

## Analgesic use for non-labour pain during pregnancy

Non-labour pain such as headache and musculoskeletal pain are common complaints during pregnancy. Like most drugs, analgesics (including paracetamol, NSAIDs and opioids) readily cross the placenta to the foetus. The potential risks of analgesic use may put practitioners off prescribing or recommending them for pregnant women. This bulletin aims to cover the use and risk of analgesic use during pregnancy.

**Paracetamol** is the analgesic of choice for the treatment of mild to moderate pain during any stage of pregnancy. The mechanism of action is unclear but it is thought to act by inhibiting prostaglandin synthesis in the central nervous system. Paracetamol is metabolised in the liver to an inactive toxic metabolite. The low concentrations of this that result from normal dosing are removed by conjugation with glutathione.

To date, there is no clear evidence to indicate that paracetamol use by pregnant women is likely to harm the developing foetus at any stage of pregnancy or have adverse effects in infancy and childhood.

**Codeine** is a 'weak' opioid that is used to treat mild to moderate pain. Codeine is metabolised by cytochrome P4502D6 in the liver to morphine, from which it probably derives its analgesic effects. Approximately one tenth of a dose of codeine is converted to morphine in the body. It may be used at any stage during pregnancy where use of paracetamol alone provides insufficient pain relief.

Although apparently 'safe', the use of codeine near term or during labour may cause problems for the foetus and neonate. Like other opioid analgesics, codeine (from in utero exposure) can cause respiratory depression in the neonate. Neonatal withdrawal symptoms such as tremor, jitteriness, diarrhoea and poor feeding have also been reported in infants following maternal use of large doses of codeine taken throughout pregnancy.

**Morphine** is a 'strong' opioid that is used to treat severe pain where use of regular paracetamol plus codeine is ineffective. Morphine may be used during pregnancy when clinically indicated.

To date, there are no reports of therapeutic use during human pregnancy being associated with major congenital defects. However, regular use and use near term or during labour has been associated with neonatal withdrawal symptoms and respiratory depression.

**Tramadol** is a synthetic opioid analogue (approximately equivalent in strength to codeine) that is used to treat mild to moderate pain. In addition to acting on the opioid receptors, it also has an effect on serotonin and noradrenaline receptors in the descending inhibitory pain pathways of the spinal cord. There are very limited data on the use of tramadol during the first trimester of pregnancy. Tramadol has been used during labour without any significant neonatal adverse events. However, it has the potential to cause neonatal withdrawal symptoms. Due to the limited data, use of tramadol during pregnancy should be avoided unless there are compelling clinical reasons for use.

**NSAIDs** such as ibuprofen and diclofenac inhibit the synthesis of prostaglandins and are used as antiinflammatories. The use of NSAIDs prior to week 28 of pregnancy does not appear to be associated with an increased risk of adverse foetal outcomes. However, it is unclear whether the disruption of prostaglandin synthesis has adverse effects on the maintenance of pregnancy and parturition as prostaglandins are intimately involved in these processes.

The use of NSAIDs after the 28<sup>th</sup> week of pregnancy is contraindicated as they can cause adverse foetal cardiovascular effects including premature closure of the ductus arteriosus and neonatal pulmonary hypertension. They may also cause oligohydramnios associated with reduced foetal renal function. NSAIDs can also inhibit uterine contraction, prolong the length of gestation and delay the onset of labour when given late in pregnancy. They may also be associated with excess bleeding in both the mother and the infant at the time of parturition.

Drug	Recommendations	Cautions
Paracetamol	Use at any stage of pregnancy	
Codeine	Use at any stage of pregnancy when stronger pain relief than paracetamol is required.	Regular use near term may be associated with withdrawal symptoms in the neonate & respiratory depression
Morphine	Use at any stage of pregnancy when maximal therapy with paracetamol plus codeine is ineffective.	Prolonged use or use near term may be associated with withdrawal symptoms & respiratory depression in the neonate
Tramadol	Very limited data. Avoid use unless there are compelling clinical reasons.	Use during labour may be associated with neonatal withdrawal symptoms & respiratory depression
NSAIDs	Use until week 28 of pregnancy if an antiinflammatory is clinically indicated	Risk of premature closure of the ductus arteriosus & other adverse foetal outcomes if used after week 28 of pregnancy

### Pink Book and Blue Book Drug use in Renal Impairment changes:

Recently the units used for reporting plasma creatinine have change from mmol/L to umol/L. This means that the Cockcroft and Gault equation on pages 142, 143 and 164 of the Pink Book – the Preferred Medicines List, Antibiotic Guidelines, Pharmacology Guidelines 12<sup>th</sup> Edition 2008 and page 142 of The Blue Book – Management Guidelines for Common Medical Conditions 12<sup>th</sup> Edition 2007 is now incorrect. Please adjust the bottom line of this equation from plasma creatinine (mmol/L) x 800 to plasma creatinine (umol/L) x 0.8.