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## **Antibiotics and Pregnancy**

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Antimicrobial drugs (antibiotics) are frequently administered to pregnant women due to the common occurrence of bacterial infections during the perinatal period. The use of antibiotics during pregnancy raises great concern about the possibility of adverse effects that these drugs may have on the fetus. This RISKIINEWSLETTER will focus on some of the more commonly prescribed antibiotics and their effects during pregnancy.

### **AMINOGLYCOSIDES**

#### **STREPTOMYCIN**

The frequency of congenital anomalies was not increased among children of 135 women who took streptomycin in the first trimester of pregnancy or among children of 335 women who took the drug anytime during pregnancy (Heinonen et al., 1977). However, congenital deafness was not included among the anomalies studied in these investigations. Two case reports which reviewed the association of streptomycin with congenital nerve deafness found that a deaf infant was born to a mother who was treated with 30 gm of streptomycin during the 8th month (Leroux, 1950), and that two congenitally deaf children were born after their mothers took 1 gm/day of streptomycin during the last trimester and during the 6th-14th weeks, respectively (Robinson & Cambon, 1964). Additionally, a study of 13 children exposed to the drug antenatally showed abnormal audiograms in 4 and abnormal caloric testing in 6 of the children. In contrast to these reports, a larger study consisting of 33 children found that only two had minor hearing loss detectable by testing. Furthermore, Varpella et al. (1969) found normal hearing among 50 children who were exposed in utero to dihydrostreptomycin and streptomycin. These latter studies suggest that streptomycin therapy during pregnancy may be associated with ototoxicity in the offspring, however, this effect occurs infrequently, if at all (Reprotox, 1991).

Streptomycin does reach breast milk in small amounts. However, the level of the drug in the milk is low and there is poor gastrointestinal absorption of the compound. Therefore, it is unlikely that streptomycin toxicity would result in a nursing infant.

#### **GENTAMICIN**

No epidemiological studies of congenital anomalies have been conducted among infants whose mothers were treated with gentamicin during pregnancy. However, nephrotoxicity has been observed in many patients receiving gentamicin, which raises the concern of whether fetal kidney damage may occur with maternal treatment. While human fetal nephropathy after maternal gentamicin treatment has not been documented, there have been instances of severe neonatal renal damage after therapy with this

drug (Chan, 1985). This may be a particular problem in premature infants and the ability to eliminate gentamicin may be dependent on postconception age and not on age from birth (Miranda, et al., 1985; Kasik et al., 1985). Furthermore, because gentamicin is an aminoglycoside, maternal treatment with this drug may be associated with an increased risk for fetal auditory nerve damage, similar to the possible risks associated with streptomycin exposure. It is important to note however, that while these theoretical risks cannot be excluded, to date no studies have demonstrated such findings with gentamicin treatment in humans.

Elevated gentamicin serum levels of 0.49ug/dL have been detected in nursing infants 1 hour after gentamicin administration (Celiloglu et al., 1994). Although these levels alone would not be expected to produce toxicity, it is undetermined whether accumulation from chronic exposure would pose a problem to the infant. It has been suggested that this issue may depend on gestational age and renal function of the infant (Reprotox, 1994).

## NEOMYCIN

No increased frequency of malformations was found upon investigation of 30 pregnancies exposed to neomycin during the first trimester (Heinonen et al., 1977). In addition, a retrospective study on human pregnancy found no evidence of adverse effects attributable to this agent (Heinonen et al., 1987). While neomycin is similar to related antibiotics such as streptomycin and gentamicin in that ototoxicity is a clearly defined side-effect, no reports have been noted that demonstrate neomycin ototoxicity in infants who were exposed in utero.

Currently, there is no data available on the possible effects of neomycin on a nursing infant.

## POLYMYXINS

### Polymyxin B

No epidemiological studies of infants who were exposed in utero to Polymyxin B have been reported. One retrospective study found no adverse effects associated with the use of Polymyxin B during pregnancy (Heinonen et al., 1977). However, these data are not sufficient to estimate the safety of using this compound during pregnancy, and therefore this drug has an undetermined risk for use during pregnancy.

Currently, there is no data available on the possible effects of polymyxin B on a nursing infant.

## TETRACYCLINES

Administration, of tetracyclines including doxycycline, tetracycline, and minocycline during the second or third trimester of pregnancy can cause staining of the teeth of the childhood and up to a 40% depression of bone growth (especially of the fibula in preterm pregnancies) (Rendle-Short, 1962; Kline et al., 1964; Kutscher et al., 1966). However, following in utero exposures to tetracyclines, rapid compensatory bone growth has been observed once antibiotic treatment is terminated (Cohlan et al., 1961).

### DOXYCYCLINE

No epidemiological studies have been reported of infants exposed in utero to doxycycline. Therefore, while a small risk cannot be excluded, there is no indication that there is an increased risk of malformations in the children of women treated with this agent during pregnancy. Although data on the specific safety of the use of doxycycline during pregnancy is limited, it is assumed that the risks of the dental staining and depression of bone growth that pertain to tetracyclines in general also pertain to doxycycline use during the second and third trimesters.

