Drug therapy during pregnancy: implications for dental practice

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IN BRIEF

- Discusses the physiological changes during pregnancy and their effects on the pharmacokinetics of drugs.
- Suggests that while the commonly used drugs in dentistry are safe during pregnancy, dentists must carefully evaluate the risks *versus* the benefits of prescribing or administering any drug to a pregnant patient.

GENERAL

Pregnancy is accompanied by various physiological and physical changes, including those found in the cardiovascular, respiratory, gastrointestinal, renal and haematological systems. These alterations in the pregnant patient may potentially affect drug pharmacokinetics. Also, pharmacotherapy presents a unique matter due to the potential teratogenic effects of certain drugs. Although medications prescribed by dentists are generally safe during pregnancy, some modifications may be needed. In this article we will discuss the changes in the physiology during pregnancy and its impact on drug therapy. Specific emphasis will be given to the drugs commonly given by dentists, namely, local anaesthetics, analgesics, antibiotics and sedatives.

INTRODUCTION

Pregnancy is a normal and healthy condition. Many physiological changes occur during that time in order to support the needs of the developing fetus. It is reported that the average pregnant patient takes two to three prescription medications during her pregnancy.[1–3] Understanding these changes and their profound impact on the pharmacokinetic properties of drugs in pregnancy is essential for dentists in order to optimise maternal and fetal health.[1] The aim of this article is to summarise the physiological changes during pregnancy and their effects on the pharmacokinetics of drugs, as well as review the current recommendations for the use of drugs commonly given by dentists, namely local anaesthetics, analgesics, antimicrobials and sedatives.

PHYSIOLOGICAL CHANGES DURING PREGNANCY

Pregnancy is accompanied by various physiological changes that may affect multiple organs. These changes are important for adaptation and to facilitate fetal growth and survival. These physiological changes should not be mistaken with pathological ones and thus dentists must recognise them. The most important alterations involve the cardiovascular system (CVS), haematological system, gastrointestinal (GI) system, respiratory system and renal system. In this section we will review these changes and link them to the effects on drug pharmacokinetics.

CVS CHANGES

The CVS undergoes significant changes at the time of pregnancy. Blood volume increases to meet maternal and fetal metabolic demands.[4] The cardiac chambers enlarge and myocardial hypertrophy is often seen on an echocardiogram. Moreover, the heart is pushed upwards and rotates forwards.[4] Cardiac output is increased up to 50% as a result of increased heart rate, and increased stroke volume.[4] Decrease in blood pressure usually occurs in the second and third trimesters. Hypotension may occur when the patient is placed in the supine position because of compression of the inferior vena cava and aorta by the developing fetus.[5] Therefore, the patient may need to lie on her left side in order to prevent the weight of the gravid uterus from blocking this blood flow. Also, changes in the positioning of the dental chair from reclining to upright should be done slowly.[5] In regard to the pharmacokinetics of drugs, the increase in total body water, blood volume and capillary hydrostatic pressure increases the volume of distribution of hydrophilic substrates, which may require an increased dose of hydrophilic drugs to obtain therapeutic plasma concentrations.[1,6] Conversely, the decrease in serum albumin and other drug-binding proteins during pregnancy may result in the need for lower doses secondary to higher free levels of many drugs, and thus higher bioactivity.[1]

RESPIRATORY SYSTEM CHANGES

Major respiratory changes occur during pregnancy. To compensate for the enlarging fetus the diaphragm is displaced 3 to 4 cm upwards. Also, oxygen consumption increases by 15 to 20%. Minute ventilation increases by 50% during the first trimester.[1] This is thought to be the result of the increase in circulating progesterone. Also, progesterone is known to directly stimulate ventilation by sensitising the central respiratory centre to carbon dioxide.[1] As a consequence, the pregnant woman takes larger tidal volumes to eliminate carbon dioxide and this causes the increase in minute volume.[1,4,5] Moreover, the increase in oestrogen production during pregnancy causes the engorgement of nasal capillaries which may result in nasal stuffiness and nasal congestion and in some cases epistaxis.[1,5] Also, with these changes, nasal breathing may become difficult and thus mouth breathing may occur and as a result there is an increased chance of xerostomia.[1,5]

HAEMATOLOGICAL CHANGES

During pregnancy, there is an overall increase in plasma, white blood cells (WBC), red blood cells and total blood volume.[4] The increase in WBC count can sometime mimic infections; however, to distinguish this from pregnancy in the case of the latter, the increase is normally associated with no change in other immature WBC forms.[1] Moreover, pregnancy is associated with an increase in all coagulation

