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Review Paper: Optimized Drug Therapy in Dental Care of Pregnant Women

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ABSTRACT

Pregnancy is a critical stage in oral health of women. The storm of hormones in pregnancy usually cause gingival problems and tooth decay. On the other hand, poor oral health during pregnancy may lead to complications such as premature delivery and preeclampsia. However, while a routine dental care is necessary during pregnancy, drug therapy may be required in some cases such as pain control or management of dental procedures or oral infections. In a pregnant patient requiring dental care, the agents routinely prescribed should be evaluated for potential risks to the mother and/or fetus. On the other hand, many physiological changes occur dur¬ing pregnancy to support the needs of the developing fetus and these changes can affect the efficacy and pharmacokinetics of drugs as well.

This article aims to provide a comprehensive review of dental drug therapy in pregnancy, including safety and recommendations for commonly used medications in dental practice. The physiological changes during pregnancy and their impact on oral health and drug therapy are discussed with an emphasize on dental therapeutic agents which can be selected in treatment of pregnant patients.

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Introduction

1. Physiological changes during pregnancy

During pregnancy some hormonal balance changes occur which causes physiological alterations to prepare body for adaptation and to ensure fetal growth and survival. These physiological changes should be distinguished from pathological states for optimal management of pregnant patients. Pregnant patients usually face some gingival and dental issues which is linked to elevated hormone levels in bloodstream. In addition to the gingival and dental issues, the most important physiological alterations involve cardiovascular system (CVS), hematological system, gastrointestinal (GI) system, respiratory system and renal system which may affect drug pharmacokinetics and necessitate some cautions in dental care and drug therapy (1).

The gingival and dental problems in pregnant patients is usually due to rising levels of progesterone in the blood stream that increases vascular permeability and may lead to excessive sensitivity to irritations in the gingiva. Therefore, gingivitis or epulis gravidarum, commonly known as pregnancy tumors, can be seen very often during pregnancy (2).

Vomiting which is very common during the first months of pregnancy, results in an acidic environment in the mouth. On the other hand, mothers usually do not pay enough attention to oral care after vomiting, and don't brush the teeth sufficiently. Hence this acidic media will be harmful for teeth and accelerates tooth decay process. On the other hand, saliva flow decreases and all these conditions accelerate the formation of caries during this period (3, 4).

Some changes also occur in CVS, for example the cardiac output is increased up to 50% and blood volume and heart rate increases to meet maternal and fetal needs. Although a decrease in blood pressure may occurs in the second and third trimesters specially in the supine position because of compression of the inferior vena cava and aorta by the developing fetus (1).

The growing fetus displaces the diaphragm about 3 to 4 cm upwards and oxygen consumption increases by 15 to 20%. Moreover, the increase in estrogen production during pregnancy causes the engorgement of nasal capillaries which may result in nasal congestion and nasal breathing may become difficult and thus mouth breathing may occur and as a result there is an increased chance of xerostomia (1, 5).

During pregnancy, there is an overall increase in plasma, white blood cells (WBC), red blood cells and total blood volume. This may alter the distribution pattern and volume of distribution of some drugs. Moreover, pregnancy is associated with an increase in all coagulation factors except for factor XI and XIII, which are decreased which may predispose the patient to deep vein thrombosis and pulmonary edema (6).

Increased progesterone levels during pregnancy cause lower esophageal tone, delayed gastric emptying and a decrease in intestinal motility. The delay in gastric emptying may result in gastro-esophageal reflux and increased incidence of nausea, vomiting and pyrosis during pregnancy.

Also, the increase in estrogen in pregnancy leads to increases in serum concentrations of cholesterol, thyroid binding globulin, and cortisol binding globulin. This increased hormone level may also alter the activity of metabolizing enzymes such as CYP 3A4 and 2C19 (7).

The increase in estrogen and progesterone levels may also have implications on the renal system. Kidney size increases about 1 to 1.5 cm in length. Also, both renal blood flow and glomerular filtration rate increase by 50-60%. Moreover, creatinine clearance increases by 25% at four weeks and by 50% at nine weeks. 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 (8).

2. Dental management during pregnancy

Pregnancy does not cause periodontal

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disease but may worsen existing conditions. Therefore, performing a good oral hygiene is highly recommended to reduce the severity of the hormone-mediated inflammatory oral changes. First of all, the patient should be well-educated to prevent maternal dental problems that may arise from the physiological changes during pregnancy. However medical interventions may be done according to the state of problem and pregnancy age.

