Pharmacotherapy of the Dental Patient during Pregnancy and Lactation

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Summary

The pregnant woman and the nursing mother present a special set of concern for the dental practitioner. Many drugs when taken by a pregnant patient or a breastfeeding mother can pass the placenta or breast alveolar cells and enter the bloodstream of the fetus or the human milk, adversely affecting fetal development or newborn child. The effect that a medication has on a fetus or a newborn child depends on the type of drug, the amount of drug taken, the duration of therapy and in pregnancy the trimester during which the drug was taken.

This is a brief review of the relative risks of drugs commonly used in dental care for the pregnant patient and the nursing mother. A list is given of possible harmful drugs in pregnancy and drugs contraindicated during breastfeeding.

Key words: *pregnancy drug effects, pregnancy risk drug category, drugs and lactation*

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Introduction

Medication exposure during pregnancy is very frequent. An international study in 1992 showed that antenatally only 14% of women received no drugs (1). Various studies show marked intercountry variations in medication habits (2,3).

In the case of pregnant women when the dental practitioner needs some therapeutic agents commonly used for dental care, he must determine the potential benefits of the dental therapy, which must clearly overweigh the potential risk. Pharmacotherapy during pregnancy is associated with special problems in the selection of medication and dosage, primarily due to potential teratogenic or toxic effects on the fetus by the drug itself and secondly due to the physiologic adjustments in the mother in response to pregnancy (4).

Maternal changes in physiology, including fluid and tissue composition, occur during pregnancy. This results in differences in the maternal pharmacokinetics of drugs administered during pregnancy. These modified pharmacokinetic variables ultimately can have an influence on drug metabolites or toxic compounds in the maternal circulation that are capable of crossing the placenta and causing fetal therapeutic and toxic responses to drugs (5).

Pharmacokinetics during pregnancy

Maternal drug *absorption* may be decreased by the combination of delayed gastric emptying and decreased motility. An increase in plasma progesterone level during pregnancy is believed to be responsible for the reduction in intestinal motility

(6). There is also a reduction in gastric acid secretions and an increase in mucus secretions, with a consequent increase in gastric pH. These may alter the dissolution and absorption of the drug. Absorption from sites other than the gastrointestinal tract may also be affected. For example, increased pulmonary absorption may result from greater minute ventilation and increased cutaneous absorption as a result of greater surface area and blood flow (7).

The apparent volume of *distribution* of many drugs increases predictably during pregnancy as maternal plasma volume expands from 30 to 50% during the first trimester (8). Some of these are indicated in Table 1. As a result of haemodilution, plasma albumin declines. The free concentration of drugs that bind to albumine increases, but the net effect for most agents is an unaltered free drug concentration, because more free drug is available for biotransformation (6). Laurence's opinion is that a useful general guide during pregnancy is to maintain drug concentrations at the lower end of the recommended range (5).

Excretion. Concomitant changes occur in cardiac output and glomerular filtration rates, which also increase approximately 30 to 50% during pregnancy (9). The expanded apparent volume of distribution, together with an increase in renal clearance leads to lower maternal circulating concentrations of drugs. The drugs which are excreted primarily unchanged in the urine such as amoxycillin, demonstrate enhanced elimination and lower steady-state serum concentrations. Its dose should be doubled for systemic infections (but not for urinary tract infections as penicillins are highly concentrated in the urine) (5).

Cholestatis frequently develops during pregnancy and may result in decreased hepatic clearance of drugs that undergo biliary excretion, but their extent can hardly be quantified (6).

Placental drug transfer

The function of the placenta during gestation is protection of the conceptus, maintenance of pregnancy, possible prevention of maternal rejection of the pregnancy, transportation of nutrients and wastes, metabolism of endogenous and xenobiotic substances and edocrine activity. However, any drug or environmental agent that gains access to the maternal bloodstream should be considered capable of crossing the placenta and reaching the fetus unless demonstrated otherwise (7).

In general, lipophilic, unionized, low molecular weight drugs in their free non-protein bound state tend to cross the placenta. A major route of placental drug transfer is a simple diffusion. As with diffusion across other biological membranes lipophilic drugs generally cross the placenta more readily than nonlipophilic compounds. Drugs which are non-ionized at the physiological pH will diffuse across the placenta more rapidly than more basic or acidic compounds. But this distinction is not absolute, since some drugs which are ionised at physiological pH such as salicylate (aspirin) rapidly and efficiently reach the fetus (10). The transfer of many substances across the placenta requires energy or special carriers.