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factors except for factor XI and XIII, which are decreased.[7] Although these changes may predispose to deep vein thrombosis and pulmonary ooedema, nonetheless, to date there is no evidence of an increase in deep vein thrombosis during dental treatment.[7]

GASTROINTESTINAL CHANGES

Increased progesterone levels during pregnancy cause lower oesophageal tone, delayed gastric emptying and a decrease in intestinal motility.[1] The delay in gastric emptying may cause an increase in gastric pressure which may in turn result in gastro-oesophageal reflux during pregnancy.[1,8] There is an increased incidence of nausea, vomiting and pyrosis. Moreover, excessive salivation is often seen in pregnant patients who suffer from nausea and vomiting.[4] This is because the vomiting process is controlled by the vomiting centre within the hindbrain which is in close proximity to the centre of salivation.[9,10] Also, the increase in oestrogen in pregnancy leads to increases in serum concentrations of cholesterol, thyroid binding globulin, and cortisol binding globulin.[1] These physiological changes may alter the pharmacokinetics of many drugs. For instance, drug absorption may be delayed during pregnancy which may result in lower plasma drug concentrations.[1,6,8] Also, in many patients gastric pH may increase during pregnancy and this may cause an increase in ionisation of weak acids, reducing drug absorption.[1] Furthermore, all of these alterations in the GI system, may change the bioavailability of many drugs.[1,6] Finally, drug biotransformation is also altered in pregnancy partly due to the increased levels of sex hormones.[1] It has been suggested that pregnancy influences drug metabolism in a metabolic enzyme-specific manner.[11] Elimination rates of drugs metabolised by CYP 2A6, 2D6, 2C9, 3A4 are increased, whereas those of CYP 1A2 and CYP 2C19 substrate drugs are decreased.[11] For instance, the decreased rates of eliminations or increased metabolic ratios of caffeine, theophylline, olanzapine and clozapine may be due to the decrease in 1A2 subtype of the CYP P450 enzymes. On the other hand, the increased clearances or decreased metabolic ratio of fluoxetine, citalopram and metoprolol may be because of the increase in 2D6 isoform of the CYP P450.[11-13]

CHANGES IN THE RENAL SYSTEM

The increase in oestrogen and progesterone levels may also have implications on the renal system. Kidney size increases by 1 to 1.5 cm in length.[4] Also, both renal blood flow and glomerular filtration rate increase by 50-60%.[1,8] Moreover, creatinine clearance increases by 25% at four weeks and by 50% at nine weeks.[4] The reduction in systemic vascular resistance, which is probably due in part to insensitivity to vasoactive hormones, may lead to activation of the renin-aldosterone-angiotensin system.[14] The increase in serum aldosterone results in a net gain of approximately 1 gram of sodium.[14] All of these changes may alter the elimination of drugs. For instance, the increase in renal blood flow and glomerular filtration rate will lead to enhanced elimination of drugs that are normally excreted unchanged.[6]

In summary, major alterations occur in the various systems during pregnancy. Many of these changes can profoundly affect the different phases of pharmacokinetics. Table 1 summarises the normal physiological changes that occur during pregnancy. Table 2 summarises the changes in pharmacokinetics.

DRUG THERAPY IN PREGNANCY

When treating the pregnant patient, special considerations may be needed. These include changes that may be required in administering and prescribing drugs.[15,16] The concern that all clinicians have is the potential adverse teratogenic effects that some drugs display. In pregnancy, it is assumed that all drugs can cross the placenta and thus affect the developing fetus.[15] During the first 90 days (first trimester), organogenesis occurs and thus the fetus is most susceptible to teratogenesis. Therefore, avoiding medications during this time is desirable, although not always possible. Similarly, the approach of not prescribing any drugs to the pregnant patient carries its own risks. For instance, inadequately managed persistent

Table 1 Normal physiological changes during pregnancy[1,4,5-8]

CVS	↑ cardiac output, ↑ stroke volume, ↑ heart rate, ↓ blood pressure
GI system	↓ in gastric emptying, ↓ GI motility, ↑ heartburn
Respiratory System	↑ tidal volume, ↓ vital capacity, ↑ residual volume
Renal System	↑ renal blood flow, ↑ glomerular filtration, ↑ creatinine clearance
Haematological System	↑ plasma volume, ↑ red blood cells, ↑ white blood cell, ↑ coagulation

Table 2 Normal physiological changes during pregnancy[1,4,5-8]

