

Management of pain and fever during pregnancy

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Pregnant women do not need to suffer unnecessary pain or potentially dangerous fever for fear of their taking medications that may be harmful to their unborn baby. Healthcare providers should be confident when prescribing appropriate treatment to such women during pregnancy.

Key points

- Pain during pregnancy should be appropriately evaluated so that women receive appropriate treatment for their stage of pregnancy.
- It is important to exclude acute (and potentially treatable) conditions.
- Overall, appropriate therapeutic doses of the commonly used analgesics have not been associated with an increased incidence of birth defects. However, narcotic and NSAID use in later pregnancy may be associated with withdrawal/adaptation problems and other sequelae, respectively.
- Sustained high fever in early pregnancy should be treated because it increases the risk of miscarriage and certain birth defects.

Pain and fever are two of the most common symptoms affecting the community at large regardless of sex or, in the case of women, pregnancy status. Pain during pregnancy may be due to acute conditions such as injury or infection, or secondary to underlying medical disorders such as rheumatoid arthritis or past injury, or it may be specifically related to pregnancy, for example, ligamentous back and pelvic pain.

It is important that pain be adequately evaluated so that women receive appropriate treatment for their stage of pregnancy. Acute (and potentially treatable) conditions such as cholecystitis or intracranial pathology must be sought and actively treated. This means that necessary investigations, including x-rays, are not withheld merely on the grounds of pregnancy. In general, diagnostic radiation (even pelvic x-ray or intravenous pyelogram) will not result in dangerous radiation levels for the developing embryo or fetus.

It is also well recognised that inadequate management of patients with chronic pain can result in depression, anxiety and hypertension, which may all impact on a woman's physical and psychological wellbeing and can have a potentially

adverse effect on her pregnancy outcome. Women with chronic pain syndromes should ideally have a comprehensive holistic pain management plan implemented by their GP or a specialist. Medications should be optimised before a planned pregnancy and consideration given to nonpharmacological modes of treatment, including physiotherapy and acupuncture.

Like pain, fever is common during pregnancy and can indicate the presence of infection or inflammation and requires appropriate investigation and treatment where necessary. It is also important to recognise that sustained high fever (above 39°C for more than 48 hours) may be associated with adverse pregnancy outcomes including miscarriage or birth defects, and thus needs to be managed appropriately.

Overall, appropriate therapeutic doses of the commonly used analgesics, including paracetamol, aspirin, NSAIDs and narcotics, have not been associated with an increased incidence of birth defects. Thus, pregnant women can be reassured that they need not suffer unnecessarily and their healthcare providers should be confident in prescribing pain relief to women during pregnancy and lactation (Table).

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PARACETAMOL

Paracetamol is probably the analgesic and antipyretic agent most widely used in the Australian community and certainly in the pregnant population. In its unconjugated form paracetamol readily crosses the placenta and in therapeutic doses does not appear to increase the risk of birth defects or other adverse pregnancy outcomes.

Despite its widespread use there are, somewhat surprisingly, no prospective controlled studies about its use in human pregnancy. Retrospective studies have found an increased risk of some birth defects, including gastroschisis and head and neck anomalies, but the data are difficult to interpret due to methodological problems. In a registry-based study from Denmark, more than 26,000 children were exposed to paracetamol in the first trimester and there was no increase in either the specific or overall rate of birth defects in exposed children compared with unexposed controls.¹

A large population-based case-control study from the US National Birth Defects Prevention Study investigated whether exposure to single-ingredient paracetamol (acetaminophen) during the first trimester of pregnancy increased the risk of major birth defects.² The prevalence of first-trimester single-ingredient paracetamol use was common in women in the case group and those in the control group, 46.9% (n = 5440) and 45.8% (n = 2059), respectively. Overall, paracetamol was not associated with an increased risk of any birth defect. In fact, it appeared to be protective in reducing the risk of certain birth defects, including anencephaly, encephalocele, cleft lip/palate and gastroschisis, in those women reporting a first-trimester infection and fever.²

There have been conflicting reports about maternal use of paracetamol during pregnancy and an association between childhood asthma and wheezing.^{3,4}

A recently published study has suggested that long-term exposure (longer than 28 days) to paracetamol during pregnancy is associated with adverse neurodevelopmental effects in children. Further studies are needed to confirm these concerning but somewhat implausible findings.⁵



NSAIDS

Aspirin

Aspirin (acetylsalicylic acid) is the oldest of the NSAIDs and is used to treat patients with mild pain and fever. It is also prescribed in doses between 40 and 150 mg/day by some obstetricians to improve pregnancy outcomes in women at risk for certain complications, including preeclampsia and intrauterine growth restriction.

Most prospective studies of aspirin use during pregnancy have involved these lower doses of less than 150 mg/day rather than analgesic doses of 300 mg every four to six hours. 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.⁶ There is a theoretical concern about premature closure of the ductus arteriosus with use of aspirin (and other NSAIDs) after about 30 weeks' gestation, although there are no reported cases of closure of the ductus arteriosus in humans specifically following third trimester aspirin use.

