Anti-infective Drug Use in Obstetrics - Part I

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1. Discuss the important background information regarding the use of drugs in pregnancy, such as reproduction studies in animals, timing in gestation, and the pharmacokinetics of the drug.
2. Describe which antibiotics (penicillins, cephalosporins, aminoglycosides, fluoroquinolones, macrolides, tetracyclines, aztreonam, and chloramphenicol), based on available information, are considered safe for use in pregnancy.
3. Describe which antibiotics (listed in number 2) have the potential for causing harm to the fetus and or newborn if used during pregnancy or lactation.

Article

Anti-infective Drug Use in Obstetrics – Part I

Author: Gerald G. Briggs, B.Pharm.

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Introduction

Antibiotics and anti-infective drugs are frequently used during all stages of gestation. For the most part, this use is not associated with embryo or fetal harm and no effect of the exposure can be noted in the newborn. There are some notable exceptions, however, such as the direct toxicity from tetracycline drugs and some aminoglycosides, and the modification of the mother’s normal bacterial flora by penicillins that may result in an increased incidence of severe sepsis in the newborn.

All drugs with a molecular weight less than 1000 daltons cross the placenta with those less than 600 crossing easily. Because most drugs have a molecular weight below 1000, exposure of the embryo and fetus should be expected when the mother is treated with these agents. The main determinant of the drug concentration in the embryo/fetus is the mother’s blood concentration. Other factors also have a role, such as lipid solubility, protein binding, and the degree of ionization at physiologic pH. Physiologic factors that can modify placental transfer include placental blood flow and the placental surface area available for transfer. The latter factor is correlated with gestational age. At term, the surface area of the placenta is at its maximum and nearly all substances can reach the fetus if present in the maternal bloodstream.

In man, the critical time for drug-induced congenital malformations is usually the period of organogenesis (which is about 20 to 55 days after conception or about 34 to 69 days after the first day of the last menstrual period). There are exceptions to this rule, however, such as the tetracycline drugs. In addition, drug-induced toxicity can occur at any time during gestation. Drug-induced toxicity is possible in the first 20 days after fertilization, but if injury occurs, it most commonly leads to spontaneous abortion, rather than to birth defects.

Reproduction testing in experimental animals has been required of all new drugs since 1966. The current regulations for reproductive and developmental toxicity were adopted in 1994, stating that new drugs must be tested in animals for fertility and...
early embryonic development, embryo-fetal development, and pre- and postnatal development. Animals commonly used, such as the rat and rabbit, have hemochorial placentas similar to the human placenta. In this type of placenta, the fetal tissue is in direct contact with the maternal blood, but the blood of the fetus and the mother do not mix.

The importance of animal reproductive data to human teratology can be appreciated by the following information: (a) all drugs, with two exceptions, that are human teratogens are also teratogenic in experimental animals (the exceptions are angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists); (b) concordance in the type of anatomical defect has been demonstrated between humans and experimental animals for all human teratogens with the exception of lithium (heart defects) and tetracycline (anomalies of the teeth). Another important fact, however, is that systemic exposure of the experimental animal should be near the maximum therapeutic exposure in humans. Animal exposures greater than 100 times the human exposure have diminished significance because most, if not all drugs can cause dose-related teratogenicity or toxicity, if administered at an appropriate time in gestation. Moreover, the systemic exposure should not cause maternal toxicity since such toxicity can also lead to adverse fetal outcomes. Therefore, with these qualifications, the presence or absence of teratogenicity in experimental animals can be a powerful, but not absolute, tool for predicting human teratogenicity.

Information is also provided on the excretion into breast milk if known. In most cases, the processes that govern the passage of a drug into milk are similar to those that determine if a drug crosses the placenta. As discussed above, maternal serum concentration is the main determinant. In addition, however, the milk pH is slightly acidic in comparison to serum pH; so weak bases could become trapped in milk (ion trapping). In general, there are few contraindications to the use of antibiotics or anti-infective drugs during nursing.