Pharmacokinetic parameter	Physiological change and effect
Absorption	↑ Gastric emptying may cause ↓ absorption ↓ GI motility may cause ↑ absorption
Distribution	↑ adipose tissue may cause ↓ volume of distribution ↑ Plasma volume may cause ↓ volume of distribution ↓ in albumin may cause ↑ free drug concentrations
Biotransformation	Some Enzymes of the CYP P450 are induced which may cause ↑ metabolism Some enzymes of the CYP P450 are inhibited which may cause ↓ metabolism ↑ CYP 2A6, ↑ CYP 2D6, ↑ CYP 2C9, ↑ CYP 3A4 ↓ CYP 1A2, ↓ CYP 2C19 ↓ Cholinesterase activity
Excretion	↑ renal blood flow may cause ↑ of clearance of the drugs ↑ GFR may cause ↑ of clearance of the drugs

Table 3 FDA pregnancy risk factors definitions[15-18]

Category A	Controlled studies in women fail to demonstrate a risk to the foetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of foetal harm appears
Category B	Either animal-reproduction studies have not demonstrated a foetal 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 foetus (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 foetus.
Category D	There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, 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 foetal abnormalities, or there is evidence of foetal 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

pain may be harmful. Likewise, an untreated apical abscess may lead to systemic infection. Thus, failure to manage these conditions may harm the mother and/or the fetus. In pregnancy, drugs should be prescribed when the benefit to the mother is maximised and when the risk to the developing fetus is minimal. To determine the risks associated with the use of drugs in pregnancy, the United States Food and Drug Administration (FDA) has classified drugs based on the level of risks they pose to the fetus.[15-18] Drugs in category A and B are considered safe as no adverse effects have been shown in humans. Drugs in category C are ones in which adverse effects on the fetus have been shown in some animal studies, but there are no adequate and well-controlled studies in humans. In this category drugs may still be used if the benefits outweigh the risks. Drugs in category D should be avoided as some studies demonstrated clear teratogenic effects in humans. Nonetheless, in rare circumstances, drugs in this category may be used.[15,16] Finally, drugs in category X clearly should be avoided as studies in humans or animals have demonstrated fetal abnormalities and positive evidence of human fetal risk.[15,16] Table 3 summarises the FDA pregnancy risks factors definitions.

Medications prescribed to pregnant patients often require modification in dosage, duration of the prescription, and the frequency with which they are taken. Here we will discuss medications commonly given in daily dental practice, namely, local anaesthetics, analgesics, antimicrobials and sedatives. Table 4 summarises the rating given to drugs commonly used in dentistry and whether or not they are safe to be given.

LOCAL ANAESTHETICS

Local anaesthetics are the most frequently used pharmaceutical agents in clinical dentistry. It is estimated that the average dentist administers approximately 1,700 cartridges of local anaesthetics per year.[19,20] Local anaesthetics administered with adrenaline are considered safe during pregnancy; this is assuming that careful aspiration is carried out to minimise the potential risk of intravascular injection.[7,21] Lignocaine and prilocaine are given a FDA category B ranking and, thus, may be considered the safest local anaesthetics to give to a pregnant patient. Of these two agents, lignocaine may be considered ideal because of its lower concentration (2%) compared to prilocaine (4%), with the result of less drug being administered per injection. Mepivacaine, articaine and bupivacaine are given an FDA category C, making them a less favourable choice during pregnancy. Among topical preparations, lignocaine is the preferred choice since it has FDA category B as opposed to benzocaine which

Table 4 Summary of medication use in the pregnant dental patient[5,7,15,16]

Agent	FDA Category	Safe during pregnancy
Local anaesthetics (injectable)		
Articaine	C	Yes
Bupivacaine	C	Yes
Mepivacaine	C	Yes
Lignocaine	B	Yes
Prilocaine	B	Yes
Local anaesthetics (topical)		
Lignocaine	B	Yes
Benzocaine	C	Use with caution
Tetracaine	C	Use with caution
Analgesics		
Paracetamol	B	Yes
Aspirin	C/D[i]	Do not use in third trimester
Dilfunisal	C/D	Do not use in third trimester
Flubiprofen	C/D	Do not use in third trimester
Ibuprofen	B/D	Do not use in third trimester
Ketorolac	B/D	Do not use in third trimester
Ketoprofen	B/D	Do not use in third trimester
Naproxen	B/D	Do not use in third trimester
Codeine	C	Use with caution (low dose)
Oxycodone	B	Yes (low does, short duration)
Meperidine	B	Yes (low does, short duration
Antimicrobials		
Penicillin	B	Yes
Amoxicillin	B	Yes
Amoxicillin + clavulanic acid	B	Yes
Erythromycin	B (do not use estolate form)	Yes
Clindamycin	B	Yes
Clarithromycin	C	Use with caution
Azithromycin	B	Yes
Tetracycline	D	No
Doxycycline	D	No
Metronidazole	B	Use with caution
Nystatin	B	Yes
Ketoconazole	C	Use with caution
Fluconazole	C	Use with caution
Chlorhexidine gluconate	B	Yes
Sedatives		
Nitrous oxide	not ranked	Use with caution
Diazepam	D	Use with caution
Lorazepam	D	Use with caution
Triazolam	X	Use with caution[ii]
Midazolam	D	Use with caution
Hydroxyzine	C	Use with caution

