INFECTIONS, ANTIBIOTICS AND PREGNANCY

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REZUMAT

Femeile gravide prezintă deseori în timpul sarcinii infecții urinare, boli cu transmitere sexuală sau pot fi purtătoare de streptococ beta-hemolitic, motive pentru care este necesară instituirea tratamentului cu antibiotice. De asemenea, se aplică o terapie standard cu antibiotice femeilor cu nașteri premature și ruptura prematură a membranelor înainte de travaliu (RPM). Antibioticele pentru RPM reduc complicațiile datorate nașterii premature și infecțiilor postnatale. Modificările fiziologice survenite în cursul sarcinii determină particularități farmacocinetice care pot afecta eficiența agenților antimicrobieni. Un motiv serios de îngrijorare este reprezentat de posibilul risc de producere al efectelor teratogene și toxice pentru făt. În general, femeile gravide sunt excluse din trialurile clinice, iar informațiile farmacocinetice referitoare la administrarea și dozarea corectă a antimicrobienelor la această populație sunt insuficiente. Deși majoritatea antimicrobienelor pot traversa bariera hemato-placentară, datele referitoare la potențialele efecte teratogene și toxicitatea fetală și neonatală provocată de aceste medicamente sunt limitate și relativ variabile. Prezentul articol recenzează datele disponibile cu relevanță clinică semnificativă referitoare la farmacologia antibioticelor celor mai frecvent utilizate în sarcină, cu preponderență pe toxicitatea fetală.

Cuvinte cheie: sarcină, infecții, antibiotice, transmitere transplacentară

ABSTRACT

Pregnant women often present in the evolution of pregnancy urinary tract infections, sexually transmitted infections and group beta streptococcus carriage requiring treatment with antibiotics. Also, it is standard practice to give antibiotics to women with pre-term, prelabor rupture of membranes (PROM). Antibiotics for PROM reduce complications due to pre-term delivery and post-natal infection. The physiologic changes that occur during pregnancy result in pharmacokinetic changes that can alter the effectiveness of antimicrobial agents. The possible risk of teratogenic and toxic effects of antibiotics on the fetus is an additional cause of concern. In general, pregnant women are excluded from clinical trials and there is little pharmacokinetic information on the use and proper dosing of antimicrobials in this population. Although most antimicrobials can cross the placental blood barrier, data on the potential teratogenic effects, fetal and neonatal toxicity caused by these drugs are also limited and off varying reliability. This article reviews the available evidence with the greatest clinical relevance regarding the pharmacology of different antibiotic agents in pregnancy, with particular focus on data related to fetal toxicity.

Key Words: pregnancy, infections, antibiotics, transplacental transmission

INTRODUCTION

1. Drug risks in pregnancy. Reproductive and developmental toxicology

Antibiotics are often prescribed during pregnancy by gynecologists and family healthcare providers due to several bacterial infections which occur during the perinatal period.[1] Their increased use is correlated with the risk of adverse effects on the fetus.[2]

Certain antibiotics can have varying levels of impact on the fetus based on when they are taken during the pregnancy. During these time periods, one must be conscious of the multiple consequences taking antibiotics can have.[3]

The care of pregnant women represents one of the paradoxes of modern medicine.[4] Practicing clinicians, who prescribe medicinal products, have to evaluate the drug exposure in women who are or may become pregnant.[5] Since the recognition of prenatal vulnerability in the early 1960s, after the maternal exposure to the mild sedative thalidomide, much has been accomplished to identify potential developmental toxicants such as medicinal products and to regulate human exposure to them.[6] The adverse developmental effects of pharmaceutical products are now recognized to include not only malformations, but also growth restriction, fetal death and functional defects in the newborn.[7]

Many reviews provide an update of anti-infective drugs used during pregnancy, known to produce fetal

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developmental anomalities.[8] In all cases it is essential to critically consider the benefit of the antibiotic therapy for the disease being treated, whether the disease is maternal, fetal or placental.[9]

1.1. Pharmacokinetics in pregnancy

Pregnancy induces many maternal physiological changes and adaptations, which can lead to clinically important reductions in the blood concentrations of certain medicinal products. The total water increases as much as 81 during pregnancy, which provides a substantially increased volume in which drugs can be distributed.[10] Serum proteins relevant to drug binding undergo considerable changes in concentration. Albumin, which binds acidic drugs and chemicals decreases in concentration by up to 10 g/L. The main implication of this change is the interpretation of drug concentrations.[11] The increased production of female hormones activates enzymes in the maternal liver, and this may result in a modified drug inactivation. The renal plasma flow will almost doubled by the last trimester of pregnancy, and drugs that are excreted unchanged by the kidney are usually eliminated more rapidly.[12]

