70. Aspirin Prophylaxis in Pregnancy

RECOMMENDATION

There is insufficient evidence to recommend for or against the routine use of aspirin to prevent preeclampsia or intrauterine growth retardation in pregnant women, including those at high risk (see ***Clinical Intervention***).

Burden of Suffering

Pregnancy-associated hypertension/preeclampsia/eclampsia syndrome (see Chapter 37 for definitions) is the second leading cause of maternal death in the U.S.[1,2] In 1992, over 112,000 pregnant women (28.5/1,000 live births) developed pregnancy-associated hypertension, of whom approximately 13% were classified as severe.[3] Maternal complications associated with preeclampsia include abruptio placentae, acute renal failure, cerebral hemorrhage, disseminated intravascular coagulation, pulmonary edema, circulatory collapse, eclampsia, and death.[4] Preeclampsia also increases the rate of cesarean delivery and prolongs the duration of hospitalization.[3,5] Neonatal complications include low birth weight (due to preterm delivery and/or intrauterine growth retardation), preterm delivery, hypoxia, and perinatal death.[6] Risk factors for preeclampsia include age (<20 or ≥40 years), Native American race, family history, nulliparity, twin gestation, chronic hypertension, diabetes, collagen vascular disease, and a previous history of pregnancy-associated hypertension or preeclampsia.[3,7,8]

Efficacy of Chemoprophylaxis

Preeclampsia may be due to endothelial dysfunction caused by the systemic effects of decreased placental blood flow.[8] Compared to women with normal pregnancies, women with preeclampsia have a relative excess of thromboxane A_2 (a platelet-derived vasoconstrictor and platelet aggregation promoter) compared to prostacyclin (an endothelial cell-derived vasodilator and platelet aggregation inhibitor).[9–11] The correction of the thromboxane A_2 to prostacyclin ratio caused by aspirin may help prevent the development of preeclampsia and its complications.[12]

A number of randomized controlled trials have evaluated the potential benefit of prophylactic aspirin in preventing preeclampsia. Two stud-

ies[13,14] were performed in routine obstetric patients. Hauth[13] et al. randomized 604 nulliparous women under the age of 28 years to 60 mg aspirin or placebo daily from 24 weeks' gestation until delivery. Compared with the placebo group, the group receiving aspirin experienced a statistically significant reduction in total and severe preeclampsia and in levels of thromboxane B_2, a metabolite of thromboxane A_2. No statistically significant differences emerged in the rates of neonatal complications (including low birth weight, prematurity, and fetal death), maternal complications, or cesarean deliveries. Sibai[14] et al. studied 3,135 nulliparous women. These women received either 60 mg aspirin (n = 1,485) or placebo (n = 1,500) daily from <26 weeks' gestation to delivery. The treated group had a 26% reduction in the incidence of preeclampsia compared with the placebo group (4.6% vs. 6.3%, p = 0.05). Women who received aspirin had a significant increase in the risk of abruptio placentae: 0.7% vs. 0.1% (p = 0.01). This outcome was not defined before the trial, however; its definition was not standardized nor was the diagnosis confirmed by external review. There were no other significant differences in maternal or fetal outcomes.

In the largest trial to date, the CLASP Collaborative Group[15] randomized 9,364 women to either 60 mg aspirin or placebo daily. Women were eligible for entry into the study for prophylactic (n = 8,021) or therapeutic (n = 1,343) treatment if they were between 12 and 32 weeks' gestation and either had signs or symptoms of preeclampsia or intrauterine growth retardation (IUGR) or were considered by the physician to be at high risk for preeclampsia or IUGR (based on a history of preeclampsia or IUGR in a previous pregnancy, chronic hypertension, renal disease, maternal age, family history, or multiple gestation). This study found a significant, small reduction in preterm deliveries in the aspirin group (12% reduction among high-risk asymptomatic women), but no difference in the incidence of preeclampsia or IUGR. An increase in transfusion rates was noted in the aspirin group; it was not associated with the occurrence or severity of postpartum hemorrhage, however, nor were there significant differences in abruptio placentae or other antepartum bleeding. No other maternal or fetal complications were noted. This trial may have failed to show an effect of aspirin on preeclampsia because of the variability and subjectivity of entry criteria (which were based on the responsible clinician's rating of risk), and the use of a more conservative statistical analysis ($\alpha = 0.01$ and two-tailed test of significance).

Three smaller trials[16–18] also examined the use of aspirin in women at increased risk of preeclampsia. These studies identified women at increased risk on the basis of results of various screening tests, including the "rollover" test,[16] wave form ultrasound,[17] and angiotensin test.[18] Intervention began between 24 and 32 weeks, and the dose of aspirin ranged from

60 to 100 mg/day. Each study found a statistically significant reduction in preeclampsia in the aspirin-treated group, but no significant differences in fetal or maternal complications. The cesarean delivery rate was significantly lower in the aspirin group in two of the studies.[17,18]

Three other randomized controlled trials enrolled women with risk factors for preeclampsia, including nulliparity, multiple gestations, chronic hypertension, and previous pregnancy with preeclampsia, IUGR, or fetal death.[19–21] All three studies showed a significant reduction in preeclampsia in the aspirin group. Two additional trials, from Finland[22] and Italy,[23] found no significant reduction in pregnancy-associated hypertension in the aspirin-treated group. These study populations included women who had pregnancy-associated hypertension or preeclampsia in the current pregnancy as well as asymptomatic high-risk women, however, which may have masked a benefit.

