

Aspirin in Recurrent Miscarriage: Is There an Indication?

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Aspirin has come into widespread use for recurrent miscarriage as it is believed to increase blood flow to the embryo and thereby prevent miscarriage. The rationale is that aspirin may act on hitherto unrecognized thrombophilias. Pregnancy itself is a hypercoagulable state associated with increased levels of procoagulant factors [1] and decreased levels of naturally occurring anticoagulants such as protein S [2]. Microthrombi are a common finding in the placental vasculature of women with recurrent miscarriage [3].

The aim of using aspirin to prevent women with recurrent pregnancy losses from suffering additional miscarriages is entirely laudable. At the Recurrent Miscarriage Clinic at Sheba Medical Center, approximately 40% of new patients were previously treated empirically with aspirin. However, the evidence for using aspirin is limited: only one small randomized study of 54 pregnant women with unexplained recurrent spontaneous miscarriage in which aspirin was compared to placebo [4]. This review explores whether aspirin use is justified as a means of preventing pregnancy loss.

ACTIONS OF ASPIRIN

Aspirin selectively and irreversibly acetylates the hydroxyl group of one serine residue in cyclooxygenase, leading to COX inhibition. COX is the enzyme that catalyzes the first two steps in prostaglandin synthesis from arachidonic acid, including PGI₂ (prostacyclin), and TXA₂ (thromboxane A₂). Since aspirin has more activity against COX-1 activity than against COX-2 [5], it has more suppressive action against thromboxane A₂ than it does against prostacyclin. Since prostacyclin causes vasodilation and prevents platelet aggregation and thromboxane A₂ is a potent platelet agonist and vasoconstrictor, aspirin tends to prevent vasoconstriction and platelet aggregation. The action is irreversible

COX = cyclooxygenase

and therefore the new enzyme must be synthesized before more prostaglandins are produced. Prostaglandins appear to be essential for implantation, although concentrations of endometrial prostaglandins are lower in pregnancy than in the menstrual cycle, and exogenous administration of high doses induces abortion. Maintenance of pregnancy may be dependent on a mechanism that suppresses prostaglandin synthesis. Aspirin, which suppresses COX, has the potential to support this mechanism.

Aspirin and other antiplatelet agents have also been reported to play a role in the inhibition of the pro-inflammatory cytokines tumor necrosis factor- α and interleukin-8 in stroke [6]. TNF α induces thrombin generation [7] and IL-8 causes polymorph accumulation [8]. Polymorphs react with fibrin and damaged tissues to form clots. In addition, aspirin is capable of stimulating IL-3 production *in vitro* [9]. Hence aspirin may also modify cytokine-mediated thrombosis. The maintenance of pregnancy has been widely reported to be dependent on a shift of pro-inflammatory to anti-inflammatory cytokines [10].

Not one study has found aspirin to confer a significant benefit on the live birth rate in antiphospholipid syndrome

ASPIRIN IN ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome is assumed responsible for pregnancy loss by causing thrombosis in the small blood vessels of the decidua, leading to subsequent fetal demise. However, placental histology shows most of the antibody to be concentrated in the cytotrophoblast. The pathological effects of antiphospholipid antibody on the trophoblast include decreased vasculosyncytial membranes, increased syncytial knots, substantially more fibrosis, hypovascular villi and infarcts than women without APS [11], and a fetal vasculopathy rather than maternal vessel thrombosis. Additionally, the dose of 75–100 mg was based on the dose required to protect against myocardial re-infarction [12]. However, it is generally believed that women with APS who use low dose aspirin have improved pregnancy outcomes. Therefore, aspirin, which has been used since the earliest studies in APS over 20 years ago, is still used widely for APS today [13] and is recommended in professional organization guidelines. Belief in the beneficial effects of aspirin is based on observational studies in which

APS = antiphospholipid syndrome

aspirin was combined with concomitant medications such as steroids or heparins.

Three placebo-controlled randomized trials assessed the subsequent live birth rate after aspirin treatment in APS [4,14,15], but none found aspirin to confer a significant benefit. These three papers were combined in a meta-analysis [16], which found no improvement in the live birth rate (relative risk 1.05, 95% confidence interval 0.66–1.68). Therefore, there is currently no evidence that low dose aspirin leads to improved pregnancy outcomes in women with APS. However, the live birth rate did increase significantly when heparin or low molecular weight heparin was added to the aspirin.

