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Rational use of antimicrobials in dentistry during pregnancy

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Abstract

The use of medicines during pregnancy deserves special attention from dentists due to the potential risks to fetal development. The prescription of antimicrobial drugs during this period must be based not only on the etiology of the disease but also on the drug's effect on the embryo, which may be toxic, possibly leading to irreversible lesions. Interest in studies of the teratogenic effects of drugs increased in response to reports of the high incidence of phocomelia in patients treated with thalidomide. Although teratogenicity has long been known, pregnant women today are still exposed to this risk. The effects of drugs depend on the level of susceptibility of the fetus and on the period of exposure during pregnancy. In this context, and considering the paucity of studies on this subject in dentistry, the aim of this review was to offer an up-to-date compilation of data on the antimicrobial drugs most frequently used during pregnancy and the effects of their use.

Key words: *Pregnancy, antimicrobials, odontology.*

Introduction

The use of antimicrobials has increased steadily since the discovery of penicillin (1). Numerous drugs have been developed since then, few of which were considered potentially toxic (2). Interest in studies of the teratogenic effects of drugs during pregnancy has increased since 1961, when the high incidence of phocomelia among patients treated with thalidomide was discovered (2). Although teratogenicity has long been known, pregnant women are still exposed to this risk (3).

Previous studies have found that 99% of pregnant women were prescribed at least one drug during pregnancy. The average consumption of drugs, excluding vitamins and supplements, is estimated to be 1.3 drugs per woman (3,4). In Brazil, this average is 4.2 drugs per woman during pregnancy, and the use of just one drug during pregnancy is 83% (2,5).

In this context, and in view of the scant studies on this subject in the field of dentistry, the purpose of this review was to make an up-to-date compilation of data on antimicrobial drugs commonly prescribed by dentists for pregnant women.

Methodology

This study consisted of a systematic bibliographic review of national and international researches involving the antimicrobials most frequently used in dentistry and their effects during pregnancy.

The bibliographic review involved journals and books containing data from the MEDLINE, LILACS (Latin-American and Caribbean Health Sciences), SciELO (Scientific Electronic Library Online - Brazil), and Scopus databases. This review found a paucity of studies published from 1990 to 2006. The

research was conducted using the keywords: "antibiotics and pregnancy", "antimicrobials and pregnancy", "antibacterial agents and pregnancy", and "puerperium".

Bibliographic review

The precise determination of the safe use of antimicrobial drugs in dentistry is not easy, particularly due to the ethical implications involved in studies on humans (2,5). The available data have been garnered through clinical observations of similar cases and cause-effect correlations in fetal abnormalities (6). Numerous studies have been based on researches with animals. However, they require careful evaluation due to the morphofunctional differences among species and considering the real correlation to adverse effects on humans (2,3).

Pregnancy is a dynamic state characterized by physiological and pharmacokinetic alterations that affect two organisms simultaneously (3,7-9). The effects of drugs depend on the level of susceptibility of the fetus and on the drug, as well as on the period of exposure during pregnancy. The genotype of mother and child may also contribute to higher susceptibility or resistance to a certain pharmacological agent. Also, the level of immaturity of essential organs may lead to different responses, according to the age of the fetus (2,8,10,11).

The use of teratogenic substances during the preimplantation phase that occurs in the first two weeks after fertilization may determine failure in embryonic fixation, leading to fetal death; therefore, the occurrence of teratogenesis is very rare (2,12, 13). Throughout this period, drugs such as metronidazol, erythromycin estolate and tetracycline must be avoided (7, 11,12,13).

During the phase of organogenesis, malformations are more frequently observed and are considered the main alterations associated with the use of some antimicrobials drugs. These drugs are responsible for the worst prognoses, such as congenital abnormalities, intrauterine growth retardation and teratogenesis (2,12,14). Throughout this period, antimetabolic drugs, especially those with activity on nucleic acid such as sulfamethoxazole, are not recommended because they are associated with several major malformations such as neural tube and cardiovascular defects (15).