For each drug that is discussed, the pregnancy risk factor category (as defined by the Food and Drug Administration) is shown in parentheses. To review:

Category A: Controlled studies in women fail to demonstrate a risk to the fetus and animal studies (if performed) also show no risk and thus, the possibility of fetal harm appears to be remote.

Category B: Either – No controlled studies in women have been done, but animal studies show no harm OR animal studies suggest a potential for harm, but controlled studies in women do not show harm.

Category C: Either – studies in animals suggest a potential for harm, and controlled studies in women have not been done OR no animal studies or human studies have been done – The potential benefit from use should exceed the potential for risk.

Category D: There is positive evidence that human fetal risk exists; however, the benefits of use may still outweigh the risk (for example, some anti-convulsive drugs).

Category X: There is positive evidence that human fetal risk exists and this risk clearly outweighs any potential benefit from using the drug. Thus the drug is contraindicated.

As you might expect, the majority of drugs are classified as category C because of the overall lack of studies in pregnant women. The purpose of this review is to provide nurses with sufficient information to understand the use of antibiotics and other anti-infective agents in women who are pregnant or who may become pregnant during treatment, and in women who are breast-feeding infants. In most cases, the maternal benefit derived from a specific agent, if no alternative is available, will outweigh any risk to the fetus or infant.

I. Antibiotics

A. Penicillins (B)

Penicillins are a large class of drugs that are frequently used during pregnancy and the postpartum period. They are sub-classified into four categories: Natural Penicillins (penicillin G, penicillin V), Penicillinase-resistant Penicillins (cloxacillin, dicloxacillin, nafcillin, oxacillin), Aminopenicillins (amoxicillin, ampicillin, bacampicillin), and Extended Spectrum Penicillins (carbenicillin, mezlocillin, piperacillin, ticarcillin). Four penicillins have been combined with a beta-lactamase inhibitor (which are clavulanic acid, sulbactam, or tazobactam sodium) to prevent inactivation by beta-lactamase-producing organisms. These are amoxicillin/potassium clavulanate, ampicillin/sulbactam, piperacillin/tazobactam sodium, and ticarcillin/potassium clavulanate.
All penicillins cross the human placenta to the embryo and fetus. Near term, the concentrations of these antibiotics in the mother, amniotic fluid, and fetus are approximately equal. Those penicillins that have undergone animal reproduction testing have not demonstrated embryo or fetal harm. Because of this, and the lack of reports showing a relationship to major congenital malformations, all penicillins are considered to be safe during human pregnancy and lactation. Small amounts of penicillins are found in human breast milk. Exposure of a nursing infant to these antibiotics may potentially cause modification of bowel flora (selection and overgrowth of resistant bacteria), an allergic reaction, or interference with the interpretation of culture results if a fever workup is required.

Reproduction studies in animals with potassium clavulanate, sulbactam, and tazobactam either alone or in combination with penicillins have revealed no evidence of embryo or fetal harm. All of these agents are rated pregnancy risk factor B in combination with a penicillin drug. The excretion of these agents into breast milk has not been studied, but the relatively low molecular weight of these agents suggests that all are excreted into milk. The effects of this exposure on a nursing infant are unknown, but probably do not represent a significant risk.

Although penicillins are not teratogenic and do not produce direct toxicity on the embryo/fetus, they do have the potential to modify the normal bacterial flora of the mother’s genital and gastrointestinal tract. The consequences of this may be the reduction in penicillin-sensitive bacteria and an increase in penicillin-resistant organisms. These resistant bacteria (under certain circumstances) can be transferred to the newborn at the time of delivery resulting in severe, life-threatening infections in the neonatal period.

