Antibiotic Use in Pregnancy and Lactation

What Is and Is Not Known About Teratogenic and Toxic Risks

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OBJECTIVE: Over ten million women are either pregnant or lactating in the United States at any time. The risks of medication use for these women are unique. In addition to normal physiologic changes that alter the pharmacokinetics of drugs, there is the concern of possible teratogenic and toxic effects on the developing fetus and newborn. This article reviews the risks and pharmacokinetic considerations for 11 broad-spectrum antibiotics that can be used to treat routine and life-threatening infections during pregnancy and lactation.

DATA SOURCES: Information from the U.S. Food and Drug Administration (FDA) product labels, the Teratogen Information Service, REPROTOX, Shepard's Catalog of Teratogenic Agents, Clinical Pharmacology, and the peer-reviewed medical literature was reviewed concerning the use of 11 antibiotics in pregnant and lactating women. The PubMed search engine was used with the search terms "[antibiotic name] and pregnancy," "[antibiotic name] and lactation," and "[antibiotic name] and breastfeeding" from January 1940 to November 2005, as well as standard reference tracing.

METHODS OF STUDY SELECTION: One hundred twenty-four references had sufficient information concerning numbers of subjects, methods, and findings to be included.

TABULATION, INTEGRATION, AND RESULTS: The teratogenic potential in humans ranged from "none" (penicillin G and VK) to "unlikely" (amoxicillin, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, and rifampin) to "undetermined" (clindamycin, gentamicin, and vancomycin). Assessments were based on "good data" (penicillin G and VK), "fair data" (amoxicillin, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, and rifampin), "limited data" (clindamycin and gentamicin), and "very limited data" (vancomycin). Significant pharmacokinetic changes occurred during pregnancy for the penicillins, fluoroquinolones and gentamicin, indicating that dosage adjustments for these drugs may be necessary. With the exception of chloramphenicol, all of these antibiotics are considered compatible with breastfeeding.

CONCLUSION: Health care professionals should consider the teratogenic and toxic risk profiles of antibiotics to assist in making prescribing decisions for pregnant and lactating women. These may become especially important if anti-infective countermeasures are required to protect the health, safety, and survival of individuals exposed to pathogenic bacteriologic agents that may occur from bioterrorist acts.

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Antibiotics are among the most commonly prescribed prescription medications for pregnant and lactating women.[1] More than 10 million women are either pregnant or lactating in the United States at any one time, and they are administered antibiotics for many reasons.[2] Because of the special considerations associated with fetal and newborn development, these women constitute a uniquely vulnerable population for which the risks of medication use must be separately assessed.

In addition to the pharmacokinetic and pharmacodynamic changes that may occur during pregnancy and lactation that can alter the effectiveness of drugs,[3] there is the added concern of the possible teratogenic and toxic effects that medications may have on the developing fetus and newborn. In general, there is a dearth of pharmacokinetic and pharmacodynamic information regarding the use and proper dosing of Food and Drug Administration (FDA)–approved

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drugs in pregnant and lactating women, as well as limited data pertaining to the teratogenic potential and the fetal or neonatal toxicity of these marketed medications. Accordingly, sparse information must sometimes be assembled from diverse sources to address these issues.

Recently, the threat of bioterrorism has expanded the context in which the potential use of antibiotic medications may be needed.[4] Although the possibility of a large-scale bioterrorist attack in the United States is unlikely, the potential for widespread antibiotic use in this situation emphasizes the need for health care professionals to be familiar with the risks and benefits of administering antibiotics to pregnant and lactating women.

This article reviews the available information concerning the risks and special circumstances to be considered in pregnant and lactating women for a group of 11 broad-spectrum antibiotics (amoxicillin, chloramphenicol, ciprofloxacin, clindamycin, doxycycline, gentamicin, levofloxacin, penicillin G, penicillin VK, rifampin, and vancomycin). By using this information, better choices can be made for the treatment of different types of bacterial pathogens in these particularly vulnerable populations.

DATA SOURCES AND METHODS OF STUDY SELECTION

Information from FDA-approved product labels, the Teratogen Information Service, Shepard's Catalog of Teratogenic Agents, REPROTOX, Clinical Pharmacology, and the peer-reviewed literature were reviewed for information concerning the use of 11 antibiotics in pregnant and lactating women. The medical literature was queried with the PubMed search engine. Papers searched were published from January 1940 to November 2005, in any language. The search terms "[antibiotic name] and pregnancy," "[antibiotic name] and lactation,", and "[antibiotic name] and breastfeeding," were used, as was standard reference tracing. A total of 124 references were accessed through these sources that contained sufficient information concerning the numbers of subjects, methods of investigation, and findings to be useful for the purpose of drawing conclusions concerning pharmacokinetic parameters, teratogenic potential, and toxicity assessments of these drugs. All materials were restricted to information from nonproprietary sources that were available in the public domain. Additionally, information concerning the potential treatment options for exposures and diseases caused by possible agents of bioterrorism were obtained from materials published by the Centers for Disease Control and Prevention in Atlanta.

RESULTS

A description of the 11 broad-spectrum antibiotics and their general modes of action are provided in Table 1.

All 11 antibiotics cross the placenta and enter the fetal compartment. For 5 of these, human umbilical cord blood levels are of the same order of magnitude as circulating maternal blood concentrations (chloramphenicol, clindamycin, gentamicin, rifampin, and vancomycin). For 4, the concentrations are of the same magnitude or higher in amniotic fluid as in maternal blood (ciprofloxacin, clindamycin, levofloxacin, and vancomycin) (Table 2).

All 11 antibiotics are excreted in human breast milk. Limited information concerning the amount in breast milk was available for 8 antibiotics (ciprofloxacin, clindamycin, doxycycline, gentamicin, levofloxacin, penicillin G, penicillin VK, and rifampin). No quantitative data concerning breast milk concentrations were available for 3 (amoxicillin, chloramphenicol, and vancomycin) (Table 2).

Using the Teratogen Information Service classification system for teratogenic risk,[44] the teratogenic potential of the 11 antibiotics during human pregnancy ranged from "none" in 2 cases (penicillin G and VK) to "unlikely" in 6 (amoxicillin, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, and rifampin) to "undetermined" in 3 (clindamycin, gentamicin, and vancomycin). Assessments were based on data that were "good" for 2 (penicillin G and VK) to "fair" for 6 (amoxicillin, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, and rifampin) to "limited" for 2 (clindamycin and gentamicin) to "very limited" for 1 (vancomycin). A summary of the human and animal data contributing to these assessments is shown in Table 3. The Food and Drug Administration Pregnancy Category classifications for the 11 antibiotics (as defined under 21 CFR [Code of Federal Regulations] 201.57 for the A, B, C, D, X Pregnancy Category system) (Table 4) were "B" in 5 cases (amoxicillin, clindamycin, penicillin G, penicillin VK, and vancomycin), "C" in 5 cases (chloramphenicol, ciprofloxacin, gentamicin, levofloxacin, and rifampin), and "D" in 1 case (doxycycline) (Table 3). In addition to the published literature, proprietary data were used to establish the FDA pregnancy category for these drugs.