TABLE. ANALGESIC AND ANTIPYRETIC MEDICATIONS SUITABLE FOR USE IN WOMEN WHO ARE PREGNANT*

Medication	Indication	Comments
Paracetamol	Mild pain and fever	Use in recommended doses to avoid hepatotoxicity (same doses as nonpregnant population)
Aspirin and other NSAIDs, e.g. ibuprofen, diclofenac, indomethacin	Mild pain and fever	Some data suggest aspirin and other NSAIDs may be associated with increased risks of miscarriage in first trimester. Aspirin and other NSAIDs should be avoided in the third trimester because of premature closure of ductus arteriosus
Codeine and other opioids, e.g. pethidine, oxycodone, tramadol	More severe pain	Can cause nausea and constipation, which may be exacerbated in pregnancy. Chronic use results in tolerance and dependence in mother as well as risks of withdrawal in infants. Women with CYP2D6 polymorphisms (and their babies) may be at greater risk of toxicity with codeine
Tricyclic antidepressants, e.g. amitriptyline (off-label use)	Chronic pain	Reassuring data with regard to pregnancy and longer-term infant neurodevelopmental outcomes. May reduce need for opioids

*Doses are the same as for nonpregnant women.

Other NSAIDs

NSAIDs such as ibuprofen, naproxen, indomethacin and diclofenac are widely used to treat mild to moderate pain and fever. NSAIDs have not been shown to increase the risk of structural birth defects or other adverse outcomes such as preterm delivery or low birthweight. There are both animal and human studies suggesting that NSAIDs may be associated with an increased risk of infertility and miscarriage.⁷ However, somewhat confusingly, there are also data reporting that low-dose aspirin (100 mg/day) improves implantation and pregnancy rates in patients undergoing in vitro fertilisation.

NSAIDs appear to increase the incidence of luteinised unruptured follicle (LUF) syndrome, a condition (also reported in rats and rabbits) where an anovulatory cycle results due to failure of normal follicular wall rupture despite normal ovarian follicular development and elevation of serum progesterone. Cyclooxygenase-2 (COX-2) is active in the ovaries during follicular development and thus inhibition via COX-2 inhibitors is thought to result

in LUF. Although similar findings have been reported for both COX-1 and COX-2 NSAIDs, a more recent paper suggested the risks were greater in patients with inactive disease and in those taking the selective COX-2 inhibitor etoricoxib rather than nonselective COX inhibitors such as ibuprofen.⁸

The phenomenon is reversible with normal ovulation documented following drug withdrawal. Thus the prolonged use of NSAIDs, which may occur in the treatment of patients with chronic pain or inflammation of rheumatological conditions, is more likely to be associated with this effect on fertility rather than occasional or intermittent use.

Two studies that primarily involved NSAIDs other than aspirin have reported findings that suggest a possible increased risk of miscarriage when these agents are taken around the time of conception or for more than one week.^{9,10} A two-armed (case-control and population-based observational cohort) study from Scandinavia demonstrated an increased risk of spontaneous abortion with use of NSAIDs in the

first trimester but with no evidence of other adverse pregnancy outcomes. A major flaw in this study, however, was 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).⁹

A study from Kaiser-Permanente in California showed an 80% increase in the risk of miscarriage associated with first trimester use of both aspirin and NSAIDs but failed to show this association with paracetamol.¹⁰

To confuse things even more, a recently published study from Israel failed to show an increased incidence of miscarriage following first trimester use of most NSAIDs apart from indomethacin.¹¹

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 cause reduction in perfusion of the fetal kidneys with resultant decrease in fetal urine output. This latter

effect is occasionally used therapeutically in fetal medicine to try and reduce liquor volume and the chances of cord entanglement in cases of mono-amniotic twin pregnancy. Most cases of reduced renal perfusion and fetal urine output are reversible but there have been reports of only partial resolution and even of death due to anuric renal failure.^{12,13}

As with the older NSAIDs, the main concerns with the COX-2 inhibitors such as celecoxib, meloxicam and piroxicam are effects on the ductus arteriosus as well as perfusion of the fetal/neonatal kidney and gut.

NSAIDs such as ibuprofen and diclofenac are considered to be compatible with breastfeeding as the relative infant doses for these agents are 0.65% and 1%, respectively, even in women taking extremely high doses, such as 75 mg diclofenac suppositories.¹⁴ The advantage of using these drugs, especially in the immediate postpartum period is the reduction in narcotic requirements and therefore reduction in the associated risks of opioid use.

Women with inadvertent NSAID use in early pregnancy should be reassured about their exposure but paracetamol should still be recommended as first-line treatment of fever and pain during all stages of pregnancy (with the addition of codeine or another narcotic analgesic for more severe pain).