B. Cephalosporins (B)

There are 24 cephalosporins available in the United States. These antibiotics are sub-classified into three categories: First Generation (cefadroxil, cefazolin, cephalaxin, cephradin, cephadine); Second Generation (cefaclor, cefmetazole, cefonicid, cefotetan, cefoxitin, cefprozil); and Third Generation (ceftriaxone, cefditoren, cefepime, cefixime, cefoperazone, cefotaxime, ceftazidime, cefixime, ceftizoxime). Similar to the penicillins, the cephalosporin antibiotics are considered safe to use during human pregnancy and lactation. All of these agents are expected to cross the placenta to the embryo or fetus and all are probably excreted into breast milk. Reproduction studies in animals (mice, rats, and rabbits) have found no evidence of impaired fertility or fetal harm with any of the cephalosporin antibiotics. Cephalosporins have been used during all stages of gestation. No association with human congenital malformations has been found in these reports. As with penicillins, small amounts of cephalosporins are excreted into human breast milk. Although adverse effects in nursing infants are rare, the same potential complications noted for penicillins (see above) may occur with cephalosporins.

C. Aminoglycosides (D)

Only the parenteral aminoglycosides (amikacin, gentamicin, kanamycin, netilmicin, streptomycin, and tobramycin) present a risk to the embryo or fetus. The oral aminoglycosides (kanamycin, neomycin, and paromomycin) are poorly absorbed into the systemic circulation. Following parenteral administration, all aminoglycosides cross the human placenta. Except for kanamycin and streptomycin, which have not been tested, the aminoglycosides are not animal teratogens, but dose-related renal toxicity has been observed. Similarly, the use of these antibiotics during human pregnancy has not been associated with congenital malformations. However, eighth cranial nerve injury (ototoxicity – nerve injury to the ear) has been reported with both kanamycin and streptomycin and this risk could potentially occur with any aminoglycoside. High, prolonged dosing, such as that used in the kanamycin and streptomycin ototoxicity cases, increases the risk of this toxicity. The American College of Obstetricians and Gynecologists (ACOG) classifies kanamycin and streptomycin as contraindicated during pregnancy because of ototoxicity and nephrotoxicity. Small amounts of aminoglycosides are excreted into breast milk, but the risk to a nursing infant from this exposure is minimal because of the poor oral absorption. However, disruption of the normal bowel flora is a potential complication.

Gentamicin can be given as a divided or single daily dose. Although a single daily dose appears to be safe for the mother, the higher serum concentration that results will allow greater amounts to cross the placenta, and thus, higher gentamicin levels in the fetus. The effects of this increased exposure have not been studied but may result in a greater risk of fetal renal or eighth cranial nerve toxicity. When given near delivery, the mean newborn gentamicin serum levels after single and divided dosing were 1.94 and 0.98 mcg/ml, respectively. Therefore, if possible, divided dosing for gentamicin is preferred.
A drug interaction between gentamicin and magnesium sulfate has also been reported. Pregnant women with pre-eclampsia (elevated blood pressure caused by the pregnancy) or preterm labor may be treated with magnesium sulfate because of its neuromuscular relaxation effect. A mother received 32 grams of magnesium sulfate over 32 hours immediately before delivery. Her depressed newborn was started on gentamicin at 12 hours of age for suspected sepsis. After the second dose, rapid onset of respiratory arrest occurred that was attributed to a gentamicin potentiation of magnesium sulfate-induced neuromuscular weakness. Thus, the combination of gentamicin (or any aminoglycoside) and magnesium sulfate should be monitored closely.

