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ASPIRIN (ACETYLSALICYLIC ACID)

Summary

Quick take: High-dose aspirin exposure in experimental animal studies causes an increase in congenital anomalies. A consistent pattern of congenital anomalies has not been identified in human reports after typical exposures to aspirin. An increase in miscarriage risk after aspirin exposure around the time of conception has been proposed. Aspirin is avoided in late pregnancy due to concerns about premature constriction of the ductus arteriosus and bleeding abnormalities. These concerns do not appear to apply to low-dose (60-100 mg/d) aspirin. Aspirin is not used during breast-feeding because of possible newborn accumulation of the drug after repeated exposures.

Aspirin (acetylsalicylic acid; ASA) is used as an analgesic and antipyretic. It is the oldest member of the large group of drugs now termed the non-steroidal anti-inflammatory drugs (NSAIDs). Aspirin and other NSAIDs act primarily by inhibiting the synthesis of prostaglandins ([1265](#)).

In very large doses, aspirin is teratogenic in rodents, with cranial and neural tube defects among the most consistent findings (1,2). Offspring of food-restricted rats that also received aspirin 250 mg/kg/d had more than twice the incidence of malformations as those that received aspirin alone (22). The most notable malformations were rib and limb defects and umbilical hernias. In even larger doses, aspirin produced similar embryotoxicity in rhesus monkeys (2). The anomalies observed included neural tube defects, skeletal malformations, and facial clefts.

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Some case-control studies have reported associations between human congenital malformations and aspirin use early in gestation, but the various studies have not uncovered a consistent outcome attributable to drug use. One study, for example, reported an increase in cleft palate among offspring of aspirin users (3), and a second found an increased stillbirth rate and reduced birth weight among women who used aspirin intermittently during pregnancy, but no increase in congenital malformations (4). A large prospective study of more than 50,000 pregnancies did not uncover any evidence of aspirin-induced teratogenicity, altered neonatal birth weight, or perinatal deaths (5). A retrospective, case-control study suggested that aspirin use during pregnancy might increase the risk of certain heart defects in the offspring (19). However, another case-control study of children with congenital heart defects found no association between these abnormalities and maternal use of aspirin during pregnancy (20). A case-control study on gastroschisis found affected pregnancies to have a significantly increased odds of having been exposed to aspirin or ibuprofen ([1096](#))(48). This association was reexamined by a different group of investigators with similar findings of a significant association between gastroschisis and self-reported use of salicylates during the first trimester of pregnancy (odds ratio 3.33; 95% confidence interval 1.05, 9.80) (49). There were only five exposed children and 45 unexposed children in the gastroschisis group.

An increased incidence of postterm pregnancy and longer duration of pregnancy in women taking aspirin has been reported (25). This observation is consistent with animal and human data on the use of other aspirin-like drugs to decrease uterine contractions and prolong pregnancy (35,36).

Near term, use of aspirin and other prostaglandin synthetase inhibitors may cause closure or constriction of the fetal ductus arteriosus with resultant pulmonary hypertension (6,7,64). Aspirin also decreases platelet adhesiveness and aggregation, and premature babies whose mothers took aspirin within one week of delivery have been found to have an increased incidence of intracranial

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bleeding (8). Thus, the available reports suggest analgesic doses of aspirin use may complicate delivery and adversely affect the newborn. For this reason, aspirin use at analgesic doses is not recommended in late pregnancy (9).

Several studies indicated that the use of small daily doses of aspirin (60 to 100 mg) by women at high risk of preeclampsia might significantly reduce the incidence of pregnancy-induced hypertension (10-14,29,30,32). Additional findings from some of these studies suggested a significant increase in fetal birth weight among at risk patients who do not become hypertensive (10,14). In a separate but related study, low-dose aspirin therapy was associated with a significant increase in birth weight, fetal head circumference, and placental weight in women with moderate hypertension who had abnormal Doppler ultrasound evaluation of the umbilical vessels (11). Aspirin did not have significant effects on pregnancy outcome in women with extreme hypertension. A randomized, placebo-controlled, double-blind study of mothers matched for parity, social and professional status, and number and nature of previous pregnancy complications, also found aspirin therapy to be effective in decreasing the frequency of IUGR, stillbirth, and abruptio placenta in mothers with a previous history of these pregnancy outcomes (21). However, the placebo group had a higher mean blood pressure than the treatment group (this difference was reported but was considered insignificant). No higher incidence of unfavorable outcomes was reported in the neonates of the treated group (21).

A large-scale Italian study of aspirin in pregnancy did not find any outcome measures that were positively influenced by aspirin (27). The small fraction of women with proteinuria and hypertension (2.7%) in the study population may have obscured a positive effect of low-dose aspirin (28). A follow-up of children in the Italian study did not find that the use of low-dose aspirin in pregnancy increased malformations or impaired development at 18 months of age (38). It should be noted that one large study performed in the US identified an increase in placental abruption associated with low dose aspirin use (32). The authors

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raised the possibility that their finding was due to an unusually low incidence of abruption in the control group (0.1%).

To address many of the limitations of previous smaller studies on this use of aspirin in pregnancy, a multinational study [CLASP (Collaborative Low-dose Aspirin Study in Pregnancy)] that involved more than 9,000 women was performed (37). Data from this study, reported in March 1994, did not support previous observations that suggested low-dose (60 mg) aspirin daily produced significant benefits for women at increased risk of preeclampsia or IUGR (37). The findings of the CLASP study did indicate that low-dose aspirin reduced fetal morbidity in a select population of women with early-onset preeclampsia. These women were typically those with preexisting disorders, such as chronic hypertension or renal disease, or those who developed preeclampsia before 32 weeks of gestation in a previous pregnancy. The CLASP results did not uncover significant adverse effects in mother, fetus, or newborn in association with the use of low-dose aspirin (46). A follow-up on infants exposed to low-dose aspirin at 12 and 18 months of age did not show any adverse developmental effects (55).