1.2. Fetal kinetics and passage of drugs to the unborn

Most studies of drug transfer across the maternal and embryonic/fetal barrier are concerned with the end of pregnancy; but little is known about the transport of substances in the early phases of pregnancy, in which, morphologically and functionally, both the yolk sac and the placenta develop and change in performance.[13,14] The placenta is a lipid barrier between the maternal and the embryonic/fetal circulations, allowing fat-soluble drugs to cross more easily than water-soluble. Drugs cross the placenta by passive diffusion, and a non-ionized drug of low molecular weight will cross more rapidly than a more polar drug. However, most drugs achieve equal concentrations on both sides of the placenta. Most drugs have a lower molecular weight than 600-800 Da, and will therefore be able to cross the placenta.

In the third month of pregnancy, the fetal liver is already capable of activating or inactivating chemical substances through oxidation.[15] It is very important that, in the fetal compartment, the detoxification of drugs and their metabolites takes place at a low level, certainly in the first half of pregnancy. The excretion in the amniotic fluid explains the accumulation of biological active substances might take place in the fetal compartment. The blood-brain barrier in the fetus is another characteristic that might be important for the possible fetotoxic effects of drugs.

Although fetal treatment is still an exception, it is of great interest that in the case of prevention of vertical infections, at the time of functioning circulation and kidney excretion, antibiotics (penicillins, cephalosporins) concentrate in the fetal compartment. Such depot effects are also enhanced by recirculation through swallowing of the antibiotics in the amniotic fluid, thus contributing to a great extent to the therapeutic effect. Obviously, this effect is lost when an early amniorrhexis (rupture of the membranes) occurs.[16]

OBJECTIVE

To review the current status of antibiotic therapy for pre-term, prelabor rupture of membranes (PROM) cesarean delivery, newly evolving strategies to enhance the effectiveness in reducing post-natal infection, and to monitor the adverse effects on the embryo and fetus.

DATA SOURCES

We conducted a full PubMed (January 1976 - August 2011) search using the key words *"pregnancy", "infections", "antibiotics"* and *"transplacental transmission"*. A total of 355 articles were identified and supplemented by a bibliographic search.

Methods of study selection

We have selected a total of 59 observational and clinical trials revealing the clinical and biological effects of antimicrobials with transplacentar transmission, administered during different stages of pregnancy.

RESULTS AND DISCUSSIONS

We conducted an analytic review of selected studies in order to reveal safety of antibiotic use in pregnancy. Although current guidelines recommend the administration of antibiotics with narrow spectrum to be delayed, only after clamping the neonate's umbilical cord, previous studies revealed the effectiveness of extended spectrum antibiotics to be used earlier, prior to surgical incision. However, the final goal is to reduce maternal infection up to 50% and to extend beneficial effects on neonatal infection as well.

1. Classification of drugs used in pregnancy

Since 1984, classification systems have been introduced in the USA, Sweden and Australia. Some of the frequently prescribed antibiotics are distributed into three groups according to their rational use during pregnancy (categories A,B,C).[17,18]

Antibiotics belonging to the first group, which should not be administered to pregnant women, are listed in Table 1:[19]

Table 1. Usual antibiotics not to be used in pregnant women.

Class of antibiotics	Representative antibiotics
Phenicols	Cloramphenicol
Aminoglycosides	Gentamycin
	Streptomycin
	Tobramycin
Antimycotics	Amphotericin B
	5-flucytosine
	Griseofulvin
Polymyxins	Colistin
	Polymyxin
Tetracyclines	Doxycicline
	Minocycline
	Tetracycline

Classification of antibiotics is general, and these systems allow for a general estimation of the safety of drugs during pregnancy and reproduction. In the European Union, a specification of the medicinal products to be used in pregnancy has to include:[20]

- Facts regarding human experience and conclusions from preclinical toxicity studies which are of relevance for the assessment of risks associated with exposure during pregnancy;
- Recommendations on the use of the medicinal product at different times during pregnancy in respect of gestation;
- Recommendations on the management of the situation of an inadvertent exposure.

