MALAYSIAN DENTAL JOURNAL

Review of Current Issues in Pregnant Dental Patients

Tuan Nadrah Naim Tuan Ismail[1], Munirah Mohd Adnan[1], Noor Huda Ismail[1], Wan Nazatul Shima Shahidan[1]

[1]School of Dental Sciences, Universiti Sains Malaysia,16150 Kubang Kerian, Kelantan, Malaysia.

ABSTRACT

Numerous physiologic effects occur within the body during pregnancy, and the oral cavity is no exclusion. Although elective dental procedures can usually be postponed until after delivery, certain conditions such as pain and infection should be addressed immediately. Recent data arising from human studies reveal a significant correlation between common medications used in dentistry and its increased risk of teratogenic effects to the fetus. This review discusses common medications used in pregnant dental patients and their potential teratogenic effects on the fetus.

Keywords: Dental; pregnant; antibiotics; analgaesics; local anaesthetic

INTRODUCTION

Pregnancy is associated with numerous transient physiological changes that return to normal in the postpartum period. The causative mechanism of the changes is inadequately understood and most of them are assumed to be caused by under hormonal changes. The oral problems which are seen in pregnancy include gingival inflammation[1], pyogenic granuloma[2], and salivary changes including variation in rate, pH, and composition.[3]

The dental management of pregnant patients requires special care. The pregnant dental patients give two important challenges to the dental practice. First, most dental procedures are elective and can be postponed until after delivery. However, dental treatment for a pregnant woman who has oral pain or infection should not be delayed. Second, not every woman of childbearing age recognise that they might be pregnant. During pregnancy, teratogenic drugs should be avoided. A drug is considered teratogenic if it has the potential or capability to cause abnormal development in an embryo or fetus.[4] Therefore when prescribing medication to any women of childbearing age, clinicians have to consider the possible adverse effects it has on a fetus.

Identification of teratogenic drugs is sometimes difficult due to several factors. First, teratogenesis in humans is very difficult to predict and cannot be compared with previously published animal studies because of considerable species variation.[5] Thalidomide, the most infamous teratogenic drug of recent times, showed no teratogenicity in mice and rats. However, corticosteroids were proven to be teratogenic in animals but not in humans.[6] Second, serious congenital deformities are present in 1-2% of all babies; and a drug is only identified as teratogenic

if its effects are frequent, unusual and/or serious. Therefore, a low grade teratogen that rarely causes minor deformities is likely to pass unnoticed.[5]

The effect of drugs on the fetus depends on the stages of pregnancy.[7] The pregnancy process starts with fertilisation and implantation. It starts from conception to 17th day of gestation. Interference by a drug with either of these processes leads to embryonic loss or survive without causing malformation.[7] Therefore, very little information is known about drugs teratogenicity during this period. The following pregnancy process is organogenesis. It occurs at 18th to 55th days of gestation.[5] This stage is the most sensitive period of pregnancy because major body organ and systems are formed. Exposure to teratogenic drugs during this period can lead to major birth defect or gross malformation.[7] The late process of pregnancy is growth and development. It occurs from 56th day onwards. During this stage, major body structures have been formed and teratogenesis is unlikely, but drugs may affect growth and function of fetal organs and tissue.[5]

The US Food and Drug Administration in 1979 had established five categories (A, B, C, D and X) to indicate the amount and quality of research done on the medication, not the safety of the medication if used during pregnancy.[8] The categories are determined by assessing the evidence-based study that categorises medications by potential risk versus benefit to the pregnant women and their offspring.[9] Category A are those medications with adequate and well-controlled studies that have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, category B are

those animal reproduction studies that have failed to demonstrate a risk to the fetus but there are no adequate and well controlled studies in pregnant women, category C are those animal reproduction studies that have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans while category D and X are those that show positive evidence of fetal harm based on investigational or marketing experience. However, since 2015, the five categories A, B, C, D and X labelling has been replaced by the FDA. This is now known as the Pregnancy and Lactation Labelling Final Rule (PLLR). Under this PLLR, pregnancy risk categories letters are now removed.[10] This is because the FDA had received comments that the old five-letter system left patients and providers ill-informed and resulted in false assumptions about the actual meaning of the letters.[11] Labelling for prescription drugs submitted after June 30, 2015 will use the new format directly, while labelling for prescription drugs approved on or after June 30, 2001, will be phased in gradually. Medications approved prior to June 29, 2001 are not subject to the PLLR rule; however, the pregnancy letter category must be removed by June 29, 2018.[10]

