

Safety of Analgesics in Pregnancy

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Abstract

During Pregnancy most women experience some kind of pain due to a pre-existing condition or a direct consequence of pregnancy. Untreated persistent pain can have adverse effects on the maternal and foetal health. Since time immemorial optimum therapeutic doses of commonly used analgesics including paracetamol, and aspirin have not been associated with increased incidence of birth defects. Chronic pain management during pregnancy and lactation remains a challenge for clinicians. Moreover, pregnant women are at risk of under treatment for painful conditions for fear about use of drugs in pregnancy. Thus, women and health professionals need to be assured about safety of analgesics and the risks of treating versus not treating pain during pregnancy and breastfeeding.

Keywords

Analgesics – paracetamol – pregnancy - breastfeeding

I. Introduction

Pain during pregnancy whether it is due to pregnancy or due to any acute conditions like injury, infection or secondary to underlying medical disorders such as rheumatoid arthritis, needs to be managed adequately. Inadequately managed pain affects the physical and psychological wellbeing of the pregnant lady by causing depression and anxiety.

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 [1-2]. Thus women and their health professionals need to understand safety of analgesics and the risks of treating versus not treating pain during pregnancy and breastfeeding. The background risk of major defects in pregnancy is 3%. Women and their health professionals should make informed decisions after knowing the risk of drug exposure, in relation to the background risk.

II. Methods

Paracetamol

Paracetamol is the analgesic and antipyretic drug most widely used in UAE and all over the world, 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.

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 [3].

Two high-quality cohort studies suggest an association between acetaminophen use in pregnancy and an increased risk of ADHD or similar behaviour in children [4]. The Danish study has been published on the website of the Danish Health and Medicines Authority also. Details of the two studies are as follows:

- In a Danish prospective cohort of 64 322 pregnancies, acetaminophen use in pregnancy was associated with significantly higher scores for behavioural problems at 7 years (risk ratio 1.13, 95% CI 1.01 to 1.27).
- In a Norwegian prospective cohort of 48 631 pregnancies with a focus on 2919 same-sex sibling pairs, acetaminophen use for 28 or more days in pregnancy correlated significantly with maternally assessed (at 3 years) reduced gross motor skills, delay in walking, increased activity, reduced communication skills, and attention-seeking or aggressive behaviour.
 - Correlation β coefficients ranged from 0.2 to 0.26, an approximate 50% to 60% relative increase.
 - Study strength was studying sibling pairs (eliminating differences in mothers or families) and a weakness was

the short duration and maternal assessment.

Research data from JAMA 2014, suggests that acetaminophen may be a hormone disruptor, and abnormal hormonal exposures in pregnancy may influence foetal brain development. This study suggests that children whose mothers used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of HKD, use of ADHD medications, or having ADHD-like behaviours at age 7 years. Stronger associations were observed with use in more than 1 trimester during pregnancy [5].

Both studies, along with the study from JAMA 2014, suggest longer use, use later in pregnancy as also use in more than one trimester, might have stronger associations. Thus, we may have to consider the timing and amount of recommended acetaminophen after further research establishes this association.

NSAIDS

NSAIDs like Ibuprofen, naproxen, indomethacin and diclofenac, are potent inhibitors of cyclo-oxygenase. In the foetus, since cyclo-oxygenase is a potent dilator of the ductus arteriosus and pulmonary resistance vessels. Its inhibition could potentially cause premature closure of these vessels, and thus their use after 30 weeks gestation is contraindicated as can cause persistent pulmonary hypertension. High doses of NSAIDs in the third trimester may also reduce perfusion of the foetal kidneys and decrease foetal urine output. This can lead to oligohydramnios with its sequelae.

A Californian study also showed an 80% increase in the risk of miscarriage associated with first trimester use of NSAIDs, possibly due to its negative effect on implantation as it affects the prostaglandin pathway. This association was not seen with paracetamol [6]. 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.

Aspirin

Aspirin is rarely used to treat pain and fever in pregnancy. Low-dose aspirin is prescribed by obstetricians (often with heparin) to reduce the risk of adverse outcomes in pregnant women with antiphospholipid syndrome and recurrent miscarriages. Overall, aspirin is not associated with an increased risk of congenital malformations. In the later stages of pregnancy, however, aspirin should be avoided since it may prolong labor, lead to greater blood loss during delivery, and increase the incidence of stillbirths.

Opioids

Opioids such as codeine, oxycodone, hydromorphone, hydrocodone and morphine, 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, miscarriages or have any adverse effect on long-term neurodevelopmental follow-up in exposed infants.

However, it may cause dependence after chronic use and tolerance in the mother with resultant withdrawal (neonatal abstinence syndrome) in the neonate. Thus, other alternatives should be looked for a pregnant lady needing chronic use of opioids.

III. Analgesics and Lactation

Paracetamol

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

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. Aspirin should be avoided for fear of Reye's syndrome in the foetus. Also, safer options are available and their use should be encouraged.

Opioids

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 with longer or chronic use, mothers

and babies should be carefully observed and monitored for signs of opioid toxicity. If a mother appears to have adverse effects of opioids there should be a low threshold for examining the baby and excluding toxicity.

IV. Conclusion

It is time to re-think about the safety of analgesics in pregnancy especially after the most trusted acetaminophen is under scrutiny. Non-medical treatments should be used to ease mild and/or short-term pain during pregnancy. If a pregnant woman needs pain relief for more than a couple of days, a consultation with a doctor should be taken to decide upon the analgesics. Further research is awaited to establish the safety of use of acetaminophen in pregnancy.

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