NARCOTIC ANALGESICS

Narcotic analgesics, including morphine-like (opioid) agonists (codeine, oxycodone, hydromorphone, hydrocodone and morphine) as well as the synthetic opioids such as pethidine and tramadol are used to treat women with moderate to severe pain. Codeine is also widely used as an antitussive in various over-the-counter preparations.

Although some studies have suggested an increased risk of some birth defects including cardiac defects, gastroschisis and spina bifida with the use of narcotic analgesics,¹⁵ overall they have not been associated with an increased incidence of birth defects or other adverse pregnancy

outcomes such as miscarriage. There is also reassuring longer-term neurodevelopmental follow-up data in exposed infants. The main concern about these drugs is that chronic use may lead to dependence and tolerance in the mother, with resultant withdrawal in the neonate (neonatal abstinence syndrome). Some common pregnancy symptoms that are recognised side effects of narcotics include nausea, postural hypotension and constipation, and these may significantly limit a woman's ability to tolerate narcotic analgesics during pregnancy. A new combination of oxycodone and naloxone (a competitive opioid antagonist) has been developed to improve tolerability of chronic narcotic pain relief but there is limited pregnancy safety information available specifically about this combination.

NSAIDs have not been shown to increase the risk of structural birth defects or other adverse outcomes such as preterm delivery or low birthweight.

Cytochrome P450 (CYP) 2D6 catalyses the O-demethylation of codeine to morphine and duplication of the gene for this enzyme results in ultrarapid metabolism of codeine and thus significantly increased production of morphine from codeine. In adults this can result in significant opioid toxicity despite small doses of drug, and thus infants of such patients are also at risk of serious toxicity if breastfed. A case report of a breastfed neonate who died following maternal codeine use postpartum highlighted the risks of opioid toxicity in patients with duplication of the *CYP2D6* gene.¹⁶ The incidence of this gene duplication varies in different populations: from about 1% in Denmark and Finland to 10% in Greece and Portugal and up to 30% in Ethiopia. Although genetic testing for this polymorphism is not routinely available, it could be considered in hospital and other

settings where chronic or high-dose opiate use is likely.

Another enzyme, uridine diphosphate-dependent glucuronyltransferase 287 (UGT287), catalyses the formation of the metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) from morphine. M6G is a highly active metabolite of morphine that is almost exclusively catalysed by UGT287. Some individuals with a genetic polymorphism (UGT287*2) have higher levels of the more active metabolite, M6G, than those with the more common UGT287*1 allele and are thus at greater risk of prolonged effects from exposure to the pharmacologically active morphine metabolite.

Caution, therefore, needs to be exercised in terms of breastfeeding and minimising the risk of opioid toxicity in both mothers and babies. Short-term opioid use is unlikely to pose a significant risk but longer-term or chronic use can be potentially dangerous, particularly in those people who are ultrarapid metabolisers due to the *CYP2D6* duplication. Mothers and babies should be carefully observed and monitored for evidence of opioid toxicity. In most cases, signs of central nervous system depression with opioids is consistent between mother and baby (although babies appear to be more sensitive to the effects of narcotics). Therefore, if a mother appears to have effects of opioid toxicity there should be a low threshold for examining the baby and excluding toxicity.

If longer-term pain relief is required in breastfeeding women then agents other than opioids – such as NSAIDs – should be considered as first-line treatment.

Women with chronic pain syndromes who may require high doses of narcotics during pregnancy should seek advice about optimising their pain management before pregnancy. It is of concern that worldwide there has been a significant increase in the prescription and use of opioids such as oxycodone, with attendant risks of tolerance, dependence and abuse in mothers and risks of withdrawal in neonates.¹⁷

ANTIDEPRESSANTS

Alternative agents including tricyclic antidepressants (used off label) may be useful in controlling chronic pain and reducing narcotic exposure. Tricyclic antidepressants have not been associated with an increased rate of birth defects and long-term neurodevelopmental studies have been reassuring.¹⁸ As mentioned above, their use in chronic pain management is off label.

ANTICONVULSANTS

Although gabapentin and pregabalin (both gamma-aminobutyric acid [GABA] analogues with anticonvulsant and anxiolytic properties) are being increasingly prescribed for the treatment of neuropathic pain, there are extremely limited data about their use in pregnancy. Therefore their use in pregnancy should not be advocated, and certainly not as first-line treatment for pain in pregnancy.¹⁹ The limited data suggest no significantly increased risk of birth defects but no long-term neurodevelopmental follow-up data are available as yet.

CONCLUSION

It is important that pain be adequately evaluated and treated so that women receive appropriate management for their stage of pregnancy. There are safe options for the management of acute and chronic pain during pregnancy and breastfeeding. It is important that women are given reassuring and evidenced-based information about their pain management options by health-care providers who are confident in their knowledge and understanding of these options. MT

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