During the last phase of embryonic development (the fetal phase), which comprises the 25th week until the end of pregnancy, exposure to drugs may lead to reduced body weight, functional disorders and carcinogenesis. These effects are correlated to high cell replication and immature biotransformation mechanism (8,14,16). During this phase, drugs such as sulfonamide, quinolone, erythromycin estolate, tetracycline and chloramphenicol are not recommended (12,16).

Other aspects that must be observed in pregnancy involve maternal physiological transformations (4,10,14). Most changes derive from hormonal alterations, which are characterized mainly by increased estrogen, progesterone, human chorionic gonadotropin (beta HCG) and prolactine levels (4,9,12,14). During pregnancy, metabolic alterations also occur, e.g., protein metabolism, lipid and glucose profiles, alterations in respiratory dynamics, changes in eating habits, gestational gingivitis, gastroesophageal reflux, constipation and immunological alterations (4,9,12).

The intake of liquids is also altered in this phase, and the plasmatic volume may be up to 50% above the normal average (2,4,10,13). According to some authors, to maintain therapeutic concentrations of a drug during pregnancy may require higher doses and lower intervals between intakes, due to increased volemia and higher cardiac deficit (4,6). These physiological alterations, allied to the pharmacokinetic characteristics of pregnancy, may even lead to failure of the therapy (7,8,16). In early pregnancy, gastrointestinal disorders, nausea and emesis associated with estrogen-related peristalsis may interfere with the absorption of antimicrobials taken orally (9,13).

The pharmacokinetic characteristics of drugs are of great importance in the maternal-fetal context (8,10,16,17). Among these characteristics, low molecular weight, lipophilic characteristics and the ability to cross through tissue compartments by concentration-dependent diffusion, and high degree of plasma-protein binding (e.g., clindamycin, doxicyclin, oxacyclin, chloramphenicol and erythromycin) are particularly important. Increased delivery from plasma to other biological sites may occur, augmenting renal elimination (7-10).

Other important aspects involve biotransformation. Special attention should focus on plasma concentrations of drugs, particularly when a drug is prescribed concomitantly with an enzyme-inducing agent that maximizes its metabolism (9,10). With regard to the elimination of antimicrobials, the increased renal blood flow and glomerular filtration rate resulting from augmented cardiac deficit lead to higher drug filtration rates. The level of unaltered drugs excreted by urine, except for some types of penicillin, increases (7, 9,17). Based on the aforementioned effects, it is clear that the ideal antimicrobial drug for pregnant woman should not pass through the placental barrier, and it is desirable to have conclusive clinical evidence of its safety is (6,10).

On the other hand, the antimicrobial resistance of microorganisms has been increasing at alarming rates worldwide. In view of this problem, it is sometimes not possible to prescribe a drug based solely on clinical evidence of its safety and effectiveness (18,19). Nevertheless, most of the antimicrobials used in dentistry are reportedly safe, allowing for their prescription during pregnancy (3,7,17,19).

In situations where evidence-based therapeutic choice is not possible, maternal-fetal monitoring is essential (6). Professionals today follow the recommendations of the Food and Drug Administration (FDA) regarding the safety of drugs for use during pregnancy, dividing them into five categories of teratogenic risk: A, B, C, D and X (1,7,16).

Category A – This category includes drugs and substances that have been tested through controlled studies in women. These studies have shown no risk to the fetus during the first semester of pregnancy and the possibility of damage to the fetus is remote.

Category B – Studies with animals have shown that the substance offers no risk to the fetus, but no controlled studies have been made in humans to verify possible adverse effects on the fetus. This category includes drugs that have shown adverse effects on animal fetuses, but controlled studies on humans did not reveal risks to the fetus.
Category C – Studies with animals have indicated that these drugs may have teratogenic or/and toxic effects on the embryo, but no controlled studies involving women have been made. A drug also falls into this category when there are no available controlled studies involving either animals or humans.
Category D – There is evidence of risk to the human fetus, but the benefits in certain situations, e.g., serious diseases or life-threatening situations with no other alternative therapy, may justify the use of these drugs during pregnancy.
Category X – Studies in animals or humans have demonstrated that the drug causes alterations of the fetus or have shown evidence of increased risk to the fetus, based on experiments in both animals and humans. The risk to the fetus outweighs any benefit.
In dentistry, the use of antimicrobials is indicated in several cases, including presurgical prophylaxis and in the endodontic treatment of periapical abscesses (18-20). Due to the magnitude of the subject under discussion, we will discuss here only the factors that may influence the selection of a drug, and the available evidence of the bacterial infections most frequently observed during pregnancy.

