REVIEW ARTICLE

Low-dose ASA in the prevention and treatment of PIH, IUGR and perinatal mortality: A review of the literature.

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Pregnancy-induced hypertension (PIH) is a major cause of maternal morbidity and is one of the top five causes of maternal death in the United States (1). Fetal and neonatal mortality are increased in the presence of maternal hypertension, presumably due to decreased uterine and intervillous space blood flow leading to intrauterine growth restriction (IUGR) (2). Women with pre-eclampsia or eclampsia stay in hospital significantly longer than normotensive women, regardless of the delivery method (1.5 to 1.8 days longer) (3). They also have a higher rate of Caesarean-section (2.4 times more likely)(3). An effective treatment or prevention strategy against PIH would be important in lowering the increased morbidity and mortality and the increased costs secondary to complications of this disorder. Recently, much interest has been generated over the use of acetylsalicylic acid (ASA) therapy in this regard. The results of several clinical trials examining the effects of ASA therapy to prevent or treat PIH and IUGR and its effects on perinatal mortality will be reviewed. Early, small trials suggested a beneficial role for using ASA to prevent the development or complications of PIH. However, later, more extensive trials have not borne out these results and thus the widespread use of ASA for prophylaxis or treatment of PIH and IUGR is not supported.

Classification of hypertensive disorders in pregnancy is sometimes confusing as different authors use different definitions. The classification scheme proposed by the National High Blood Pressure Education Working Group in 1990 (4) is a concise one and will be used to interpret the results of reviewed literature (Table 1). Based on this scheme, there are three major classes of hypertension in pregnancy:

1. Pregnancy-induced hypertension
2. Chronic hypertension and
3. Chronic hypertension with superimposed PIH.

Several risk factors have been recognised that predispose a woman to the development of PIH. Teens under 15 years have a 2.8 times greater risk of developing pre-eclampsia than older women up to 35 years (4). At this point, the risk also increases with advancing maternal age (i.e. age over 35-40 years), especially if the woman is nulliparous (2- to 3-fold increase) (5). Other risk factors include a 6- to 8-fold increase in primiparous versus multiparous women (2), pre-eclampsia in the first pregnancy (10-15 times increased risk) (6), chronic hypertension (3-7 times greater risk) (7), family history of eclampsia (8 times increased risk) (7), diabetics (2 times greater risk) (8), hydatidiform mole and fetal hydrops (each 10 times higher risk) (4), and twin pregnancy (2-3 times increased risk) (7).

Table 1: Classification of hypertensive disorders of pregnancy (4).

Pregnancy-induced hypertension (PIH)
•Transient (gestational): during pregnancy or within 24 hours of the birth and without associated proteinuria or edema
•Pre-eclampsia: edema, and/or proteinuria (may be mild or severe)
•Eclampsia:development of convulsions not attributable to another cause
Chronic hypertension (HTN)
•Of any cause preceeding pregnancy
Chronic HTN and PIH
•Superimposed pre-eclampsia
•Superimposed eclampsia

Many theories about the etiology and pathophysiology of this disorder have been proposed, ranging from cardiovascular-based explanations to allergy-based ones. The physiologic response that increases cardiac output in pregnancy may

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be overcompensating in women who become hypertensive (9). It has also been suggested that some women with PIH have an increased sensitivity to the exposure of sperm (2).

The most current theory is that poor uteroplacental perfusion secondary to inadequate invasion of the trophoblast into the uterine spiral arteries eventually leads to hypertension in the mother (10). The invasion of trophoblast normally occurs in two phases. The first is during early pregnancy (between 10-16 weeks gestation), and the second between 16 and 22 weeks gestation. If the trophoblast does not erode away the spiral arteries effectively, the spiral arteries continue to respond to local and humoral agents (e.g. thromboxane A_2, angiotensin II and catecholamines) causing local vasospasm, with resultant compromise in uteroplacental flow (11). Thus, the initial manifestations of PIH are local, and the decrease in uteroplacental perfusion may cause fetal growth restriction. The maternal response may be variable, and may or may not lead to the development of maternal hypertension (12).

In order for the trophoblast to invade the spiral arteries, placental vasodilation must be maintained. It has been proposed that prostacyclins (e.g. prostaglandin I_2 or PGI_2) produced by the trophoblast may serve in this regard (10). Prostacyclins, produced by the endothelial cells and by the trophoblast act as vasodilators and have anti-aggretory effects on platelets. They have the opposite effect of another prostaglandin, thromboxane A_2 (TxA_2) produced by platelets and the trophoblast (i.e. TxA_2 causes vasospasm and platelet aggregation). Both prostaglandins are increased in normal pregnancy. It is thought that if the balance between TxA_2 and PGI_2 is shifted to favour TxA_2, its vasoconstrictor effects become dominant and the trophoblast fails to erode the spiral arteries effectively.