During the first trimester there is a great concern about doing dental procedures due to high risk of teratogens in organogenesis of the developing fetus and risk of spontaneous abortions. The interventions should be limited to periodontal prophylaxis and emergency treatments only (3).

By the second trimester, the organogenesis is complete, and the risk to the fetus is low. The mother has also had time to adjust to pregnancy, and the fetus has not grown to a potentially uncomfortable size that would make it difficult for the mother to sit for long periods. It is safe to perform a routine dental treatment in the second trimester and early part of the third trimester, but from the middle of the third trimester, routine dental treatments are avoided (3, 4, 9).

Although most elective dental procedures can be postponed, treatment of a pregnant patient with oral pain, advanced disease, or infection should not be delayed. Therefore, optimized drug therapy in dental management of pregnant patients is an important issue. The pregnancy risk categories, teratogenicity and alterations of drug pharmacokinetics must be considered in drug therapy of these patients.

3. Alterations of drug pharmacokinetics in pregnancy

As discussed earlier some alterations occur in the various body systems during pregnancy including cardiovascular and renal system. Many of these changes can profoundly affect the different aspects of pharmacokinetics.

Regarding the pharmacokinetics of drugs, delayed gastric emptying may change the bioavailability of many drugs. For instance, drug absorption may be delayed during pregnancy which may result in lower plasma drug concentrations. Also, in many patients gastric pH may increase during pregnancy and this may cause an increase in ionization of weak acids, reducing drug absorption (1, 10).

The increase in total body water, blood volume and capillary hydrostatic pressure increases the volume of distribution of some drugs, which may require an increased dose to obtain proper therapeutic plasma concentrations. However, in the dose adjustments the pharmacist should consider other physiological alterations such as decrease in serum albumin and other drug-binding proteins during pregnancy which may result in higher free drug levels in plasma and the need for lower doses (6, 10).

Finally, drug biotransformation is also altered in pregnancy partly due to the increased levels of estrogen and progesterone concentrations to stimulate the pregnane X receptor. Elimination rates of drugs metabolized by CYP 2A6, 2D6, 2C9, 3A4 are increased, whereas those of CYP 1A2 and CYP 2C19 substrate drugs are decreased. 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 (7, 10).

The physiological changes in renal system may alter elimination of drugs. Renal excretion is likewise increased because of the elevated cardiac output and glomerular filtration. For instance, the increase in renal blood flow and glomerular filtration rate will lead to enhanced elimination of drugs that are normally excreted unchanged (1, 8).

Alterations in liver function are common, and the hepatic toxicity of tetracycline and certain other compounds is markedly accentuated by pregnancy (1, 10).

Understanding the physiological changes and their profound impact on the pharma¬cokinetic

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properties of drugs in pregnancy is essential in optimized drug therapy while managing maternal and fetal health.

4. Selection of dental therapeutic agents for pregnant patients

According to the reports an average pregnant patient takes two to three prescription medications during her pregnancy. Special considerations may be required while treating the pregnant patient. It is generally assumed that all drugs can cross the placenta and thus affect the developing fetus and the major concern is the potential teratogenic effects of some drugs; specifically, during the first trimester that organogenesis occurs. Therefore, avoiding medications during this time is desirable, although not always possible. On the other hand, the approach of not prescribing any drugs to the pregnant patient carries its own risks. For instance, inadequately managed persistent pain may be harmful or an untreated apical abscess may lead to systemic infection. Thus, failure to manage these conditions may harm the mother and/or fetus [9]. In pregnancy, drugs should be prescribed when the benefits to the mother and the developing fetus outweigh the risks. This evaluation should be based on pregnancy category classification and stages of pregnancy. However, drug therapy in pregnancy often require modifications in dosage, duration of the prescription, and the frequency of dosing due to physiological changes during this period.

4.1. Pregnancy risk categories

The Food and Drug Administration (FDA) established 5 categories for classifying potential risks associated with drug therapy in pregnancy. This is a useful guide for safety considerations of drug therapy in pregnancy. Category A includes drugs that have been adequately studied in humans and have evidence supporting their safe use. Drugs in Category B have no evidence of risk in animal studies or human therapeutic use. Category C includes drugs where teratogenicity risk has been demonstrated in animals and cannot be ruled out in humans. Category D includes drugs that have demonstrated risks in humans, but their therapeutic benefit may outweigh the risks, while Category X includes agents that have been shown to be harmful to the mother or fetus with an unfavorable benefit-versus-risk profile.

