Objectives

1. Describe the potential concerns for using clindamycin, imipenem-cilastatin, meropenem, metronidazole, spectinomycin, and vancomycin during pregnancy or lactation.
2. Discuss the potential concerns of using sulfonamide drugs, nitrofurantoin, or trimethoprim during pregnancy or lactation.
3. Describe the potential concerns of using certain amebicide drugs and anti-malarial agents during pregnancy or lactation.

Article

Anti-infective Drug Use in Obstetrics – Part II

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3. Describe the potential concerns of using certain amebicide drugs and anti-malarial agents during pregnancy or lactation.

This article is a continuation of Part I. Again, for each drug that is discussed, the pregnancy risk factor category (as defined by the Food and Drug Administration) is shown in parentheses. To allow for easy reference as these drugs are discussed the categories are as follows:

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 stated in Part I, the majority of drugs are classified as category C because of the overall lack of studies in pregnant women.

I. Antibiotics

G. Miscellaneous Antibiotics Continued from Part I:
Clindamycin (B)

Clindamycin is used frequently in pregnancy, especially in the latter half of gestation for treating potential anaerobic infections. The antibiotic is not an animal teratogen and there are no reports of human congenital malformations attributable to its usage. Clindamycin crosses the human placenta, but this has only been studied near delivery. Clindamycin is excreted into breast milk. In one study, two grossly bloody stools were observed in a nursing infant whose mother was treated with clindamycin and gentamicin. The condition resolved when breast-feeding was stopped. Other potential complications are similar to those of the penicillins (discussed in Part I).

Imipenem-Cilastatin (C)

Imipenem is a carbapenem antibiotic, one of two available in the United States. It is combined in a 1:1 ratio with cilastatin sodium, a reversible inhibitor of the enzyme dehydropeptidase I (which is found in the proximal renal tubular cells of the kidney). Dehydropeptidase I will inactivate imipenem; therefore, the inhibition of this enzyme will result in higher urinary concentrations of imipenem. Animal reproduction tests with imipenem-cilastatin have shown no evidence of teratogenicity, but embryonic loss (spontaneous abortion) was observed in pregnant monkeys given doses about 3 times the maximum recommended human dose. Both imipenem and cilastatin cross the human placenta with measurable concentrations in fetal blood and the amniotic fluid. Although the reported pregnancy experience with the antibiotic is limited (no experience in the first trimester), the combination is considered safe in the second half of gestation. Similarly, there is no experience during breast-feeding, but small amounts of the antibiotic can be found in milk. The drug is probably safe during this period with a similar potential for complications as seen with the penicillins (discussed in Part I).

Meropenem (C)

Meropenem is the other carbapenem antibiotic that is available in the United States in the same class as imipenem. Reproduction tests in rats and monkeys found no evidence of impaired fertility or fetal harm, except for slight changes in fetal weight. No reports describing the use of meropenem in human pregnancy or during lactation have been published. Its relatively low molecular weight suggests that it crosses the placenta as well as being excreted into breast milk.

Metronidazole (B)

Reproduction studies in mice and rodents revealed no evidence of fetal harm. Of interest though, the antibiotic markedly increased the fetal toxicity and teratogenicity of alcohol in mice. Metronidazole crosses the human placenta throughout gestation with fetal concentrations approximately equal to those in the mother. A large number of studies have described the use of metronidazole during human pregnancy with most finding no association with birth defects. A possible association with oral clefts was found in two studies, but confirmation from other studies is lacking. Two meta-analyses of the published literature relating to first trimester exposure to metronidazole found no association with birth defects (odds ratio near 1 with confidence intervals overlapping 1). In addition, two large population-based studies found no evidence of an association between the antibiotic and major birth defects.

The antibiotic is frequently used in the second and third trimesters for the treatment of bacterial vaginosis. The American College of Obstetricians and Gynecologists (ACOG) considers the use of metronidazole for bacterial vaginosis or trichomoniasis in the first trimester to be contraindicated, but acceptable for use during the rest of pregnancy. The main concern with the use of metronidazole during gestation relates to the mutagenicity observed in bacteria and the carcinogenicity seen in rodents. Neither of these potential adverse effects, however, has been demonstrated in humans. A 1998 retrospective cohort study involving 328,846 children in Tennessee under the age of 5 years investigated the relationship between childhood cancer and in utero exposure to metronidazole (8.1% of the cohort). No statistically significant associations were found for all cancers, leukemia, neuroblastoma, or other cancers. Although this study had several limitations (relatively small number of subjects exposed to the drug, rarity of childhood cancer, young age of subjects), it is the largest such study to date.