D. Fluoroquinolones (C)

Ten fluoroquinolones are available in the United States (ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin, and trovafloxacin). Alatrofloxacin is a pro-drug of trovafloxacin that is given intravenously. Animal reproduction studies have not demonstrated a teratogenic effect, but embryo and fetal toxicity at systemic exposures close to those obtained in humans have been observed with these agents. The relatively low molecular weights are suggestive that all agents in this drug class cross the placenta to the embryo and fetus. However, only three of the antibiotics (ciprofloxacin, norfloxacin, and ofloxacin) have had placental transfer actually documented. Human pregnancy exposure has been reported for four fluoroquinolones (ciprofloxacin, enoxacin, norfloxacin, and ofloxacin). No information is available for the other agents. Although a number of birth defects have occurred in pregnancies exposed to the four antibiotics, the lack of a pattern among the anomalies suggests that there may be no association with the drugs. However, the number of pregnancy exposures is too small to exclude a causal relationship with some of the defects. ACOG classifies all fluoroquinolones as contraindicated during gestation because of the lack of information for most agents and the arthropathy (joint abnormalities) observed in immature animals when given a fluoroquinolone directly.

The use of fluoroquinolones during lactation is not recommended. The relatively low molecular weight of these antibiotics is suggestive that all are excreted into breast milk. Documentation of this, however, has only occurred with ciprofloxacin, ofloxacin, and sparfloxacin. In each, the maternal milk and plasma concentrations were approximately equivalent. Because of animal carcinogenicity (squamous cell carcinoma) in mice exposed to ultraviolet light during the chronic usage of some fluoroquinolones (e.g. lomefloxacin) and the potential for arthropathy and phototoxicity, women should not nurse when they are taking these antibiotics.

E. Macrolides (B or C - see text)

Of the five macrolides, erythromycin (except erythromycin estolate) has the most reported pregnancy data and is considered safe to use during gestation. Erythromycin estolate is contraindicated during pregnancy because of the risk of maternal hepatotoxicity. Less information is available for the other four macrolides (azithromycin, clarithromycin, dirithromycin, and troleandomycin). No evidence of teratogenicity or fetal toxicity has been observed in animals administered azithromycin or erythromycin. Doses nearly equivalent to the human dose of clarithromycin produced a low incidence of cardiovascular defects in one strain of rats and a variable incidence of cleft palate in another strain of mice. Dirithromycin did not cause congenital malformations in mice, rats, and rabbits, but fetal toxicity (growth retardation) was observed in mice. Animal studies have not been conducted with troleandomycin. Azithromycin and erythromycin have been shown to cross the human placenta, but there is no data for the other three agents. No reports associating a macrolide antibiotic with human congenital malformations have been published but the data is very limited for all of the macrolide drugs except erythromycin. Pregnancy risk factor ratings of B have been assigned to azithromycin and erythromycin, whereas the other three agents are rated C.

There is no reported experience with clarithromycin, dirithromycin, and troleandomycin during human lactation. Because both erythromycin and azithromycin are excreted into milk, however, the other three antibiotics should also be expected to produce measurable levels in milk. The milk to plasma ratio for erythromycin was 0.5 after both the 1.2 g/day and 2 g/day dosing. Accumulation in milk was observed with daily doses of azithromycin (1 g, then followed by 500 mg every day for 3 days): 0.64 mcg/ml, 1.3 mcg/ml, and 2.8 mcg/ml after the first, second, and fourth doses, respectively. The patient's infant was not allowed to nurse. No adverse effects have been reported in nursing infants whose mothers were being treated with these antibiotics, but disruption of the normal bowel flora is a potential complication (as seen with most antibiotics).

F. Tetracyclines (D)

The tetracycline class of antibiotics (tetracycline, demeclocycline, doxycycline, minocycline, and oxytetracycline) is generally considered to be contraindicated during gestation. Tetracyclines were used extensively in pregnancy in the 1950’s and 1960’s, but the documentation of maternal and fetal toxicity markedly reduced their use during gestation. The most serious maternal
toxicities appear to be acute fatty metamorphosis of the liver and renal failure.

