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SAFETY OF COX-2 INHIBITORS IN PREGNANCY

Question:
Is there any evidence to suggest that selective COX-2 inhibitors are safer than conventional NSAIDs in pregnancy?

Answer:
Background: conventional NSAIDs
First trimester: The use of non-steroidal anti-inflammatory drugs (NSAIDs) in the first trimester of pregnancy does not appear to be considered teratogenic[1-4]. However, there have been anecdotal reports associating the use of NSAIDs with bilateral phocomelia and penile agenesis (n=1, indomethacin), hydrops (n=1, indomethacin), cerebral palsy (n=2, ibuprofen), generalized seizures (n=1, ibuprofen) and anencephaly (n=2, ibuprofen), although a causal relationship between these events and NSAID exposure has not been made[1,3-5].

Second and third trimesters: As a class, NSAIDs are generally considered contraindicated in the latter stages of pregnancy. All NSAIDs inhibit prostaglandin synthesis and, when given in the third trimester of pregnancy, may cause adverse foetal cardiovascular effects including constriction of the ductus arteriosus and neonatal pulmonary hypertension. NSAIDs may also inhibit uterine contraction, prolong the length of gestation and delay the onset of labour when given in the later stages of pregnancy. They may also cause oligohydramnios associated with reduced foetal renal function[1-5].

Selective COX-2 inhibitors
We are not aware of any data describing the use of celecoxib or rofecoxib in human pregnancy[1,3,6,7].

Prostaglandins are intimately involved in many of the processes of reproduction including ovulation, fertilisation, implantation, pregnancy maintenance and parturition. There is evidence from animal and/or in vitro studies to suggest that selective cyclo-oxygenase-2 (COX-2) inhibitors may be associated with reproductive complications including low fertilisation rates, implantation failure and uterine relaxation[8,9]. Celecoxib has also been associated delaying preterm labour and constriction of the ductus arteriosus[10,11].

These features suggest that the selective COX-2 inhibitors may carry significant risks, similar to those observed with conventional NSAIDs. However, it is possible that dual blockade of COX-1 and COX-2 may carry greater risks than blockade of COX-2 alone[12]. This is supported by the observation that indomethacin produced greater ductal constriction compared with celecoxib in foetal lambs[11]. However, further research is needed.

Conclusions:
We are not aware of any data describing the outcomes of selective COX-2 inhibition on human pregnancy. Prostaglandins mediate many of the reproductive processes indicating that alteration in their production may be undesirable. Selective COX-2 inhibition has been associated with some of the effects apparent with conventional agents such as premature closure of the ductus arteriosus.

Current data is insufficient to determine whether they are less likely to cause these effects than conventional NSAIDs. In general, it is preferable to avoid all COX inhibitors during pregnancy.

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