Despite numerous concerns regarding the potential for maternal and fetal or neonatal toxicity of these

Table 1. Description of the Eleven Broad-Spectrum Antibiotics Investigated

Antibiotic	Description	Year of Initial FDA Approval
Amoxicillin	Semi-synthetic beta-lactam antibiotic. Inhibits the final stage of bacterial cell wall synthesis, leading to cell lysis.	1974
Chloramphenicol	Broad-spectrum antibiotic isolated from *Streptomyces venezuela* in 1947, now synthetically available. Binds to the 50S subunit of bacterial ribosomes, inhibiting peptide bond formation and protein synthesis.	1950
Ciprofloxacin	Fluoroquinolone antibiotic. Exerts its bactericidal effect by disrupting DNA replication, transcription, recombination, and repair by inhibiting bacterial DNA gyrase.	1987
Clindamycin	Antibiotic derived from lincomycin that has wide-ranging antimicrobial activity. Binds to the 50S ribosomal subunit, thereby inhibiting bacterial protein synthesis.	1970
Doxycycline	Broad-spectrum antibiotic that binds to the 30S bacterial ribosomal subunit. Blocks the binding of transfer-RNA to messenger-RNA, thereby disrupting protein synthesis.	1967
Gentamicin	Aminoglycoside antibiotic with broad-spectrum activity. Binds irreversibly to 30S bacterial ribosomal subunit, thereby inhibiting protein synthesis.	1966
Levofloxacin	Fluoroquinolone antibiotic. L-isomer of ofloxacin, which provides its principal antibiotic effect. Inhibits bacterial DNA replication, transcription, recombination, and repair by inhibiting bacterial type II topoisomerases.	1996
Penicillin G	Beta-lactam antibiotic that is primarily bactericidal. Inhibits the final stage of bacterial cell wall synthesis, leading to cell lysis.	1943
Penicillin V (phenoxymethyl penicillin)	Naturally derived beta-lactam antibiotic. Inhibits the final stage of bacterial cell wall synthesis, leading to cell lysis. Considered preferable to penicillin G for oral administration because of its superior gastric acid stability.	1956
Rifampin	Rifamycin B derivative that inhibits bacterial and mycobacterial DNA-dependent RNA polymerase activity. Used primarily for the treatment of tuberculosis, with additional utility for the treatment of both leprosy and meningococcal carriers.	1971
Vancomycin	Glycopolypeptide antibiotic. Binds to the precursor units of bacterial cell walls, inhibiting their synthesis and altering cell wall permeability while also inhibiting RNA synthesis. Because of its dual mechanism of action, bacterial resistance is rare.	1964

FDA, U.S. Food and Drug Administration.

11 drugs–including idiosyncratic and dose-related bone marrow suppression with chloramphenicol, arthropathies and bone and cartilage damage with ciprofloxacin and levofloxacin, dental staining and hepatic necrosis with doxycycline, and ototoxicity and nephrotoxicity with gentamicin and vancomycin–none of these toxicities has been documented in human mothers or offspring either during pregnancy or breastfeeding with these antibiotics (Table 3).

Very limited information was available pertaining to maternal pharmacokinetics in pregnancy for 8 antibiotics (amoxicillin, ciprofloxacin, clindamycin, gentamicin, levofloxacin, penicillin G, penicillin VK, and vancomycin), and none was available for 3 (chloramphenicol, doxycycline, and rifampin) (Table 2). For 4 antibiotics (amoxicillin, gentamicin, penicillin G, and penicillin VK), lower circulating drug concentrations were measured in pregnant women than nonpregnant, suggesting that a shorter dosing interval or increased maternal dose or both may be necessary to obtain similar circulating drug concentrations as for women in the nonpregnant state. In the case of ciprofloxacin and levofloxacin, circulating concentrations were generally reduced in pregnant women, also suggesting that an increased maternal dose or a shorter dosing interval or both may be necessary. In 3 cases (chloramphenicol, gentamicin, and vancomycin), therapeutic drug monitoring of serum peak and trough levels is recommended to assess circulating drug levels. In 1 case (clindamycin), the standard pharmacokinetic parameters did not change appreciably during the first, second, or third trimester of pregnancy (Table 2). Very little pharma-

Table 2. Current Information for Eleven Broad-Spectrum Antibiotics That May Be Used in Pregnant and Lactating Women