Some other agents, such as barbiturates, narcotic analgesics, and local anesthetics, are "flow limited" in their placental transfer because a decrease in maternal blood flow to the placenta may reduce the placental passage of these agents.

Normal uterine contractions during labor, oxytocic drugs, exogenously administered sympathomimetics, or ß-adrenergic receptor blocking agents all affect maternal and fetal hemodynamics and therefore may modify maternal drug distribution and placental transfer.

Adverse effects of drugs on the fetus

Since 1920 it has been known that external agents can affect fetal development, when it was discovered that X-irradiation during pregnancy could cause fetal malformation or death. The drugs as causative agents in teratogenesis were recognised in 1960 with the shocking affair with thalidomide (11). Drug or chemical exposure during pregnancy are believed to account for about 1% of all fetal malformations (12).

Drugs may act on the embryo and fetus directly or indirectly. Any drug affecting cell division, enzymes, protein synthesis or DNA synthesis is directly a potential teratogen. Indirectly dangerous

drugs are those acting on the uterus (vasoconstriction reduce blood supply and cause fetal anoxia; misoprostol /a synthetic analogue of prostaglandin E/ cause uterine contraction leading to abortion) and on the mother's hormone balance.

The most vulnerable period for major anatomical abnormality is that of organogenesis which occurs during weeks 2-8 of intrauterine life. The adverse actions of drugs taken by the mother at this time may result in permanent birth defects (13). After the organs are formed abnormalities are less anatomically dramatic, but although developing fetus continues to be vulnerable to drug effects.

The use of drugs during the final weeks of pregnancy may have a damaging effect on the fetus at birth. At that time the newborn has an incompletely developed metabolic system which cannot process and eliminate drugs rapidly and effectively. As a result, overdosage may occur.

Drugs known to be teratogenic, probably or suspected or being teratogenic, are listed in Table 2.

The drugs known to be *teratogenic* are:

- *Ethanol* in pregnancy causes impaired fetal development, associated with small size, abnormal facial development and other physical abnormalities and mental retardation (14,15, 16).
- *Cytotoxic drugs* can cause malformations when used in early pregnancy, but more often lead to abortion (5).
- *Retinoides* such as *isotretinoine* and *etretinate*, used by dermatologists to treat different skin diseases (psoriasis, acne etc.), are known teratogens and cause a high proportion of serious abnormalities (skeletal deformities) in exposed fetuses (17).
- *Anticonvulsant drugs*. The incidence of congenital anomalies among babies born to epileptic women is 2-3 times higher than in the healthy population. None of the major anticonvulsants is to be regarded as free from teratogenic effects and no one drug is clearly safer than any other in this regard. *Phenitoin* (18) can cause cleft lip/palate, *valproate* (19) neural tube defects and *carbamazepine* spina bifida and hypospadias (a malformation of the male urethra) (20). However a pregnant epileptic woman under anticonvulsant treatment has a 90% chance of having a normal child (with regular controle of serum α-fetoprotein, uterine ultrasonography and diagnostic amniocentois) (21).
- *Anticoagulant*, *warfarin* administered in the first trimester is associated with nasal hypoplasia and various central nervous system abnormalities, affecting roughly 25% of babies. In the last trimester there is as risk of intracranial hemorrhage in the baby during delivery (22).

For the drugs under suspicion there has been some reluctance to their use in pregnancy. However, most large-scale controlled studies conclude that these agents can be used safely during pregnancy. But in general the best recommendation is to **avoid any drug during the first trimester**.

The drugs *probably teratogenic* are: *cocaine* and *sex hormones*. The data suggested that cocaine--exposed infants may be at increased risk for congenital malformations (23,24,25) and for the sex hormones the results of numerous studies have lead to the conclusion that they are slightly teratogenic and that caution is needed (26,27).

The US Food and Drug Administration (FDA) has established five categories for classifying drugs according to the risks they pose to pregnant women and their fetuses (28).

These categories, labeled A, B, C, D and X are listed below (Table 3) with a description for each. Drugs in category A and B are usually considered safe for use in pregnancy. Drugs in category C may be used despite possible risks. Drugs in category D should usually be avoided and category X is contraindicated because the risks involved clearly outweigh potential benefits. These five categories provide a guide to the relative safety of drugs prescribed to pregnant woman.

Selecting drugs for the pregnant dental patient

In the case of a pregnant patient, the dental practitioner must determine that the potential benefits of the dental therapy required for her care outweigh the risks to the fetus.