ASPIRIN IN UNEXPLAINED RECURRENT PREGNANCY LOSS

In our clinic approximately 40% of new patients are failures of empiric aspirin treatment. There is only one prospective randomized trial of aspirin for the prevention of miscarriage in unexplained pregnancy losses [4]. In that study 27 women were randomized to receive aspirin, and 27 received placebo. There was no difference in the live birth rate or the incidence of late obstetric complications. The authors concluded, “Low dose aspirin is ineffective in the prevention of miscarriage in recurrent spontaneous abortion.” Rai et al. [12] carried out a prospective observational study to assess the effect of low dose aspirin (75 mg daily) in improving the subsequent live birth rate in women with either unexplained recurrent early miscarriage (< 13 weeks gestation, n = 805) or unexplained late pregnancy loss (n = 250). There was no significant difference in the live birth rate between those who took aspirin and those who did not (odds ratio 1.24, 95% CI 0.93–1.67). In contrast, women with a previous late miscarriage who took aspirin had a significantly higher live birth rate than those who did not (OR 1.88, 95% CI 1.04–3.37). The authors concluded that empiric use of low dose aspirin in women with unexplained recurrent early miscarriage is not justified. The increased live birth rate in women with a previous late miscarriage indicates that a number of cases of second-trimester miscarriage may have a thrombotic etiology. However, it is important to note that hereditary thrombophilias were not excluded in the study by Rai and team [12].

No study has assessed aspirin in unexplained recurrent late pregnancy losses after the exclusion of hereditary thrombophilias, thus casting doubt on the relevance of aspirin in unexplained late losses.

ASPIRIN IN HEREDITARY THROMBOPHILIAS

Hereditary thrombophilias are associated with an increased tendency to venous thrombosis, but they do not definitely cause thrombosis. Both the Royal College of Obstetricians and the American College of Obstetricians guidelines for the management of recurrent miscarriage state that there is insufficient evidence to recommend thrombophilia testing in recurrent miscarriage. ESHRE (European Society of Human Reproduction and Embryology) recommends that thrombophilia testing be reserved as an advanced investigation. Thrombophilia screening is widely carried out in Israel and is recognized to be within the “Basket of health services” of three of the four major health funds (Leumit, Maccabi and Meuhedet). Aspirin is often recommended for hereditary thrombophilias. However, hereditary thrombophilias cause thrombosis directly without the intervention of platelets or changes in the thromboxane prostacycline balance. In the factor V Leiden mutation, factor Va becomes resistant to degradation by activated protein C, increasing the risk of venous thromboembolism three to fivefold. The prothrombin gene mutation, G20210A, was found to be associated with increased prothrombin levels and a threefold increased risk for venous thrombosis.

Low dose aspirin has been reported to be ineffective in the prevention of miscarriage in recurrent spontaneous abortion

The only study to assess aspirin in the hereditary thrombophilias is that of Gris and colleagues [17], which compared the live birth rate after aspirin therapy versus enoxaparin in 160 patients with hereditary thrombophilia and at least one prior pregnancy loss. The patients treated with enoxaparin had a significantly higher live birth rate than those treated with low dose aspirin (86% vs. 29%, respectively). Therefore, there is little rationale or evidence to prescribe aspirin in recurrent pregnancy loss in the presence of hereditary thrombophilias.

CONFOUNDING FACTORS

The most important confounding factor in assessing the effect of aspirin or any other treatment for maternal causes of pregnancy loss is either congenital malformations in the embryo or fetal chromosomal aberrations. In women with recurrent miscarriages 75% are missed abortions with either embryonic demise or blighted ova. In missed abortions 200 of 233 embryos were found to be structurally abnormal on embryoscopy [18]. These defects included anencephaly, encephalocele, spina bifida, syndactyly, pseudo-syndactyly, polydactyly, cleft hand and cleft lip. Without embryoscopy these embryos would not have been diagnosed and the patients might have been treated empirically with aspirin for a presumed clotting factor. Although there are no embryo-

CI = confidence interval
OR = odds ratio

scopic analyses of recurrent miscarriages, the incidence of malformations is known to be higher in women with recurrent miscarriage than in the general population [19]. Structural abnormalities that are incompatible with life could confound the results of aspirin therapy.

In recurrent miscarriage, approximately 30% of embryos are karyotypically abnormal [20]. Aberrations, such as 16 trisomy and triploidy, are incompatible with life and invariably cause fetal demise. A 30% incidence of fetal chromosomal aberrations has been reported in two small series of patients with antiphospholipid syndrome [21,22]. The author has also found chromosomal aberrations in the abortus of four patients with hereditary thrombophilias [23]. Aspirin cannot correct chromosomal aberrations. Unfortunately, since the abortus is not usually karyotyped in Israel, it is not known if pregnancy loss after aspirin therapy is due to failure of treatment or confounding of the results by fetal chromosomal aberrations. In an ideal trial assessing the effect of aspirin, subsequent abortions will be karyotyped in order to accurately assess the results.

Rather than preventing miscarriage, aspirin was associated with an increased risk of miscarriage. Teratogenicity has been reported in animals and there may be a higher risk of gastroschisis in humans.