Australian categorisation system for prescribing medicines in pregnancy has seven categories (A, B1, B2, B3, C, D and X). Category A are drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Human data are lacking or inadequate for drugs in the B subcategories and the information is based on animal data. Similar with FDA, the allocation of a B category does not imply greater safety than a C category and medicines in category D are not absolutely contraindicated during pregnancy.[12]

ANTIBIOTICS

Most of the antibiotics used in dental management are US FDA category B, which means the animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.[8] These include penicillin, cephalosporin, and macrolide antibiotics.[13] A recent study showed that use of macrolide antibiotics during pregnancy slightly increased the risk of cerebral palsy or epilepsy in children when compared with penicillin.[14] On the other hand, few previous studies have shown the relationship between maternal infection and cerebral palsy.[15,16] It is possible that an underlying infection may be responsible for the association rather than the treatment itself.

Metronidazole is the other commonly prescribed antibiotic in dentistry as this drug acts specifically against anaerobes. Use of metronidazole has been controversial over the years. A previous study had suggested an association between metronidazole and a rise in various birth defects.[17] Greenberg and Reynolds (1985) found that there were two infants born with cleft and optic atrophy in mothers who were treated with metronidazole for trichomoniasis. However, the study was not established because of the small sample size. On the other hand, there are few studies showing the relationship between trichomoniasis and preterm birth, but no published studies reported that trichomoniasis was related with teratogenicity.

However, Koss and Baras found no association between metronidazole treatment during the first or afterward trimesters of pregnancy and preterm birth, low birth weight, or congenital anomalies, based on analysis of chart review and electronic data from a cohort of women in urban

New York State hospital.[18] According to US FDA, metronidazole is a category B drug. These letter categories are often misinterpreted as a 'grading system', thus making prescribing decisions based on the pregnancy category. The pregnancy letter designations were classified based on available human and animal data, not hierarchical structure.[9,19] Australian categorisation system for prescribing medicines in pregnancy has categorised metronidazole under category B2 drug[12] which means studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Its effects on the human fetal organogenesis are not known. Furthermore, the recent animal study found that metronidazole has been shown to be carcinogenic in mice and rats.[20] The use of metronidazole should be reserved for the certain conditions only such as in the treatment of serious anaerobic bacterial infections. Unnecessary use of the drug should be avoided.[21]

ANALGAESICS

Chronic and severe pain that is ineffectively treated is associated with hypertension, anxiety, and depression.[22] However, it is important to weigh the benefits and risks of using analgaesics during pregnancy. New reports query the safety of pain medicines when used during pregnancy. Recently published studies showed that all analgaesics have potential risk to the fetus.[23-25] Exposure to NSAIDs during pregnancy is associated with increased risk of spontaneous miscarriage.[26] Example of NSAIDs is ibuprofen, naproxen, diclofenac, and celecoxib. Therapeutic Goods

Administration (TGA) has recommended all over the counter NSAIDs, to include an advisory statement on their packaging which appropriately addresses the risk of spontaneous abortion.[27] Current guideline by US FDA states that NSAIDs should not be used by pregnant women in their third trimester of pregnancy because of the risk of premature closure of the ductus arteriosus in the fetus.[28] In a normal full-term baby, closure of the ductus arteriosus occurs within 18 to 24 hours after birth. NSAIDs are US FDA category B in first and second trimester and category D in the third trimester.[29]

Maternal exposure to opioid during the first trimester is associated with increased risk of neural tube defect in newborn.[25] Example of opioids is oxycodone, hydrocodone, hydromorphone, morphine, codeine, and tramadol. The commonly used opioid in dentistry is tramadol. It is classified as a category C by FDA which means there is lack of human data on effects of usage of opioids during pregnancy. TGA also categorised it was a category C which means the drug has caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations due to its pharmacological effects.[12] Therefore, tramadol should not be used in pregnant women before or during labour, unless the potential benefits outweigh the risks.