2. Safety of antibiotic use in pregnancy

Among the anti-infective agents, the use of common antibiotics prescribed in therapeutic doses is very important for family healthcare providers. Fetal monitoring is recommended regarding the safety in pregnancy of the following classes of antibiotics:

2.1. Penicillins

Penicillins are widely used during pregnancy, including ampicillin, amoxicillin, azlocillin, mezlocillin, penicillin G, penicillin V, piperacillin, ticarcillin, etc. Many studies have revealed their lack of fetal adverse effects, even if it has been proved that they accumulate in the amniotic fluid.[21]

Penicillins, belonging to the β-lactam antibiotics, inhibit cell-wall synthesis in bacteria and have bactericidal properties. They have a low toxicity profile for both, the pregnant woman and the fetus, when used in therapeutic doses. Penicillins cross the placenta in low concentrations, and can be detected in amniotic fluid. Elimination is more rapid in pregnant women and therefore dosage or dosage intervals should be adjusted if necessary.[22]

There is no evidence that penicillins have teratogenic or embryo/fetotoxic properties.[23] A higher prevalence of cleft palate after prenatal exposure to ampicillin in the second and third month of pregnancy was revealed though by Czeizel.[24]

Recommendation: penicillins are the antibiotics of choice in pregnancy and can be safely recommended in usual doses.

2.2. 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 four generations. Many of the first and second generation cephalosporins have been studied extensively in pregnant patients.[25] Cephalosporins also belong to the β-lactam antibiotics, but their pharmacokinetic and antibacterial properties are different from those of penicillins.

Although further research is still needed, the first and second generation cephalosporins can be considered safe, with no side-effects for the fetus if used during pregnancy.[26] The third and generation of cephalosporins, however, have not been used extensively during pregnancy; therefore, there is little information known about their effects. Forth generation cephalosporins (cefipime) are useful in in pregnancy, but only for cases of severe bacterial sepsis.[27]

Cephalosporins cross the placenta, and can reach therapeutic levels in amniotic fluid and fetal tissues. It has been revealed that elimination in pregnant women is faster and it may be necessary to adjust dosage.[28]

Among the first-generation cephalosporins, cephalotin was widely used before it has been proved that it crosses the placental barrier being bound to plasma proteins in an average of 60-70%; thus, when extended to the fetus, many researchers have revealed cases of neonatal kern icterus produced at decreased bilirubin levels.[29]

Concerning the use of cephalosporins during the perinatal period, the drug of choice is cefuroxime, because its ability to cross the placenta after the second trimester of pregnancy, without fetal toxic side-effects.[30]

Second and third generation of cephalosporins, especially cefotetan, are increasingly associated with severe immune hemolytic anemia.[31]

Recommendation: cephalosporins can be used safely during pregnancy if needed; the older, first generation cephalosporin antibiotics are preferred.

2.3. Macrolide antibiotics

Erythromycin is the oldest of the macrolides. The most extended and suggestive study included the infants of 398 women who received erythromycin for different infectious diseases during the second and third trimesters of pregnancy; the safety of this common used macrolide antibiotic was proved by the lack of congenital anomalies in the pediatric study group. When considering the different side-effects affecting the neonate's liver, only the estolate ester of erythromycin was correlated with an increased rate of hepatotoxicity. The levels of serum glutamic oxaloacetic transaminase ranged from 44 to 130 IU/L, but the subclinical and biological changes were reversible.[32]

Many studies revealed a better understanding of the beneficial effects of erythromycin treatment upon delaying premature rupture of membranes, as well as improving pregnancy evolution in the last trimester with no side-effects on neonatal outcome.[33]

In a recent study, Källén reported an increased rate of cardiovascular malformations (1.8%), especially ventricular and atrial septal defects; he concluded that even the association is causal, the individual risk for an infant is still low.[34]

The association between prenatal exposure to erythromycin and infant pyloric stenosis is still controversial; thus, an increased risk (0.2%), was revealed by Cooper.[35]

Clarithromycin has a similar chemical structure to erythromycin. Relatively few epidemiological studies have examined the congenital anomalies induced in neonates following in utero exposure. There have been often reported cardiovascular abnormalities, and in some cases cleft palate, fetal growth retardation, and embryonic loss, but these results are controversial.[36] Even if further research is needed, these data suggest the higher toxicity of clarithromycin during development in comparison with its parent compound, erythromycin.[37] The defined underlying relationship between experimental study findings and neonatal risks is still unclear.