Doxycycline is excreted into breast milk. A theoretical possibility exists that a nursing infant could

experience dental staining or inhibition of bone growth from breast milk containing doxycycline. However, it is not known whether the amount of antibiotic in the breast milk is sufficient to cause these effects. Furthermore, unlike other tetracyclines, the oral absorption of doxycycline is not substantially inhibited by foods or milk. As a result, increased neonatal toxicity might be possible from this agent in breast milk. Exposure to low levels of doxycycline may cause modifications in bowel flora and interfere with the interpretation of culture results if a fever work-up is necessary for a nursing infant (Reprotox, 1994). The WHO Working Group in Drugs and Human Lactation concluded that the use of this agent for a short (one week) period during breastfeeding was probably safe (WHO Working Group, Bennet, 1988).

## TETRACYCLINE

The frequencies of congenital anomalies was not increased over the expected rate among children of 341 women treated with tetracycline during the first trimester of pregnancy (Heinonen et al., 1977). Similarly, two cohort studies examined 274 infants of women who took tetracycline during the first trimester, and found there was no increased incidence of malformations (Jick et al., 1981; Aselton et al., 1985). Additional findings showed the frequency of congenital anomalies was no greater among 1,336 children exposed to tetracycline in utero anytime during pregnancy (Teris, 1991). Only one case-control study which observed 46 infants found an association with maternal use of tetracycline during pregnancy and transposition of the great arteries (Zierler & Rothman, 1985).

Generally, only the deciduous teeth are involved in the staining. However, if administration of the drug occurs close to term, the crowns of the permanent teeth may be stained. This staining appears to be of cosmetic significance and does not affect development of the enamel or increase the likelihood of caries (Genot et al., 1970; Rebich et al., 1985). Similar staining has been observed in the bones and lenses of fetuses who were exposed to tetracycline in utero (Cohlan et al., 1963; Totterman & Saxen, 1969; Krejci & Brettschneider, 1983; Glorieux et al., 1991). The association between the use of tetracyclines in pregnancy and decreased rate of bone growth has been observed with tetracycline use in premature infants (Cohlan et al., 1963). Although it has been reported that four infants with congenital or infantile cataracts were exposed to tetracycline during the first trimester (Farrar & Mackie, 1964; Harley et al., 1964), these findings are not the results of controlled studies; therefore no definite conclusion can be drawn regarding a possible association between tetracycline use in pregnancy and development of cataracts.

Tetracycline is excreted into breast milk in low concentrations. The American Academy of Pediatrics considers tetracycline compatible with breastfeeding (Committee on Drugs, American Academy of Pediatrics, 1989), and the WHO Working Group on Human Lactation noted that the risk to the nursing infant appears low when the antibiotic is used for 7-10 days.

## 5-NITROIMIDAZOLE

### METRONIDAZOLE

Of twenty-six reports that examined a total of 1,323 pregnant women, only four (Morgan, 1978; Peterson et al., 1966; Greenberg, 1985; Cantu, 1982) found evidence of congenital anomalies in infants exposed to metronidazole during the first trimester. Among these four studies, no consistent pattern of congenital malformations was found. Furthermore, the study conducted by Peterson et al., (1966) found congenital malformations including coronal hypospadias, syndactyly, calcaneous valgus, hydrocele, and pyloric stenosis, which may not necessarily be related to the first trimester. Given the limited information available, and no conclusive human studies, there is probably no increased risk of birth defects due to exposure to metronidazole during pregnancy.

Relatively large amounts of metronidazole are excreted into breast milk. As a result, the WHO Working

Group on Drugs and Human Lactation suggest that breastfeeding be discontinued by mothers using repeated doses of this drug.

## PENICILLINS

Penicillins are a widely used group of antibiotics which include ampicillin, amoxicillin, azlocillin, mezlocillin, penicillin G, penicillin V, piperacillin, ticarcillin, etc. Although penicillins accumulate in amniotic fluid in large amounts during maternal ingestion, no adverse fetal effects have been associated with this group of compounds (Hutter, 1985). It must be noted that all penicillins may produce anaphylaxis during pregnancy or immediately after delivery. If anaphylaxis is severe and uncontrolled, it could result in compromising placental circulation, and cause fetal damage or death (Reprotox, 1993). However, in general, the penicillins have not been shown to be teratogenic in humans, and there have been no recognized adverse effects due to exposure of these drugs.

Penicillins are excreted into breast milk in small amounts, yet this exposure is unlikely to have detectable effects in the newborn. However, it is possible that nursing infants exposed to these antibiotics may experience alterations in bowel function. Furthermore, exposure to penicillins through breastfeeding may be sufficient to cause allergic sensitization in the infant.

## CEPHALOSPORINS

Cephalosporins are the most widely used class of antibiotics. Based on their spectrum of activity against gram-negative bacteria, these antibiotics are classified into three generations. Many of the first and second generation cephalosporins have been studied extensively in pregnant patients. Although there is limited data available at this time, it is thought that most of the first and second generation cephalosporins are not associated with any known or suspected teratogenic effects and are assumed safe for use during pregnancy (Landers et al., 1983). The third generation cephalosporins, however, have not been used extensively during pregnancy; therefore, there is little information known about their effects.