Drugs in categories A and B are generally considered appropriate for use during pregnancy, while Category C drugs should be used with caution; drugs in categories D and X should be avoided or are contraindicated. The labeling requirements for use of drugs during pregnancy are being revised by FDA to provide a more detailed description of safety considerations, dosing protocols, duration of exposure, and gestational timing of exposure (11, 12)

4.2. Teratogenicity of drugs

A teratogen is any agent that causes permanent alterations in the function or form of the fetus and induce birth anomalies. Among thousands of marketed drugs, only a few are proven to be teratogenic in humans. Thalidomide was the most popular human teratogens which was administered as a tranquilizer and antiemetic in the 1950s. Warfarin, retinoids, valproic acid, and heavy metals are also known to produce significant physical birth defects. Unfortunately, accurate pregnancy risk assessment in human is somehow impossible and full of uncertainty for many newly marketed or infrequently prescribed drugs. In most cases the risks associated with drug use during pregnancy is obvious just when the frequency of birth defects increases. Some other adverse effects that are subtle and delayed, such as behavioral changes and cognitive effects, are nearly impossible to determine. On the other hand, animal data, which are the result of high and prolonged exposures to drugs, are highly affected by species variability. In some congenital defects, such as cleft lip which have high background rates, it is often difficult to determine whether the etiologic factor was the drug or some other underlying factors (11).

Fortunately, the therapeutic agents used in dental practice are used quite frequently, and enough evidence is available to evaluate their potential risk.

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4.3. Commonly used drugs in dental practice

4.3.1. Local anesthetics

Local anesthetics are the most frequently used agents in dentistry. Most local anesthetics administered with adrenaline have not shown teratogenicity in humans and are considered relatively safe for use in dentistry with the assumption that careful aspiration is carried out to minimize the risk of intravascular injection. Lignocaine and prilocaine with an FDA category B ranking are the safest local anesthetics in pregnant patient. Mepivacaine, benzocaine, and bupivacaine are in the FDA category C and are not favorable choices during pregnancy (13).

The administration of adrenaline with local anesthetics is recommended and justified in dental practice. Although high doses of adrenaline, as used in the management of hypotension, may be problematic in pregnancy, adrenaline used in the dental practice is of very low concentration, and therefore is unlikely to affect uterine blood flow. Moreover, it will decrease the systemic uptake of anesthetics and reduce their toxicity, increase their duration of action and decreases bleeding at the site of administration (14).

However, almost all local anesthetics can cross the placenta, limiting the anesthetic dose to the minimum required dose is advisable. Diluted blood volume and decreased protein binding during pregnancy may lower the maximum safe dosage. Intravascular injection combined with decreased protein binding could conceivably increase local anesthetic toxicity. However, the maximum recommended local anesthetic doses used in dentistry are very conservative and unlikely to reach significant fetal blood levels (9, 13).

Prilocaine and benzocaine are recognized as inducers of methemoglobinemia. Although there have been no published reports in the literature of any added hazard to mother or fetus compared to other anesthetics, limiting the dose of these drugs is recommended to avoid potential methemoglobinemia (14).

4.3.2. Peripheral and Centrally acting analgesics

If a pregnant patient reports dental pain, first of all the underlying reason should be identified and subsequently eliminated. However, usually an analgesic may be needed as an adjunctive therapy. Generally, most of analgesics used in dental practice are safe. The most common analgesic is paracetamol which. Paracetamol is the most common analgesic prescribed during pregnancy that has an FDA category of B and has been labelled as the safest analgesic during pregnancy as it is not associated with any teratogenicity. Recent studies have shown that prolonged use of paracetamol may increase the future risk of attention deficit hyperactivity disorder (ADHD) in babies. Although definite conclusions were not drawn. However, taking 500–1000 mg of paracetamol every four hours to a maximum of 4 grams per day is considered safe during pregnancy. The dosage of acetaminophen should be closely monitored to preclude potential hepatic toxicity (15, 16).

Another group of commonly used analgesics are the nonsteroidal anti-inflammatory drugs (NSAIDs), which have both anti-inflammatory and analgesic properties. Aspirin and NSAIDs have the common mechanism of inhibiting prostaglandin synthesis. Prostaglandin E2 is one of the hormones involved in the induction of labor and NSAIDs may prolong labor by inhibiting the production of prostaglandins and cause ineffective contractions during labor. In addition, there are also concerns of increased bleeding during delivery and premature closure of the ductus arteriosus. prostaglandin inhibitors raise concerns about premature fetal ductus arteriosus constrictor, resulting in pulmonary hypertension in the fetus. These concerns were derived from studies on patients taking large doses of aspirin and extrapolated to apply to other NSAIDs. There may be a slightly increased risk of congenital anomalies, including cardiac defects, when NSAIDs—such as ibuprofen, naproxen, or celecoxib—are taken early in pregnancy as well (16, 17).

