

# By using a low dose aspirin (150 mg) we can prevent the complication of preeclampsia in primigravida

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To evaluate the importance of using low doses Aspirin 150mg from 16 weeks of gestation in order to prevent eclampsia in primigravida. It is a Prospective randomized control study demonstrating the effects of low dose Aspirin (150 mg) in prevention of eclamptic fit and reducing the maternal and fetal morbidity, all cases were collected from the Obstetric department in Misurata central hospital.

Four thousand six hundred and seventy primigravida had entered this study in January 1999 until December 2002. They had been distributed according to their booking status. As all booked primigravida receiving prophylactic Aspirin (150mg). There were significant differences between the booked group (4590) and unbooked group (80) in the incidence of pre-eclampsia (4.1%) in the booked group compared with (12.5%) in other groups. There had been one mild eclamptic fit in booked primigravida 0.02% compared to four in the unbooked group (5%).

The results & conclusion gives evidence that by using a low dose aspirin in primigravida reduces the incidence of eclamptic fit and avoids the maternal and fetal morbidity.

## Introduction

Hypertension is the most common medical problem encountered during pregnancy, complicating 5-6% of pregnancies (14, 20). When hypertension is identified during pregnancy at or less than 20 weeks' of gestation, blood pressure elevations usually represent chronic hypertension. (14) In contrast, new onset of elevated blood pressure readings after 20 weeks' gestation mandates the consideration and exclusion of pre-eclampsia. (14) Pre-eclampsia occurs in approximately 5% of pregnancies and 10% in first pregnancies.

Hypertensive disorders in pregnancy may cause maternal and fetal morbidity and remain a leading source of maternal mortality. (14)

Hypertension during pregnancy remains a major cause of maternal and perinatal morbidity and mortality. These complications often follow the development of severe hypertension or pre-eclampsia. There is less agreement on the management of mild to moderate hypertension in the mid-trimester. (25,26) Anti-hypertensive medication prevents the development of severe hypertension later in pregnancy but it has not shown a reduction in the inci-

dence of pre-eclampsia or perinatal mortality. Although the exact patho-physiologic mechanism is not understood clearly, pre-eclampsia can be thought of as a disorder of endothelial function with vasospasm. (14)

Hypertension occurring in pre-eclampsia is due to vasospasm, with arterial constriction and relatively reduced intravascular volume compared to a normal pregnancy. Usually, the vasculature of pregnant women demonstrates decreased responsiveness to vasoactive peptides such as angiotensin II and epinephrine. Women who develop pre-eclampsia show a hyper responsiveness to these hormones; their blood pressure is labile, and their normal circadian blood pressure rhythm may be blunted or reversed. (2; 3; 4; 5,11,12)

Prostaglandin has an important role in pregnancy and the mechanism of parturition in all mammalian species that have been studied. (4,5,13,25)

For instance there is evidence that prostaglandin is critical in mechanisms that regulate cervical ripening and uterine contractions moreover it is likely that prostaglandin plays a significant role in the regulation of uterine and fetal placental haemodynamics. The presence of prostaglandin in amniotic fluid was first demonstrated by Karim in 1966 and shortly thereafter he demonstrated that labour was associated greatly with increased concentrations of amniotic fluid prostaglandin ( Karim 1966, Karim and Devlin 1967).

There is general agreement in PIH, that the balance is tilted in favour of the action thromboxane. Several groups have demonstrated a deficiency of prostaglandin production by measuring residual plasma levels of stable prostacyclin metabolite (Lewis etal 1981, Ylikorkala etal 1981, Yamaguchi and Mori 1985) and urinary prostacyclin metabolite (Goodman etal 1982, Fitzgerald etal 1987) in PIH. Overall it is probable that there is a decrease in prostacyclin production with an increase in thromboxane production.

Other investigations have been done to study prostacyclin and thromboxane

production in fetal rather than maternal tissues. The results are more consistent with demonstrating an altered prostacyclin / thromboxane ratio than in the maternal compartment. The source of excess thromboxane production is of some dispute with Walsh etal (1985) suggesting that the placenta is the most likely source. (Fitzgerald etal 1987) has performed a study which suggests that platelets may be the main source on the basis that the recovery of thromboxane

## All booked primigravida women were assigned low dose aspirin 150mg

B2 excretion paralleled the recovery of platelet cyclo-oxygenase following aspirin administration.

