REVIEW

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Antibiotics and pregnancy

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Like anybody else, pregnant women are susceptible to infections. The correct treatment of these women, however, must consider along with pathogens, the infection site and antibiotic pharmacokinetics, the fetus and possible side effects to the child. When prescribing over this special condition, the physician must remember that the prescription will affect two organism and the drug must treat the mother without affecting the fetus. Beta-lactams having a long history of use without significant deleterious effects on the fetuses still are the safest choice during pregnancy. However, considering the constant increase of multi-resistant microorganisms, the physician has been forced to use different antimicrobial agents. Usually, data regarding safety during pregnancy are very limited, which causes serious doubts during prescription. In addition, many studies regarding the safe use of antibiotics during pregnancy are inconclusive or demand more evidence. The present study is a wide revision regarding the use of antibiotics during pregnancy, considering their pharmacokinetics and the clinical experience in recent years. It also intends to assist the physician during prescription and to give information to the pharmacists to help pregnant women.

Topics:

1. Introduction

Pregnancy can be considered as the unique situation that two different organisms – mother and fetus – are exposed to the same drug. Exogenous substances may have unpredictable and irreversible consequences in the physical development of the child (Mantovani and Calamandrei 2001).

The number of drugs usually prescribed during pregnancy is considered very high. Previous studies in the 1990's have shown that in Denmark and Finland between 44% and 46% of pregnant women were exposed to at least one drug. In other European countries, such as The Netherlands (86%), Germany (96%) and France (94% to 96%) the rate is higher (Egen-Lappe and Hasford 2004). Similarly, Brazilian data show that more than 80% of women are exposed to at least one drug during pregnancy (Gomes et al. 1999). In Brazilian pregnant women antibiotics are mainly prescribed against urinary or respiratory infections (between 11 to 15%) (Mengue et al. 2001). An American study observed 152,531 women in the 270 days before delivery, between 1996 and 2000. It showed that amoxicillin was dispensed to 34,304 women and more than 90,000 prescriptions were antibiotics (Andrade et al. 2004).

Generally, antimicrobial agents present low-molecular weight and high lipid solubility allowing the diffusion across the placenta and excretion in the milk, which expose the fetus and the newborn to toxic effects (Dashe and Gilstrap 1997). A careful risk-benefit evaluation must be established before the use of antibiotics during pregnancy, i.e., the benefit of the antibiotic must be greater

than the risk to the fetus. If the antimicrobial therapy is established, the physician must be familiarized to all possible risks of the chosen agent.
Data on the antibiotic efficacy and safety during pregnancy are very scarce due to legal and ethical issues, which forbid studies about the action of these drugs during pregnancy or in newborn babies. Usually, the clinical and epidemiological studies about drug safety are performed on non-pregnant women and the results are extrapolated to pregnant ones.
Many physiological alterations observed in pregnancy could interfere directly with the pharmacokinetics of the antibiotics, leading to increasing plasmatic concentration and toxic effects or, in opposite, to sub-inhibitory levels, which diminish the antimicrobial effect, cause therapeutic failure and the selection of resistant strains (Preston 2004).
The aim of the present study is to summarise the recent clinical experience about the pharmacological aspects and the use of antibiotics in pregnancy. This review could help the physician and the pharmacist in the guidance and prescription to treat infections in pregnant women.

2. Physiological changes during pregnancy

The prescription of antibiotics for pregnant women must consider the physiological changes during pregnancy that could significantly alter the pharmacokinetics of an antimicrobial agent. Functional alterations in the gastrointestinal tract due to estrogen cause gastric emptying delay, dyspepsia, nausea, vomit and can considerably decrease absorption and bioavailability of antibiotics taken orally (Loebstein et al. 1997).
Around the twentieth week of pregnancy, an increase of approximately 40% in the blood volume is verified (Weller and Rees 2000). In addition, both glomerular filtration and hepatic activity increase causing a significant reduction in serum concentration of some antibiotics. These phenomena could explain the lower plasmatic concentrations in pregnant women in comparison to non-pregnant ones when usual doses of cephalosporins are used (Philipson et al. 1987).
The increase in blood volume induces a reduction in the plasmatic albumin concentration, which also influences antibiotic pharmacokinetics (Hedstrom and Martens 1993). The immediate effect is the proportional increase of the free fraction of the antibiotic, allowing more antibiotic molecules available to cross the placenta and to reach the fetus, faster metabolization and excretion (Loebstein et al. 1997).
Faster metabolization and excretion also contribute to the reduced antibiotic plasmatic concentration in pregnant women in comparison to non-pregnant ones. An altered volume of distribution associated to an increased glomerular filtration rate (Niebyl 2003) and increased urinary elimination were pointed out as co-factors inducing differences in the antibiotic concentrations between pregnant and non-pregnant women (Loebstein and Koren 2002).

3. Transport across the placenta

The mechanism of drug transportation to the fetus blood is simple diffusion. This process is influenced by physicochemical factors of the antibiotic such as molecular weight, lipid solubility, ionization rate and the plasmatic protein binding.
The great majority of antimicrobial agents has highly lipid solubility and low molecular weight allowing a very easy diffusion across the placenta, quickly reaching the intrauterine compartment, exposing the fetus and decreasing the maternal antibiotic plasmatic concentration (Niebyl 2003). The antibiotics having low plasma protein binding usually reach the highest concentrations in the fetal serum (Boobis and Lewis 1982).
All physiological alterations observed during pregnancy could significantly alter the antibiotic pharmacokinetics, resulting in a decrease of approximately 10% to 50% in the maternal plasmatic concentrations. This decrease could result in sub-inhibitory concentrations and consequent therapeutic failure (Loebstein and Koren 2002). In addition, high concentration in the fetal blood could induce malformation or compromised development.
In order to establish safety standard references for drugs used during pregnancy, the FDA (Food and Drug Administration of United States of America) created a division of five categories.