Friedman et al. (11) postulated that poorly perfused trophoblast releases toxic substances into the maternal vasculature that damage endothelial cells. Endothelial cell damage results in the release of vasoconstrictor substances and other mediators leading to local vasospasm, increased permeability of blood vessels and hence clinical manifestations of hypertension, edema and proteinuria.

Thus, it seems that the balance between vasoconstrictive TxA_2 and vasodilative PGI_2 plays an important role in the development of PIH and IUGR. ASA irreversibly acetylates cyclo-oxygenase, the enzyme that converts arachidonic acid into both PGI_2 and TxA_2. However, production of TxA_2 seems to be selectively inhibited over the production of PGI_2 with low doses of ASA (60-150 mg) (13). The mechanism is unclear, but Dekker and Sibai (14) propose that platelets are more sensitive to ASA than the PGI_2-producing endothelium, thus tipping the balance to favour PGI_2 in the circulation.

The interest in using ASA as prophylaxis/treatment for PIH and IUGR has been so great that some clinicians have implemented its use before results from large, randomized-controlled trials have become avail-

Table 2: Summary of results from small trials.

Dosing regimens and agents used are given in text. p-Value given for statistically significant results. DNA=data not available. AST=angiotensin sensitivity test. See comments on individual studies in text.

Study	No. of patients	IUGR		Perinatal mortality		Pre-eclamptic proteinuria		Gestational hypertension	
		N	%	*N*	%	*N*	%	*N*	%
Beaufils *et al.*, 1985 (17)	Treatment: 48	4 (p<0.005)	8	0 (p<0.02)	0	0 (p<0.01)	0	19	40
	Control: 45	13	19	5	11	6	13	22	49
Wallenburg *et al.*, 1986 (18)	Treatment: 23	4	17	1	4	0 (p<0.01)	0	2	9
	Control: 23	6	26	1	4	7	30	4	17
Wallenburg & Rotmans, 1987 (19)	Treatment: 24	4 (p<0.02)	17	1	4	DNA		2	8
	Control: 24	16	67	0	0	DNA		4	17
Schiff *et al.*, 1989 (13)	Treatment: 34	2	6	0	0	1 (p<0.019)	3	3	9
	Control: 31	6	19	0	0	7	23	4	13
Benigni *et al.*, 1989 (20)	Treatment: 17	2 (p<0.05)	12	0	0	DNA		0	0
	Control: 16	6	38	1	6	DNA		3	19
McParland *et al.*, 1990 (21)	Treatment: 48	7	15	1	2	1 (p<0.02)	2	6	13
	Control: 52	7	13	3	6	10	19	13	25

able. As an example of this trend, one study of changes in prescription patterns in the Netherlands (15) reported that ASA use for prevention of PIH increased from 53% to 79%, and its use for treatment of PIH increased from 25% to 48%. The authors also point out that the greater use of ASA by clinicians may have been responsible for the steady decline in recruitment of patients for a large, international trial (Collaborative Low-dose Aspirin Study in Pregnancy or CLASP). In fact, CLASP could not start at all in New Zealand because physicians there were so convinced of the effectiveness of ASA.

REVIEW OF STUDIES

Small studies

The first report that ASA may be effective in the prevention of pre-eclampsia (16) sparked several small trials that found large reductions in the incidence of PIH (including pre-eclampsia) and IUGR (13,17-21). The results of each of the trials is summarized in Table 2. However, the subjects of these studies were selected because they appeared to be at particularly high risk of developing PIH and/or IUGR and each trial consisted of less than 100 subjects. The first, by Beaufils et al. (17) in 1985, reported significant reductions in the incidence of pre-eclampsia, IUGR and perinatal mortality. Patients were selected on the basis of an obstetrical history that put them at high risk for pre-eclampsia and/or IUGR, or because they had a history of hypertension or an otherwise complicated past pregnancy. This study was not double-blinded (for "ethical reasons" not made known by the authors) and there was no placebo-controlled group. Furthermore, most of the subjects were multiparous, so the applicability of the study to the highest risk group (i.e. primiparous women) is questionable. Dipyridamole (300 mg daily), another antiplatelet agent, was used in conjunction with ASA treatment (150 mg daily) from "3 months" gestation until delivery. It is unlikely that the addition of dipyridamole influenced the outcomes to a significant extent as it has been shown that there is no difference between therapy with ASA and dipyridamole and treatment with ASA alone (22).