## CEPHALOTHIN

Cephalothin is a first-generation cephalosporin antibiotic. This compound does cross the placenta, and 60-70% is bound to plasma proteins once entering the fetal circulatory system (Reprotox, 1994). As a result, cephalothin may potentially increase the risk of neonatal kernicterus at low levels of bilirubin (Bernard et al., 1977). Nevertheless, cephalothin is not currently associated with any known teratogenic effects and, according to Landers et al. (1983), it is assumed safe for use during pregnancy.

## CEPHALEXIN

No epidemiological studies of congenital anomalies among infants exposed to cephalixin in utero have been reported. Having reviewed several reports of women taking this drug during pregnancy, Briggs et al. (1986) found no increase in defects or toxicity of newborns who were exposed to cephalixin in utero. The amount of data supporting these findings, however, is quite limited.

## CEFAZOLIN

No epidemiological studies of congenital anomalies have been conducted on infants who were exposed to cefazolin in utero. Among offspring of rats who were given 2-4 times the human therapeutic dose of cefazolin during pregnancy, fetal growth retardation was observed (Hasegawa & Yoshida, 1980; Hasegawa et al., 1987). However, it is important to note that the relationship between animal study findings and human risks is not known.

Small amounts of all three of these cephalosporins pass into breast milk. It has been suggested that this might cause modification of bowel flora for the nursing infant, or interfere with the interpretation of

culture results if a fever work-up is required (Briggs et al., 1986).

## CEFUROXIME

Cefuroxime is known to cross the placenta during the third trimester of pregnancy. There have been no reports of adverse effects associated with the clinical use of this drug, although controlled studies on possible human reproduction are not available.

One manufacturer of cefuroxime states that this compound does reach breast milk, however, there are no reports concerning the possible toxicity of this agent for the nursing infant.

## MACROLIDES

### ERYTHROMYCIN

No increase in the frequency of congenital anomalies was observed among children of 79 women treated with erythromycin during the first 4 months of pregnancy, or among children of 230 women treated anytime in pregnancy (Heinonen et al., 1977). Similarly, no increased incidence of congenital anomalies was found among two groups studied, including 100-200 and 260 women, respectively, who were treated with the drug during the first trimester of pregnancy (Jick et al., 1981; Aselton et al., 1985). In addition, infants of 398 women treated with erythromycin during the second or third trimester showed no increased frequency of congenital anomalies (McCormack et al., 1987). The estolate ester of erythromycin has been associated with a relatively high incidence of subclinical, reversible hepatotoxicity when used during pregnancy (McCormack et al., 1977).

Some investigations which looked at the treatment of chlamydia and mycoplasma infections with erythromycin during pregnancy, found an association with improved gestational outcomes such as increased birth weight and reduced morbidity (Schachter et al., 1986; McGregor et al., 1986; McCormack et al., 1987; FitzSimmons et al., 1986; Cohen, 1990; Ryan et al., 1990). Specifically, one study found that women with a history of spontaneous abortion who were mycoplasma positive in the urogenital tract experienced significant decreases in their pregnancy loss rate after treatment with erythromycin (Quinn et al., 1983). However, a large multicenter study did not find this drug to have significant effects on women who had infections with *Ureaplasma urealyticum* (Eschenbach et al., 1991). Other investigators have found that treatment with erythromycin has resulted in significant decrease of premature rupture of membranes as well as prolonging pregnancy and improving neonatal outcome (McGregor et al., 1990; McGregor, 1991).

This antibiotic is excreted into the breast milk in small amounts. The American Academy of Pediatrics classified erythromycin as compatible with breastfeeding (Committee on Drugs, American Academy of Pediatrics, 1989).

### CLARITHROMYCIN

Clarithromycin is structurally similar to erythromycin. Currently, there have been no epidemiological studies of congenital anomalies conducted on infants who were exposed to this antibiotic in utero. Animal studies have reported adverse effects such as cardiovascular abnormalities, cleft palate, fetal growth retardation, and embryonic loss. Although these findings occurred when the animal was given doses much higher than the typical therapeutic dose for humans, these reports stand in sharp contrast to the minimal effects reported in animal studies in which erythromycin was given during pregnancy. Therefore, these data suggest that clarithromycin may be more toxic during development than its parent compound, erythromycin (Reprotox, 1994). It is important to note that the precise relationship between animal study findings and human risks is unknown.

Clarithromycin is excreted into human breast milk in considerable concentrations although the safety of nursing while using this antibiotic has not been investigated.

## **SUMMARY**

Although antibiotics are commonly prescribed to pregnant women, details relating to the effects of many of these drugs remains poorly understood. If an antibiotic must be prescribed , it is important to be aware of the effects such drugs can have on pregnancies, in order to prescribe the most suitable treatment with the least risk to the pregnancy.