Antibiotic	Microbiologic Spectrum of Activity*	Placental Transmission	Transmission Into Breast Milk	Possible Pregnancy Dosage/Schedule Adjustments, Metabolism, Excretion, and Recommendations for Monitoring
Amoxicillin	Gram-positive aerobes, most gram-positive anaerobes, gram-negative aerobes including some enteric bacilli, Helicobacter, spirochetes, actinomyces*	Crosses the human placenta.[5–7] Penicillins transferred to the fetus and amniotic fluid reach therapeutic levels.[5]	Excreted in human breast milk in small amounts.[8] Considered "usually compatible with breastfeeding."[9†] Following therapeutic doses, mean human milk concentrations were 0.1–0.6 μg/mL.[10] No adverse effects seen in nursing infants whose mothers have been treated with amoxicillin.	Shorter dosing interval and/or increased dose have been suggested during pregnancy to attain similar plasma concentrations as for nonpregnant women.[6,11] Penicillins are primarily renally excreted via tubular secretion and glomerular filtration. Volume of distribution and renal clearance are increased during the 2nd and 3rd trimesters.[6,11]
Chloramphenicol	Gram positives, gram negatives, anaerobes, chlamydia, rickettsiae	Crosses the human placenta readily. Umbilical cord serum concentrations 29–106% of maternal levels.[12]	Excreted in human breast milk.[13–15] In 5 patients with minor obstetrical lacerations who received 1 g PO qD for 8 days, mean milk concentrations were 0.5–2.8 μg/mL. In 5 patients receiving 2 g PO qD for 8 days for mastitis, mean milk concentrations were 1.8–6.1 μg/mL.[13] Human milk concentrations are 51–62% of blood levels.[14] Percentage of administered dose in human breast milk per day is 1.3%.[15] Effect on breastfed infants considered "unknown but may be of concern."[16]	Unknown whether dose adjustments during pregnancy are necessary. Pharmacokinetics during pregnancy has not been specifically studied. Serum concentrations can be monitored to keep peak and trough levels in the ranges of 10–20 and 5–10 μg/mL, respectively. CBC monitored to detect bone marrow depression.
Ciprofloxacin	Gram-negative aerobes, some staphylococci	Crosses the human placenta and concentrates in amniotic fluid (Product information Cipro, 2001).[17] In 20 women at 19–25 weeks of gestation who received two 200-mg IV doses q 12 hours, the mean amniotic fluid level 2–4 hours after dosing was 0.12 ± 0.06 μg/mL (n = 7; amniotic fluid: maternal serum concentration [AF:MS ratio] = 0.57), 0.13 ±0.07 μg/mL at 6–8 hours (n = 7; AF:MS ratio = 1.44), and 0.10 ± 0.04 μg/mL at 10–12 hours (n = 6; AF:MS ratio = 10.00).[17]	Excreted in human breast milk (Product information Cipro, 2001).[17] Considered "usually compatible with breastfeeding."[9†] In 10 women given 750 mg q12 hours PO, serum and milk concentrations were obtained 2, 4, 6, 9, 12, and 24 hours after the 3rd dose. Concentrations were 3.79 ± 1.26, 2.26 ± 0.75, 0.86 ± 0.27, 0.51 ± 0.18, 0.20 ± 0.05, and 0.02 ± 0.006 μg/mL at these times and the ratios of breast milk: serum concentration were 1.84, 2.14, 1.60, 1.70, 1.67, and 0.85, respectively.[17] For breastfeeding infants consuming 150 mL/kg per day, the estimated maximum dose is 0.569 mg/kg per day or ≤ 2.8% the approved dose for infants of 20 mg/kg per day.[18]	Circulating fluoroquinolone concentrations are lower in pregnant than in nonpregnant women, but no specific pharmacokinetic data is available regarding ciprofloxacin in pregnant women.[19] It is unknown whether dose adjustments during pregnancy are necessary. Approximately 50–70% of a dose is excreted in the urine and, if renal function is impaired, the serum half-life is slightly prolonged (Product information Cipro, 2001).

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Table 2. Current Information for Eleven Broad-Spectrum Antibiotics That May Be Used in Pregnant and Lactating Women (*continued*)

Antibiotic	Microbiologic Spectrum of Activity*	Placental Transmission	Transmission Into Breast Milk	Possible Pregnancy Dosage/ Schedule Adjustments, Metabolism, Excretion, and Recommendations for Monitoring
Clindamycin	Gram-positive anaerobes, gram-negative anaerobes, aerobic gram-positive cocci, streptococci, *Clostridia* strains	Crosses the human placenta readily.[44,20–23] In 54 women undergoing cesarean delivery who received 600 mg IV 30 minutes before surgery, umbilical cord blood concentrations were 46% of maternal serum levels.[20] After multiple oral doses prior to therapeutic abortion, fetal blood concentrations were 25% and amniotic fluid levels were 30% of maternal blood levels.[21]	Excreted in human breast milk (Product information Clindamycin, 1970). Considered "usually compatible with breastfeeding."[9†] At maternal doses of 150 mg orally to 600 mg IV, breast milk concentrations range from 0.7 to 3.8 μg/mL (Product information Clindamycin, 1970).	Pharmacokinetic parameters do not change during pregnancy in women studied during the 1st, 2nd, and 3rd trimesters of gestation.[20,24] There are no studies to indicate that dosing should be modified during pregnancy. C_{max} and T_{max} (after a single standard dose) and C_{ss} (after multiple doses) do not change appreciably at any time during pregnancy.
Doxycycline	Gram-positives, gram-negatives, rickettsiae, chlamydiae, mycoplasma, spirochetes, actinomyces	Crosses the placenta (Product information Vibramycin, 2001).	Excreted in human breast milk.[25] Use for a short period (1 week) during breastfeeding is considered probably safe.[9,16] Breast milk concentrations are 30–40% of that found in maternal blood.[25]	Unknown whether dose adjustments during pregnancy are necessary. Pharmacokinetics during pregnancy has not been specifically studied. Enterohepatically recirculated. Excreted in urine and feces as unchanged drug. From 29% to 55.4% of a dose can be accounted for in the urine by 72 hours (Product information Vibramycin, 2001).
Gentamicin	Gram-negative aerobic rods, many streptococci, *Staphylococcus aureus*, mycobacteria	Crosses the human placenta.[20,26–28] In 2 different studies, peak umbilical cord blood levels were 34%[26] and 42%[20] of associated maternal blood concentrations.	Excreted in human breast milk.[29,30] Considered "usually compatible with breastfeeding."[9†] Poorly absorbed from the GI tract.[29] Only half of nursing newborns had detectable serum levels, which were low and not likely to cause clinical effects.[29] No adverse signs or symptoms in nursing infants as a result of maternal treatment.[9]	Increased dosage suggested due to decreased serum half-life in pregnancy and lower maternal serum levels.[20,31] In 54 women undergoing cesarean delivery, levels were lower than nonpregnant women.[20] Eliminated mainly by glomerular filtration (Product information Gentamicin, 1966). Clearance decreased in preeclamptic patients.[32] Dose/ dosing interval adjusted via peak and trough levels (Product information Gentamicin 1966).

(*continued*)

Table 2. Current Information for Eleven Broad-Spectrum Antibiotics That May Be Used in Pregnant and Lactating Women (*continued*)