4. FDA categories

Category A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
Category B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X: Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant (Briggs et al. 2002).
The Table shows the antibiotics classes according to their clinical use, adverse effects and FDA classification.

5. Classes of antibiotics

5.1. Inhibitors of cell wall synthesis

5.1.1. Penicillins

A Hungarian study monitored 38,151 pregnant women over 16 years and found that 6,554 (17.2%) women used antibiotics, which were mainly penicillin (5,525 cases or 84.3%) prescriptions (Czeizel et al. 1998). A similar study carried out in Brazil showed 539 (54%) women using penicillin and cephalosporins representing 234 (23.4%) of the total of antibiotics used during pregnancy (Fonseca et al. 2002). There is no doubt that penicillins are the most prescribed antibiotics for pregnant women (Czeizel et al. 2001c). Penicillins are classified as natural (penicil-

Table: Antimicrobial agents according to class, clinical use, adverse effects and FDA classification

Class	Clinical Indication in pregnancy	Adverse effects	FDA category
Penicillins [a]	Puerperal sepsis Gonorrhea Syphilis Community-acquired pneumonia Urinary tract infection Bronchitis	Allergy Skin rash Diarrhea	B
Cephalosporins [a, b]	*S.aureus* infections Surgical chemoprophylaxis Acute pyelonephitis Pelvic inflammatory disease Gram negative sepsis (ceftriaxone) *P. aeruginosa* sepsis (ceftazidime)	Cross allergy with penicillin	B
Other beta-lactams Carbapenems [a] Imipenem Meropenem Ertapenem [c, d]	Postpartum infections Severe pyelonephitis Perinatal infections	Diarrhea Skin rash Nausea	 C C B
Monocyclic Aztreonam [e]	Aerobic gram-negative infections (alternative to aminoglycosides) Urinary tract infections Uncomplicated gonorrhea	Nausea Gastrointestinal effects Eosinophilia	B
Vancomycin [f]	MRSA infections *C. difficile* induced colitis	Ototoxicity Nephrotoxicity Red man syndrome	C
Teicoplanin [g]	Gram positive infections	Injection site intolerance	Not been evaluated
Fosfomycin [b, h]	Uncomplicated lower tract infections	Gastrointestinal effects Diarrhea	B
Macrolides Erythromycin [i, j]	*Legionella, Mycoplasma* and *Chlamydia* infections *T. pallidum*	Hepatotoxicity (estolate) Gastrointestinal	B
Clarithromycin [k]	Upper respiratory tract infections *H. pylori* eradication *Mycobacterium avium* complex prophylaxis in HIV positive patients	Gastrointestinal effects	C
Roxithromycin [j]	*Chlamydia trachomatis* and *Ureaplasma urealyticum* infections	Gastrointestinal effects Stevens-Johnson syndrome	B
Azithromycin [l]	*Chlamydia trachomatis* urethritis Pharyngeal infections and pneumonias Lyme disease [f]	Gastrointestinal effects Headache	B
Telithromycin [m, n]	*Chlamydia trachomatis* urethritis *Neisseria gonorrhoeae*	Gastrointestinal effects	C
Lincosamides [f, j]	Postpartum metritis Anaerobic infections	Gastrointestinal effects Skin rash	B
Aminoglycosides [f, o] Gentamicin Streptomycin Amikacin	(In general) Septicaemia and other severe infections of Gram negative aerobic infections	(In general) Nephrotoxicity Ototoxicity Neuromuscular blockade	 C D D
Tetracyclines [f, p]	*Mycoplasma, Chlamydia* and *Spirochets* infections	Hepatotoxicity Yellow-brown teeth discoloration	D
Chloramphenicol [q]	Salmonellosis Rocky Mountain fever [r] Typhoid fever [s]	Haemolytic anaemia Grey Baby Syndrome [t]	C
Oxazolidinones [u] Linezolid	MRSA, *E. faecalis* and *E. faecium* infections	Gastrointestinal effects Tongue discoloration	C
Metronidazole [f, j, v]	Anaerobic sepsis *Trichomonas vaginlis, Giardia lamblia* and *Entamoeba histolytica* infections	Gastrointestinal effects Metalic taste Headache	B
Quinolones [f, w]	Urinary tract infections (alternative to beta-lactams) Upper respiratory tract infections	Gastrointestinal effects Headaches Dizziness Eosinophilia	C

Table: (continued)

Class	Clinical Indication in pregnancy	Adverse effects	FDA category
Sulfonamides [f, j]	Toxoplasmosis Prophylactic protocols for pneumonia by *Pneumocystis carinii* in HIV positive pregnant women	Kernicterus (neonate) Allergic ski rash Stevens-Johnson syndrome Haematological effects	B
Trimethoprim [f, j]	Associated with sulfonamides	Causes palatine cleft Malformations in the urinary tract and cardiovascular system	C
Polymixins			
Colistin [x, y, z]	Gram negative infections Prophylaxis in Ceasarean section (Assoc. ampicillin)	Nephrotoxicity, neuromuscular blockade, ataxia, dizziness	C