In 1986, Wallenburg et al. (18) demonstrated in a randomised, placebo-controlled, double-blinded study that there was a significant effect of ASA in preventing pre-eclampsia, but not in preventing IUGR. Perinatal mortality was not affected. A statistically significant increase in the rate of Caesarean-section was also noted in the placebo group. The treatment group in this study took 60 mg ASA daily from 28 weeks gestation until delivery. Study subjects were selected from a group of 207 healthy, primiparous women screened for possible development of PIH with an angiotensin II infusion test. Those with an increased blood pressure response to infused angiotensin II at 28 weeks gestation were enrolled in the study and randomly allocated to either treatment or placebo groups.

Wallenburg published another trial of low-dose ASA with Rotmans in 1987 (19). They studied multiparous women with a history of at least two pregnancies greater than 20 weeks gestation that had been complicated by severe IUGR and placental infarction. They originally intended to perform a randomized, placebo-controlled trial. However, it was subsequently found that the high-risk patients they approached to take part in the study all wanted treatment and refused to participate in randomization, even if placebo was not used. Thus, the investigators had to resort to using historical controls selected by an obstetrical record search. Their treatment group took 1-1.6 mg/kg/day of ASA (rounded off to the nearest 10 mg) and 225 mg dipyridamole daily in three divided doses from 16-34 weeks of pregnancy. The control group had no treatment but had received comparable antenatal care. The investigators found a significant reduction in the incidence of IUGR in the treatment group, but no difference in the rates of perinatal mortality or gestational hypertension. The difference in pre-eclamptic proteinuria was not assessed. This study lacked a concurrent, placebo-controlled group. The subjects in the study were all multiparous, high-risk patients and again, the applicability of the results to low-risk primiparous women is questionable. Also, two patients in the treatment group were later found to have lupus anticoagulant, and this may have biased the results either for or against ASA treatment.

Another randomised, double-blinded, placebo-controlled trial by Schiff et al. (13) in 1989 studied 65 primiparous and multiparous women who had a positive roll-over test at 28-29 weeks gestation. A roll-over test consists of the measurement of blood pressure (BP) while the woman is lying on her left side and then when she "rolls over" onto her back. A positive test is indicated by a rise in diastolic BP of 15 mm Hg or more when the woman moves to the supine position from what it was while lying on her left side. The treatment group in this study received 100 mg ASA daily from the time of their positive roll-over test to 10 days prior to the estimated time of delivery. The results showed a significant decrease in the incidence of proteinuric pre-eclampsia in the treated as compared to the control group, but no significant differences between the two groups in reduction of IUGR or total perinatal mortality.

Benigni et al. (20) published a single-blinded study of 33 women in 1989 who had pregnancies judged to be at high risk because of a history of essential hypertension or a past pregnancy complicated by placental insufficiency, severe IUGR, or pre-eclampsia before 32 weeks gestation. Treatment consisted of 60 mg ASA daily from 12 weeks gestation until delivery. The treatment group reached statistical significance in lower rates of IUGR and also a later week of delivery than the placebo group. The overall reduction in PIH was not significant, and the rates of proteinuric pre-eclampsia were not evaluated. The reason why the evaluator of clinical

Table 3: Summary of results from larger trials.

Dosing regimens and agents used are given in text. p-Value given for statistically significant results. DNA=data not available. AST=angiotensin sensitivity test. See comments on individual studies in text.

Study	No. of patients	IUGR		Perinatal mortality		Pre-eclamptic proteinuria		Gestational hypertension	
		N	%	*N*	%	*N*	%	*N*	%
Uzan *et al.*, 1991 (22)	Treatment: 156	20 (p<0.05)	13	7	4	5 (p<0.02)	3	35	22
	Control: 73	19	26	6	8	8	11	25	34
Italian study 1993 (27)	Treatment: 583	117	20	18	3	12	2	69	12
	Control: 523	95	18	19	4	9	2	42	8
Hauth *et al.*, 1993 (24)	Treatment: 302	17	6	1	0	5 (p<0.009)	2	19	6
	Control: 302	19	6	1	0	17	6	17	6
Viinikka *et al.*, 1993 (25)	Treatment: 97	4	4	2	2	9	9	12	12
	Control: 100	9	9	0	0	11	11	14	14
Sibai *et al.*, 1993 (26)	Treatment: 1485	68	5	30	2	69 (p<0.05)	5	100	7
	Control: 1500	87	6	21	1	94	6	89	6
CLASP 1994 (23)	Treatment: 4659	371	8	129	3	313	7	DNA	
	Control: 4650	401	9	136	3	352	8	DNA	

outcomes was not blinded is unknown, but this introduces the possibility of bias. Furthermore, since only three women developed PIH in the placebo group as compared to none in the treatment group, it seems unlikely that there would have been a significant decrease in the incidence of pre-eclampsia with ASA treatment even if this outcome had been measured.