Antibiotic	Microbiologic Spectrum of Activity*	Placental Transmission	Transmission Into Breast Milk	Possible Pregnancy Dosage/ Schedule Adjustments, Metabolism, Excretion, and Recommendations for Monitoring
Levofloxacin	Gram-positives and gram-negatives	Crosses the human placenta and concentrates in amniotic fluid (based on data for racemic ofloxacin) (Product information Levaquin, 1996).[17] In 20 women at 19–25 weeks of gestation receiving two IV 400-mg doses of ofloxacin q12 hours, mean amniotic fluid concentration 3–6 hours after dosing was 0.25 ± 0.11 μg/mL (n = 6; amniotic fluid: maternal serum concentration [AF:MS ratio] = 0.35), 0.15 ± 0.11 μg/mL at 6–10 hours (n = 8; AF:MS ratio = 0.67), and 0.13 ± 0.11 μg/mL at 11–12 hours (n = 6; AF:MS ratio = 2.57).[17]	Excreted in human breast milk in high concentrations (based on data for racemic ofloxacin) (Product information Levaquin, 1996).[17] Considered "usually compatible with breastfeeding."[9†] In 10 women given 400 mg of ofloxacin q12 hours PO, serum and milk concentrations were obtained 2, 4, 6, 9, 12, and 24 hours after the 3rd dose. Concentrations were 2.41 ± 0.80, 1.91 ± 0.64, 1.25 ± 0.42, 0.64 ± 0.21, 0.29 ± 0.10, and 0.05 ± 0.02 μg/mL at these times, with breast milk: serum concentration ratios of 0.98, 1.30, 1.39, 1.25, 1.12, and 1.66, respectively.[17] For breastfed infants consuming 150 mL/kg per day, the estimated maximum infant dose of ofloxacin is 0.362 mg/kg per day.[18]	Circulating fluoroquinolone concentrations are lower in pregnant than in nonpregnant women, but no specific pharmacokinetic data is available regarding levofloxacin in pregnant women.[19] There are no data to support dosing adjustments during pregnancy.
Penicillin G	Gram-positive aerobes including most streptococci/ enterococci, gram-positive anaerobes, spirochetes, actinomyces, some gram negatives*	Crosses the human placenta.[5,33,34] Penicillins are transferred to the fetus and amniotic fluid reaching therapeutic levels.[5]	Excreted in human breast milk in small amounts (Product information Bicillin, 2001; product information Penicillin V, 1997).[15] Considered "usually compatible with breastfeeding."[9†] In women with serum concentrations of penicillin ranging from 6 to 120 μg/dL, corresponding breast milk concentrations were 1.2–3.6 μg/dL, and the amount of the maternal dose appearing in breast milk per day was estimated at 0.03%.[15]	Shorter dosing interval and/ or increased dose have been suggested during pregnancy to attain similar plasma concentrations as for nonpregnant women.[6,11] Penicillins are primarily renally excreted via tubular secretion and glomerular filtration. Volume of distribution and renal clearance are increased during the 2nd and 3rd trimesters.[6,11]
Penicillin VK	Gram-positive aerobes including most streptococci/ enterococci, gram-positive anaerobes, gram negatives	Crosses the human placenta readily.[5,7,10,33,34,35] Penicillins are transferred to the fetus and amniotic fluid reaching therapeutic levels.[5]	Excreted in human breast milk in small amounts (Product information Penicillin V, 1997).[15,36] Considered "usually compatible with breastfeeding."[9†] In 18 women, penicillin V milk concentration depended on presence of mastitis, with peak levels 2.6–5.4 hours after a single PO 1,320-mg dose.[35] Peak concentration was 30–72 μg/dL with mean concentration 26-37 μg/dL. AUC over 8 hours after dosing was 2.1–3.0 mg-h/L.[35] Estimated dose of penicillin V ingested per day by breastfed infants is 40–60 μg/kg, or 0.09–0.14% of maternal dose per kg body weight.[35]	Shorter dosing interval and/or increased dose have been suggested during pregnancy to attain similar plasma concentrations as for nonpregnant women.[6,11] Penicillin V is excreted renally, primarily via tubular secretion. Volume of distribution and renal clearance are increased during the 2nd and 3rd trimesters.[6,11]

(*continued*)

Table 2. Current Information for Eleven Broad-Spectrum Antibiotics That May Be Used in Pregnant and Lactating Women (*continued*)

Antibiotic	Microbiologic Spectrum of Activity*	Placental Transmission	Transmission Into Breast Milk	Possible Pregnancy Dosage/ Schedule Adjustments, Metabolism, Excretion, and Recommendations for Monitoring
Rifampin	Mycobacteria, *Neisseria meningitidis*, *S aureus*, *Haemophilus influenzae*, *Legionella pneumophila*, Chlamydia	Crosses the human placenta (Product information Rifampin, 1971).[37–39] Umbilical cord concentrations between 12% and 33% of maternal blood levels, with peak levels occurring concurrently after drug administration.[37–39]	Excreted in human breast milk (Product information Rifampin, 1971).[15,40,41] Considered "usually compatible with breastfeeding."[9†] After a single oral dose of 600 mg, a nursing infant would ingest approximately 0.05% of the maternal dose per day, or approximately 0.3 mg/day.[15,40,41]	Unknown whether dosing adjustments during pregnancy are necessary. Pharmacokinetics during pregnancy has not been specifically studied. Hepatically deacetylated to active metabolite. Parent compound and metabolites excreted via biliary elimination (60%). Enterohepatic re-circulation; plasma levels elevated in hepatic disease. Up to 30% excreted in urine; renal clearance is 12% of GFR.[38]
Vancomycin	Gram positives, *S aureus*, *Staphylococcus epidermidis*, streptococci, enterococci, *Clostridium*, *Corynebacterium*	Crosses the human placenta (Product information Vancomycin, 1964).[42,43] Appears in umbilical cord blood after IV maternal treatment (Product information Vancomycin, 1964).[42,43] Amniotic fluid and umbilical cord blood concentrations during the early 3rd trimester comparable to maternal blood levels (fetal-maternal serum concentration ratio of 0.76).[43]	Excreted in human breast milk when administered IV (Product information Vancomycin, 1964).[42] When administered orally, vancomycin is poorly absorbed from the GI tract (Product information Vancomycin, 1964). It is, therefore, not likely to cause adverse effects in nursing infants.	There are no studies to indicate that vancomycin dosing should be modified during pregnancy. Volume of distribution and plasma clearance both increased, but half-life similar to that for nonpregnant women (4.55 versus 4–6 hours) in a woman administered IV vancomycin twice daily from 26–28 weeks of pregnancy.[43]

CBC, complete blood count; AF, amniotic fluid; MS, maternal serum; GI, gastrointestinal; AUC, area under the curve; GFR, glomerular filtration rate.

* Listed in the product label and the clinical pharmacology monograph as active against most strains; bacterial resistance occurs commonly in some species of otherwise susceptible bacteria due to beta-lactamase production.

† Based on assessment by the American Academy of Pediatrics.