The most elective dental procedures must be postponed until after the pregnancy is over, although dental treatment for a pregnant woman who has oral pain, advanced disease or infection should not be delayed.

The therapeutic agents commonly used in dental care for pregnant women are local anesthetics, non-narcotic analgesics, antimicrobials and sedatives/ /anxiolytics.

Risks associated with specific drug classes

Local anesthetics and the admixture

Local anesthetics are considered relatively safe for use during pregnancy. *Lidocain* (Anelok, Lidokain) is a widely used local anesthetic agent of the amide type with low toxic potential. Pregnancy risk for lidocaine is B. Lidocaine like all local anesthetics can cross the placenta. Within the fetus there is a significant decrease in serum α_1-acid glycoprotein (the binding proteins for lidocaine and other basic drugs) and therefore the unbound ("free") drug increases. This could cause fetal depression. The dental practitioner must limit the dose to the minimum required for effective pain control (29).

The *adrenaline*, a naturally occurring hormone, pregnancy risk C is generally considered to have no teratogenic effects when administered with dental anesthetics. Adrenaline can stimulate cardiovascular functions and its administration demands careful technique and proper dosing (30). Adrenaline may delay the second stage of labor in a pregnant woman because the drug inhibits spontaneous or oxytocin-induced uterine contractions. It may also cause anoxia to the fetus (31).

Non-narcotic analgesics

For management of oral pain during pregnancy, among a number of peripherally acting analgesics, *paracetamol* (*acetaminophen*) is considered to be the best choice (32,33). Pregnancy risk for paracetamol is B. The second analgesic is *aspirin*, pregnancy risk D. Aspirin has widespread use in pregnant woman, and in moderate doses has shown no evidence of teratogenesis in humans. There are very few reports in which aspirin can be implicated as a human teratogen (34,35,36). Possibly the increased production of prostaglandins during pregnancy overrides the effects of aspirin in the usual dosages. But aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) such as *ibuprofen* and *naproxen* should be avoided particularly during the third trimester of pregnancy because they have the common mechanism of inhibiting prostaglandin synthesis. By blocking synthesis of the prostaglandins involved in induction of labor, NSAID may prolong pregnancy. Additionally, prostaglandin inhibitors may cause constriction of the *ductus arteriosus* in the fetus, resulting in pulmonary hypertension in the infant. The role of aspirin as an antithrombotic agent and its ability to promote bleeding mean that it should be very definitely avoided at parturition, to avoid delivery complications and postpartum hemorrage in the mother (37).

Antimicrobials

Penicillin G, *penicillin V*, *ampicillin*, *amoxicillin* and *cephalosporins* (all pregnancy risk B) are generally thought to be safe during pregnancy. As remarked above the pharmacokinetic of ampicillin and amoxicillin is altered in pregnant women and this can lead to lower plasma concentrations of the drug when compared with nonpregnant women (38). Pregnancy significantly increases the elimination rate of ampicillin (39). Similar results of the significantly faster elimination rate have also been demonstrated in a pharmacokinetic study on pregnant women and phenoxymethylpenicillin (Penicillin V) (40). *Erythromycin* (except erythromycin estolate) (41,42), *clindamicin* - both pregnancy risk C, and *metronidazole* - pregnancy risk B, are believed to have minimal risk (43).

The greatest concern regarding antimicrobial use is the agents that have limited indications in dentistry: *aminoglycosides* (*gentamycin*) cross the placenta and might theoretically cause otological and perhaps nephrological damage to the fetus. No proven cases of intrauterine damage by gentamicin and tobramycin have been recorded (41).

Tetracycline therapy in the second and third trimester of pregnancy have been implicated for causing tooth discoloration and inhibition of bone

development in infants. In view of their effects on the teeth and the bones, as well as in view of an increased risk of potentially fatal fatty liver degeneration in pregnant women, tetracycline preparations should not be prescribed during pregnancy with the exception of a vital indication (44,45).

Chloramphenicol is contraindicated in pregnancy because of maternal toxicity and fetal circulatory failure called *gray baby syndrome* (46).

Sedatives - anxiolytics

Benzodiazepines (pregnancy risk D) are anxiolytic drugs commonly prescribed in pregnancy. They readily pass from the mother to the fetus. Pregnant women may have some risk of congenital malformation if exposed to benzodiazepines during the 1 st trimester, although data are contradictory and any real effect would appear to be minimal (47,48). The pregnant women should avoid benzodiazepines if possible, during late pregnancy and labour, because floppiness, apnea and withdrawal in the infant can pose obvious clinical problems (49). A single exposure to a clinically acceptable dose of any benzodiazepine, as compared to chronic therapy throughout pregnancy, would have minimal risk (50).