A physiological balance between prostacyclin and thromboxane is likely to be a major importance in maintaining the Vasodilated State of normal pregnancy and it is probable that the imbalance that exists in PIH is responsible for the generalized vasoconstriction and platelet aggregation. Vasoconstriction would result in reduced fetal placental blood flow with subsequent infarction and growth retardation whilst systemic, vasoconstriction leads to hypertension. An imbalance favouring thromboxane would increase platelet aggregation and activate the coagulation system leading to thrombocytopenia. Theoretically it has been suggested that low dose aspirin may restore the balance and thus be of use in preventing and possibly treating preeclampsia. (13,25)

### **Aims and Objectives of our study**

To evaluate the effect of low dose aspirin (150mg) in:

- 1 The severity of pregnancy induced hypertension (PIH).
- 2 Incidence of eclampsia.

### **Methods and Material**

Women were entered into the trial at the Misurata central hospital. They began in January 1999 until December 2002. Women were distributed according to booking status as all booked primigravida receiving aspirin 150mg. Four thousand six hundred and seventy primigravida had been registered in a delivery book then recruited into the trial. Base line details were recorded blood pressure (diastolic phase v) had been measured by trial midwives using an appropriate cuff size.

All booked primigravida women were assigned low dose aspirin 150mg. The dose of aspirin was chosen to be sufficient to inhibit platelet aggregation and was one that had been reported to prevent and decrease complication of pre-eclampsia while keeping side effects to a minimum. Women were asked to take aspirin every day until delivery unless advised otherwise. Most women continued their antenatal care at the antenatal polyclinic, only to return to the hospital clinic for delivery or if any other problem. Doctor on duty or at discharge completed aspirin single page follows up form after delivery.

### **The main prespecified outcomes were**

- ◆ Proteinuric pre-eclampsia.
- ◆ Estimated duration of pregnancy.
- ◆ Birth weight.
- ◆ Intrauterine growth retardation.
- ◆ Intrauterine fetal death.
- ◆ Number of days in the special care nursery.
- ◆ Number of days since birth to discharge and bleeding problems of the new-born.
- ◆ Other maternal events such as use of antihypertensive and anticonvulsant drugs.
- ◆ Antepartum all postpartum Haemorrhage and Caesarean section were also considered.

## Results

4670 Cases were randomized to either the booked group or un-booked group (not taking aspirin) 4590 were booked group and 80 women were un-booked group.

Hypertensive disorder of pregnancy: -

Proteinuric pre-eclampsia developed in 202 women (4.3%) in the whole study group (table no. 1) developed in 192 women (4.1%) in booked group compared with 10 women (12.5%) in un-booked group table (2). The difference was statistically significant ( $p < 0.05$ ).

Neither proteinuria nor pre-eclampsia was reported in this study group, no difference was found between the groups in the medians of the highest systolic or diastolic blood pressure recorded between randomisation and the onset labour.

## Aspirin inhibits the conversion arachidonic acid to the unstable endoperoxide intermediate PGE2

### Incidence of eclampsia

Eclamptic fit was developed in 5 women (0.1%) in all study group. Developed in one patient in booked group (0.02%) and in four patients in un-booked group (5%). Table 3. The difference was statistically significant ( $p < 0.05$ ).

### Mode of delivery

The incidence of operative delivery in booked patients was 5.6% compared to the un-booked group 37.5% ( $p < 0.01$ ) table 4.

Birth weight out come: -

Birth weight < 10th centile in booked group was 3% compared to 10% in un-booked group ( $p < 0.05$ ) table 5.