Table 3. Teratogenic and Toxic Potential of Eleven Broad-Spectrum Antibiotics Based on Available Human and Animal Data

Antibiotic	Human Data: Teratogenic and Toxic Effects	Animal Data: Teratogenic and Toxic Fetal Effects	Magnitude of Human Teratogenic Fetal Risk (Based on TERIS Assessment)[44]	FDA Pregnancy Category*
Amoxicillin	OR for major congenital anomalies = 1.4 (95% CI 0.9–2.0) for women using amoxicillin + clavulanic acid during pregnancy in a case-control study of 6,935 malformed infants (no increased risk).[45] OR (adjusted) for congenital anomalies = 1.16 (95% CI 0.54–2.50) in a Danish study (1991–2000) of 401 primiparous women who filled prescriptions for amoxicillin during pregnancy (rate = 4.0%) compared with 10,237 controls who did not redeem any prescription drug (rate = 4.1%).[46] No increased rate of congenital malformations among 147 women who received prescriptions for amoxicillin during the 1st trimester.[46] No increased rate of congenital anomalies among 284 infants whose mothers were administered amoxicillin or ampicillin during the 1st trimester, or in 1,060 infants whose mothers were treated at any time during pregnancy.[47] No significantly increased rate of major or minor anomalies in the children of 14 women treated with amoxicillin and probenecid during the first 14 weeks of gestation or among 57 women treated after the 14th week in a controlled clinical trial on the treatment of gonorrhea during pregnancy.[48] No adverse effects in offspring exposed to amoxicillin during the 2nd and 3rd trimesters in 3 controlled clinical trials of antibiotic treatment for premature preterm rupture of membranes.[49–51] An association of necrotizing enterocolitis in newborns and maternal amoxicillin and clavulanic acid treatment during the 3rd trimester was observed in a randomized controlled trial including 4,826 pregnant patients.[52,53]	No increased congenital malformations in mice treated with 3–7 times the maximum human therapeutic dose of amoxicillin.[54] No adverse reproductive effects in rats given amoxicillin-clavulanic acid at doses of 400 and 1,200 mg/day prior to fertilization and during the first 7 days of gestation (Product information Amoxil, 2001).[55] No adverse fetal effects in pigs given amoxicillin with clavulanic acid at doses of 600 mg/kg on days 12–42.[56] Increased frequency of embryonic death in mice treated with amoxicillin at 6–7 times the maximum therapeutic human dose.[54]	Increased risk of teratogenicity is "unlikely," based on "fair" data.	B
Chloramphenicol	OR for major congenital anomalies = 1.7 (95% CI 1.2–2.6) for oral administration at any time during pregnancy in a case-control study of 22,865 malformed infants (risk marginally increased).[57] RR for congenital malformations = 1.19 (95% CI 0.52–2.31) in 348 offspring born to women who took chloramphenicol at any time during pregnancy (no statistically increased risk).[58] Potential for both dose-related and idiosyncratic bone marrow toxicity. Caution should be used near term, during labor, and while breastfeeding due to the possibility of inducing "gray-baby" syndrome.[59]	No increased congenital anomalies in monkeys.[60] No teratogenicity in mice or rabbits at 10–40 times the recommended human dose.[61] No teratogenicity in rats at 2–4 times the usual human dose,[62] but various fetal anomalies at 10–40 times the human dose.[61,63] Increased fetal death and decreased fetal weight in mice, rats, and rabbits.[61–63]	Increased risk of teratogenicity is "unlikely," based on "fair" data. "Therapeutic doses of chloramphenicol are unlikely to pose a substantial teratogenic risk."	C

(*continued*)

Table 3. Teratogenic and Toxic Potential of Eleven Broad-Spectrum Antibiotics Based on Available Human and Animal Data *(continued)*

Antibiotic	Human Data: Teratogenic and Toxic Effects	Animal Data: Teratogenic and Toxic Fetal Effects	Magnitude of Human Teratogenic Fetal Risk (Based on TERIS Assessment)[44]	FDA Pregnancy Category*
Ciprofloxacin	Congenital malformation rate = 4.0% and spontaneous abortion rate = 10.7% among liveborns to 56 women who continued their pregnancies after exposure to ciprofloxacin (ENTIS registry, 1986–1994). Rates of spontaneous abortion/fetal death, post-natal disorders, prematurity and intra-uterine growth retardation did not exceed background rates.[64] In a prospective registry of 116 pregnancies exposed to ciprofloxacin, 91 resulted in live births and 69% of these were exposed during the 1st trimester. Six liveborns were malformed (congenital malformation rate = 6.6%). There was no pattern of minor or major malformations.[64] OR for major congenital anomalies = 0.85 (95% CI 0.21–3.49) in a controlled, prospective, observational study of 200 human pregnancies exposed to fluoroquinolones during the 1st trimester (2.2% rate versus 2.6% in controls) [53% ciprofloxacin exposures, with 68% during the 1st trimester] (no increased risk).[65] No clinically significant musculoskeletal or developmental dysfunctions in offspring.[65] No congenital malformations and no increase in musculoskeletal problems in offspring of 28 pregnant women exposed to ciprofloxacin during the 1st trimester.[65] Permanent quinolone-induced cartilage or bone damage has not been documented in humans.[66,67] Seven women exposed to ciprofloxacin during 2nd or 3rd trimester delivered healthy, normal babies. Motor, adaptive, social, and language milestones were consistent with age, and there was no evidence of cartilage damage on regular clinical assessments up to 5 years of age.[68]	No detectable adverse effects on embryonic or fetal development in monkeys.[69] No evidence of teratogenicity in the offspring of mice, rats, and rabbits.[70]	Increased risk of teratogenicity is "unlikely," based on "fair" data. "Therapeutic doses of ciprofloxacin during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no [increased] risk".	C
Clindamycin	Major congenital anomalies in 31 of 647 infants (4.8%) whose mothers were given prescriptions for clindamycin during the 1st trimester of pregnancy; expected rate 4.3%.[71] No increased rate of congenital malformations in 104 women treated with clindamycin during the 2nd or 3rd trimester of pregnancy for the prevention of preterm delivery.[72] No increased rate of congenital anomalies in 65 infants born to women who received clindamycin and quinine during the 2nd or 3rd trimester of pregnancy for the treatment of malaria.[73]	No increased congenital malformations in mice and rats given 1–12 times the therapeutic human dose.[77,78]	Increased risk of teratogenicity is "undetermined" based on "limited" data. "Although a small [increased] risk cannot be excluded, a high risk of congenital anomalies in the children of women treated with clindamycin during pregnancy is unlikely".	B

(continued)

Table 3. Teratogenic and Toxic Potential of Eleven Broad-Spectrum Antibiotics Based on Available Human and Animal Data *(continued)*