a – (Heikkila and Erkkola 1994); b – (Christensen 2000); c – (Teppler 2004); d – (Merck & Co. 2004); e – (Clark 1992); f – (Dashe and Gilstrap 1997); g – (Campoli-Richards et al. 1990); h – (Stein 1998); i – (Larsen and Glover 1998); j – (Garland and O'Reilly 1995); k – (Einarson et al. 1998); l – (Bush and Rosa 1994); m – (Boswell et al. 1998); n – (Mensa 2003); o – (Czeizel et al. 2000a); p – (Hautekeete 1995); q – (Mathai et al. 2003); r – (Stallings 2001); s – (Seoud 1988); t – (Johnson 2003); u – (Clemett and Markham 2000); v – (Sorensen et al. 1999); w – (Dinsmoor and Gibbs 1988); x – (Knothe and Dette 1985); y – (Parke-Davis 1997); z – (Birkenfeld and Anteby 1983)

lin G, penicillin V), penicillinase-resistant (cloxacillin, dicloxacillin, nafcillin, oxacillin), aminopenicillins (amoxicillin, ampicillin) and extended spectrum (carbenicillin, piperacillin, ticarcillin).

All penicillins are considered "category B" due to a higher selective toxicity occasioned by their mechanism of action, i.e., alteration on the cell wall, which is a structure present only in bacteria. In addition, these antimicrobial agents are among the oldest known antibiotics, with approximately 60 years of clinical experience (Czeizel et al. 2001c).

Penicillins are indicated during pregnancy mainly to treat syphilis, infections in the upper respiratory tract associated to group B Streptococci, enterococcal infection and for prophylaxis of bacterial endocarditis (Dashe and Gilsatrap 1997). The use of beta-lactam agents in urinary tract infections has decreased due to the increasing rates of resistant *E. coli* strains, which is the main pathogen.

The mostly prescribed penicillins are penicillin G, phenoximethylpenicillin (penicillin V), ampicillin and amoxicillin combined with clavulanic acid (Christensen 2000). This association is used mainly to surpass resistance mediated by beta-lactamases (Sa Del Fiol et al. 2000). At usual doses neither ampicillin (250/500 mg, QID, during 5 days) nor amoxicillin/clavulanate (250/500 mg amoxicillin and 125 mg clavulanate, TID, during 3 to 10 days) were able to induce significative congenital abnormalities (Czeizel et al. 2001c, 2001d).

Previous studies showed that clavulanic acid could interfere in some laboratory tests commonly recommended during pregnancy, like the *Coombs test*, which is used to detect fetal erythroblastosis. The use of clavulanic acid could induce false-positive results (Blanchard et al. 1989; Williams et al. 1985). Despite this interference, the clavulanic acid has no direct toxicity since a study showed no alteration at birth of 556 children exposed to the drug during the first trimester (Briggs et al. 2002).

Many clinical studies carried out recently contributed to the establishment of penicillin safety. Reports about phenoxymethylpenicillin (Czeizel et al. 2000b; Dencker et al. 2002), pivampicillin (Larsen et al. 2000), oxacillin (Czeizel et al. 1999a), dicloxacillin (Aselton et al. 1985), amoxicillin (Jepsen et al. 2003), amoxicillin plus clavulanic acid (Czeizel et al. 2001d) and ampicillin (Czeizel et al. 2001c) confirmed the safety of these drugs during pregnancy.

Usually, the major concern about beta-lactam antibiotics is not their direct toxicity, but the allergic reactions, which are almost impossible to prevent. Approximately 5% to 10% of the population can be affected by some kind of allergic reaction (Shepherd 2003) varying from a simple skin rash to anaphylactic shock. In addition, allergic reactions may cause premature birth due to the large release of histamine.

Previous studies showed alterations in penicillin pharmacokinetics in pregnant women since the maternal blood concentration markedly decreased due to increased kidney blood flow and glomerular filtration rate (Neibyl 2003; Heikkila and Erkkola 1994). Due to increased blood volume and renal clearance, both causing distribution volume augmentation, plasmatic concentration of the antibiotic can be reduced by up to 50% in pregnant women compared to non-pregnant ones (Einarson et al. 2001). Higher doses should be used in order to obtain antibiotic blood concentration.

Penicillins can easily cross the placenta by passive diffusion reaching the fetus. Close to the birth event, the concentrations of these antibiotics are the same in the maternal plasma, the amniotic fluid and the fetus. The renal clearance is considerably lower in newborn babies and breast-feeding women than in the children and adults, remaining higher concentrated in the newborn blood (Briggs et al. 2002).

Briefly, it is very clear that penicillin does not represent direct toxicity to the fetus or the mother and it could be used whenever is necessary during pregnancy.

5.1.2. Cephalosporins

The cephalosporins are very similar to the penicillins since these antibiotics also have a beta-lactam ring and the same mechanism of action, interfering with the synthesis of the bacterial cell wall. They also have high selective toxicity being, after the penicillins, the most prescribed antibiotics during pregnancy. The Hungarian study (Czeizel et al. 1998) observed that 458 (1.2%) women used some kind of cephalosporin.

First discovered in Italy in the 1940s, cephalosporins are in clinical use since the 1960s. They are divided into four generations according to the spectrum of activity. The main representatives belong to the first generation, consisting of cephalexin and cefadroxil. The second generation is represented by cefuroxime and cefaclor; the third generation by ceftriaxone and cefotaxime; and the fourth generation by cefepime and cefpirome.

