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Antibiotics in Pregnancy: Toxicity and Teratogenicity

The primary concern in the use of drugs during pregnancy is the adverse effects that these chemicals may produce on the embryo and fetus. Following the thalidomide disaster, the awareness of the risk of drug intake during pregnancy has generally increased. However, in a prospective study (1) with pregnant women, all of the subjects had taken at least two drugs and 93% of them had taken more than five drugs. About 37% of the drugs used were antibiotics. In another study (2), 28% to 38% of the pregnant mothers had taken antibiotics.

Considering carefully the advantages and the possible damage related to drug use, antibiotics in particular well illustrate the situation of the prescriber, who is often sailing between Scylla and Charybdis. First we should remember the frequency of anomalies of the fetus. The frequency of idiopathic or spontaneous malformations of the fetus amounts to 2%. About 30% of all observed congenital malformations are related to chromosomal anomalies etc., and the frequency of other (often unknown) related factors, e.g. drugs, is as high as about 60% (3). Among the antibiotics, only a few classes of compounds have been convincingly shown to be completely harmless when used during pregnancy. However, our knowledge of most antibiotics is limited, as can be seen from the warnings of antibiotic manufacturers not to administer that particular drug during pregnancy, especially in the first trimester. It is now evident that any substance present in the maternal blood should be able to cross the placenta to an extent which is dependent on drug metabolism or other factors such as concentration gradients, lipophilicity, molecular size and binding effects etc. However, as mentioned above, the currently available information on the pharmacokinetics of many antibiotics in the maternal-fetal unit is fragmentary.

Some of the frequently prescribed antibiotics will be distributed below into three groups according to their rational use during pregnancy. Antibiotics belonging to the first group, which should not be administered to pregnant women, are listed in Table 1.

In adults the main adverse reaction pattern of aminoglycosides consists of ototoxicity and kidney damage. The aminoglycosides cross the placenta (4) and their concentration in the amniotic fluid ranges from 30% to 60% of the average maternal concentration in blood. Severe intrauterine otological damage has been reported after the administration of aminoglycosides to mothers (5). Moreover, there is also a risk of nephrotoxicity in the fetus, although no proven cases have been published. Tumor-inducing effects due to aminoglycosides are unknown.

Table 1: Antibiotics not to be used by pregnant women.

Aminoglycosides
Gentamicin
Streptomycin
Tobramycin etc.
Antimycotics
Amphotericin B
5-flucytosine
Griseofulvin etc.
5-nitroimidazoles
Metronidazol etc.
Polymyxins
Colistin
Polymyxin
Tetracyclines
Doxycycline
Minocycline
Tetracycline etc.
Vancomycin

Most of the antimycotics exhibit a high potential for severe adverse reactions in adults, involving, for example, the nervous system, the blood, the liver and the kidney. This general toxicity has led to the recommendation that antimycotics should not be given during pregnancy. Depending on the nature of the antimycotic compound, animal studies have shown hepatomas, mutagenicity or teratogenic effects (6, 7). In humans, griseofulvin taken during pregnancy led to the observation of abortion and malformation (6).

The 5-nitroimidazoles are generally well tolerated. The warnings with respect to administration during pregnancy are the result of increased mutation rates found *in vitro* in bacteria (8). In some animal experiments tumor-inducing effects (malignant lymphoma, lung tumors, liver carcinoma and mammary tumors) could be demonstrated (9, 10). Evidence of fetal malformations in animals or in humans has not been reported.

The nature of the side-effects of polymyxins is in some ways similar to that of the aminoglycoside group, i. e. nephrotoxicity to acute renal failure and neurotoxicity, e. g. neuromuscular blockade and ataxia, dizziness, convulsions and circumoral paraesthesias. Because colistin and polymyxin B can cross the placenta, these rather toxic

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drugs, which act by destructing biological membranes, should not be used in pregnancy. Teratogenicity of the polymyxins has not been reported. Nowadays, the polymyxins can in most cases be replaced by other antibiotics of lower toxicity.

The concentration of tetracyclines in umbilical cord blood amounts to about 50% of the concentrations in the maternal blood (11). Corresponding to these concentrations, typical adverse effects of tetracyclines were also seen in the fetus following intrauterine exposure.