It should be noted that CLASP administered aspirin to 38% of participants after 20 weeks gestation. When results were analyzed for women beginning aspirin prior to 20 weeks, a reduction in preeclampsia was identified. This effect is consistent with recognized pathophysiologic mechanisms for preeclampsia. In addition, the blood pressure definition for preeclampsia was more stringent in CLASP than in other studies, introducing another possible explanation for CLASP's failure to show the benefits identified in other trials. However, subsequent large-scale studies (56-58), including one in Jamaica (57) that focused on possible beneficial effects of starting aspirin before 20 weeks' gestation, have not supported the prospect that low-dose aspirin will alter the onset or clinical course of preeclampsia. The use of aspirin in women with established preeclampsia is not recommended (53,54).

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In women with and without SLE who have lupus anticoagulant and anticardiolipin antibodies, several reports showed that the use of low-dose (60 to 80 mg/d) aspirin in conjunction with prednisone ([1169](#))(20 to 80 mg/d) improved pregnancy outcome and prevented most thrombotic events (reviewed in ref 23). Two additional reports did not find any benefit from the use of prednisone in conjunction with low-dose aspirin in women with serum autoantibodies and a history of recurrent fetal loss (34,50). The discrepancies in these observations may be based on how each study defined its test populations (51). Another study reported that pretreatment for four week with prednisone and aspirin improved the pregnancy rate after in vitro fertilization in autoantibody seropositive patients (67). This observation awaits further investigation. The use of heparin and aspirin in this patient population is also under investigation (68).

Newborns exposed in utero to low dose aspirin have not been found to have an excessive risk of bleeding abnormalities (10,11). Detailed biochemical investigations have indicated that exposed newborns had significantly reduced levels of platelet cyclooxygenase (63%) but enzyme levels were not completely suppressed (14-16). These findings have been interpreted to suggest that low doses of aspirin may permit normal hemostatic competence in the fetus and newborn (14,15). Despite this optimism, some proponents of the use of low dose aspirin recommend that treatment be stopped at least five days before the estimated date of delivery to avoid possible hematologic abnormalities in the newborn (10,16). However, in a prospective randomized controlled study of women in the third trimester of pregnancy treated until delivery with up to 80 mg/d of aspirin, neonatal levels of 6-keto- prostaglandin F1 alpha and thromboxane B2 were unaffected (24). Platelet aggregation was not inhibited, and all infants had normal echocardiograms, and no evidence of cephalohematoma, gastrointestinal bleeding, or purpura (24). Low dose aspirin has also been found not to alter fetal cardiovascular waveforms on pulsed Doppler evaluation, suggesting a negligible effect of this therapy on the ductus arteriosus or other vascular smooth muscle (31,39,65). Other studies have

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confirmed that low-dose aspirin therapy during pregnancy did not increase neonatal bleeding complications (32) or decrease fetal urine excretion (33). Data from one study indicated that the use of epidural analgesia does not appear to be contraindicated in women using low-dose aspirin in late pregnancy (45).

Aspirin and other salicylates are transferred into breast milk (40-43). A milk: plasma ratio of less than 1.0 was found from the available studies involving salicylates, suggesting that only a small fraction (4 to 8%) of a single maternal dose would be ingested by a suckling infant (42,43). However, in one clinical report, metabolic acidosis developed in the infant of a woman who ingested a salicylate daily while breastfeeding (42). Animal and human data suggest that the reduced clearance of salicylates by neonates may result in drug accumulation and toxic effects even when repeated exposures are small (41,44). Because of these concerns, the WHO Working Group on Human Lactation classified the salicylates as unsafe for use by nursing women (26). In Britain, the use of aspirin during breastfeeding has been categorized as contraindicated due to a theoretical risk of Reye's Syndrome (52). This however, does not refer to low dose aspirin specifically. For mothers who need to be on aspirin during the postpartum period, a safe way to use aspirin is to take the aspirin at night after the last breast-feeding and then pump and discard the first milk in the morning. This will eliminate most of the aspirin that may have been excreted in the milk.

Aspirin and other NSAIDs may play a role in at least one type of female infertility. Prostaglandin inhibition appears to increase the incidence of luteinized unruptured follicle syndrome, a condition in which normal ovarian follicular development is followed by an elevation of serum progesterone compatible with ovulation, but the cycle remains anovulatory because the follicular wall remains unruptured (69,70). Rat and rabbit studies have reported ovulation inhibition in association with aspirin and other prostaglandin inhibitors (47,71,72). In women, ultrasound scans of follicular development have been used to show a fivefold increase in the incidence of this syndrome in the presence of some NSAIDs (70).

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The prolonged use of NSAIDs, which may occur in the treatment of chronic pain and inflammation of rheumatologic conditions, is most likely to be associated with this antifertility effect. Similar findings have been reported for both COX-1 and COX-2 NSAIDs (70,73). In contrast to this observation, one group of investigators has reported that low-dose aspirin (100 mg/d) improved implantation and pregnancy rates in patients undergoing in vitro fertilization (59). They hypothesize that this effect may be mediated by improved ovarian and uterine blood flow associated with this low dose of aspirin. The significance of these findings has been questioned (60-63). In a subsequent report, a higher pregnancy rate and better endometrial pattern were achieved in patients with thin endometrium after low-dose aspirin administration (66). No mechanism for this effect was proposed. Two studies that primarily involved NSAIDs other than aspirin have reported findings that suggest a possible increased risk of miscarriage when these agents have been taken around the time of conception or for more than a week (74,75). For a detailed discussion of these studies, see the NSAID summary,