Metronidazole is excreted into breast milk with milk to plasma ratios of about 1. Because of the mutagenicity and carcinogenicity noted above, the use of this antibiotic during breast-feeding is controversial. If a 2-gram oral dose is used for trichomoniasis, it is recommended that breast-feeding be held for 12 to 24 hours to allow excretion of the drug (peak milk levels after a 2-gram dose are in the 50-60 mcg/ml range). No adverse effects in nursing infants attributable to metronidazole have been reported with the possible exception of a single case of diarrhea and secondary lactose intolerance. The American Academy of Pediatrics (AAP) recommends using the drug with caution during lactation.
Spectinomycin (C)

No pregnancy data, human or animal, are available for this antibiotic that is used for the treatment of Neisseria gonorrhea. Consequently, the safest course is to avoid this agent during the first trimester. It is not known if the agent crosses the human placenta. Because the antibiotic is poorly absorbed after oral administration, its use during lactation probably presents a negligible risk to a nursing infant.

Vancomycin (B)

Vancomycin is occasionally indicated in pregnancy for the treatment of Gram-positive bacteria resistant to less toxic anti-infective agents. Animal reproduction studies have revealed no evidence of fetal harm. Vancomycin crosses the human placenta and produces measurable levels in fetal blood and the amniotic fluid. No major birth defects, ototoxicity, or renal impairment have been reported after the use of vancomycin during human pregnancy, but the number of exposures is limited. Vancomycin is excreted into breast milk with a milk to plasma ratio of approximately 1. Systemic levels in the nursing infant would not be expected because of the poor oral absorption. The potential complications of exposure to vancomycin in milk are the same as those identified for the penicillins (discussed in Part I).

II. Other Bacterial Anti-infective Drugs

A. Sulfonamides (C/D)

Although they do not appear to pose a significant teratogenic risk, all of the agents in this class of anti-infective drugs share the potential of causing toxicity in the fetus and in the newborn, if given to the mother near delivery. Teratogenicity (mainly cleft palate) has been observed in rats with sulfamethoxazole at doses approximately 10 times the maximum recommended human dose on a weight basis. Most other sulfonamides have not undergone animal reproduction testing. Sulfonamides readily cross the human placenta resulting in fetal levels that are up to 90% of the mother's concentration. Equilibrium between the maternal and fetal compartments is usually established within 2 to 3 hours. Sulfonamides are categorized as pregnancy risk factor C (but considered D if used near term).

Hemolytic anemia and death have been reported in a fetus with glucose-6-phosphate dehydrogenase (G6PD) deficiency, whose mother was treated with sulfisoxazole in the third trimester. Hemolytic anemia has also been reported in newborns exposed in utero to other sulfonamides. In addition to hemolytic anemia, two other toxicities in the newborn, hyperbilirubinemia and, theoretically, kernicterus, may also occur when these agents are given near term. Sulfonamides compete with bilirubin for binding to plasma albumin, a well-known effect when administered directly to neonates. Before birth, free bilirubin is cleared from the fetus by the placental circulation, but after birth, this mechanism is no longer available. Therefore, when given to the mother within a few days of delivery, severe jaundice (hyperbilirubinemia) in the newborn is a possible consequence. Kernicterus, resulting from the passage of unbound bilirubin across the blood-brain barrier, is also a potential complication but has not been reported following in utero exposure.

Surveillance studies, other retrospective reports, and case histories have found some associations between sulfonamides and congenital malformations, but the relationships require confirmation from controlled studies before they can be considered anything other than hypotheses. However, the current use of sulfonamides as single agents during gestation is relatively uncommon, so confirming studies are unlikely. Therefore, the safest course is to avoid sulfonamides during the first trimester, because of the possible risk of congenital anomalies, and close to term, because of the risk of toxicity.

Low concentrations of sulfonamides are excreted into breast milk. The maternal use of these relatively short-acting agents (sulfadiazine, sulfamethizole, sulfamethoxazole, and sulfisoxazole) does not appear to pose a risk for a healthy, full-term infant. The AAP classifies only one of these agents (sulfisoxazole) as compatible with breast-feeding, but this probably reflects the lack of data available for the other agents rather than concerns of safety. Exposure to sulfonamides in breast milk is contraindicated for ill, stressed, or premature infants and in infants with hyperbilirubinemia or G6PD-deficiency.

B. Nitrofurantoin (B)

Nitrofurantoin is commonly used in pregnancy for the treatment and prophylaxis of urinary tract infections. No evidence of impaired fertility, teratogenicity, or toxicity were observed in mice and rats at doses close to those used in humans. A low
incidence of congenital malformations and growth retardation, however, were produced in mice at higher doses. Nitrofurantoin was carcinogenic (fetal lung papillary adenomas) in mice, but the relationship of this to potential human cancer is unknown. Although it has not been studied, nitrofurantoin probably crosses the placenta, especially near term.