1. Penicillin
Penicillins are bactericides that belong to the betalactamic group. Their mechanism of activity is based on the inhibition of bacterial cell wall synthesis through inactivation of the transpeptidase enzyme (17,21).
The penicillins most frequently used in dentistry are classified as natural penicillin: crystalline penicillin G (endovenous-EV), penicillin G procaine (intramuscular-IM), and penicillin G benzatine (IM); and semisynthetic penicillin: phenoxymethylpenicillin (via oral-VO), betalactamase-resistant penicillin: oxacillin, cloxacillin and methicillin; and aminopenicillin: ampicillin, amoxicillin (3,21).
With regard to their activity spectrum, they generally act on Gram-positive rods. Oxacillin, methicillin and dicloxacin, and also larger spectrum penicillin (such as amoxicillin associated with clavulanic acid and ampicillin associated with sulbactam) are effective on Gram-negative microorganisms (3,17,21).
Undoubtedly this antimicrobial drug is the most indicated for pregnant women, since it has highly selective toxicity (14, 17). Penicillin can be described as safe and is classified as category B by the FDA. Few side effects are described, and the most important reactions are gastrointestinal disorders and hypersensitivity (1,22). The occurrence of hypersensitivity reactions may vary from 1% to 10% of patients and may be fatal for 0.02% of cases. Acute reactions occur after 22 minutes following intake, and are characterized by urticaria, angiodema, bronchospasm, hypotension or anaphylactic shock. Immediate reactions occur between 30 minutes and 48 hours after penicillin intake and are represented by urticaria, angiodema, bronchospasm, wheezing and local inflammation. Late reactions occur after 72 hours of penicillin intake, with characteristic symptoms: skin reactions, exfoliative dermatitis, serious stomatitis and acute glossitis (22,23). In dentistry, its use is indicated in endodontics, implantology, surgery and for bacterial endocarditis prophylaxis, according to the American Heart Association (1,19).

2. Cephalosporins
These drugs also belong to the betalactamic group and show similar activity and resistance mechanisms as those of the penicillins. They are subdivided into generations: first generation: cefazolin, cefalexin, cefadroxil, and cefradine; second generation: cefuroxime, cefprozile, and cefmetazol; third generation: cefotaxime, cefdinir, ceftriaxone, cefoperazone and ceftazidime; fourth generation: cefepime, and cefpiroma (21,23). The cephalosporins, in addition to penicillin, are one of the antimicrobial drugs most frequently indicated during pregnancy and are classified as category B by the FDA (7, 21). Like penicillin, cephalosporins show low occurrence of adverse reactions, except for hypersensitivity, which affects 10% of patients with hypersensitivity to penicillin due to cross-hypersensitivity (23).

3. Macrolides
Erythromycin, clarithromycin, roxithromycin, and azithromycin are macrolides that interfere with the bacterial synthesis of leucine, by their action on 50S subunits of ribosomes, inhibiting the translocation of t-RNA (21,24). They are bacteriostatic, but may be bactericide, depending on the microbial species and inoculum microorganisms involved in the infectious process, as well as the drug concentration in the infected area (21,25).
They show similar spectrum of activity as that of penicillin. They are effective against Gram-positive, anaerobic and a wide spectrum of Gram-negative microorganisms (24). Their toxicity is low due to the absence of subunit 50S in human cells (12). However, erithromycin may cause cholestatic hepatitis, general hepatoxicity and gastrointestinal alterations, mainly in estolate form (24). Erythromycin is classified as category B by the FDA and the base form is considered the best form for use during pregnancy (1). In dentistry, besides erithromycin associated with metronizadol, azithromycin and clarithromycin are indicated for penicillin-allergic patients, treatment of endodontic infections after root canal decontamination, and periapical abscesses (19,22). It is considered the third choice for the prophylaxis of bacterial endocarditis (18).