Antibiotic	Human Data: Teratogenic and Toxic Effects	Animal Data: Teratogenic and Toxic Fetal Effects	Magnitude of Human Teratogenic Fetal Risk (Based on TERIS Assessment)[44]	FDA Pregnancy Category*
Clindamycin (continued)	No congenital malformations among 16 children of women treated with clindamycin during the 1st trimester of pregnancy for attempted prevention of recurrent miscarriage.[74] Can be a causative factor in the development of pseudomembranous colitis due to overgrowth of *Clostridium difficile*. Occurs infrequently and no more common among pregnant women using clindamycin than nonpregnant.[75] Has occurred with use of nearly all antibacterial agents, including clindamycin (Product information Clindamycin, 1970). An infant developed bloody stools after exposure to clindamycin and gentamicin in breast milk; no blood and breast milk samples were obtained and a causative relationship was not established.[76]			
Doxycycline	OR for major congenital anomalies = 1.6 (95% CI 1.1–2.3) for women receiving doxycycline at any time during pregnancy in a case-control study of 18,515 infants with congenital abnormalities (risk marginally increased).[79] OR of 1.6 was not significantly increased (95% CI 0.8–3.6) for a separately analyzed subgroup exposed during organogenesis (2–3 months of pregnancy).[79] No association of congenital malformations with doxycycline exposure for any of 6 anomalies (cardiovascular defects, oral clefts, spina bifida, polydactyly, limb reduction defects, and hypospadias) among 1,795 doxycycline-exposed pregnancies in 229,101 completed pregnancies in a surveillance study of Medicaid recipients.[71] All mothers reported that exposed infants were normal at 1 year of age in a prospective study of 81 pregnancies treated with doxycycline for 10 days during the early 1st trimester.[80] Tetracycline class antibiotics may induce hepatic necrosis in some pregnant women.[81–83] Some tetracyclines can cause cosmetic staining of primary dentition for exposures during the 2nd or 3rd trimester,[84,85] and there is some concern about possible enamel hypoplasia and reversible depression of fetal bone growth.[86] No staining from doxycycline has been documented in humans.	No increase in congenital anomalies in mice treated with 2–6 times the maximum human dose.[87] Increased skeletal anomalies and decreased fetal weight in mice at 17 times the maximum human dose.[87] No teratogenicity in rabbits given 2–17 times the maximum human dose, but decreased fetal weight and increased fetal death at higher doses.[87,88] No teratogenicity in rats or monkeys at more than 100 times the human dose.[89] Delayed long bone skeletal differentiation in albino rats given 8 mg/kg of doxycycline intraperitoneally from gestational day 8 to 19.[90] Delayed appearance of primary ossification centers in the humerus, ulna, radius, femur, tibia, and fibula compared with controls ($P < .001$).[90]	Increased risk of teratogenicity is "unlikely," based on "fair" data. "Therapeutic doses of doxycycline are unlikely to pose a substantial risk of fetal malformations, but the data are insufficient to state that there is no [increased] risk." Increased risk of dental staining is "undetermined" based on "very limited" data.	D

(continued)

Table 3. Teratogenic and Toxic Potential of Eleven Broad-Spectrum Antibiotics Based on Available Human and Animal Data *(continued)*

Antibiotic	Human Data: Teratogenic and Toxic Effects	Animal Data: Teratogenic and Toxic Fetal Effects	Magnitude of Human Teratogenic Fetal Risk (Based on TERIS Assessment)[44]	FDA Pregnancy Category*
Gentamicin	OR for major congenital anomalies = 1.7 (95% CI 0.9–3.2), in a case-control study of 22,865 infants with congenital anomalies (no increased risk); included 19 critical exposures, with the majority occurring during the 2nd or 3rd month of pregnancy.[91] A randomized trial of 3 parenteral antibiotic regimens showed no congenital abnormalities among 57 infants whose mothers were treated with gentamicin during the 1st or 2nd trimesters.[92] The frequency of newborn hearing screening failures was not different between 46 infants whose mothers were treated with gentamicin during pregnancy and 92 unexposed control infants.[93] Renal cystic dysplasia was reported in a child whose mother was given gentamicin during the 7th week of pregnancy.[94] There is no proof of a causal relationship between the gentamicin treatment and the nephrotoxicity, but it cannot be excluded.[94] No ototoxicity or nephrotoxicity has been documented in human fetuses.[44]	Mice given 1–12 times the maximum human dose had a slight statistically nonsignificant increase in the rate of congenital anomalies at lower doses, but not higher ones.[95] Fetal deaths were increased.[95] In mice treated with 11–18 times the maximum human dose, dose-dependent ultrastructural vestibular system damage was demonstrated in offspring.[96] In rats treated systemically with daily doses up to 500 times the maximum human ophthalmic dose, gentamicin depressed median glomerular counts and kidney and body weights in newborns (Product information Gentamicin, 1966). Rats given 9–25 times the maximum human dose had nephrotoxicity in offspring of type typically expected from aminoglycoside exposure.[97]	Increased risk of teratogenicity is "undetermined" based on "limited" data. "A small [increased] risk cannot be excluded, but there is no indication that the risk of malformations in children of women treated with gentamicin during pregnancy is likely to be great."	C
Levofloxacin	No well-controlled studies of the safety and efficacy of levofloxacin in pregnant or lactating women have been reported.	No teratogenicity in rats at oral doses up to 810 mg/kg per day (9.4 times the maximum human dose based on BSA) or IV doses up to 160 mg/kg per day (1.9 times the maximum human dose) (Product information Levaquin, 1996).	There are no well-controlled studies of the safety and efficacy of levofloxacin in pregnant or lactating women. Comprehensive reviews of published data concerning norfloxacin and ciprofloxacin (2 related fluoroquinolone antibiotics) conclude that an increased risk of teratogenicity is "unlikely" based on "fair" data.	C

(continued)

Table 3. Teratogenic and Toxic Potential of Eleven Broad-Spectrum Antibiotics Based on Available Human and Animal Data *(continued)*

