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## **Non-narcotic Analgesics and Pregnancy**

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The non-narcotic analgesics, aspirin (acetylsalicylic acid), acetaminophen and ibuprofen, are among the most common over-the-counter drugs used during pregnancy (Collins, 1981). The Collaborative Perinatal Project (Heinonen et al., 1977) reports that of the 50,000 women in the study, approximately 30% used non-narcotic analgesics during the first trimester of gestation. Over 60% of the study participants used analgesics some time during their pregnancies. Furthermore, because these medications are self-administered, the potential exists for inappropriately extending their use and increasing their doses with medical implications for both mother and fetus (Peterson et al., 1985). This RISK||NEWSLETTER will focus on the effects of acetylsalicylic acid, acetaminophen and ibuprofen when used during pregnancy.

### **MECHANISMS OF ACTION**

All three agents are prostaglandin synthetase inhibitors. The pathway that is affected involves the enzyme which catalyzes the conversion of arachidonic acid to the cyclic endoperoxide, prostaglandin G<sub>2</sub>. The enzyme, cyclo-oxygenase, either is inactivated or inhibited by aspirin, acetaminophen and ibuprofen. Prostaglandin G<sub>2</sub> is a precursor for the larger family of prostaglandins responsible for vascular and uterine regulation (Barton et al., 1991). Prostaglandins are also important in the regulation of systemic and pulmonary vessels and the ductus arteriosus (Needs, 1985). Acetylsalicylic acid, acetaminophen and ibuprofen are known to cross the placenta and acetylsalicylic acid has been shown to remain longer in the neonatal system than in the adult system.

### **ACETYLSALICYLIC ACID (ASA)**

The effects of ASA on a pregnancy have been disputed in the literature. In a large prospective study of 50,000 women who were treated with ASA, 14,000 during the first four lunar months of pregnancy, there was no evidence of increased risk for congenital anomalies in exposed infants, compared to those infants who were not exposed (Sloan et al., 1976). ASA use during pregnancy had no significant effect upon mean birth weight, neonatal death or the rate of stillbirths (Collins et al., 1981). Available data indicate that the risk of birth defects was not increased substantially when women took doses of ASA during their first trimester considered to be common occasional use (650-1300mg/day) (Teris, 1994). In the studies that have observed an increase in the frequency of birth defects, no specific, nor reproducible, pattern of anomalies has been described.

Two British studies showed salicylates could be a teratogen. In these studies, more than 1,200 mothers of children with birth defects were analyzed for salicylate use during pregnancy. A significant number of mothers had taken salicylates (Collins et al., 1981). An increase in oral clefts among exposed infants

was seen in a study of almost 600 Finnish women whose consumption of aspirin was 3X that of controls (Collins et al., 1981). In another study, an increase in frequency of gastroschisis was associated with first trimester use of ASA (Werler et al., 1992). It is generally accepted that in women who take ASA during pregnancy, gestation length might be increased. Near-term use (within one week of deliver) has been associated with an increased risk of intracranial hemorrhage in infants that are premature or low-birthweight (Briggs, 1994). Analgesic use late in pregnancy may complicate delivery and adversely effect the neonate and is therefore not recommended.

In larger doses, for example those used in the treatment of rheumatic diseases (up to 5000 - 6000 g/day), ASA has been associated with a number of congenital birth defects including neural tube defects, facial clefts and skeletal malformations (Teris, 1994). An association between high doses of ASA and the premature closure of the ductus arteriosus has been suggested (Levin et al., 1978). This closure might result in neonatal pulmonary hypertension and hypoxemia (Barton et al., 1991). Other studies showed no association between children with congenital heart defects and occasional maternal use during pregnancy (Werler et al., 1989). If maternal high doses cause premature closure of the patent ductus arteriosus, it occurs infrequently. Chronic use of ASA during pregnancy is thought to increase the risk of stillbirth, anemia, prepartum hemorrhage and preeclamptic toxemia (Needs, 1985).