[i]where B/D or C/D is listed, the first letter refers to the category for 1st and 2nd trimester and the second letter refers to the category in the 3rd trimester. [ii]Although Triazolam is given a category 'X' risk factor ratings, there is no data to support an association between this drug and foetal malformations and thus this drug may be used with caution.[7,15,16,52]

has an FDA category C ranking.[21] Although high doses of adrenaline, as used in the management of hypotension, may be problematic, adrenaline used in the dental setting is of very low concentration, and therefore is unlikely to affect uterine blood flow.[21] Moreover, its use in local anaesthetics is beneficial as it will decrease their uptake systemically, helping to minimise the likelihood of toxicity. Moreover, adrenaline increases the duration of local anaesthetics and decreases bleeding at the site of administration and thus its administration is important and justified.[21,22] Furthermore, Gurbet et al. investigated the effects of adrenaline added to local anaesthetics used for epidural anaesthesia as an analgesic during labour.[23] The authors of this study randomly assigned patients who were 37 weeks into pregnancy to five groups receiving different dosages of adrenaline. Their research showed no significant side effect differences between the groups.[23] In summary, in the pregnant patient, any amide local anaesthetic is considered safe with the ideal agent being 2% lignocaine with 1:100,000 adrenaline.[5,21]

ANALGESICS

The pregnant patients should not have to suffer from dentally-related pain. It is important to note that if a pregnant patient presents with pain, its origin should be identified and subsequently eliminated. Then, if symptomatic relief is needed, an analgesic should be given as an adjunctive measure. In general, if used properly, the analgesics used commonly in dental practice are safe. The most common analgesic prescribed during pregnancy is paracetamol which has an FDA rating of B. It has been labelled as the safest analgesic during pregnancy as it is not associated with any teratogenicity. However, recent studies demonstrated that taking paracetamol during pregnancy may increase the future risk of attention deficit hyperactivity disorder (ADHD) in the newborn.[24,25] Although definite conclusions were not drawn and other factors might have affected the outcome of these studies, nonetheless, prolonged used of paracetamol may have a very small risk associated with it. Thus, taking paracetamol as advised, 500–1000 mg every four hours to a maximum of four grams per day is considered safe in the pregnant patient.[7,15,16,26]

Another group of commonly used analgesics are the nonsteroidal anti-inflammatory drugs (NSAIDs), which include drugs such as ibuprofen and naproxen. These drugs have anti-inflammatory and analgesic properties and although their use in dentistry is very advantageous, their application during pregnancy is less favourable.[15,27] For instance, ibuprofen is given a Category B ranking in the first and second trimesters; however, in the third trimester it is given category D and thus should not be prescribed during that time. This is because it has been shown that the use of NSAIDs late in pregnancy may prolong the length of the pregnancy through ineffective contractions during labour. There are also concerns of increased bleeding during delivery and premature closure of the ductus arteriosus.[7,28,29] Also, although these drugs were not shown to cause fetal malformations or increased risk of birth defects, they have been implicated with an increase incidence of miscarriage, particularly when prescribed during the first trimester.[30,31] In summary, if needed, ibuprofen can be prescribed in the first and second trimesters but should be avoided during the third trimester.

In some cases, where pain is moderate to severe and cannot be managed with paracetamol alone (or NSAIDs in the first and second trimesters), opioids can be given. In this category, commonly prescribed drugs include codeine and oxycodone, usually given in combination with paracetamol or acetylsalicylic acid (ASA). Oxycodone is the safest as it has a category B ranking, whereas codeine has a category C ranking since its use has been reported to cause increased risk of congenital malformations including cleft lip and palate and other cardiac and circulatory malformations.[15,16] Nonetheless, prescribing codeine (preferably in the second or third trimesters) for a short duration, when needed, is acceptable.[15,16] Also, it should be noted that chronic opioid use has been associated with fetal dependence, premature delivery, neonatal respiratory depression and delayed growth.[27,32] If there is severe chronic pain, an interprofessional approach is best. General recommendations for the use of analgesics in the pregnant patient are outlined in Table 5.