Paracetamol or acetaminophen is the most commonly used analgaesic and antipyretic in pregnancy and has been available as an over the counter drug. Although it has been on the market since the 1950s, recent finding shows that paracetamol use at any trimester during pregnancy is associated with a higher risk for attention deficit hyperactivity disorder.[24,30] However, the study

has potential limitation in their studies' design, therefore additional well-designed cohort studies are necessary to prove or disprove the association between paracetamol exposure to the fetus and attention deficit hyperactivity disorder or hyperkinetic disorder.[31]

LOCAL ANAESTHETIC AGENTS

Local anaesthetics use during pregnancy for dental treatment has been considered safe, as there is no factual evidence of harmful effects to the fetus. A recent study on the safety of dental treatment and local anaesthetics during pregnancy do not represent a major teratogenic risk.[32] Lidocaine and prilocaine are category B US FDA drug. Lidocaine may be considered ideal because of its lower concentration (2%) compared to prilocaine (4%), with the result of less drug being administered per injection.[33] While mepivacaine, articaine, and bupivacaine have a US FDA category C making them a less favourable choice during pregnancy.[33] Drugs that are listed as category C indicates that there is limited information about the safety of these medications however do not imply worse safety than drugs that are listed as category B.

CONCLUSION

Active surveillance on the safety of certain drugs used during pregnancy should be continued and as a precaution, they are only ever used if the benefits of treatment are thought to outweigh potential risks. Dental practitioners also need to keep up to date with current medication information to improve the standard of care for their patients.

ACKNOWLEDGEMENTS

The author declares that there are no conflicts of interest and no funding were received for this work.

*Corresponding author:

Dr. Tuan Nadrah Naim Tuan Ismail,

School of Dental Sciences, Universiti Sains Malaysia,16150 Kubang Kerian, Kelantan, Malaysia

E-mail: tnadrah@usm.my

Tel: +6097675896; Fax: +609767 5505

REFERENCES

1 Russell, S. L. Pregnancy Is Associated With Various Degrees of Increased Gingival Inflammation in Healthy Women. *Journal of Evidence Based Dental Practice* 13, 155-156 (2013).

2 Armitage, G. C. Bi-directional relationship between pregnancy and periodontal disease. *Periodontology 2000* 61, 160-176 (2013).

3 Naveen, S., Asha, M., Shubha, G., Bajoria, A. & Jose, A. Salivary flow rate, ph and buffering capacity in pregnant and non pregnant women–a comparative study. *JMED Research* 2014, 1-8 (2014).

4 Freeman, J., Bwire, R., Houn, F., Sheehan, P. & Backstrom, J. Teratogenic Drugs and Risk Management An Implementation Assessment. *Therapeutic Innovation & Regulatory Science* 48, 420-427 (2014).

5 McKay, G. A., Reid, J. L. & Walters, M. R. *Lecture notes: clinical pharmacology and therapeutics*. Vol. 63 283 (John Wiley & Sons, 2011).

6 Bjørn, A.-M. B. *et al.* Use of corticosteroids in early pregnancy is not associated with risk of oral clefts and other congenital malformations in offspring. *American Journal of Therapeutics* 21, 73-80 (2014).

7 Buhimschi, C. S. & Weiner, C. P. Medications in pregnancy and lactation: part 1. Teratology. *Obstetrics & Gynecology* 113, 166-188 (2009).

8 US Food and Drug Administration. Labeling and prescription drug advertising: Content and format for labeling for human prescription drugs. *Federal Register* 44, 37434-37467 (1979).

9 Ramoz, L. L. & Patel-Shori, N. M. Recent changes in pregnancy and lactation labeling: retirement of risk categories. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 34, 389-395 (2014).

10 Food and Drug Administration HHS. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. *Federal Register* 79, 72063-72103 (2014).

