparently the likelihood to deliver a malformed infant in women who used oral contraceptives at the beginning of pregnancy is increased by smoking.<sup>155</sup></li> <li>• One study concluded that early, high-dose <i>in utero</i> exposures to Depo-Provera may affect fetal growth.<sup>156</sup></li> <li>• Others suggested that medroxyprogesterone acetate cannot be demonstrated to have a measurable teratogenic risk and certainly does not present a risk for congenital heart disease and limb reduction defects.<sup>157</sup></li> <li>• Several studies addressed the issue related to fetal exposure to levonorgestrel in women who seek emergency contraception: <ul style="list-style-type: none"> <li>–If hormonal emergency contraception is inadvertently taken in early pregnancy, neither the woman nor the fetus will be harmed.</li> </ul> </li> </ul>	
Retinoids Isotretinoin (Accutane)	<ul style="list-style-type: none"> <li>• Contraindicated during pregnancy.</li> <li>• Before prescribing, physicians must be sure that patients are capable of complying with mandatory contraceptive measures. (Only manufacturer-approved physicians may prescribe it.<sup>158</sup>)</li> </ul>	<ul style="list-style-type: none"> <li>• This drug and its active metabolites cross the human placenta and are known human teratogens.</li> <li>• Multiple organ systems are affected including CNS, cardiovascular, and endocrine and thus damage can be severe.<sup>160</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Unknown if enters human breast milk.</li> <li>• Considering its potential adverse impact on the fetus, breast-feeding is contraindicated.</li> </ul>

(continued)



**Table 3. Considerations for Teratogenic Drugs Commonly Prescribed in Pregnant and Breast-feeding Women (continued)**

Drug	Maternal Considerations	Fetal Considerations	Breast-feeding Considerations
Retinoids Isotretinoin (Accutane) (continued)	<ul style="list-style-type: none"> <li>The most recent and most stringent system aimed to avoid exposure is an Internet-based, performance-linked system called iPLEDGE.<sup>*159</sup></li> <li>Two reliable forms of birth control must be used at the same time (unless abstinence is the chosen method of birth control) for 1 mo before starting treatment, during treatment, and for at least 1 mo after the end of the treatment.</li> </ul>	<ul style="list-style-type: none"> <li>Mental retardation without malformations has also been reported.</li> </ul>	<ul style="list-style-type: none"> <li>Unknown if enters human breast milk.</li> <li>Considering its potential adverse impact on the fetus, breast-feeding is contraindicated</li> </ul>
Radioactive iodine (iodine- <sup>131</sup> ) Iodine- <sup>131</sup> (I- <sup>131</sup> )	<ul style="list-style-type: none"> <li>Contraindicated in pregnant women.</li> <li>Cost-effective, safe, and reliable treatment for hyperthyroidism in non-pregnant women.<sup>161</sup></li> <li>Although excreted from the body within 1 mo, the current ACOG recommendation is that women should avoid pregnancy for 4–6 mo following treatment.<sup>113</sup></li> </ul>	<ul style="list-style-type: none"> <li>No adequate reports or well-controlled studies in human fetuses.</li> <li>Detrimental effects on the thyroid of the developing fetus as a result of I-<sup>131</sup> treatment for thyrotoxicosis of the mother in the first trimester of pregnancy are reported.<sup>162</sup></li> </ul>	<ul style="list-style-type: none"> <li>Breast-feeding should be avoided for at least 120 d after treatment.<sup>163</sup></li> </ul>

ACE, angiotensin-converting enzyme; CNS, central nervous system; SSRI, selective serotonin reuptake inhibitor; IUGR, intrauterine growth restriction; STD, sexually transmitted disease; IV, intravenous; INR, international normalized ratio; IQ, intelligence quotient; LGA, large for gestational age; ACOG, American College of Obstetricians and Gynecologists; FDA, U.S. Food and Drug Administration; NSAID, nonsteroidal antiinflammatory drug.

\* Available at <http://www.fda.gov/cder/drug/infopage/accutane/iPLEDGEupdate>.

† Saxén I. Cleft palate and maternal diphenhydramine intake [letter]. *Lancet* 1974;1:407–8.

‡ Tuffli GA. Testosterone and micropenis [letter]. *J Pediatr* 1974;84:927.

## CONCLUSION

Whether to prescribe a drug to a pregnant or breast-feeding woman is a decision that must be made in consideration of many factors, including, but not limited to, gestational age of the embryo or fetus, route of drug administration, absorption rate of the drug, whether the drug crosses the placenta or is excreted in breast milk, the necessary effective dose of the drug, molecular weight of the drug, whether monotherapy is sufficient or if multiple drugs are necessary to be effective, and even the mother's genotype. Potential harm to the fetus or nursing infant is paramount among these factors. Equally important is assessment of the potential harm to the mother that withholding a drug can cause. The decision, then, typically comes down to, "Does the benefit of the drug outweigh its risks?"