Newborns of mothers who have ingested 5g

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to 10 g of aspirin 5 days before delivery are associated with bleeding tendencies, specifically intracranial hemorrhage. No bleeding tendencies were found if aspirin was taken no fewer than 6 days prior to delivery. Aspirin and other NSAIDs should be avoided, especially during the third trimester of pregnancy (17).

However, the administration of NSAIDs must be done with caution according to the stage of pregnancy. For instance, ibuprofen is given a Category B ranking in the first and second trimesters but in the third trimester it is given category D and thus should not be prescribed during that time. 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 not controlled with paracetamol or NSAIDs, opioids can be administered. Codeine and oxycodone usually given in combination with paracetamol or acetylsalicylic acid (ASA) are the most commonly prescribed drugs in this category. Oxycodone is safer as it is in the category B, whereas codeine has a category C ranking since there are some reports of congenital malformations including cleft lip and palate and other cardiac and circulatory malformations. However, codeine administration (preferably in the second or third trimesters) for a short duration is acceptable. Chronic opioid use has been associated with fetal dependence, premature delivery, neonatal respiratory depression and delayed growth [18]. It should be noted that if there is severe chronic pain, a professional approach rather than drug therapy is recommended.

4.3.3. Antimicrobials

When dental infection is observed in a pregnant patient, the first line of treatment is incision and drainage of the infected site, but if extensive swelling and/or other systemic symptoms like fever is observed an antibiotic should be prescribed. Generally, most antibiotics used in the dental practice are safe during pregnancy and the greatest concerns are with the antimicrobial agents that have limited indications in dentistry. The penicillin and cephalosporin antibiotics most commonly used in dentistry (penicillin V, amoxicillin, and cephalexin) are generally considered safe for use during pregnancy. 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 because the estolate salt of erythromycin may be more likely to induce cholestatic hepatitis in a pregnant mother and is, therefore, not recommended (19). Data concerning the fetal safety of other macrolides including clarithromycin, azithromycin, and roxithromycin have been limited but significant increased fetal risks were not reported. A clinical study in 2020 examined the association between the use of macrolides including azithromycin, clarithromycin, erythromycin, and roxithromycin in pregnancy and the risk of major birth defects compared to penicillin and reported no significant association (20). However, as there is no conclusive evidence regarding the adverse outcomes of macrolides in off springs, may be recommended when the benefits of treatment are expected to outweigh the potential risks (21, 22).

Metronidazole is another antibiotic commonly used in dentistry. The FDA ranking of metronidazole is B, but its use during pregnancy is controversial. There are some reports of increased risk for preterm birth, teratogenesis and fetal harm while others did not find any association between first trimester use of metronidazole and congenital anomalies. Thus, metronidazole can be used with caution and when needed. Aminoglycosides, such as gentamicin, may induce ototoxicity when administered late in pregnancy (9, 19).

One exception in the antimicrobial therapy in dentistry is tetracycline and its derivatives like doxycycline. These antimicrobials cause tooth discoloration and impaired bone metabolism and are given category D, and thus any of these, whether administered orally or buccal, should

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not be prescribed during pregnancy.

Chlorhexidine gluconate mouth rinse can be safely used during pregnancy as it is given category B ranking. Among the antifungals, nystatin is the safest with category B ranking. Ketoconazole and fluconazole have category C ranking, but they are acceptable to prescribe for short durations when necessary (11, 19).

4.3.4. Sedative agents

If a pregnant patient experience fear and anxiety of dentistry in a way that require sedation, sedative drugs can be administered to reduce the risks of undue stress. Nitrous oxide (N2O) and the benzodiazepines are the most commonly used sedatives for pregnant patients. N2O is not given any rating by the FDA. However, it seems that short exposures during general anesthesia with nitrous oxide, halothane, and thiopental are not thought to be teratogenic. There is some controversy over prolonged and high-dose exposure to N2O in rats. It has demonstrated skeletal and behavioral teratogenic effects. N2O has been shown to inhibit methionine synthase, which can affect DNA synthesis, in animal studies and N2O related anomalies were thought to occur from inhibition of this enzyme, however, studies failed to demonstrate this effect in humans. As in dental applications the administration of N2O is short term, no adverse consequences have been found and therefore its administration is considered safe. It is ideal to avoid N2O in the first trimester if possible, and if given at pregnancy, it should be administered for less than 30 minutes and with at least 50% oxygen (23).