Antibiotic	Human Data: Teratogenic and Toxic Effects	Animal Data: Teratogenic and Toxic Fetal Effects	Magnitude of Human Teratogenic Fetal Risk (Based on TERIS Assessment)[44]	FDA Pregnancy Category*
Levofloxacin (continued)		No teratogenicity or adverse effects on fertility in rats at oral doses up to 360 mg/kg per day.[91] Decreased fetal body weight and increased fetal mortality in rats given 810 mg/kg per day, with retardation of fetal skeletal ossification/skeletal variations (Product information Levaquin, 1996).[98] No teratogenicity in rabbits given up to 50 mg/kg per day orally (1.1 times the maximum recommended human dose based on BSA), or IV at doses up to 25 mg/kg per day (0.5 times the highest recommended human dose) (Product information Levaquin, 1996).[98]		
Penicillin G	OR for major congenital anomalies = 1.3 (95% CI 1.1–1.5) for women who used penicillin G during pregnancy in a case-control study (1980-1996) of 22,865 malformed infants (marginally increased risk suggested attributable to recall bias by the authors).[99] RR for congenital malformations = 0.92 (95% CI 0.78–1.10) among 7,171 infants whose mothers were treated with a penicillin derivative at any time during pregnancy (no increased risk).[58] The frequency of 1st-trimester penicillin use was no greater than expected in a prospective study of 194 infants with major malformations born in Sweden (1963–1965).[100] OR for neural tube defects = 0.90 (95% CI 0.37–2.17). Rate of 1st-trimester penicillin use was no greater than expected in a case-control study of 538 infants with neural tube defects and 539 controls in California from 1989 to 1991 (no increased risk).[101] No adverse effects noted in offspring despite widespread use of penicillins during pregnancy.[10,44,58,99,102]	No teratogenicity in mice administered up to 500 units/g on gestation day 14.[103] No teratogenicity or increased abortions in rabbits maintained on 100 mg/kg per day during pregnancy.[104] No teratogenicity or impaired fertility in mice, rats and rabbits (Product information Bicillin, 2001).	Increased risk of teratogenicity is "none" based on "good" data.	B

(continued)

Table 3. Teratogenic and Toxic Potential of Eleven Broad-Spectrum Antibiotics Based on Available Human and Animal Data *(continued)*

Antibiotic	Human Data: Teratogenic and Toxic Effects	Animal Data: Teratogenic and Toxic Fetal Effects	Magnitude of Human Teratogenic Fetal Risk (Based on TERIS Assessment)[44]	FDA Pregnancy Category*
Penicillin VK	OR for congenital anomalies = 1.25 (95% CI 0.84–1.86) (not increased) among 654 users of penicillin VK with or without other drug use during the 1st trimester (1991–1998). The rate of congenital anomalies (4.6%) was no greater than for 9,263 controls who did not redeem any prescription drug during pregnancy (3.6%).[105] Nine cardiovascular abnormalities occurred in the group exposed to penicillin VK (OR 1.74; 95% CI 0.83–3.65) (not statistically increased).[105] OR for congenital anomalies = 1.3 (95% CI 1.1–1.6) in a case-control study (1980–1996) of 22,865 infants with congenital anomalies (173 [0.8%] treated with penicillin V during pregnancy). Adjusted OR for medically documented penicillin V use during the 1st trimester showed no significant association between maternal exposure and congenital anomalies.[106]	No evidence of impaired fertility or harm to the fetus due to penicillin in reproduction studies in mouse, rat, and rabbit (Product information Penicillin V, 1997).	Increased risk of teratogenicity is "none" based on "good" data.	B
Rifampin	In a meta-analysis of case reports (1971–1977; 15 different authors),[111] congenital malformations among 410 offspring in 442 gravidas treated with rifampin–usually in combination with other drugs–was 3.3% and no higher than expected for human populations.[44,107] Exposure was during the first 4 months in 109 cases. The spontaneous abortion rate = 1.7% was below expected for a general obstetrical population.[108] In 226 women exposed during 229 conceptions, 9 offspring had congenital malformations among 207 births (4.3%)[37,109]; this was no greater than the historical rate for women afflicted with tuberculosis.[37,109] The spontaneous abortion rate = 2.4% and was below expected for general obstetric populations.[108] No congenital anomalies in the offspring of 13 women treated with rifampin for leprosy,[110] or 18 women treated for brucellosis.[111] Treatment occurred during all trimesters.	No increased rate of congenital anomalies in rats or mice treated with 2.5–10 times the usual human dose.[112] In rats and mice treated with ≥ 15 times the human dose (≥ 150 mg/kg per day), there was an increased rate of spina bifida, cleft palate, and nonossified skeletal elements (Product information Rifampin, 1971).[37,109] The malformation rate was dose-dependent. No increase in rate of congenital anomalies in rabbits treated with similar doses (200 mg/kg per day). No fetal malformations in rabbits administered doses of 50 mg/kg per day for 20 days beginning on day 2.[113] In rabbits given doses of up to 20 times the usual human dose, imperfect osteogenesis and embryotoxicity were reported (Product information Rifampin, 1971).	Increased risk of teratogenicity is "unlikely" based on "limited to fair" data. "The data are insufficient to state that there is no [increased] risk".	C

(continued)

Table 3. Teratogenic and Toxic Potential of Eleven Broad-Spectrum Antibiotics Based on Available Human and Animal Data *(continued)*

Antibiotic	Human Data: Teratogenic and Toxic Effects	Animal Data: Teratogenic and Toxic Fetal Effects	Magnitude of Human Teratogenic Fetal Risk (Based on TERIS Assessment)[44]	FDA Pregnancy Category*
Vancomycin	No congenital anomalies in the offspring of 10 women who received 1 g q12 hours IV for at least 1 week during either the 2nd or 3rd trimester, with peak and trough blood levels 24.4–65.7 μg/mL and 5.6–16.7 μg/mL, respectively.[42] No congenital abnormality in the newborn of a woman who received 28 days of 1 g q12 hours IV beginning at 13 weeks of pregnancy.[114] The highest peak level measured was 20 μg/mL. A fetal bradycardia occurred in a pregnant woman who developed hypotension when vancomycin was infused rapidly IV during labor, but there were no adverse effects on the child.[115] Vancomycin is potentially ototoxic and nephrotoxic. However, 10 pregnant women who received 1 g q12 hours IV for at least 1 week had no maternal ototoxicity or nephrotoxicity.[42] In a pregnant woman who was treated IV twice daily for 13 days, there was no maternal ototoxicity or nephrotoxicity.[43] The risk of these toxic effects in the fetus is considered low.[42,44]	No congenital malformations in rats given up to 200 mg/kg per day IV (1,180 mg/m^2, or 1 times the maximum human dose on a mg/m^2 basis) or in rabbits given up to 120 mg/kg per day IV (1,320 mg/m^2 or 1.1 times the maximum recommended human dose on a mg/m^2 basis). No effects on fetal weight or development in rats at the highest dose or in rabbits given 80 mg/kg per day (880 mg/m^2 or 0.74 times the maximum recommended human dose based on mg/m^2) (Product information Vancomycin, 1964).[116] No increase in congenital malformation rate in rats or rabbits treated with 1–5 or 1–3 times the human dose, respectively.[116,117]	Increased risk of teratogenicity is "undetermined" based on "very limited" data.	B

TERIS, Teratogen Information Service; OR, odds ratio; RR, relative risk; CI, confidence interval; ENTIS, European Network of Teratology Information Services; BSA, body surface area.
* A, B, C, D, X Pregnancy Category system, as defined under 21 CFR 201.57.

