Nonsteroidal anti-inflammatory drugs for rheumatoid arthritis during pregnancy

Ana Florescu, MSC  Gideon Koren, MD, FRCPC

ABSTRACT

QUESTION I am treating two pregnant patients who have rheumatoid arthritis with nonsteroidal anti-inflammatory drugs. Are these medications safe at high doses during pregnancy?

ANSWER While these medications do not appear to increase overall rates of congenital malformations, they do increase the risk of ductus arteriosus constriction or closure.

RHEUMATOID ARTHRITIS (RA) is a systemic autoimmune inflammatory disease of the joints. It affects women of reproductive age, so pregnancy complicated by RA is not uncommon. Most pregnant women find that RA tends to improve during pregnancy; it most often improves during the second and third trimesters.

Treating RA during pregnancy is particularly challenging. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of therapy, despite reported and confirmed adverse effects on both mothers and fetuses when they are used for long periods. The principal mode of action of this class of anti-inflammatory drugs is their non-selective inhibition of cyclooxygenase 1 and 2 (COX-1 and COX-2). In addition to the desired effect of reducing inflammation, non-selective COX inhibitors also inhibit gastric, platelet, and renal production of prostaglandin.1

All NSAIDs cross the human placenta and are distributed to the fetus at term. Prenatal exposure to NSAIDs has been shown to increase the incidence of pulmonary hypertension, premature closure of the ductus arteriosus, and periventricular hemorrhage, and to impair fetal renal function leading to oligohydramnios.2 These effects have been reported for indomethacin, ibuprofen, ketoprofen, and diclofenac.1 Although risk of ductal closure increases during late pregnancy in women exposed to NSAIDs, closure is frequently resolved within 24 hours of stopping therapy.

Fetuses exposed to NSAIDs often have decreased urinary output,1 but as with ductal closure, the amniotic fluid usually returns to normal after therapy is stopped. Renal complications appear to be rare, considering the number of women treated with NSAIDs.3 Adverse renal effects reported include fatal anuria, renal failure, oliguria, and oligohydramnios.

A population-based retrospective study on use of NSAIDs showed that they did not increase adverse birth outcomes, but did increase risk of...
A recent meta-analysis completed by Motherisk\(^\text{10}\) found a 15-fold increased risk of ductal constriction after brief (up to 48 hours) exposure to NSAIDs near term. No such risk seems to exist with use of NSAIDs during the first two trimesters. These data suggest a cautious approach, as it is likely that chronic use of NSAIDs in high doses, such as is necessary in the treatment of RA, is associated with an increased risk of adverse fetal effects.

### References