A recent study by McParland et al. (21) in 1990 selected 100 women with abnormal Doppler uteroplacental flow-velocity waveform at 18-20 weeks gestation, and then again at 24 weeks gestation. They were randomised to either 75 mg ASA daily or identical placebo from 24 weeks of pregnancy. Over 1200 primiparous women were screened to obtain the study groups in this double-blinded trial. The only significant result obtained was a decrease in the rate of proteinuric pre-eclampsia in the ASA group. There were no differences in the rates of IUGR, perinatal mortality or gestational hypertension.

Altogether, the results of these studies suggest that low-dose ASA is effective in reducing the incidence of pre-eclampsia by 85-90% in high risk women. The reduction in IUGR is about 50% and the overall decrease in the incidence of PIH is about 40% (23).

Large studies

In 1991, the results of several larger studies (22-27) indicated that the large effects observed by the small trials may not be accurate. These study results are summarized in Table 3. A French study in 1991 (Essai Pre-eclampsie Dipyridamole Aspirine or EPREDA by Uzan et al. (22) was the first of these larger studies to be published. Two-hundred and twenty-nine multiparous women with a high-risk obstetrical history (i.e. one or more of IUGR, fetal death or *abruptio placentae* in at least one previous pregnancy) were randomly assigned to one of three groups. The first group received 150 mg ASA daily; the second took 150 mg ASA daily and 225 mg dipyridamole daily. The third group was the placebo control. All groups began treatment or placebo from 15-18 weeks gestation and continued until delivery. This study had two objectives: to study the effectiveness of ASA in preventing IUGR and PIH and to compare the effects of treatment with ASA and dipyridamole to the effects of treatment with ASA alone. No outcome differences were demonstrated between the two treatment groups. The pooled results of both treatment groups versus controls showed a significant decrease in the rates of IUGR and proteinuric pre-eclampsia in the treatment groups. No primiparous women were included in the study, so the results may not be applicable to this group.

In 1993, an Italian study (23) of 1106 primiparous and multiparous women judged to be at high risk for PIH based on age, pre-pregnancy hypertension or nephropathy with normal renal function and blood pressure, a complicated obstetrical history or PIH and/or early signs of IUGR in the current pregnancy. Treatment consisted of 50 mg ASA daily from the date of

randomisation (range 16-32 weeks gestation) until delivery. The control group received comparable antenatal care, but no placebo. Patients were randomized to either the treatment or control groups, but the investigator knew who was receiving ASA and who was not. The study could not demonstrate any significant differences in outcome between the two groups, and the investigators concluded that there was little support for using low-dose ASA in women at moderate risk for PIH or IUGR. The results have been challenged because of biases that could easily have arisen due to lack of placebo control or double-blinded technique. However, given the general acceptance of ASA therapy in pregnancy among clinicians at this point, (15) it seems more likely that the results should have been biased in favour of ASA treatment and not against.

Hauth et al. (1993) (24) studied over 600 healthy, normotensive, primiparous women with singleton gestations, all of whom were of lower socioeconomic status and many of whom were African Americans. Patients were randomised to either 60 mg ASA daily from 24 weeks gestation until delivery or matching placebo. Significant results were demonstrated in the reduction of pre-eclamptic proteinuria in the treatment group. No significant reductions were found for IUGR or perinatal mortality. This data may better reflect the results that could be expected if ASA was used as universal prophylaxis against PIH and IUGR in healthy, primiparous women. However, their study population appeared to have a higher "background" rate of pre-eclampsia, and the results in a population with an overall lower incidence of pre-eclampsia may be less dramatic.

A smaller study from 1993 by Viinikka et al. (25) enrolled primiparous and multiparous women with pre-existing hypertension or a history of severe pre-eclampsia in a previous pregnancy. The study was randomized, double-blinded and placebo-controlled. The treatment group received 50 mg ASA daily from 15 weeks gestation until delivery. No significant differences between the treatment and control groups could be demonstrated. However, the investigators did note a trend toward improvement in fetal hemodynamic performance as assessed by Doppler and a decreased need of intensive neonatal care in the treatment group.

