



Analgesics and pain relief in pregnancy and breastfeeding

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Summary

Women should be reassured that pain can be treated during pregnancy and lactation and that they need not suffer unnecessarily. Overall, appropriate therapeutic doses of the commonly used analgesics including paracetamol, aspirin and opioids have not been associated with an increased incidence of birth defects. The use of non-steroidal anti-inflammatory drugs in the third trimester is not recommended. Untreated persistent pain can have adverse effects for the mother and her pregnancy and women with persistent pain should ideally have optimisation of their pain management before pregnancy.

Key words: codeine, non-steroidal anti-inflammatory drugs, opioids, paracetamol.

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Introduction

Pain during pregnancy may be due to acute conditions such as injury or infection, or secondary to underlying medical disorders such as rheumatoid arthritis. Pain related to pregnancy can also occur.

Inadequately managed persistent pain can result in depression and anxiety. These may impact on a woman's physical and psychological wellbeing and can potentially have an adverse effect on her pregnancy.

Women should not suffer unnecessarily from pain during pregnancy and lactation. If used appropriately, common analgesics such as paracetamol, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are relatively safe.

In counselling women about taking medicines during pregnancy it is always important to emphasise that all couples have a background risk of around 3% of having a baby with a major birth defect and that approximately 15% of all recognised pregnancies end in miscarriage, regardless of any drug exposures. Over 85% of women use some medication during pregnancy and analgesics are the most common preparations used, after vitamins, in all trimesters of pregnancy, with over 50% of women using analgesics during their pregnancy.¹

The risks or otherwise of drug exposures need to be put into the context of this background risk. Women and their health professionals can then make informed decisions and weigh up the potential risks of treating versus not treating pain during pregnancy and breastfeeding.

Paracetamol

Paracetamol is the analgesic and antipyretic drug most widely used in Australia, particularly by pregnant women. Although it readily crosses the placenta in its unconjugated form, in therapeutic doses it does not appear to increase the risk of birth defects or other adverse pregnancy outcomes. Despite paracetamol's widespread use there are, somewhat surprisingly, no prospective controlled studies about its use in pregnancy.

The drug is not considered to be teratogenic although some retrospective studies including the US Collaborative Perinatal Project found an increased risk of any congenital abnormality and specifically an increase in congenital dislocation of the hip in exposed infants. A registry-based study from Denmark of 26 424 children who were exposed to paracetamol *in utero* during the first trimester found no increase in either the specific or the overall rate of birth defects compared with unexposed controls.²

Aspirin

Aspirin is used to treat mild pain and fever, and low-dose aspirin is also prescribed by some obstetricians (often with heparin) to reduce the risk of adverse outcomes in pregnant women with antiphospholipid syndrome and recurrent miscarriages.³ Overall, aspirin is not associated with an increased risk of congenital malformations, although one meta-analysis suggested an association between first trimester aspirin use and increased risk of gastroschisis*.⁴

NSAIDs

NSAIDs including ibuprofen, naproxen, indomethacin and diclofenac are widely used to treat mild to moderate pain and fever. They are inhibitors of cyclo-oxygenase. In the fetus and newborn, cyclo-oxygenase is a potent dilator of the ductus arteriosus and pulmonary resistance vessels. Its inhibition could potentially cause premature closure of these vessels. These

* an abdominal wall defect resulting from rupture of the amniotic membrane during gut-loop herniation or, later, due to delayed umbilical ring closure

drugs have not been shown to increase the risk of structural birth defects or other adverse outcomes such as preterm delivery or low birth weight. However, a case-control and population-based observational cohort study from Scandinavia demonstrated an increased risk of spontaneous abortion with first trimester use of NSAIDs but with no evidence of other adverse pregnancy outcomes. Major flaws in this study, however, were that it was prescription-based and retrospective and did not control for the indications of use of NSAIDs (such as underlying fever or viral illness).⁵

A Californian study also showed an 80% increase in the risk of miscarriage associated with first trimester use of both aspirin and NSAIDs. This association was not seen with paracetamol.⁶

A suggested mechanism to explain the increased risk of miscarriage is interference with implantation as a result of effects on the prostaglandin pathway. Women who have used NSAIDs inadvertently during the first trimester should be reassured about the use, but other analgesics such as paracetamol should be recommended as preferable options for subsequent use.

Use of NSAIDs after 30 weeks gestation is contraindicated because of their potential to cause premature closure of the fetal ductus arteriosus and persistent pulmonary hypertension. High doses of NSAIDs in the third trimester may also reduce perfusion of the fetal kidneys and decrease fetal urine output. This is why NSAIDs are occasionally used as an intervention to try and reduce liquor volume and the chances of cord entanglement in cases of mono-amniotic twin pregnancy. Most of the cases of reduced output are reversible, but there have been reports of only partial resolution and even of death due to anuric renal failure.^{7,8}

As with the older NSAIDs, the main concerns with the COX-2 inhibitors are effects on the ductus arteriosus as well as perfusion of the fetal/neonatal kidney and intestine. Topical NSAIDs generally result in negligible blood levels and would be considered to be relatively safe in pregnancy although absorption is increased by use over a large surface area or the application of heat.