Table 4. U.S. Food and Drug Administration Pregnancy Labeling Categories*

Pregnancy Category	Category Description
A	Well-controlled studies available in humans with no adverse effects observed in human pregnancies
B	No adverse effects in well-controlled studies of human pregnancies with adverse effects seen in animal pregnancies OR no adverse effects in animal pregnancies without well-controlled human pregnancy data available
C	Human data lacking with adverse pregnancy effects seen in animal studies OR no pregnancy data available in either animals or humans
D	Adverse effects demonstrated in human pregnancies; benefits of drug use may outweigh the associated risks
X	Adverse effects demonstrated in human or animal pregnancies; the risk of drug use clearly outweigh any possible benefits

* Defined under 21 CFR 201.57 for the A, B, C, D, X Pregnancy Category system.

cokinetic data were available in lactating women for any of the antibiotics (Table 2).

CONCLUSION

The safety of drug use in pregnancy is often an enigma. Many drugs have a long usage history in pregnancy without any controlled clinical trials ever having been conducted to ascertain their safety or efficacy during human pregnancy. Although there is little reason to believe that medications that have been demonstrated to be effective for particular conditions in nonpregnant subjects will not also prove effective when delivered in proper doses to pregnant women, the changes in basic physiology that occur in the maternal volume of distribution, renal clearance, and hepatic metabolism–as well as the potential for pharmacokinetic effects related to the distribution and metabolism of the drug in the fetal compartment–make the issue of proper pregnancy-specific dosing difficult to predict in the absence of empirical data. To further complicate this issue, these physiologic changes of pregnancy vary greatly from the first to the third trimester.

Often, because of inadequate data regarding the prevalence of use, timing, and duration of exposure of sufficient numbers of pregnant women to drugs, there is insufficient information to formulate conclusive judgments about their safety and efficacy that are different from that for nonpregnant patients. Concerns regarding potential teratogenicity and fetal or neonatal toxicity are often incompletely addressed by the limited amount of pregnancy and lactation exposure data and adverse event reports that are available. Because of this, conflicts can arise between the theoretical fear of adverse fetal or neonatal consequences and the general bias among most healthcare professionals that the successful treatment of medical conditions in the mother is in the offspring's best interest. This is especially true in the case of potentially life-threatening illnesses, as is the case with many agents of bioterrorism. These issues are particularly relevant to emergency response professionals, as well as to primary health care providers who manage the pregnancies of the nearly four million women who deliver newborns each year in the United States.[2]

The difficulty with the assessment of drug effects

Table 5. Eleven Broad-Spectrum Antibiotics That May Be Used in Pregnant and Lactating Women in Cases of Exposure to Potential Agent(s) of Bioterrorism[4,70,118-123]

Antibiotic	Potentially Useful Against Bioterrorist Agent(s)*
Amoxicillin	*Bacillus anthracis*†
Chloramphenicol	*Bacillus anthracis*†
	Yersinia pestis†
	Francisella tularensis†
Ciprofloxacin	*Bacillus anthracis*
	Yersinia pestis†
	Francisella tularensis†
	Coxiella burnetii†
Clindamycin	*Bacillus anthracis*†
Doxycycline	*Bacillus anthracis*
	Yersinia pestis
	Francisella tularensis
Gentamicin	*Bacillus anthracis*†
	Yersinia pestis†
	Francisella tularensis†
Levofloxacin	*Bacillus anthracis*†
	Yersinia pestis†
	Francisella tularensis†
	Coxiella burnetii†
Penicillin G	*Bacillus anthracis*
Penicillin VK	*Bacillus anthracis*†
Rifampin	*Bacillus anthracis*†
Vancomycin	*Bacillus anthracis*†

* As cited by the Centers for Disease Control and Prevention based on in-vitro microbiologic susceptibility data from a limited set of clinical isolates.

† Not currently a Food and Drug Administration–approved indication.

in pregnant women is typically related to a lack of well-controlled clinical data concerning the pharmacokinetics and pharmacodynamics of their use in pregnancy. Assessments that pertain to rare adverse events typically rely on the analysis of retrospective case-control data and, less often, on prospective cohort series. By using these data, it is often possible to place bounds on the risk of teratogenicity and fetal or neonatal toxicities that may result from medication use during pregnancy and lactation and to make reasonable judgments as to the safety of different medications, in addition to estimates concerning their proper dosing. A summary of these findings—based on the available data for 11 widely used broad-spectrum antibiotics—is presented in Tables 2 and 3. When indicated and properly administered, all of these agents seem to have sufficient evidence to allow for their use during pregnancy and lactation.

Antibiotic use in pregnant and lactating women has become an increasing concern due to the threat of bioterrorism. Because the timing and type of a bioterrorist attack is necessarily unpredictable, health care providers must be aware of the different types of diseases and potential treatment options that may be needed in these circumstances (Table 5). The situation is further complicated because the data that pertain to medications for combating these agents are derived primarily from in vitro susceptibility studies in limited numbers of clinical isolates that were obtained from nonpregnant patients. Many of the treatment regimens that are currently recommended by the Centers for Disease Control and Prevention for these bioterrorist agents and their associated diseases are not currently FDA-approved indications because of the lack of adequate and well-controlled clinical trials to support their efficacy and safety under these circumstances. Sometimes they may have been approved based on surrogate markers or endpoints (ie, 21 CFR 314 Subpart H) or only animal data based on the animal efficacy rule (ie, 21 CFR 314 Subpart I).[124,125] Thus, the issues of teratogenicity and fetal toxicity, as well as additional concerns surrounding the potential need for differential dosing of these drugs during pregnancy under these circumstances, have an intrinsically limited amount of data from which to draw.

The focus of this article has been to evaluate the existing data within the public domain with regard to 11 broad-spectrum antibiotics that can be of potential use in pregnant and lactating women. All are currently available for the treatment of routine and life-threatening bacterial infections, in addition to exposures associated with some known potential agents of bioterrorism. In the unlikely case of a bioterrorist attack, all health care providers must be able to provide their patients with appropriate treatment or prophylaxis after critical exposures. Pregnant and lactating women are a particularly vulnerable population and health care professionals should be familiar with the antibiotics that can be used under such adverse circumstances to feel confident in treating such pathogenic exposures.

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