Almost 3000 normotensive primiparous women were subjects in a randomized, double-blinded, placebo-controlled trial by Sibai et al. (26), also in 1993. A dose of 60 mg ASA daily was given to those in the treatment group from the date of randomization (range 13-26 weeks gestation) until delivery. The investigators demonstrated a significant reduction in the rate of proteinuric pre-eclampsia in the treatment group, but no significant reduction in the rate of IUGR or perinatal mortality.

Finally, the largest trial to-date to evaluate the effectiveness of ASA in preventing or treating pre-eclampsia and IUGR (Collaborative Low-dose Aspirin Study in Pregnancy or CLASP) (23) published its results in March, 1994. This multicentre (213 centres) study recruited 9364 women over 5 years, of which follow-up was obtained and data analyzed for 9309 women. The subjects were of varying gravidity, were entered for either prophylactic or therapeutic means, and were randomised to either treatment or control groups. Treatment consisted of 60 mg ASA daily from the date of randomisation (range 12-32 weeks) until delivery. The control group received a matching placebo. The results were analyzed separately for those entered for prophylaxis or therapy and the data was also pooled to show the results for all women regardless of the reason for entry into the trial. The investigators could not show a difference between the two groups in the rates of pre-eclampsia, IUGR or perinatal mortality. The only significant difference found was a reduction of 14% in the likelihood of the ASA group to have a preterm delivery (delivery before 37 weeks).

The authors of the CLASP study pooled the results of all the larger studies done to-date, and found a reduction in the incidence of pre-eclampsia with antiplatelet therapy of about one-quarter. If the CLASP results are included in this analysis, the reduction falls to about one-sixth. This means that pre-eclamptic proteinuria would be prevented in only 1 of 100 women treated with ASA (23). As discussed earlier, pooled data from the smaller trials suggested an almost 90% reduction in the incidence of pre-eclamptic proteinuria with ASA. When the data regarding perinatal deaths is pooled, no significant reduction can be demonstrated (27).

DISCUSSION

There are several reasons for the wide discrepancies in the results of large versus small trials. First, trials with positive data are much more likely to be published than those that find no treatment effect. It is known that at least as many women as were enrolled in all of the smaller studies were randomised in other small trials (23). However, these results were not published, presumably because the data was not as favourable as that in the published trials. This may explain why the larger trials showed much less extreme results.

Many of the studies had much potential for bias in their study design. The lack of placebo controls, blinding techniques and randomisation in some of the studies make the results less reliable and could possibly have contributed to the apparent beneficial effect of ASA prophylaxis/therapy in PIH.

Another explanation may be that the trials that showed the best results selected a group of patients for whom antiplatelet therapy was directed more at the pathophysiology behind their disease. The most promising results, especially in the larger trials, in prevent-

ing proteinuric pre-eclampsia come from the studies that enrolled healthy, normotensive primiparous women and used ASA as prophylaxis. Perhaps once the disease process develops or has developed in a previous pregnancy, it is too late to prevent it with antiplatelet therapy, even in a subsequent pregnancy. If this is true, a better early diagnostic tool may help to select those at risk of developing PIH and its attendant maternal and fetal complications for early antiplatelet therapy. The best-designed smaller studies (13,18,21) did use a diagnostic test (angiotensin II sensitivity, roll-over test, Doppler uteroplacental flow-velocities) to select their patients, and two of these trials studied only primiparous women who were otherwise thought to be healthy until their abnormal test result.

All of the reviewed studies reserved ASA use until after the 12th week of gestation. Presumably this was to avoid the risk of teratogenic effects on organogenesis in the first trimester. It is possible that the process that leads to the development of PIH and IUGR is already well underway by the beginning of the second trimester. In this case, ASA therapy early in the first trimester may make a difference in outcomes. The CLASP investigators do recommend beginning ASA therapy before 20 weeks gestation, since later entry into their trial for therapeutic reasons was associated with a higher perinatal mortality (23). It is reassuring that none of the trials showed a significant risk to either the mother, fetus or neonate of hemorrhagic or other complications of ASA.

Altogether, the results of the available trials do not support the widespread use of ASA as prophylaxis or treatment of PIH or IUGR in all pregnant women. Those judged to be at particularly high risk for developing PIH complications may arguably still be candidates for early antiplatelet therapy. However, because hypertensive disorders in pregnancy are so common and because they are the cause of so much perinatal mortality, it is disappointing that the earlier, promising results were not substantiated in the larger trials. Research should now perhaps be directed at a better understanding of the complicated pathophysiology behind PIH and IUGR in hopes of finding another avenue of therapy to direct against it.

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