Tetracyclines given during the period of calcification of the teeth are deposited as a calcium complex in the mineralization zones and cause a greyish-brown or yellow discolouration of the teeth as well as hypoplasia and enamel defects (12–15). Similarly, tetracyclines demonstrate a deposition in growing bones (16) with possible disturbances of longitudinal growth (17). In tissue culture studies an inhibition of osteogenesis has been observed in the presence of tetracyclines (18). Furthermore, the occurrence of congenital limb malformations due to tetracyclines has been discussed (19). Severe adverse effects, such as lethal fatty liver degeneration, were reported in pregnant women undergoing tetracycline therapy (often after a high dosage) (20, 21). The danger of side-effects with respect to the mother is probably greatest during the last trimester of pregnancy.

The adverse reactions of vancomycin resemble those of the aminoglycosides. Dose-dependent ototoxicity with transient or permanent deafness and sometimes nephrotoxicity predominate. Although vancomycin transfer across the placenta has not been studied in detail, pregnant women, as a precaution, should not take vancomycin.

Antibiotics other than those listed in Table 1 may be carefully given but only at certain stages of pregnancy. Under therapy with chloramphenicol, thiamphenicol, pyrimethamine and rifampicin, cytotoxic and teratogenic effects cannot be excluded during the first trimester of pregnancy. One serious adverse effect of chloramphenicol, the well-known “gray syndrome” (22), has been seen not only when the antibiotic had been administered to pretermatures or full term babies, but also in newborns borne by women who had taken chloramphenicol during the final stage of pregnancy. Chloramphenicol penetrates well into the fetal circulation; the levels reach 30% to 80% of the concentrations in maternal blood.

Pyrimethamine, an antiprotozoal drug, inhibits the dehy-

drofolate reductase involved in the biosynthesis of folic acid. Animal studies have shown that pyrimethamine exhibits teratogenic potencies causing malformations and fetal death. In humans, the teratogeny is dubious.

Rifampicin therapy during pregnancy in humans is suggested to be related to intrauterine death, malformations of the urinary tract, hydrocephalus and anomalies of the auditory meatus (23).

The sulfonamides are also capable of penetrating the placenta. In animals, malformations could be experimentally produced by sulfonamides (24), but in man there is only little evidence to suggest teratogenic effects. Only a few retrospective studies suggest a slight association of sulfonamides with malformations (2, 25). Another side-effect of sulfonamides is caused by the competition of sulfonamides with bilirubin at common serum binding sites (26). Sulfonamides administered to newborns or to mothers in the third trimester of pregnancy can displace the unconjugated bilirubin from the plasma albumin. The liberated bilirubin may then enter the tissues and the brain and produce the so-called kernicterus (27, 28).

The last compound listed in Table 2, trimethoprim, distributes well across the placenta. The concentrations of trimethoprim in fetal blood may equal the concentrations in maternal blood. Like pyrimethamine, trimethoprim acts as a folic acid antagonist and may be related to congenital anomalies (29).

In contrast to the antibiotics listed above, which should be excluded from therapy during pregnancy or at certain stages of pregnancy, the antibiotics listed in Table 3 may be administered at any time. As a general principle, pregnant women should not take any drugs, but if an antibiotic must be prescribed, the doctor should choose one from this last table containing compounds which, to our present knowledge, have never been shown to cause harmful adverse effects.

Table 3: Antibiotics to be used at any time during pregnancy.

Penicillins
Ampicillin
Azlocillin
Isoxazolyl penicillins
Mezlocillin
Penicillin G
Penicillin V
Piperacillin
Ticarcillin etc.
Cephalosporins
Cefaclor
Cefamandole
Cefazolin
Cefotaxime
Cefuroxime
Latamoxef etc.
Erythromycin
Lincomycin

Table 2: Antibiotics to be used only at certain stages of pregnancy.

	Not administered	
	before 12th week	after 28th week
Chloramphenicol	(+)	+
Pyrimethamine	+	+
Rifampicin	+	
Sulfonamides	+	+
Trimethoprim	+	+

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