Drugs and breast milk

Breastfeeding of the newborn child has increased during the past ten years in the US and European countries. This, in combination with the explosive growth in the number of new pharmacologic agents concerns over environmental contaminants could be a risk for the breastfeeding infant. Medical professionals too often simply discourage breastfeeding instead of investigating whether the drug enters breast milk and poses a risk to child or not (51,52).

Human milk represents a complex solution of proteins, carbohydrates, fat, and liquid with a composition similar to that in serum. Its composition varies during the weeks and the months of lactation as well as during a single feeding. Human milk has a pH of approximately 7.0, which influnces the distribution of drugs from the maternal circulation into milk. To enter human milk, a drug leaves the maternal circulation and enters the breast alveolar cells by diffusion across cell membranes or into water-filled channels or through binding to carrier proteins. Since milk is more acidic than plasma basic compouds may be slightly concentrated in this fluid, and the concentration of acidic compounds in milk is lower than in plasma. Non-electrolites, such as ethanol and urea, readily enter breast milk and reach the same concentration as in plasma, independent of the pH of the milk (53). For most drugs, the milk concentration is similar to that in the maternal circulation. The usual percentage of the maternal dose transferred to the infant ranges from 0.05% to 2%. Most drugs taken by the mother pose no hazard to the child, but there are exceptions. Practical measures can be used to minimize the passage of drug into milk, e.g., breastfeeding just before the administration of medication so that a significant amount of the drug can be eliminated before the next feeding. Few drugs are considered to be contraindicated during breastfeeding and should be avoided. For some drugs a temporary cessation of breastfeeding is required, some of them must be given with caution during breastfeeding and for some with unknown drug effects care is necessary (Table 4).

When dental treatment is needed to maintain a breastfeeding womans oral health selecting the safest agents is the basic principle of therapy (54). The therapeutic agents most commonly used in dental care are local anesthetics. Low concentrations of *lidocaine* and its metabolite monoethylglycinexylidide have been found in breast milk after a dental procedure, but no risk seems to be involved (55).

Tetracaine (20 times as toxic as procaine) marked serious systemic side effects can develop owing to rapid absorption following topical use (56).

For alleviation of the mother's oral pain peripherally acting analgesic-antipyretic can be used. However *salicylates* are distributed into breast milk and the use of aspirin should be avoided during breastfeeding (possible association with Reyes syndrome!) (5). *Paracetamol* is also excreted into breast milk in low concentrations, but no adverse effects have been reported, so it can be a drug of choice.

Administration of any of the central nervous system depressants commonly used for sedation is problematic. *Benzodiazepines* are safe if their use is

brief. Prolonged use may cause a somnolence or poor suckling (50).

The infection of the orodental system in the breastfeeding mother must also be treated, but only a few antiinfectives pose no hazard (57).

Penicillins and *cephalosporins* are excreted in breast milk and their use, particularly penicillin G and V, in breastfeeding women may sensitize the infant to penicillins (31).

Aminoglycosides are excreted in small amounts in breast milk. An alternative feeding method is recommended during therapy, because the half-life of aminoglycosides is prolonged in neonates owing to the immaturity of their renal system (58).

Tetracyclines are excreted in breast milk and should not be used in breast feeding women because of the risk of discoloration of teeth, enamel defects and retardation of the childs bone growth (59).

Chloramphenicol is unsafe. The drug is excreted in milk in low concentrations, posing a risk of bone marow depression and a slight risk of "gray baby sindrome" (60).

Clindamycin, *lincomycin*, *metronidazole* and *sulphonamide* should be avoided (5).

Erythromicin can be used with cautioun (30).

Conclusion

When treating pregnant patients or breastfeeding mothers the dental practitioners needs to determine that the potential benefits of the drug required for the mothers dental care outweigh the risks to the fetus or neonate.

Some drugs routinely used are more unsafe than others and these should be avoided.

A list of unsafe drugs is not practicable, because much depends on the timing of the drug administration (during first, second or third trimester), the dosage and the duration of therapy. Dental practitioners, who usually use drugs with short metabolic half-lives, administered for limited periods and in reduced dosages, are less likely to cause complications during pregnancy and lactation.