Generally, benzodiazepines are administered for dental anxiety requiring sedation. Nonetheless, sedative agents are neuronal function inhibitors and generally cross-placental barriers and their use during pregnancy is viewed with apprehension. Among the anti-anxiety drugs, diazepam (Valium) has been most frequently assessed in pregnancy. Animal and human investigations have noted an association between diazepam exposure during pregnancy and oral clefts. Although further review showed that the link with cleft lip and palate was not valid. Chronic applications of these drugs in the third trimester, were shown to cause fetal dependence and withdrawal. Thus, benzodiazepines may be used with caution when sedation for dentistry is required (24, 25).

Table 1. Medication use in the pregnant dental patient

Medication	FDA category	Safety of use during pregnancy
Local anesthetics		
Lignocaine	B	Safe
Prilocaine	B	Safe but limited dose is recommended to avoid potential methemoglobinemia
Mepivacaine	C	Safe
Benzocaine	C	Safe but limited dose is recommended to avoid potential methemoglobinemia
Bupivacaine	C	Safe
Analgesics		
Paracetamol	B	Safe but caution is recommended in prolonged use due to the risk of ADHD
Aspirin	C in the 1st and 2nd trimester/D in 3rd trimester	Use with caution according to the stage of pregnancy, do not use in 3rd trimester

Medication	FDA category	Safety of use during pregnancy
Ibuprofen	B in the 1st and 2nd trimester/ D in 3rd trimester	Use with caution according to the stage of pregnancy, do not use in 3rd trimester
Ketorolac	B in the 1st and 2nd trimester/D in 3rd trimester	Use with caution according to the stage of pregnancy, do not use in 3rd trimester
Ketoprofen	B in the 1st and 2nd trimester/D in 3rd trimester	Use with caution according to the stage of pregnancy, do not use in 3rd trimester
Naproxen	B in the 1st and 2nd trimester/D in 3rd trimester	Use with caution according to the stage of pregnancy, do not use in 3rd trimester
Codeine	C	Use with caution preferably in the second or third trimesters with low dose and short duration
Oxycodone	B	Safe just with low dose and short duration
Antimicrobials		
Penicillin	B	Safe
Amoxicillin	B	Safe
Amoxicillin + clavulanic acid	B	Safe
Erythromycin	B	Safe but not the estolate form
Clindamycin	B	Safe
Clarithromycin	C	Use with caution
Azithromycin	B	Safe but use when benefits of treatment are expected to outweigh the potential risks
Tetracycline	D	Not safe
Doxycycline	D	Not safe
Metronidazole	B	Use with caution
Nystatin	B	Safe
Ketoconazole	C	Use with caution
Fluconazole	C	Use with caution
Sedatives		
Nitrous oxide	Not ranked	Use with caution for less than 30 minutes with at least 50% oxygen
Diazepam	D	Use with caution
Lorazepam	D	Use with caution
Triazolam	X	Use with caution
Midazolam	D	Use with caution

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Conclusion

Dental care during pregnancy needs special attention and considerations. Some hormonal and subsequently physiological changes through this period may increase the possibility of dental and gingival problems or can worsen the existing issues. Pregnant women are strongly recommended to have special attention to dental care during pregnancy. However, some situations such as routine dental problems may necessitate drug therapy. Today there is a lot of information about safety of drugs in pregnancy and drugs vary widely in their relative risk during this period. Physiological changes during pregnancy can also modify drug pharmacokinetics which may necessitate dose adjustments in pregnant patients.

FDA category of drugs are available and extracted from animal and human studies, and a health care provider can decide about drug therapy according to the state of disease, the toxicity rate and teratogenicity of drug, duration of usage and stage of pregnancy. Fortunately, there are a lot of information about commonly used drugs in dental practice and there are safe options in each category of drug to control the situation. However, one should note that the available data is being updated all the time and it is recommended to check the references before any administrations.

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None

Authors'contributions

Masoud Faghih Akhlaghi: Conceptualization, Methodology, Writing - Review & Editing **Marjan Daeihamed:** Writing - Original Draft, Data Curation, Supervision

Conflict of Interests

The authors declare no conflict of interest

Ethical declarations

Not applicable

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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