The cephalosporins are largely used in pregnant women for the prophylaxis of post-cesarean section infections, minor urinary infections caused by gram-negative rods,

acute pyelonephritis and, in some cases of bacterial resistance to other antibiotics (Christensen 2000).
FDA considers these antibiotics as category B. They easily cross the placenta by passive diffusion and the plasmatic levels of the mothers are usually lower than in non-pregnant women, which makes it necessary to increase the dose to obtain usual minimum inhibitory concentrations (Niebyl 2003). Their plasmatic protein binding could vary from 20% to 80% and the fetal plasmatic concentration is approximately 15% to 20% of the concentration observed in the pregnant woman. However, this concentration is enough to present a bactericidal effect against pathogens in the amniotic liquid and fetal tissue (The Medical Letter 1987).
There is no doubt that cephalexin is the most widely used cephalosporin during pregnancy. Until now, no risks of teratogenicity were observed in women using these antibiotics. Czeizel et al. (2001b) studied 22,865 pregnant women who had fetuses or newborn infants with congenital abnormalities and 38,151 pregnant women who had infants without any defects from 1980 to 1996. Three hundred and eight (1.35%) pregnant women (440 or 1.15%, in the control groups) were treated with cephalosporins. The comparison of the occurrence of medically documented cephalosporin treatments did not indicate a detectable teratogenic potential in humans.
Einarson et al. (2001) showed 177 (4.9%) malformations in 3,613 newborn babies previously exposed to cephalexin during the first trimester of pregnancy. The same study showed 76 (5.7%) malformations of 1,325 exposures to cefaclor; 27 (3.7%) of 722 exposures to cefadroxil; 3 (2.1%) of 143 exposures to cefuroxime, and 4 (6.7%) of 60 exposures to ceftriaxone. Although some of these rates are slightly above the 3% baseline, no clear patterns of malformations were detected, confirming a very low teratogenic risk for this group of drugs. Other studies confirmed that there is no evidence associating the use of cephalosporins during pregnancy and the presence of congenital abnormalities or fetal teratogenic potential (Briggs et al. 2002; Czeizel et al. 2001b).

5.1.3. Other beta-lactams

Imipenem and meropenem are considered carbapenemic antibiotics, which also have the beta-lactam ring. Imipenem is administered with cilastatin, a therapeutic adjuvant that inhibits dehydropeptidase, minimizing the renal metabolization of the antibiotic (Heikkila et al. 1992). Studies carried out on monkeys using doses of imipenem three times greater than the usually recommended dose for humans did not showed teratogenicity, but an increasing number of spontaneous abortions was observed (Briggs et al. 2002).
This antibiotic has been very successfully used in the treatment of post-delivery infections (Matsuda et al. 1998). However, there is little or no substantiated clinical experience about the use of imipenem in pregnancy and no reports on teratogenicity exist. It is classified as Category C by FDA (Heikkila et al. 1992).
Ertapenem is a carbapenem Group 1 agent, introduced in the late 2001 in the USA and 2002 in Europe. It is a once-a-day, parenteral beta-lactam antibiotic, showing a large spectrum of activity, which is similar to imipenem including all anaerobes and many gram-negative bacilli, except *P. aeruginosa* and Acinetobacter (Teppler et al. 2004). Ertapenem crosses the placental barrier of rats but doses up to 700 mg/kg/day administered (i.v.) in mice and rats did not show toxicity during external, visceral and skeletal examination of the fetuses. However, the mice showed slight decreases in average fetal weights and an associated decrease in the average number of ossified sacrocaudal vertebrae (Merck & Co. 2004).
No adequate and well-controlled studies in pregnant women were carried out until now and, once animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Ertapenem is also classified as Category B agent according to FDA (Merck & Co. 2004). Recent studies showed that ertapenem could be useful during pregnancy to treat severe pyelonephritis or community-acquired pneumonia, which are not caused by *P. aeruginosa* (Ortiz-Ruiz et al. 2004).
Aztreonam is a monocyclic beta-lactam antibiotic with great activity against gram-negative aerobic bacilli. The spectrum of activity is similar to that of the aminoglycoside agents, but without side effects such as ototoxicity and nephrotoxicity (Dashe and Gilstrap 1997). The drug crosses the placenta but it is found in low concentrations in both fetal serum and breast milk (Dinsmoor and Gibbs 1988). The great majority of studies about the use of aztreonam in pregnant women were carried out during the perinatal period and all of them concluded that the drug is safe (Chimura et al. 1990). Very few inconclusive studies were performed during the first semester of pregnancy (Bristol-Myers Squibb 2004). Thus, the teratogenic potential of aztreonam has not been well established.
The recommendations of the manufacturer of aztreonam clearly state "*...there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, aztreonam should be used during pregnancy only if clearly needed*". Aztreonam is classified as category B by FDA but there is no guaranty on the safety use of this drug, especially in the first three months of pregnancy (Clark 1992).

5.1.4. Vancomycin

Once vancomycin kills bacteria by inhibiting the cell wall synthesis in a very specific location, it could not supposed to be harmful for pregnant women or fetuses. In addition, it is a large molecule with antimicrobial activity restricted to gram-positive microorganisms, especially the methicillin-resistant *Staphylococcus aureus* (Greenwood 1997) and *Clostridium difficile* strains (Dashe and Gilstrap 1997). However, the use of vancomycin during pregnancy has been discussed controversly due to the potential risk for fetal ototoxicity or nephrotoxicity (Dashe and Gilstrap 1997). In addition, the "red man" syndrome, which is characterized by large histamine liberation after the drug injection causing intense uterine contraction and maybe premature labor, has been associated to vancomycin use (Davey and Williams 1991; Campoli-Richards 1990).
Despite the use of vancomycin could be indicated during the second and third trimesters of pregnancy, there is little experience regarding this issue. Although usual doses of vancomycin pose no threat to the fetus, it is still classified by FDA as category C.