A large body of data on human pregnancy experience has accumulated since nitrofurantoin became available. No evidence of an association with congenital malformations has been discovered in these studies. A 1995 meta-analysis of four studies that met the inclusion criteria of the investigators failed to find a significant correlation between nitrofurantoin use in early gestation and congenital defects (pooled odds ratio 1.29, 95% confidence interval 0.25-6.57).

Although not teratogenic, hemolytic anemia is a potential complication in subjects who are G6PD deficient or whose red blood cells are deficient in reduced glutathione. Newborns have immature erythrocyte enzyme systems (glutathione instability). Therefore, pregnant women should avoid nitrofurantoin near term because of the risk of hemolytic anemia. A number of cases of this rare toxicity have been reported.

Nitrofurantoin is excreted into human breast milk, possibly by an unknown active transport mechanism, producing a milk to plasma ratio of 6.21 (or 6 times greater than the mother’s plasma concentration). The AAP considers the anti-infective to be compatible with breast-feeding, but notes that hemolytic anemia is a potential complication in nursing infants with G6PD deficiency. In spite of the high milk concentrations suggested by the above study and the AAP precautions, no reports have been located describing toxicity in nursing infants exposed to nitrofurantoin in milk. Thus, toxicity in the nursing infant may occur, but it appears to be rare.

C. Trimethoprim (C/D)

Trimethoprim is used during gestation for the treatment of urinary tract infections either alone or in combination with sulfamethoxazole. It is a folate antagonist that acts by binding to and inhibiting the enzyme dihydrofolate reductase, thereby blocking the formation of tetrahydrofolic acid from dihydrofolic acid. The anti-infective is teratogenic and/or embryo toxic in rats and rabbits. Trimethoprim readily crosses the human placenta producing similar levels in the fetal and maternal serum and in amniotic fluid. A pregnancy risk factor of C has been assigned to trimethoprim, but it should be rated a D in the first trimester because of its anti-folate action. A low folic acid level in the mother at the time of conception and in the first few weeks after conception has been suggested as a possible cause for the development of neural tube defects. A number of reports have described congenital malformations following exposure to trimethoprim in the first trimester, including two reports published in 2000. The malformations observed were oral clefts, spinal anomalies, urinary tract abnormalities, and cardiovascular defects, and these were attributed to its action as a folate antagonist. Low levels of trimethoprim are excreted into breast milk. The risk to a nursing infant from this exposure is thought to be negligible. The AAP classifies trimethoprim as compatible with breast-feeding.

III. Amebicide Drugs

A. Chloroquine (C)

(see the Anti-malarial section below)

B. Iodoquinol (C)

This agent is used for intestinal amebiasis and is poorly absorbed from the gastrointestinal tract. It contains 64% organically bound iodine. No evidence of human teratogenicity has been reported when iodoquinol was used during any stage of gestation. One surveillance study reported a possible association with congenital dislocation of the hip, but this finding is not interpretable without confirming evidence. Use of the drug during lactation has not been reported. The poor oral bioavailability will limit the amount of drug available for excretion into breast milk. In non-pregnant adults, elevations of protein-bound serum iodine levels may persist for up to 6 months after treatment. Because iodine is concentrated in breast milk, serum and urinary iodine levels may be elevated in a nursing infant.

C. Metronidazole (B)

(see Miscellaneous Antibiotic section above)
D. Paromomycin (C)

Paromomycin is an oral aminoglycoside antibiotic used for intestinal amebiasis. Oral absorption of the agent is essentially non-existent. Published human pregnancy experience is very limited, but because of its poor absorption it should have no effect on the embryo or fetus. In addition to its lack of systemic bioavailability, it also has poor lipid solubility. Both of these characteristics suggest that it is not excreted into breast milk.

IV. Anti-malarial Agents

A. Atovaquone/Proguanil (C)

Atovaquone/proguanil is a fixed dose combination drug used for the treatment and prophylaxis of malaria. Neither agent, either alone or in combination, has caused fetal harm in pregnant rats and rabbits at doses less than those producing maternal toxicity. Both agents probably cross the human placenta, but this has not been studied. Studies of the combination drug in human pregnancy have apparently not been published. A number of reports, however, have described the use of proguanil during human gestation. Proguanil is considered by some to be the least toxic prophylactic anti-malarial agent available. Because the agent is a folate antagonist (inhibits parasitic dihydrofolate reductase), women taking the drug either alone or in combination should be supplemented with folic acid. Supplementation with folic acid has no effect on its anti-malarial properties. However, this folate antagonist action raises similar concerns for causing neural tube defects as discussed above under trimethoprim (though no reports have been published on this topic). Thus, because of this theoretical concern, the drug should be used with caution in the first trimester. Small amounts of proguanil are excreted into human breast milk. Atovaquone has been found in animal milk, but has not been studied in humans. Studies are needed to determine the safety of these agents for the nursing infant.