Three trials, two randomized[15,24] and one nonrandomized,[25] tested the efficacy of low-dose aspirin in the prevention of IUGR in asymptomatic high-risk women. The CLASP trial[15] (see above) of women at increased risk of IUGR found no difference in incidence of IUGR between those who were randomized to receive aspirin prophylaxis compared to placebo. In the other randomized controlled trial,[24] pregnant women with a history of poor outcomes (including IUGR) in two earlier pregnancies were randomized to receive either aspirin 150 mg/day or a placebo, beginning at 15 to 18 weeks' gestation. Those given aspirin had significantly heavier babies (mean 225 g higher; $p = 0.03$), and the proportion weighing less than the 10th percentile was decreased from 26% to 13% in the treated group ($p < 0.02$). The nonrandomized trial also found a significant reduction in IUGR in the aspirin group. Two other randomized controlled trials cited above found no difference in IUGR incidence with aspirin prophylaxis, but the inclusion of both symptomatic and asymptomatic high-risk women may have concealed an effect.[22,23]

The safety of aspirin prophylaxis in pregnancy must be carefully considered. While there have been sporadic reports of congenital heart defects associated with aspirin use in the first trimester of pregnancy, no causal link between aspirin and birth defects has been established.[26] Preterm closure of the ductus arteriosus has also been reported. High-dose aspirin consumption close to delivery can result in maternal and fetal clotting abnormalities such as increased maternal bleeding and neonatal intracranial hemorrhage.[12,27] Maternal effects were seen with doses of 1,500–2,500 mg/day, and neonatal effects with doses of 325–1,500 mg/day. Bleeding problems have not generally been reported at low doses (60–150 mg/day),[28–30] although most trials were too small to detect rare adverse effects. The two largest trials each found a significantly increased risk of bleeding: abruptio placentae in one trial[14] and an increased risk of

postpartum maternal transfusion in the other.[15] A meta-analysis of 11 randomized controlled trials of low-dose aspirin prophylaxis in pregnancy did not find an association, however, between aspirin and either abruptio placentae or perinatal mortality.[31]

Effectiveness of Counseling

Little information on compliance with daily aspirin prophylaxis during pregnancy is available. In one trial, 315 of 919 women failed a 2-week run-in period due to poor compliance with either visits or medication.[13] In another trial, 35 of 39 women recruited for a placebo-controlled study of low-dose aspirin therapy in the prevention of preeclampsia refused participation.[32] Reasons for refusal included fear that aspirin would harm the fetus or the pregnant woman, the belief that pregnant women should not participate in experimental studies of drugs, and the belief that women should avoid medications during pregnancy.

Recommendations of Other Groups

No organization currently recommends routine aspirin prophylaxis in pregnancy for the prevention of preeclampsia or intrauterine growth retardation.

Discussion

Numerous randomized controlled trials among both low-risk and high-risk pregnant women indicate that aspirin prophylaxis reduces the incidence and severity of preeclampsia. Nevertheless, no consistent reductions in other fetal or maternal complications have been seen. Although the CLASP trial found a significant reduction in preterm delivery, most trials to date have had insufficient power to identify clinically important differences in rates of prematurity, respiratory distress syndrome, and perinatal death. A meta-analysis of controlled trials reported no significant effect of aspirin on perinatal mortality.[31] In addition, the largest trial in healthy low-risk women[14] found a significant increase in the risk of abruptio placentae, a potentially life-threatening complication for both the fetus and the woman, while the CLASP trial[15] reported an increased risk of maternal transfusion postpartum. Hence, the net health impact of routine aspirin prophylaxis remains uncertain. While aspirin appears to reduce the incidence of preeclampsia, it is unknown whether it improves other, perhaps more important, fetal and maternal outcomes. Preeclampsia may be only one manifestation of a broader underlying pathophysiologic defect. Complications commonly attributed to preeclampsia may be due to the underlying pathology and not to preeclampsia per se. If so, prevention of preeclampsia may not translate into an overall clinical benefit.

One randomized trial found a beneficial effect of aspirin on birth weight among women at increased risk for delivering an infant with IUGR. While statistically significant, this effect may have little clinical impact due to problems with the definition of "growth retardation." This study did not differentiate constitutionally small infants with progressive intrauterine growth from infants with faulty growth patterns. In addition, other randomized trials in asymptomatic and symptomatic women have not reported significant effects on IUGR. Further studies are warranted to confirm any benefit, to determine the optimal gestational ages for administration, and to find the lowest effective dose of aspirin.

CLINICAL INTERVENTION

There is insufficient evidence to recommend for or against routine aspirin prophylaxis in pregnancy for the prevention of either preeclampsia ("C" recommendation) or intrauterine growth retardation ("C" recommenda tion). Clinicians may wish to inform patients at high risk of preeclampsia that aspirin prophylaxis has been shown to decrease this risk, but such patients should also be informed that aspirin has not been proven to improve overall fetal or maternal outcomes, that one large trial raised the possibility of an increased risk of abruptio placentae, and that aspirin can have additional unpleasant and occasionally serious side effects.

The draft of this chapter was prepared for the U.S. Preventive Services Task Force by Peter W. Pendergrass, MD, MPH, and Carolyn DiGuiseppi, MD, MPH.

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