5.1.5. Teicoplanin

This glycopeptide antibiotic has a molecular structure similar to that of vancomycin. Besides its long half-life, which allows once-daily intramuscular or intravenous administration, the incidence of "red man" syndrome is low-

er than under vancomycin (Davey and Williams 1991). It is indicated against resistant gram-positive microorganisms (Campoli-Richards et al. 1990) or in patients who have limited venous access or are hypersensitive to beta-lactam antibiotics (Bibler et al. 1987). Until the moment, there are no studies regarding the use or the safety of teicoplanin during pregnancy and it is still not approved by FDA.

5.1.6. Fosfomycin

No teratogenic effects have been associated with the use of fosfomycin in clinical studies or in animal models (Stein 1998). Fosfomycin crosses the placental barrier of rats and it does not produce teratogenic effects in pregnant rats at very high doses such as 1000 mg/kg/day, which is approximately 9 times the human dose based on body weight. Maybe the mechanism of action of fosfomycin could explain the absence of teratogenic effects. This synthetic antibiotic inhibits bacterial cell wall synthesis by inactivating the enzyme enolpyruvyl transferase. It is useful against a wide range of common urinary tract pathogens and is well absorbed orally. A single dose results in high serum levels, which provides concentrations above the MIC for common urinary pathogens for up to 3.5 days (Patel et al. 1997). Comparative clinical trials suggest that a single dose of fosfomycin is as effective clinically as a 7–10 day treatment regimen of nitrofurantoin, norfloxacin or co-trimoxazole (Stein 1998). Since adequate and well-controlled studies in humans have not been performed, FDA classifies it as category B (Forrest Pharmaceuticals 2002).

5.2. Protein synthesis inhibitors

5.2.1. Macrolides

First isolated in 1952 from a *Streptomyces erythreus* strain in the Philippines, the macrolides have become the group of choice for the "allergic-to-penicillin" patients. These agents are bacteriostatic and they act in the bacterial ribosome, linking to the 50S sub-unit inhibiting protein synthesis (Mensa et al. 2003), which is different from the human ribosome.

The spectrum of activity is preferentially against gram-positive cocci with little action against *Staphylococcus aureus*. The use of macrolides in pregnant women is restricted to treat syphilis and upper-respiratory tract diseases in patients with allergic history to penicillin. In addition, it has been used to treat toxoplasmosis and urethritis caused by *Chlamydia trachomatis* (Hedstrom and Martens 1993; Einarson et al. 2001).

Erythromycin is the oldest known macrolide and it is usually presented as estolate or stearate formulation. Plasmatic concentration in pregnant women greatly varies according to the stage of pregnancy leading to sub-inhibitory concentrations or over-exposition, which causes toxicity to the baby (Larsen and Glover 1998). Erythromycin freely passes across the placenta barrier, resulting in low (5% to 20% of mother's plasmatic concentration) plasmatic fetal concentration (Czeizel et al. 1999b).

Pregnant women should avoid the estolate formulation because it causes hepatoxicity in 2% up to 10% of the users, increasing 2 to 10 times the AST (aspartate aminotransferase) and ALT (alanine aminotransferase) concentrations and up to three times the level of alkaline phosphatase (Lewis 2000).

FDA classifies erythromycin as a category B agent. There are no reports about the teratogenic effects of this antimicrobial agent. The *Collaborative Perinatal Project* could not detect any risk of malformation in 230 babies exposed to erythromycin throughout pregnancy stages (Einarson et al. 2001). Other similar studies, like the *Hungarian Case-Control Surveillance of Congenital Abnormalities* (previously described here), observed that only 0.5% of both malformed (22,865) and non-malformed (38,151) babies were exposed to erythromycin (Czeizel et al. 1999b; Neibyl 2003). Thus, there is no increased risk of teratogenicity due to use of erythromycin.

A study carried out by the *Center for Disease Control and Prevention* (CDC) observed a greater risk of pyloric stenosis in children born from mothers exposed to erythromycin. CDC concluded that the use of erythromycin in pregnancy should be reassessed and analyzed very carefully (Honein et al. 1999). However, another study using a bigger sample did not observe evidence of increased risk for pyloric stenosis among infants born from mothers exposed to erythromycin during pregnancy (Louik et al. 2002). A recent study (Sorensen et al. 2003) observed a relationship between pyloric stenosis in newborn babies and breast feeding mothers exposed to erythromycin. While no conclusive results exist, the use of erythromycin in pregnancy should be carefully analyzed.

Clarithromycin is another macrolide mainly used for the treatment of infections of the upper-respiratory tract, for *H. pylori* eradication and for prophylaxis against the *Mycobacterium avium* complex in HIV positive patients, especially in the pregnant ones.

Data on clarithromycin use during pregnancy are few and contradictory. Einarson et al. (1998) compared 157 women exposed to clarithromycin during pregnancy to women not exposed to any kind of teratogenic agents (drugs, cigarettes, alcohol, etc.). No significant differences were observed regarding malformation between the two groups, considering that 122 pregnant women used the antibiotic in the first trimester. However, the rate of spontaneous abortion was significantly leigher (14%) in the group exposed to clarithromycin than in the control group (7%).

The use of doses 2 to 4 times greater than the usual dose in human beings did not show any teratogenic effect in rats or rabbits. However, these doses in other strains of rats caused cardiovascular anomalies in the offspring. In addition, doses four times the usual human dose caused a variable incidence of palatine cleft in rats (FDA 2000). FDA classified clarithromycin as a category C agent. Thus, it should be used during pregnancy only when no other safe therapeutic option is available (FDA 2000).

