

ASPIRIN (Commentary)

Pharmacology

Salicylates in general, and aspirin in particular, have antipyretic, anti-inflammatory and analgesic properties. They also inhibit prostaglandin synthesis. Some aspirin is excreted unchanged in the urine, but most is first metabolised by a series of saturable rate-limiting steps. Toxic levels of salicylate (which is what is formed when aspirin is first de-acetylated in the liver, and which is itself metabolically active) can accumulate very rapidly with high dose treatment once this limit is breached. Aspirin and salicylate both have an effect of platelet adhesion, but only aspirin seems to inhibit platelet aggregation.

Use during pregnancy

There is no known contraindication to **regular daily low-dose** aspirin use (50–100 mg/day) either at the time of conception, or later in pregnancy (Kozer *et al.*, 2003). While salicylate will reach the fetus (Garrettson *et al.*, 1975), the amount of aspirin in fetal blood will be less than a tenth of what it is in the mother (Wolff *et al.*, 1977). Neither is there any clear evidence that **occasional full-dose use** carries much risk either, and teratogenicity does not seem to be an issue (see below). However there are two studies showing that such use around the time of conception may cause a measurable increase in the risk of miscarriage (Li *et al.*, 2003; Nielsen *et al.* 2004).

Conflicting reports have appeared with regard to **regular full-dose use**. While teratogenicity does not seem to be a problem when normal therapeutic doses are used, but there has been concern that treatment could increase the risk of maternal or fetal haemorrhage. Exposure to aspirin does not commonly cause premature duct closure or later persistent pulmonary hypertension as was once feared (de Swiet and Fryers, 1990). It is, however, clear that regular full dose usage (> 3.2 g/day) in late pregnancy can delay the onset of labour (Lewis and Schulman, 1973) and may also, if taken during labour, slow the progress of labour itself (Waltman *et al.*, 1973).

Most of the reports suggesting that aspirin use in pregnancy could be hazardous related to pregnancies where there was regular, unregulated, **addictive high-dose use**. Many of the women in the study from Sydney (Collins and Turner, 1975), which was the first to report that salicylate use was associated with an increased risk of stillbirth, and of fetal growth retardation, were also self-medicating with a range of other drugs. No such hazards could be detected in the large prospective study of non-abusive use published by Shapiro *et al.* in 1976. There are suggestions that the sudden impulsive use of aspirin in attempted **suicide** may put the fetus at more risk than the mother (Palatnick and Tenenebin, 1998). The underlying reason for any such vulnerability remains imperfectly established, but haemorrhagic complications are a possibility. These have not generally been a feature, however, in the few cases where the gross maternal over-medication shortly before delivery resulted in the delivery of a baby who showed features of florid salicylate poisoning after birth (Buck *et al.*, 1983).

Teratogenicity: The large prospective study of 50,000 pregnancies by Slone *et al.*, 1976, at a time when aspirin was more widely used than it is now, found no evidence of teratogenicity. In other much smaller, retrospective, case control studies where a weak link was found it is difficult to exclude the possibility of biased recall. It could also have been the intercurrent illness that triggered the use of aspirin in some of these studies, rather than the aspirin that caused the fetal abnormality. A report appeared in 1987 suggesting that even intermittent full dose use in the first half of pregnancy could cause a reduction in the child's IQ, but this observation could not be replicated. There are reports suggesting that such use increases the risk of gastroschisis (Kozer *et al.*, 2002), and this is a plausible hypothesis if, as many believe, gastroschisis is caused by a vascular insult. However, it is difficult to see how this can be a major cause of this particular birth defect given that the incidence of gastroschisis seems to be rising at a time when the use of aspirin in pregnancy is declining. While exposure to doses higher than are ever used therapeutically can produce malformations in animals, only one of the 31 women who took an overdose in McElhatton's short report gave birth to a malformed baby.

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Use during lactation

No study has even looked to see how much aspirin appears in human milk – studies have simply looked at salicylate transfer, and the accuracy of any blood levels reported may have been affected, in the past, by the fact that bilirubin gives a false positive colour reaction with ferric chloride, the reagent most frequently used to estimate blood salicylate levels. However, a mother who takes a *single* dose of aspirin while breast feeding will not have exposed her child to a dose of salicylate that (on a weight-for-weight basis) equates to more than 5% of what she had exposed herself to. The effect of *regular* low dose maternal treatment has never been studied, but is almost certainly equally safe. Much less is known about the level of exposure that results from regular high dose treatment and, because the enzymes responsible for drug elimination are saturatable, and the baby's ability to eliminate the drug limited, it would be possible for toxic levels to accumulate. Indeed, most authorities hold that paracetamol or ibuprofen are much safer analgesics to use during lactation anyway because any ingestion of aspirin could, in theory, trigger Reye's syndrome. In addition, salicylates bind competitively with plasma proteins in the same way as sulphonamides, making kernicterus at least a theoretical possibility in any very jaundiced baby (Ahlfors *et al.*, 1982).

There is, at the moment, only a single published report of toxicity caused by breast feeding. This occurred to the 16 day old baby of a mother who was said to be taking 3.9 grams of aspirin a day (Clark and Wilson, 1981). It is, however, very difficult to see how this child could have ingested enough salicylate from breast milk to still have a serum salicylate level of 240 mg/l three days after admission. Since levels in the mother's blood and milk were never examined, it remains unclear where the salicylate in the child's blood stream actually came from. This single report should *not* be used to discourage the very occasional mother who has good reason to take regular high dose aspirin from breast feeding: it would however seem wise, in the light of this report, to actively monitor the salicylate levels achieved. Subsequent publication of the findings would also be of great help to others faced with a similar decision.

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