4. Lincosamines
In this group, clindamycin is the only drug that is indicated

for pregnant women in dentistry (19,21). It is bacteriostatic, although it may have bactericidal effects in high dosages. It is effective against anaerobic and a wide spectrum of Gram-positive microorganisms (21,26). Its mechanism of activity is the bacterial inhibition of protein biosynthesis through activity on ribosome 50S and inhibition of peptidil transferase in tRNA translocation (26).

The drugs of this group have a spectrum of activity similar to that of penicillin, but they are active against betalactamase-producing strains (7,21,26). The adverse reactions most frequently observed are chronic diarrhea and pseudomembranous colitis (27).

There is no evidence of teratogenic risks related to this drug, which is classified as category B by the FDA (3,6,14). In dental practice, it belongs to the group of drugs that can be prescribed for penicillin-allergic patients (19,21). This group is indicated in clinical situations such as osteitis or other bone infections caused by anaerobic microorganisms. It is highly effective in the treatment of abscesses because it is macromolecular, easily phagocyted by macrophages and leukocytes (19,20). Moreover, it can also reach the gingival fluid, maintaining higher concentrations when compared to the minimum inhibitory concentration (MIC) for Gram-negative anaerobic bacteria associated with periodontal disease. This feature eliminates the need for association with metronidazol during pregnancy (7,20). They are usually selected for the treatment of advanced and chronic periodontal diseases, particularly those refractory to penicillin (18).

5. Tetracyclines

These drugs are bacteriostatic with a wider spectrum of activity than penicillin and macrolides. They block bacterial protein synthesis by binding to 30S unit ribosomes and inhibit RNA aminoacyl transferase. They are active against Gram-positive, Gram-negative, microaerophilic and anaerobic microorganisms (1,27).

The high affinity of this drug group to bivalent ions (such as calcium) affects bone development, inducing significant reductions in gingival colagenase and also high periodontal bone loss. Moreover, it may cause dental alterations such as dentin pigmentation and dental enamel hypoplasia (6,21). It shows direct interference in mineralized tissue, formation of dental germs in permanent teeth and deciduous fetal dentition (7,21). Because of these effects, they are classified as category D by the FDA and are considered unsuitable for use during pregnancy. Tetracycline may cause reactions such as nausea, epigastric pain, abdominal distention, oral ulcerative lesions, diarrhea, hepatic and renal disorder and photosensitivity (1, 12,14).

6. Metronidazol

Metronidazol is an essentially antiprotozoan prodrug (28). It is widely used in dentistry in association with other antimicrobials such as betalactamics and macrolides. Metronidazol is the third most frequently prescribed antimicrobial drug in dentistry during pregnancy (3,7,29). It has a narrow spectrum of activity, acting against anaerobic and microaerophilic microorganisms, with no effect on aerobic microorganisms (21, 29). Its mechanism of activity involves decrease of the level of nicotinamide adenine dinucleotide (NADH) synthesis and reduced level of nicotinamide adenine dinucleotide phosphate (NADPH) due to its interference in the hydrogen pathway (28). In dentistry, it is prescribed in association with amoxicillin for the treatment of advanced and/or acute periodontitis, mainly for necrotizing ulcerative gingivitis (NUG) (21,29). It is also indicated for the treatment of acute infections such as pericoronaritis and periapical abscesses (18). This drug shows few adverse effects if used during a limited period. It may cause blood dyscrasias, gastrointestinal disorders, and a metallic taste in the mouth (12,18,29). It is not recommended during the first trimester of pregnancy, although it is classified as a relatively safe antiprotozoan, and is classified as category B by the FDA (1,29).

Final Considerations

There are no definitive and complete answers for the safe use of antimicrobials during pregnancy. However, the available information provides the dentist with a choice of various therapeutic and prophylactic options within relatively safe limits. The prescription of drugs during pregnancy must be evaluated carefully, weighing the risks versus benefits for both fetus and mother. Antimicrobial drugs with toxic potential should therefore be prescribed by the physician only if the infectious disease is life-threatening and there is no other choice for its treatment.

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