Roxithromycin (a macrolide derivative from erythromycin) shows more predictable absorption, higher plasmatic levels and prolonged half-life in both serum and tissue (Chastre et al. 1987). It can be used against *Chlamydia trachomatis and Ureaplasma urealyticum*, which causes gynecological infections in pregnant women (Garland and O'Reilly 1995) or in association with isoniazid or rifampicin to treat tuberculosis (Rastogi et al. 1995). It penetrates the placental barrier penetration (4.3%) better than erythromycin (3.0%) and azithromycin (2.6%). Reproductive studies in rats, mice and rabbits at doses of 100, 400 and 135 mg/kg/day, respectively, did not show developmental abnormalities. In rats, doses above 180 mg/kg/day caused embryotoxicity and toxicity to the mother. Although no teratogenic effects were demonstrated at usual doses, the safety in human beings is still not well established. It is classified as category B by FDA (Aventis Pharmaceutical 2000).

Azithromycin is a macrolide mainly used to treat pharyngeal infections and pneumonia. Its pharmacokinetics allow

the once-a-day administration during a short period improving patient compliance (Schonwald et al. 1999). It is very often used to treat urethritis caused by *Chlamydia trachomatis* in pregnant women (Bush and Rosa 1994) showing the same efficacy as to amoxicillin (Jacobson et al. 2001). Despite intensive reports of the use of azithromycin against chlamydial infections during pregnancy, there are few data on the literature about its safety. These reports have been indicated no significant teratogenic potential. The FDA classifies it as category B (Pfizer 2003).

Telithromycin is a semisynthetic erythromycin derivative with enhanced activity against macrolide-resistant *Streptococci* (Bryskier 2000). This enhanced activity probably occurs due to its binding to accessory sites of the 23S subunit of the bacterial ribosome (plus the binding to the 50S portion) inhibiting more intensely the protein synthesis (Douthwait et al. 2000). The antibacterial spectrum of telithromycin includes gram-positive bacilli and cocci, gram-negative cocci, some gram-negative bacilli, enteric pathogens and some anaerobic microorganisms (Jamjian et al. 1997).

At present, there are no studies on pregnant women and the data about telithromycin's teratogenic potential were obtained through animal models including rabbits and rats. The doses used in these studies were larger than the doses usually administered to human beings, but no evidence of teratogenic effects was found. FDA classifies it as category C agent and, like other agents with the same classification, it should be used during pregnancy only if a clear potential benefit could justify the potential risk (Aventis 2004).

5.2.3. Lincosamides

Of the two clinically important lincosamides: lincomycin (extracted originally from *Streptomyces lincolnensis*) and clindamycin (chemically derived from lincomycin), only the second one has been used during pregnancy. Like the macrolides, these drugs inhibit the protein synthesis, presenting activity against *Staphylococci*, *Streptococi* and, in particular, against *Bacteriodes fragilis* and many anaerobic organisms (Greenwood 1997).

The clindamycin plasmatic concentration seem not to differ between pregnant and non-pregnant women (Weinstein et al. 1976). In fetal blood, it reaches about 50% of the concentration verified in the maternal blood (Philipson 1973). No increased teratogenic risk was observed in 647 babies previously exposed to clindamycin during the first trimester of pregnancy (Einarson et al. 2001). FDA classifies both lincomycin and clindamycin as category B agents.

5.2.4. Aminoglycosides

Aminoglycosides like gentamicin, tobramycin, kanamycin, streptomycin and amikacin are bactericidal antibiotics that inhibit protein synthesis by binding to the 30S sub-unit of the bacterial ribosomes, particularly of gram-negative aerobic organisms (Greenwood 1997).

The aminoglycosides have been used in association to penicillins against *Pseudomonas aeruginosa* infections (Dashe and Gilstrap 1997) during pregnancy. No other teratogenic effect than ototoxicity has been associated with the use of these drugs, markedly with streptomycin and kanamycin, during the first trimester of pregnancy (Niebyl 2003). A previous study that observed 1,619 newborns from mothers exposed to several agents used for the treatment of tuberculosis, failed to associate streptomycin with congenital defects (Marynowski and Sianozecka 1972). However, FDA classifies streptomycin as a category D agent due to many other reports on ototoxicity and nephrotoxicity in newborn babies of mothers exposed to the drug in the first trimester of pregnancy (Conway and Birt 1965; Donald and Sellars 1981).

There are very few data regarding the use of amikacin during pregnancy. A retrospective study in 391 mothers, which used the antibiotic, showed hearing disturbs in 2.3% of the babies. Amikacin is also classified as a category D agent by FDA, but there are no reports of its teratogenicity in the literature (Einarson et al. 2001).

In addition, the use of any aminoglycoside agent with neuromuscular blockers in myasthenic patients could cause difficulties during the labor or respiratory disturbance in the parturient women due to an enhancement in neuromuscular blockage (Murphy 1984). Besides, the concomitant use of aminoglycosides and cephalosporins could enhance the nephrotoxicity (Niebyl 2003).

Gentamicin is the most widely used aminoglycoside, especially used to treat pyelonephritis resistant to beta-lactam agents (Christensen 2000). It freely crosses the placenta reaching fetal concentration peaks of approximately 40% of the maternal blood concentration, one to two hours after intramuscular administration (Weinstein et al. 1976). FDA classifies this antibiotic as a category C agent. There are no reports about gentamicin's teratogenicity (Czeizel et al. 2000a), but some studies showed nephrotoxicity in newborn babies (Chan and Ng 1985). As a rule, among aminoglycosides only gentamicin could be used with some safety in pregnancy but, in general, the aminoglycosides should be reserved for cases with restricted indication and they must be used in the smallest dose during the shortest time possible.