SIDE EFFECTS

The general adverse effects of aspirin have been described elsewhere [24]. Aspirin has been shown in a meta-analysis to increase gastrointestinal hemorrhage [25]. The risk of gastrointestinal hemorrhage with aspirin (less than 163 mg daily) was 2.3% compared to 1.45% with placebo (OR 1.59, 95% CI 1.40–1.81). Hence, one additional case of hemorrhage would occur in every 100 patients taking low dose aspirin. Aspirin was also found to lead to deterioration of renal function in the elderly [26].

In pregnancy, rather than preventing miscarriage, aspirin has been associated with an increased risk of miscarriage. The increased risk has been shown in a case-control study [27] in which pharmacy data were linked with birth registry data. The increased risk has also been described in a population-based cohort study by Li and co-authors [28]. After adjustment for confounding factors, aspirin use begun at conception was associated with an increased risk of miscarriage (RR = 4.3, 95% CI 1.3–4.2). However, a meta-analysis of low dose aspirin during the first trimester did not find an increase in the miscarriage rate [29]. In later pregnancy, the likelihood of bleeding antenatally, intrapartum and postpartum has been reported to be higher in women taking low dose aspirin [30].

The risk to the developing fetus from exposure to aspirin is difficult to quantify. Salicylates administered to the

mother cross the placenta easily, inhibiting fetal prostacyclin and thromboxane activity [31]. The fetus has lower plasma protein binding of salicylates compared to adults [32]. Additionally, elimination is less efficient, so the resulting fetal concentration of salicylates is much higher than in the mother. A dose-response adverse effect has been reported in the fetus. The risk of bleeding in the neonate (particularly intracranial hemorrhage) increases with increasing maternal exposure to aspirin before delivery. There have been case reports of preterm occlusion of the ductus arteriosus and pulmonary hypertension in fetuses exposed *in utero* to salicylates, but with low dose aspirin taken late in gestation such abnormalities were not seen in the study by Hertz-Picciotto et al. [32]. However, because the event rates

are low and sample sizes are small, the studies have insufficient power to detect such rare outcomes.

Teratogenicity has been reported in laboratory animals including diaphragm, cardiac and midline defects [33]. Embryos exposed to aspirin are edematous with facial malformations and tail abnormalities. Aspirin has also been associated with cardiac defects in several species [34]. In humans, an elevated risk of cardiac defects, such as hypoplastic left ventricle, coarctation of the aorta and aortic stenosis, has been estimated [32]. In the study by Dolitzky and co-authors [35], 50 women received 100 mg aspirin; one of them had tricuspid regurgitation. Two cases of cyclopia were associated with daily maternal ingestion of up to 4 g of aspirin in the first trimester. Although the low dose that is usually used in recurrent miscarriage may be insufficient to cause structural anomalies of the central nervous system, the exposure may be sufficient to cause functional impairment manifesting as deficits in cognitive or behavioral development [32]. Aspirin has been associated with a significantly lower IQ in 4 year olds and attention span deficits in children whose mothers used aspirin in the first half of pregnancy [36]. The explanation for such an adverse effect may be a decreased cerebral fetal circulation to the brain induced by prostaglandin inhibition by aspirin [37]. Additionally, a significantly higher risk of gastroschisis has been detected in infants born to women using aspirin in the first trimester compared with non-aspirin users (OR 2.37, 95% CI 1.44–3.88) [38]. The Spanish Collaborative study of Congenital Malformations [39] has confirmed an increased risk of gastroschisis after first-trimester prenatal exposure to salicylates (OR 3.47, $P = 0.015$) after controlling for maternal age and maternal smoking. However, several population-based cohort and case-control studies [40] did not find an increased risk of congenital malformations.

RR = relative risk

CONCLUSIONS

The use of aspirin to prevent pregnancy loss stems from the assumption that pregnancy loss is due to a thrombotic mechanism in APS and the fact that aspirin has cardioprotective effects. Hereditary thrombophilias are assumed to act by similar mechanisms and to warrant similar treatment. Even unexplained pregnancy losses are sometimes assumed to have an as yet unexplained underlying thrombotic process. At present, no report in the medical literature has shown a role for aspirin in preventing recurrent pregnancy loss. On the contrary, three placebo-controlled trials and a meta-analysis of aspirin in APS show no beneficial effect. In unexplained pregnancy loss, one placebo-controlled trial and one observational study demonstrated that aspirin had no beneficial effect. However, the study by Rai and associates [13] does show a positive effect in late pregnancy losses when hereditary thrombophilias were not excluded. There is no study of aspirin in the hereditary thrombophilias. The results of Rai's study [12] suggest that the positive effects of aspirin in late losses may be due to its action in patients with hereditary thrombophilias. In the work by Gris et al. [17] enoxaparin was shown to be more effective. However, all of these results may have been confounded by the failure to assess fetal karyotypic aberrations.

In conclusion, the possibility of side effects such as the increased risk of miscarriage, gastroschisis, etc., and the fact that there is no evidence that aspirin is efficacious in treating women with recurrent miscarriage contraindicate prescribing aspirin in early pregnancy.

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