Recommendation: Erythromycin is still the drug of choice among the macrolides during pregnancy. Erythromycin estolate and troleandomycin should not be given in the second and third trimesters. Newer macrolides such as azithromycin, clarithromycin, josamycyn, and roxithromycin are second-choice macrolides. Spiramycin is the drug of choice for the treatment of toxoplasmosis during the first trimester.

2.4. Lincomycin and clindamycin

These antibiotics are only indicated during pregnancy when penicillins, cephalosporins, erythromycin or the other macrolides are not effective. Nor teratogenic or fetotoxic effects have been reported for lincomycin in 302 pregnancies.[38]

Intravaginal clindamycin is very effective in the treatment of bacterial vaginosis.[39]

2.5. Tetracyclines

Several clinical reports point out that the exposure to tetracycline after the third trimester (since week 13 following conception) affects the color of deciduous teeth, which appear yellowish and even darker: brown or gray-brown. At the light of Wood lamp they have the typical fluorescence.

Alterations arerelated to the type of tetracycline, its dosage, the length of treatment and the stage of teeth calcification at the moment of exposure. In case of exposure to tetracyclines in the last period of pregnancy also the crown of permanent teeth may possibly be stained.[40]

Most authors agreed the fact that only the deciduous teeth are involved in the staining process. Thus, if the drug administration occurs close to term, the crowns of the permanent teeth are affected by the antibiotic and may be stained. This process has only cosmetic signification, without affecting the development of the enamel, or increasing the caries rate. After in utero exposure to tetracycline were pointed out similar staining affecting the bones of the fetus. Important consequences on bone status during childhood with teeth staining and a 40% depression of bone growth have been revealed after tetracycline, doxycycline, and minocycline administration during the second or third trimester of pregnancy.[41]

Interesting researches in the field of premature infants have reported the correlation between the use of tetracyclines during pregnancy and decreased rates of bone growth.[42]

Recommendation: Tetracyclines are contraindicated beyond the fifteenth week of gestation. In the first trimester – they are considered to be second-line therapy. Doxycycline should be preferred in such cases.

2.6. Sulfonamides and trimethoprim

Sulfonamides cross the placenta well and fetal concentrations are 50-90% of maternal plasma concentrations. Due to their bilirubin-mobilizing capacity, they may increase the risk of hyperbilirubinemia in the neonate when used near the delivery.[43] Very high doses of trimethoprim have produced teratogenic effects (cleft palate) in rats. However, there is no strong evidence to suggest that trimethoprim or co-trimoxazole cause a serious risk of teratogenicity in human.[44]

Recommendation: Sulfonamides, trimethoprim, and co-trimoxazole may be safe alternative drugs for antibiotic treatment of urinary tract infections when penicillins and cephalosporins are ineffective. When trimethoprim or co-trimoxazole are needed in the first trimester, folic-acid supplementation (0,5 mg/day) is recommended.[45,46]

2.7. Quinolones

Quinolones cross the placenta and are found in the amniotic liquid in low concentrations. Umbilical cord concentrations of ciprofloxacin, pefloxacin, and ofloxacin have been found to be lower than maternal blood concentrations.[47]

The use of quinolones in the first trimester of pregnancy has not been associated with an increased risk of major malformations or other adverse effects on pregnancy outcome.[48]

The relationship between the prenatal use of fluoroquinolones and the increased risk of bone malformations was studied by Wogelius in 2005; he pointed out that the study on 130 women who redeemed a prescription of fluoroquinolones during the first trimester or 30 days before conception did not find a significant increase of (such) birth defects.[49]

Recommendation: Quinolones should only be used in case of complicated infections resistant to the antibiotics of choice in pregnancy. Ciprofloxacin and norfloxacin should then be chosen, because of their relatively large documented experience. Even the first-trimester use of a quinolone antibiotic is not an indicator for termination of pregnancy, but detailed ultrasonography is needed.[50]

2.8. Aminoglycosides

Currently, there is a lack of epidemiological studies concerning congenital fetal anomalies among pediatric population when mothers received gentamycin during pregnancy. It is well known that gentamycin use is correlated with nephrotoxicity; many researchers tried to understand the mechanisms involved in fetal kidney damage after maternal therapy during pregnancy.[51] While maternal gentamycin side-effects, like fetal nephropathy after maternal therapy, are still in debate, severe neonatal renal damages have been revealed. A special concern affects premature infants, and the ability to eliminate gentamycin may be correlated with post-conception age and not with the age from birth.[52]