However, accurately weighing benefit against risk requires a thorough understanding of those benefits and risks. Current methods to assess and classify drug risk are spotty at best. Pharmaceutical companies gain approval to market drugs before follow-up studies have been conducted on their long-term effects. Moreover, pregnant and breast-feeding women are not appropriate test subjects precisely because of the risk of drug teratogenicity.

Novel approaches in the field of theranostics are being developed to address this research shortfall. Theranostics involves a diagnostic test to classify disease subtypes or stages to select and qualify a specific course of treatment and to monitor patient response to the specific targeted therapy. In contrast to current inadequate research methods, theranostics can potentially address several important questions:



**Table 4. Resources for Drug Effects in Pregnancy\***

Resource Name	Web Site
Reprotox	<a href="http://www.reprotox.org">http://www.reprotox.org</a>
Teris	<a href="http://depts.washington.edu/terisweb">http://depts.washington.edu/terisweb</a>
FDA	<a href="http://www.fda.gov/womens/registries/paxil_letter_e3.pdf">http://www.fda.gov/womens/registries/paxil_letter_e3.pdf</a>
Paroxetine	<a href="http://www.gskus.com/news/paroxetine/paxil_letter_e3.pdf">http://www.gskus.com/news/paroxetine/paxil_letter_e3.pdf</a>
Isotretinoin	<a href="http://www.fda.gov/cder/drug/infopage/accutane/iPLEDGEupdate">http://www.fda.gov/cder/drug/infopage/accutane/iPLEDGEupdate</a>
STD	<a href="http://www.cdc.gov/std/treatment/2006/updated-regimens.htm">http://www.cdc.gov/std/treatment/2006/updated-regimens.htm</a>

FDA, U.S. Food and Drug Administration; STD, sexually transmitted diseases.

\* Web sites listed and recommended for relevant information in regard to the effect of exposure to a large number of drug medications during pregnancy (Reprotox, Teris), U.S. Food and Drug Administration, paroxetine and isotretinoin exposure during pregnancy, and the most up-to-date recommendations for treatment of sexually transmitted diseases during pregnancy.

Why do pregnant women present with different signs and symptoms and of varying degrees? Why do pregnant women respond differently to treatments? Why do they require different medication doses?

Bioinformatics, genomics, and functional proteomics are molecular biology tools essential for the progress of “molecular theranostics.” The increasing availability of rapid and sensitive diagnostic tools already allows personalized treatment, which addresses the heterogeneity of both the disease and the subject. Theranostics offers the opportunity of building bridges between research and clinical development (translational medicine). Although theranostics is still in its infancy, it is expected to grow rapidly. In March 2004, the FDA released a white paper entitled, “Innovation or Stagnation?—Challenge and Opportunity on the Critical Path to New Medical Products.”<sup>164</sup> This report describes the inefficiencies in the translation of novel research from the bench to bedside, with a focus on drug discovery and development processes. This “critical path” initiative has already demonstrated success in several areas. For example, trastuzumab (Herceptin, Genentech, S. San Francisco, CA) targets the her2/neu receptor, which is a biomarker for an aggressive subset (25%) of breast cancer. Molecular diagnostics can detect HER2/neu from biopsy samples of breast tumor tissue.<sup>165</sup> Trastuzumab is not indicated for the general population of breast cancer patients, because it does not have a beneficial effect on patients whose tumors do not express the her2/neu receptor. However, treatment with trastuzumab in the her2/neu-expressing breast cancer subpopulation cuts the 4-year recurrence rate by 50% and thus extends the life of appropriate breast cancer

patients. An example of a “theranostic strategy” here would be the development of rapid genotyping assays for pregnant women that are predictive of phenotype expression in the mother and fetus.<sup>166</sup> As more mutations are identified and clinical, pharmacologic, biologic, and pharmacokinetic relationships are established, rapid genotyping may soon become a clinical reality for the targeted treatment of maternal and fetal disease.

Meanwhile, physicians should look more critically at a drug’s classification and at evidence of its teratogenicity before prescribing it. Information about the effect of exposure to a large number of medications during pregnancy can be obtained in electronic format through consultation of several Web sites (Table 4). In particular, the Reprotox resource was developed to provide summary information to health care providers on the effects of chemical and physical agents on fertility, pregnancy, and lactation. Agents include industrial and environmental chemicals as well as over-the-counter, prescription, and recreational drugs. There are summaries for more than 4,000 agents included, along with references for the data.

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