5.2.5. Tetracyclines

Tetracyclines are bacteriostatic agents that bind to the 30S sub-unit of the bacterial ribosome inhibiting protein synthesis. They are broad-spectrum antibiotics with activity against aerobic and anaerobic gram-positive and gram-negative organisms, *Rickettsiae*, mycoplasms, and *Chlamydiae* (Dashe and Gilstrap 1997).

All tetracyclines freely cross the placenta reaching significant levels in the fetal blood. The plasmatic concentration of the umbilical cord reaches 60% and the amniotic liquid reaches 20% of the level in the mother's blood. These drugs can also be found at relative high concentrations in motheŕs milk (Czeizel and Rockenbauer 2000).

Tetracyclines form very strong chelates with calcium in developing bones and teeth (Niebyl 2003), leading to yellow-brownish stains on the teeth and bones due to deposition in these tissues during the calcification process. Tetracyclines are absolutely contra-indicated in pregnant women during calcification stage of hard tissues, i.e., after the 20th week of pregnancy (Einarson et al. 2001). Permanent teeth are affected just when the administration occurs before birth and less than 8 years of age (Briggs et al. 2002). Tetracyclines could also cause acute-fatty hepatic necrosis in pregnant women (Hautekeete 1995).

FDA classifies all tetracyclines as category D agents. The literature is very controversial concerning their teratogenicity. While some authors consider tetracyclines safe during the first three months of pregnancy (Niebyl 2003) other authors consider that these drugs, particularly oxytetracycline, present a teratogenic risk to the fetus if they are

used during the second month of pregnancy and could cause neural-tube defects, palatine cleft and severe congenital cardiovascular abnormalities (Czeizel and Rockenbauer 2000).
Based on FDA recommendations and the controversial studies, tetracyclines are not recommended during any stage of pregnancy.

5.2.6. Chloramphenicol

First discovered in 1947, chloramphenicol is obtained from *Streptomyces venezuelae* strains. It is a bacteriostatic agent, which inhibits the protein synthesis trough binding to the 50S sub-unit of the bacterial ribosome. Chloramphenicol freely crosses the placenta (Czeizel et al. 2000c).
The drug is metabolized by hepatic conjugation and forms a glucuronide that is excreted in urine. The liver of newborn babies cannot perform the conjugation process causing high plasmatic concentrations of free drug that is called the *Grey Baby Syndrome* (Johnson 2003). This syndrome is characterized by cyanosis, paleness, abdominal distension, vomiting and circulatory collapse resulting in 50% mortality (Knight 1994). A study based on the Hungarian Case-Control Surveillance of Congenital Abnormalities during a period between 1980 to 1996, did not found any teratogenic risk to fetuses of mothers exposed to chloramphenicol during early stages of pregnancy (Czeizel et al. 2000c). However, FDA classifies chloramphenicol as category C and it should be used just in case of absolute necessity.

5.2.7. Oxazolidinones

Oxazolidinones are synthetic antibacterial agents that inhibit bacterial protein synthesis (Swaney et al. 1998). Linezolid is the main representative of this group and it is mainly used to treat skin and soft tissue infections, pneumonia and bacteremia (Clemett and Markham 2000). It is bacteriostatic against gram-positive organisms including methicillin-resistant *Staphylococci*, penicillin-resistant *Pneomococci* and vancomycin-resistant *Enterococcus faecalis* and *E. faecium* (Clemett and Markham 2000).
Linezolid did not show teratogenic potential in mice at levels four fold higher than in humans (450 mg/kg/day) or in rats at levels equivalent to that observed in humans (15 and 50 mg/kg/day). However, those linezolid levels caused embryotoxicity and fetal toxicity. Increased postimplantational embryo death, including total loss of the litter, decreased fetal body weights, and an increased incidence of costal cartilage fusion was observed in mice. Decreased fetal body-weights and reduced ossification of sternebrae were observed in rats. There are no adequate and well-controlled studies in pregnant women. Thus, linezolid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. FDA classifies it as category C agent (Pharmacia & Upjohn Company 2004).

5.3. DNA synthesis inhibitors

5.3.1. Metronidazole

Metronidazole is derived from nitroimidazol that inhibits the replication of bacterial DNA. Originally, it was used to treat infections caused by protozoa, first for trichomoniasis and later for amebiasis and giardiasis. The drug showed also intensive antibacterial activity, especially against anaerobic organisms (Greenwood 1997). During pregnancy, it is restricted to treat infections caused by *Trichomonas vaginalis* or caused by anaerobic microorganisms (Sorensen et al. 1999). This antibiotic freely crosses the placenta and reaches the fetal blood and amniotic liquid at high concentrations (Rodin and Hass 1966).
Chronic exposition to high doses has been shown to cause cancer in rodents and mutation in microorganisms. In addition, it has been associated to a possible teratogenic or cancer-inductor agent in fetuses (Niebyl 2003). Prospective and retrospective studies did not confirm these possibilities and they have failed to show any toxic effect on pregnant women or newborn babies (Beard et al. 1988; Piper et al. 1993; Sorensen et al. 1999; Czeizel and Rockenbauer 2000). FDA classifies metronidazole as category B agent.