B. Chloroquine (C)

Chloroquine is a drug of choice for the prophylaxis and treatment of sensitive malarial species during pregnancy. At high doses, it is embryo toxic and teratogenic (producing microphthalmia and anophthalmia – small or absent eyes) in rats. In fetal mice and monkeys, chloroquine accumulates for long periods in the melanin structures of the eyes and inner ears. In humans, fetal concentrations of the drug are approximately equal to maternal levels. Chloroquine should not be withheld during pregnancy because the risk of complications from malarial infection in pregnancy is increased, which may have severe consequences for the fetus (abortion, stillbirth, prematurity, low birth weight, fetal distress, and congenital malaria). Chloroquine is excreted into human breast milk. This exposure has not been reported to cause adverse effects in the nursing infant, but the amount is too low for protection against malaria. The AAP classifies chloroquine as compatible with breast-feeding.

C. Dapsone (C)

(see Leprostatic Agents in Part III)

D. Halofantrine (C)

There are no reports on halofantrine use in human pregnancy. The agent is embryo toxic and teratogenic (skeletal malformations) in rabbits and is embryo toxic in rats. Because of this toxicity and the lack of human reports, halofantrine should be avoided in human pregnancy. Fetal exposure to the drug after crossing the placenta should be expected.

E. Hydroxychloroquine (C)

Animal reproduction studies have not been conducted with hydroxychloroquine. However, chloroquine, a closely related agent, has undergone such tests (see above). Limited use in human pregnancy suggests that hydroxychloroquine does not pose a significant risk to the fetus. The Centers for Disease Control and Prevention (CDC) states that the drug may be used during pregnancy for anti-malarial prophylaxis because the prophylactic dose (400 mg/week) has not been shown to cause fetal harm. Similarly, prophylactic use during breast-feeding does not appear to represent a risk to the nursing infant. Continuous, daily dosing, however, may result in accumulation of a toxic amount in the nursing infant and should be avoided.

F. Mefloquine (C)
A number of studies have reported the use of mefloquine during human pregnancy. No increase in the incidence of adverse outcomes has been found. The use of mefloquine for malaria chemoprophylaxis, however, is controversial because of the potential for drug-induced fetal toxicity. Consequently, first trimester use of mefloquine should be reserved for those regions where chloroquine-resistant malaria is present. Use after the first trimester is acceptable in any geographic region. The agent has shown a dose-related toxicity and teratogenicity in mice, rats, and rabbits. Although it has not been studied, the molecular weight of mefloquine is low enough that it probably crosses the placenta. Mefloquine is excreted into human breast milk. The long-term effects of this exposure are unknown.

G. Primaquine (C)

Animal reproduction studies have not been conducted with primaquine. Similarly, no human reports describing the use of this agent in human pregnancy or during lactation have been published. The molecular weight of primaquine is low enough that passage across the placenta is expected. Primaquine may cause hemolytic anemia in subjects with glucose-6-phosphate dehydrogenase deficiency. If possible, use of the drug should be withheld until pregnancy is completed.

H. Pyrimethamine (C)

Pyrimethamine, a folic acid antagonist (inhibits parasitic dihydrofolate reductase), is teratogenic in mice, rats, hamsters, and pigs. The relatively low molecular weight suggests that transfer across the placenta to the fetus readily occurs. This folate antagonist action raises similar concerns for causing neural tube defects as discussed above under trimethoprim (though no reports have been published on this topic). Thus, because of this theoretical concern, the drug should be used with caution in the first trimester. Most human pregnancy reports have not described embryo/fetal toxicity or teratogenicity. However, one case of severe congenital malformations (abdominal and thoracic wall defects with exteriorization of the heart, lungs, and most of the abdominal viscera; absent left arm) has been reported. Folic acid supplementation (5 mg/day) is recommended, especially during the first trimester, to prevent folic acid deficiency. Pyrimethamine is excreted into human breast milk in quantities sufficient to treat and prevent malaria in a nursing infant. The AAP classifies pyrimethamine as compatible with breast-feeding.

References or Suggested Reading:


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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.