The placental transfer of tetracycline was first reported in 1950. In 1961, following in utero exposure to tetracycline close to delivery, the first case of intense yellow-gold staining under fluorescent light of the fetal skeleton was reported, followed the next year by a report that described the staining of deciduous teeth. The stained teeth eventually changed to yellow-brown. The mechanism of bone and tooth enamel staining was related to the potent chelating ability of tetracycline. The antibiotic forms a complex with calcium orthophosphate that becomes incorporated into bones and teeth undergoing calcification. In teeth, the discoloration is permanent because remodeling and calcium exchange do not occur after calcification is complete. The deciduous teeth begin to calcify at approximately 5 to 6 months of gestation; therefore, the use of a tetracycline after this time will result in staining. The permanent teeth are not affected unless tetracyclines are administered after birth. In addition to discoloration, tetracycline can transiently inhibit bone growth of the fetus (after in utero exposure) and the premature infant (given tetracycline shortly after delivery). In both, however, bone growth goes through a catch-up phase after exposure ceases, so the long-term effect of growth inhibition is clinically insignificant.

Surveillance studies and other evaluations have reported congenital malformations after pregnancy exposure to tetracyclines, but a relationship between the drug exposures and the defects could not be established. In contrast, a 2000 population-based case-control study did find statistically significant associations between oxytetracycline treatment during the second month of pregnancy and neural-tube defects, cleft palate, and multiple congenital malformations (mainly neural tube defects and cardiovascular malformations).

Tetracycline and doxycycline are excreted into breast milk in low concentrations. Data for the other tetracyclines are lacking, but they are probably also excreted into milk. A theoretical risk exists for inhibition of bone growth and tooth staining in the nursing infant. However, at least for tetracycline, the risk is considered to be remote because the antibiotic chelates the calcium in the milk and thus, absorption is negligible. The American Academy of Pediatrics (AAP) classifies the maternal use of tetracycline as compatible with breast-feeding.

G. Miscellaneous Antibiotics

Aztreonam (B)

Aztreonam is a monocyclic, beta-lactam antibiotic. No evidence of teratogenicity or embryo/fetal toxicity was observed in animal reproduction tests. The antibiotic crosses the human placenta. Because there are no reports describing its use in pregnancy, the safest course is to avoid the antibiotic during the first trimester. Very low concentrations of aztreonam have been detected in breast milk after a single 1-gram parenteral dose, but infants were not allowed to nurse. The low levels were attributed to the acidic nature of the agent and its low lipid solubility.

Chloramphenicol (C)

This antibiotic has not undergone animal reproductive tests, but the limited human pregnancy experience is not suggestive of embryo or fetal risk. As with most antibiotics, chloramphenicol readily crosses the human placenta. Because there are no reports describing its use in pregnancy, the safest course is to avoid the antibiotic during the first trimester. Very low concentrations of aztreonam have been detected in breast milk after a single 1-gram parenteral dose, but infants were not allowed to nurse. The low levels were attributed to the acidic nature of the agent and its low lipid solubility.

The antibiotic is excreted into breast milk. The AAP classifies chloramphenicol as an agent whose effect on a nursing infant may be of concern because of the potential for idiosyncratic bone marrow suppression. Disruption of the normal newborn bowel flora is another potential complication.

References or Suggested Reading:

7. Towers CV, Briggs GG. Antepartum use of antibiotics and early-onset neonatal sepsis - the next four years. (submitted for publication, 2002).

About the Author(s)

Gerald G. Briggs is a Pharmacist Clinical Specialist in the Perinatal Center of Women’s Hospital, Long Beach Memorial Medical Center in Long Beach, California. He is also a Clinical Professor of Pharmacy for the University of California, San Francisco and an Adjunct Associate Clinical Professor of Pharmacy at the University of Southern California, Los Angeles.

He is the primary author of the textbook entitled Drugs in Pregnancy and Lactation, currently in its 6th Edition, copyright 2001, Lippincott, Williams, and Wilkins, Philadelphia, Pennsylvania. He also has several publications in peer-review medical journals and has lectured at many institutions across the United States and Canada regarding the use of drugs in pregnancy and lactation.