Table 5 General recommendations for the use of analgesics during pregnancy

General	Eliminate the source of pain, if at all possible.
For paracetamol	Paracetamol is the analgesic of choice in the otherwise healthy pregnant patient. Use a dose of 500–1,000 mg every 4 hours to a maximum of 4 grams per day.
For NSAIDs	NSAIDs can be used cautiously in first and second trimesters. NSAIDs should be avoided during the third trimester. If NSAIDs are used in the pregnant patient, it is recommended to use the lowest effective dose for as short a period of time as possible.
For opioids	Opioid analgesics can be cautiously prescribed to the pregnant dental patient. If opioid analgesics are prescribed, low dose and short duration are recommended.

ANTIMICROBIALS

As a general rule, antimicrobials used in the dental practice are safe during pregnancy. One exception to this is tetracycline and its derivatives. These antimicrobials are contraindicated during pregnancy and are given category D, and thus any of these, whether administered orally or applied subgingivally, should not be prescribed during pregnancy.[5,7] In general, it should be noted that antibiotics are not a substitute to incision and drainage and thus, if a patient presents with an infection, the first line of treatment should be drainage of the infected site. If, however, the patient presents with extensive swelling and/or other systemic involvement (for example, fever) an antibiotic should be prescribed. Specifically, penicillin and amoxicillin are category B drugs and thus can be prescribed safely. If a patient is allergic to penicillin, clindamycin can be given as it is also in category B. Erythromycin is given category B ranking, nonetheless, it is no longer considered a preferred alternative and is best avoided. Furthermore, it has been recommended not to use the estolate form of this drug as it has been associated with cholestatic hepatitis.[33] Another antibiotic commonly used as an adjunct to control periodontal disease is metronidazole. Although the FDA ranking of metronidazole is B, its use during pregnancy is controversial. Specifically, some authors reported that this drug has been associated with increased risk for preterm birth, teratogenesis and fetal harm[34-37] while others did not find any association between first trimester use of metronidazole and congenital anomalies.[38-41] Thus, metronidazole can be used cautiously and when absolutely needed. Chlorhexidine gluconate mouth rinse can be safely used during pregnancy as it is given category B ranking. Among the antifungals, nystatin is the safest as it is given category B ranking. Ketoconazole and fluconazole are less favourable as they both have category C ranking, nonetheless, it is acceptable to prescribe these drugs when necessary.[15]

SEDATIVES

In common with many patients, the pregnant patient may have fear and anxiety of dentistry that will require the use of sedation. If this fear is significant enough, sedation can be justified in order to minimise the risks of undue stress. The most common sedatives applied for this purpose are nitrous oxide (N_2O) and the benzodiazepines. N_2O is not given any rating by the FDA; however, its use during pregnancy is considered acceptable. There is some controversy as N_2O has been shown to inhibit methionine synthase, which can affect DNA synthesis, in animal studies.[42] The anomalies

associated with N_2O were previously thought to occur from inhibition of this enzyme, however, studies failed to demonstrate this effect in humans.[7,15] Moreover, studies examining the literature on the safety of N_2O found that adverse consequences of N_2O were associated with large doses (concentration higher than 50%) and long duration exposures.[43,44] Thus, because in the dental setting the administration of N_2O is of short term, no adverse consequences have been found and therefore its administration is considered safe. Nonetheless, as with any drug, N_2O should only be given if it is indicated. It is ideal to avoid N_2O in the first trimester if possible, and if given at all in pregnancy, it should be administered for less than 30 minutes and with at least 50% oxygen.[15] For dental personnel, a relevant issue is that chronic occupational exposure to N_2O was linked to infertility and spontaneous abortions in offices where scavenging was not used.[45–47] Therefore, scavenging is mandatory whenever N_2O is used and, provided that it is in place, dental personnel will not be exposed to potential toxicity.[48]

Benzodiazepines are commonly administered for patients with anxiety requiring sedation. These drugs, when taken during pregnancy, were linked to fetal malformations, fetal abortion and craniofacial defects such as cleft lip and palate,[49–51] yet further review showed that the link with cleft lip and palate was not valid.[52] When prescribed chronically in the third trimester, these drugs were shown to cause fetal dependence and withdrawal,[16,53,54] a situation that is avoided by the single use administration as occurs in sedation in dentistry. Thus, benzodiazepines may be used with caution when sedation for dentistry is indicated.

CONCLUSION

Fortunately, the commonly used drugs in dentistry are safe in pregnancy. Nevertheless, dentists must evaluate carefully the risks versus the benefits of prescribing or administering any drug to a pregnant patient. As always, it is important to note that if a patient presents with pain or infection, the first line of treatment should be removal of its source. If pharmacotherapy is initiated, prescribe the lowest dose for the shortest duration required.

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