The use of gentamycin as an aminoglycoside during pregnancy may be also correlated with an increased risk for fetal auditory nerve damage, as previously reported with streptomycin exposure. The higher incidence of side-effects is considered to be the first four month of pregnancy after aminoglycoside exposure.[53,54]

Elevated gentamycin serum levels have been detected in nursing infants one hour after gentamycin administration. It is important to find out if accumulation from chronic drug exposure affects the vital organs of the newborn; several previous studies have suggested that this process may be correlated with the gestational age and with the fetal renal function.[55]

Recommendation: Aminoglycosides are not recommended for parenteral use during pregnancy. They should only be administered in case of life-threatening infections; in those cases, maternal serum levels should be carefully monitored and dose should be adjusted if necessary. When higher doses have been used, renal function should be monitored in the neonate and an auditory test should be performed.

2.9. Cloramphenicol

Cloramphenicol is relatively toxic, and can cause severe agranulocytosis. It crosses the placenta well and can reach therapeutic concentrations in the fetus. It should not be used in the last weeks of pregnancy as, owing to inadequate metabolism in the neonate, toxic concentrations can be reached which may cause the "gray baby syndrome" (feeding problems, vomiting, ash-gray skin, respiratory distress, and cardiovascular collapse), which may be fatal in the neonate.[56]

Recommendation: Cloramphenicol and thiamphenicol are contraindicated during pregnancy unless there is a serious indication. Treatment during the first trimester is not an indication for termination of pregnancy or for massive prenatal diagnostic procedures.

2.10. Polypeptide antibiotics

Only few epidemiological studies concerning in utero exposure to colistin and polymyxin B have been reported. In a retrospective clinical survey, there were no adverse effects associated with the use of polymyxin B during pregnancy. However, the safety of using this compound during pregnancy is needed to be evaluated in further longitudinal studies, and therefore these antibiotics have an undetermined risk for use during pregnancy.[57] There is a case report of a woman who became hypotensive when vancomycin was infused too rapidly during labor; the fetus exhibited bradycardia during the hypotensive episode.[58]

Recommendation: Vancomycin should only be used in case of life-threatening bacterial infections.[59]

Even if the majority of antimicrobial drugs can cross the placental blood barrier, there are few data

Table 2. Overview of published trials of transplacental passage of antibiotics.

Study	Design	Sample size	Antibiotic in pregnant women	Study outcome - Fetal risk
Czeizel AE[24]	RCT	105	Ampicillin	Cleft palate
SumnerJY[29]	RCT	69	Cephalotin	Kernicterus
Mitchell TF[27]	RCT	58	Cefazolin	High risk of neonatal kernicterus
Garraty G[31]	RCT	128	Cefotetan	Severe immune hemolytic anemia
Mc Cormack WM[32]	RCT	268	Erythromycin estolate	Hepatotoxicity (SGOT – 44-130 IU/L)
Czeizel AE[33]	RCT	275	Erythromycin	Increased rates of PROM
Källén B[34]	RCT	1585	Erythromycin	Cardiovascular malformations
Cooper WO[35]	RCT	448	Erythromycin estolate	Innfantile hypertrophic pyloric stenosis
Einarson A[36]	RCT	350	Clarithromycin	Cardiovascular abnormalities, cleft palate, fetal growth retardation
CzeizelAE[41]	RCT	1247	Oxytetracycline	Decreased rates of bone growth in premature infants
Boskovic R[46]	RCT	1336	Cotrimoxazole	Preterm birth reduction
Wogelius P[49]	RCT	215	Fluoroquinolones	Increased risk of bone malformations
Jin ZK[55]	RCT	320	Gentamycin	Nephrotoxicity
Basim I[56]	RCT	1345	Cloramphenicol	Gray baby syndrome

RCT: Randomized Clinical Trial

referring to the teratogenic effects, and toxicity upon fetus and neonate; the clinical experience with these drugs during pregnancy is also limited and of varying reliability.

This article reviews the available clinical trials mostly suggestive for the pharmacology of various antibiotic agents administered during pregnancy, with special interest on evidence related to fetal toxicity. (Table 2)

CONCLUSION

Even if the use of antibiotics prescribed to pregnant women is a requirement in many infectious conditions, most of the side-effects and mechanisms induced by these drug exposure remain unclear. If in certain situations an antibiotic must be prescribed, it is important to be well informed about the effects of such drug on pregnancy, in order to choose the most appropriate treatment with the lowest risk to the fetus and neonate.

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