11 Pernia, S. & DeMaagd, G. The new pregnancy and lactation labeling rule. *Pharmacy and Therapeutics* 41, 713 (2016).

12 Therapeutic Goods Administration. *Prescribing medicines in pregnancy database*, <http://www.tga.gov.au/prescribing-medicines-pregnancy-database#searchname>

13 Sannerstedt, R. *et al.* Drugs During Pregnancy. *Drug Safety* 14, 69-77, doi:10.2165/00002018-199614020-00001 (1996).

14 Meeraus, W. H., Petersen, I. & Gilbert, R. Association between antibiotic prescribing in pregnancy and cerebral palsy or epilepsy in children born at term: a cohort study using the health improvement network. *PLoS ONE* 10, 1-14 (2015).

15 Neufeld, M. D., Frigon, C., Graham, A. S. & Mueller, B. A. Maternal infection and risk of cerebral palsy in term and preterm infants. *Journal of perinatology* 25, 108-113 (2005).

16 Bear, J. J. & Wu, Y. W. Maternal infections during pregnancy and cerebral palsy in the child. *Pediatric neurology* 57, 74-79 (2016).

17 Greenberg, F. & Reynolds, J. F. Possible metronidazole teratogenicity and clefting. *American Journal of Medical Genetics Part A* 22, 825-825 (1985).

18 Koss, C. A. *et al.* Investigation of metronidazole use during pregnancy and adverse birth outcomes. *Antimicrobial agents and chemotherapy*, AAC. 06477-06411 (2012).

19 Mosley JF II, Smith, L. & Dezan, M. An overview of upcoming changes in pregnancy and lactation labeling information. *Pharmacy practice* 13, 605-608 (2015).

20 Abrevaya, X. C., Carballo, M. A. & Mudry, M. D. The bone marrow micronucleus test and metronidazole genotoxicity in different strains of mice (Mus musculus). *Genetics and molecular biology* 30, 1139-1143 (2007).

21 Löfmark, S., Edlund, C. & Nord, C. E. Metronidazole is still the drug of choice for treatment of anaerobic infections. *Clinical Infectious Diseases* 50, S16-S23 (2010).

22 Babb, M., Koren, G. & Einarson, A. Treating pain during pregnancy. *Canadian Family Physician* 56, 25-27 (2010).

23 Edwards, D. R. V. *et al.* Periconceptional over-the-counter nonsteroidal anti-inflammatory drug exposure and risk for spontaneous abortion. *Obstetrics and gynecology* 120, 113 (2012).

24 Liew, Z., Ritz, B., Rebordosa, C., Lee, P.-C. & Olsen, J. r. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA pediatrics* 168, 313-320 (2014).

25 Yazdy, M. M., Mitchell, A. A., Tinker, S. C., Parker, S. E. & Werler, M. M. Periconceptional use of opioids and the risk of neural tube defects. *Obstetrics and Gynecology* 122, 838-844 (2013).

26 Nakhai-Pour, H. R., Broy, P., Sheehy, O. & Bérard, A. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. *Canadian Medical Association Journal* 183, 1713-1720 (2011).

27 Therapeutic Goods Administration. 33 (Australian Government Department of Health, 2016).

28 Koren, G., Florescu, A., Costei, A. M., Boskovic, R. & Moretti, M. E. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Annals of Pharmacotherapy* 40, 824-829 (2006).

29 Moses, S. *Analgesic medications in pregnancy*, <http://www.fpnotebook.com/Pharm/OB/AnlgscMdctnsInPrgncy.htm>

30 Thompson, J. M. *et al.* Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. *PLoS ONE* 9, 1-6 (2014).

31 Fays, L. *et al.* Use of paracetamol during pregnancy and child neurological development. *Developmental Medicine & Child Neurology* 57, 718-724 (2015).

32 Hagai, A., Diav-Citrin, O., Shechtman, S. & Ornoy, A. Pregnancy outcome after in utero exposure to local anesthetics as part of dental treatment: A prospective comparative cohort study. *The Journal of the American Dental Association* 146, 572-580 (2015).

33 Ouanounou, A. & Haas, D. Drug therapy during pregnancy: implications for dental practice. *British Dental Journal* 220, 413-417 (2016).