5.3.2. Quinolones

Quinolones are wide-spectrum bactericidal antibiotics that inhibit the DNA-gyrase of bacteria. Ciprofloxacin, norfloxacin, gatifloxacin, levofloxacin and ofloxacin are representatives of this group (Saravanos and Duff 1992). There is great concern to use these agents during pregnancy because the mammalian gyrase is very similar to the bacterial one.
The quinolones reach high concentrations in the amniotic fluid and umbilical cord blood (Loebstein et al. 1998). They are used to treat urinary infections that do not respond to conventional treatment because they usually reach high concentrations in the urinary tract (Hootn and Stamm 1997). However, the use of these drugs in pregnancy is still very controversial.
Some studies carried out on animals have shown damage to the fetal cartilages after the mothers were exposed to quinolones (Grady 2003). Other studies in animals have also shown that offspring exposed to quinolones have developed severe arthropathies caused by these antibiotics (Yabe et al. 1997; Nagai et al. 2002). A recent study carried out by the author of the present paper (not yet published) showed that ciprofloxacin administered to pregnant rats at doses of 20 and 40 mg/kg caused alteration in body weight, cranium and thorax measurements in the fetuses. Cranial flattening and alteration in the number of ossifications of the sternum bone were also verified.
Despite these serious adverse effects observed in animal models, other studies in human beings did not found any alterations in the joints of babies from mothers exposed to many quinolones in several periods of pregnancy (Berkoivitch et al. 1994; Danisovicova et al. 1994; Loebstein et al. 1998). Anyway, these drugs are relatively new in the global market and there is not enough clinical experience to guarantee their safety. Thus, the use of these agents in pregnancy should be avoided. FDA classifies all the quinolones listed above as category C agents.

5.4. Bacterial metabolism inhibitors

5.4.1. Sulfonamides

First introduced in the medical therapeutics in the 1930s, the sulfonamides are the oldest class of antibiotics known. They are bacteriostatic agents that inhibit folic acid synthesis in bacteria (Reid et al. 1975). The main indication to use these agents during pregnancy in the past was to treat urinary tract infections caused by gram-positive cocci or gram-negative rods (Dashe and Gilstrap 1997).

Two hours after drug administration, a balance between maternal and fetal blood concentration is reached (Czeizel et al. 2001a). Sulfonamides can compete with bilirubin for binding sites of plasmatic albumin when administered right before the birth, causing a high concentration of free bilirubin in the fetal blood, which is called *kernicterus* (Ahlfors 2000). In addition, the sulfonamides could cause hemolytic anemia in the baby due to a glucose-6-phosphate dehydrogenase deficiency (Perkins 1971).

FDA classifies the sulfonamides as category B agents. There is no relationship between teratogenic effects and the use of sulfonamides (Dashe and Gilstrap 1997).

Trimethoprim is usually associated with sulfonamides because it competitively inhibits the bacterial folate-reductase that results in a synergistic action, which is very important to treat urinary infections. Other indications of this association include prophylaxis of pneumonia caused by *Pneumocystis carinii* in HIV-positive pregnant women (Dashe and Gilstrap 1997). The association of trimethoprim-sulphonamide produces similar concentrations in both maternal and fetal blood (Reid et al. 1975).

The affinity of trimethoprim for folate-reductase of bacteria is around 50,000 times greater than the affinity for mammalian folate-reductase. However, studies have shown the ability of this drug to interfere in fetal formation, causing palatine cleft, malformation in the urinary tract and in the cardiovascular system (Hernandez-Diaz et al. 2000; Czeizel et al. 2001a). Folic acid supplementation in mothers using folate antagonists reduces these malformations in the babies (Hernandez-Diaz et al. 2000). Trimethoprim is classified as category C agent by FDA and should not be used in the first three months of pregnancy.

5.4.2. Polymyxins

Among the polymyxins, colistin (polymyxin E) is the mainly representative. It is a basic polypeptide that binds to anionic phospholipid sites in bacterial cytoplasmic membranes, which induces the disruption of the membrane structure, modifying the membrane permeability and inducing the leakage of intracellular contents.

The antimicrobial activity of colistin is restricted to gram-negative bacteria, including *Enterobacter*, *E. coli*, *Klebsiella*, *Salmonella*, *Pasteurella*, *Bordetella*, and *Shigella*, which are usually sensitive to concentrations between 0.05 to 2.0 μg/mL. Most strains of *Pseudomonas aeruginosa* are inhibited *in vitro* by less than 8 μg/mL (Chambers 1996).

The use of colistin during pregnancy must be restricted to treat infection caused by *P. aeruginosa* or associated to ampicillin when a ceasarean-sectioning prophylaxis is indicated (Birkenfeld and Anteby 1983). In general, the use of colistin during pregnancy is not recommended because it is usually possible to use other less-toxic drugs and due to a large number of side effects (nephrotoxicity, neurotoxicity, neuromuscular blockade, ataxia, dizziness, convulsions and circumoral paraesthesia) caused by colistin (Knothe and Dette 1985). FDA classifies it as category C agent (Parke-Davis 1997).

6. Conclusions

The present review shows that a high number of antibiotics could be used with relatively great safety during pregnancy. However, those classified in the categories C and D by FDA should be avoided. The physician must keep in mind the teratogenic potential and the bacterial sensitivity of the antibiotic classes to promote a safe and quality therapy for the pregnant women. The pharmacist must know the teratogenic potentials of all antibiotics to guide the women about the real risks and the safety of these medications. Statements such as "*Use with caution, especially in the first trimester*" or "*the benefits should be analyzed along the toxic potential or unknown hazards to the fetus*", usually found in the manufacturer data sheets, rather than helping, could cause confusion in the future mothers. The present review could help the physician and the pharmacist in the guidance and prescription to treat infection in the pregnant women.

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