Opioids

Opioids such as codeine, oxycodone, hydromorphone, hydrocodone and morphine, as well as drugs such as pethidine and tramadol, are used to treat moderate to severe pain. Codeine is also widely used in various over-the-counter preparations. Overall, opioid analgesics have not been associated with an increase in birth defects or other adverse outcomes such as miscarriage. There are also reassuring data on longer-term neurodevelopmental follow-up in exposed infants. The main concern about these drugs is that persistent use may lead to dependence and tolerance in the mother with resultant withdrawal (neonatal abstinence syndrome) in the neonate.

Women with persistent pain who may require high doses of opioids during pregnancy should seek advice about optimising their pain management before pregnancy. Sometimes alternative drugs including tricyclic antidepressants may help to control persistent pain and reduce opioid exposure. Tricyclic antidepressants have not been associated with an increased rate of birth defects or long-term neurodevelopmental effects.⁹

Breastfeeding

Paracetamol is considered to be safe for use during lactation.

The estimated dose received via breast milk is 6% of the maternal dose. It should be remembered that paracetamol is widely used at doses far greater than this for children.

NSAIDs, such as ibuprofen and diclofenac, are considered to be compatible with breastfeeding. The infant doses relative to the maternal doses are 0.65% and 1% respectively, even in women taking high doses – for example diclofenac suppositories 75 mg.¹⁰ The advantage of using these drugs, especially in the immediate postpartum period, is a reduced need for opioids and the potential risks associated with them.

Aspirin is generally not recommended for treatment of pain during breastfeeding mainly because there may be significant adverse effects in infants (the relative infant dose may be as high as 10%) and safer alternatives are available. There is also the theoretical concern that aspirin can cause Reye's syndrome in infants.¹⁰

Genetic polymorphisms and opioids

Cytochrome P450 2D6 catalyses the O-demethylation of codeine to morphine and genetic polymorphisms in the CYP2D6 gene can affect the metabolism of codeine. One of the polymorphisms may result in reduced efficacy of codeine which can be a potential clinical problem.

The case report of a breastfed neonate, who died following maternal codeine use postpartum, highlights the risks of opioid toxicity in patients with another polymorphism – duplication of the CYP2D6 gene.¹¹ This results in ultra-rapid metabolism of codeine and significantly increases the production of morphine. In adults this can lead to significant opioid toxicity despite small doses of drug, and thus breastfed infants of such patients are also at risk of serious toxicity. The incidence of this gene duplication varies in different populations, from approximately 1% in Denmark and Finland to 10% in Greece and Portugal and up to 30% in Ethiopia.

There are also other genetic polymorphisms involved in morphine metabolism that theoretically could reduce its clearance.

Caution needs to be exercised in terms of breastfeeding and minimising the risk of opioid toxicity in both mothers and babies. Short-term use is unlikely to pose a significant risk but longer-term or chronic use can be potentially dangerous, particularly

Use of NSAIDs after 30 weeks gestation is contraindicated

in those people who are ultra-rapid metabolisers due to the CYP2D6 duplication. Mothers and babies should be carefully observed and monitored for signs of opioid toxicity. In most cases the occurrence of central nervous system depression with opioids is consistent between mother and baby (although babies appear to be more sensitive to the effects of opioids) and so if a mother appears to have adverse effects of opioids there should be a low threshold for examining the baby and excluding toxicity.¹² If longer-term pain relief is required, then other drugs such as NSAIDs should be considered as first-line treatment.

Conclusion and recommendations

At MotherSafe we reassure women regarding inadvertent NSAID use, but recommend paracetamol as first-line treatment of fever and pain during pregnancy. Codeine or another opioid analgesic can be added to treat more severe pain. NSAID use is contraindicated in the third trimester and alternative analgesics should also be considered in the first trimester.

Women and their doctors should however be reassured that there are safe options to treat pain, both acute and chronic, during pregnancy and breastfeeding.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 31)

3. Paracetamol does not cross the placenta.
4. NSAIDs should be avoided during the third trimester.

Dental notes

Prepared by Michael McCullough, Chair, Therapeutics Committee, Australian Dental Association

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Dentists often advise patients regarding pain management for dental pain and generally the recommendation for pregnant women to use paracetamol, as the first-line treatment of fever and pain, is reasonable. However, on occasions the dental pain experienced will warrant the short-term use of drugs which include therapeutic doses of codeine. The use of these drugs for short-term treatment (2–3 days) in women who are pregnant or breastfeeding should not pose any adverse risk.

It is probably prudent for dentists not to prescribe non-steroidal anti-inflammatory drugs for pain relief during pregnancy. If their patients are experiencing profound, persistent pain it would be advisable to liaise with the patient's medical practitioner for appropriate management. Importantly, accurate diagnosis and timely dental treatment will dramatically and effectively reduce the pain for these patients. This will diminish the requirement for systemic pain relief.