It has been suggested that the use of ASA in low doses (40-150 mg/day) throughout pregnancy or in the second and third trimesters may guard against preeclampsia, intrauterine growth retardation and maternal immunologic conditions associated with fetal loss such as lupus (Barton et al., 1991). More recently, however, a multinational study involving more than 9,000 women who were treated with very low doses of ASA (60 mg/day) showed no protection against an increase in preeclampsia or intrauterine growth retardation (CLASP, 1994). Thirty-eight percent of the study sample did not receive ASA treatment until after the 20th week of gestation. When studied separately, those women who received ASA treatment prior to 20 weeks did show a reduction in preeclampsia (Reprotox, 1995). Studies on this treatment have involved thousands of women and no adverse effects on their offspring have been observed (Teris, 1994).

#### ACETAMINOPHEN

Acetaminophen was used as an analgesic beginning in 1893, six years before the introduction of ASA (Peterson, 1985). If used in therapeutic doses for short amounts of time, there is no known teratogenic effect associated with acetaminophen. Generally, acetaminophen has a less “noteworthy” role as a prostaglandin synthesis inhibitor (Peterson, 1985). Routinely used during all phases of pregnancy, it is safe as a short-term analgesic.

Werler and her colleagues found a nonsignificant elevation of gastroschisis associated with first trimester use (1991); the prenatal exposures to acetaminophen in seventy-six infants with gastroschisis were studied. The Collaborative Perinatal Project studied the maternal use of acetaminophen during the first trimester and anytime in gestation in almost 1,000 women; no increase in frequency of congenital abnormalities was seen (Heinonen, 1977). A retrospective study on congenital heart defects found no association with the use of acetaminophen (Zierler et al., 1985). Aselton et al., (1985) studied 687 women with first trimester exposure to acetaminophen and found no increase in the rate of congenital abnormalities.

When maternal toxic levels of acetaminophen are reached, various adverse effects have been noted including facial cleft, spina bifida, and pyloric stenosis (Briggs, 1994).

#### IBUPROFEN

The effects of ibuprofen during pregnancy have not been delineated as thoroughly as acetaminophen or ASA. There is a “none to minimal” risk of congenital anomalies associated with its use during

pregnancy (Teris, 1994). The frequency of birth defects was not increased among the children of women who were treated in the first trimester (Aselton, 1985), or at various doses during pregnancy (Barry, 1984). Use of ibuprofen has been reported in over 100 human pregnancies without evidence of a syndrome of congenital anomalies.

Similar to the other prostaglandin inhibitors, high doses of ibuprofen during the third trimester may be a factor in the premature closure of the ductus arteriosus. Hendricks et al., (1990) studied a group of 309 women with preterm labor who received ibuprofen and found a relationship with premature closure of the ductus arteriosus. This potential toxicity is the basis for the recommendation against its use in the third trimester. One case report described a woman who had taken large doses of ibuprofen during the second and third trimesters; constriction of the ductus arteriosus was observed in the fetus. A causal relationship was not assessed due to confounding factors in the case (Baker, 1993).

## **SUMMARY**

The non-narcotic analgesics discussed above belong to a class of drugs termed prostaglandin synthetase inhibitors. These agents inhibit cyclo-oxygenase, an enzyme which catalyzes the conversion of arachidonic acid to endoperoxide, a precursor of the prostaglandins. Vasoconstriction, uterine activity, uteroplacental blood flow and platelet aggregation are regulated by the prostaglandins.

Acetylsalicylic acid, acetaminophen and ibuprofen are common drugs taken during pregnancy. Self-administration has the potential for incorrect dosages or prolonged use. Women should be aware that any medication, even over-the-counter drugs, taken during pregnancy has the potential for disrupting the development of the fetus. Due to the association of ASA and ibuprofen with premature closure of the ductus arteriosus, their use is usually not recommended during the third trimester. When these agents are used as tocolytic treatment in the third trimester, weekly or biweekly ultrasounds may be useful to monitor for this condition (Wiggins et al., 1990). Acetaminophen is considered safe during pregnancy.