## Discussion

Although, therapeutic effects of aspirin had been appreciated for nearly a century it was not until 1971 that Vane described elaborated experiments guinea pig lung, which suggest that aspirin inhibit synthesis of prostaglandin. Aspirin inhibits the conversion arachidonic acid to the unstable endoperoxide intermediate PGE<sub>2</sub>, which is catalyzed by cyclo-oxygenase. A few years later this inhibition effect was shown to result from acetylation of the cyclo-oxygenase enzyme (Roth and Majerns 1975). The discovery of thromboxane A<sub>2</sub> and prostacyclin as the predominant endoperoxide products in the platelet and in the endothelium, respectively, raised the possibility of a differential inhibitory effect of aspirin on cyclo-oxygenase in the two tissues (Moncado and Vane 1979). According to this hypothesis low doses of aspirin preferentially inhibit platelet thromboxane synthesis leaving endothelial prostacyclin synthesis relatively intact.

Effect in platelet aggregation: - Aspirin inhibit platelet aggregation by irreversible acetylation as described above, dosages as low as 160mg inhibit platelet cyclo-oxygenase activity by more than 80% and large doses have little additional effect (Burch et al 1978). Platelet lack nuclei and is unable to re-synthesize cyclo-oxygenase following aspirin administration, and therefore impaired for the duration of their life span. Nevertheless these platelets can respond to endoperoxides and thromboxanes released from other platelets, and it has been estimated that only 10% concentration of non-acetylated platelets is needed to restore normal function to the entire platelet population (O'Brien 1968, Cerskus et al 1980).

Teratogenesis: - The balance of evidence suggests that large doses of aspirin during organogenesis may slightly increase the risk of malformation. However it is possible that the symptoms or diseases requiring analgesia in form of salicylates may be contributory. There is no evi-

Blood pressure		
Normal	High	eclampsia
4468	202	5
95.6%	4.3%	0.1%

Table 1 - Hypertensive disorder of pregnancy incidence of pre-eclampsia in primigravida

Pre-eclampsia	
Booked group (4590)	Un-booked group (80)
192	10
4.1%	12.5%

Table 2 - The incidence of hypertensive disorder in pregnancy according to the booking group.

Incidence of Eclampsia	
Booked group	Un-booked group
1	4
0.02%	5%

Table 3 - Incidence of eclampsia according to the booked and un-booked group.

	Booked	Un-booked
Caesarean section	426	8
Indication Pre-eclampsia	42	3
	5.6%	37.5%

Table 4 - Mode of delivery

	Booked	Un-booked
Out come	4590	80
Birth weight <10th percentile	136	8
	3%	10%

Table 5 - Birth weight out come

dence that low dose aspirin (<150mg / day) is teratogaic.

Altered haemostasis: - Aspirin is known to inhibit platelet function. Dosages in the range of 50-100mg of aspirin inhibit platelet function for 5-10 days after ingestion.

Maternal haemostasis: (Lewis and Schulman (1973)) demonstrated that the average blood loss at delivery in patients with heavy aspirin ingestion within the last 6 month of pregnancy was significantly increased. (Collins and Turner (1975)) reported a higher inci-

dence of antepartum and postpartum haemorrhage as well as the need for transfusion at delivery in mothers who chronically ingested large amounts of salicylates. Prolonged maternal bleeding times (up to 25 min) with doses of aspirin 50mg /day has recently been reported (Uzan et al 1989).

fetal haemostasis : In (1971 Corby and Schulman) suggested that aspirin taken shortly before delivery might cause a decrease in platelet function in new born infants. This report was followed by several case reports of minor bleeding tendencies ("Purpura, Petechiae and Cephalohematorra", in infants whose mothers had ingested aspirin prior to delivery) (Bleyar and Breckenridge 1970, Haslan et al 1974)

Length of gestation and labour: As aspirin inhibits prostaglandin synthesis it may be anticipated that uterine contractions might be inhibited and Aspirin would therefore delay the onset and increase the length of labour. (Collins and Turner (1975)) in their study of Australian women who dramatically had taken large doses of salicylates throughout pregnancy also found prolonged gestation and an increase in complicated deliveries.

Effects on fetal circulation: - Doppler echo cardio graphic studies showed that low doses of aspirin (20-80mg) 30 patients did not close the ductus arteriosus and pulmonary pressures were not elevated (Sibai 1989).

Perinatal mortality: - (Collins and Turner (1975)) found on very limited data significantly decreased birth weights, increased fetal wastage and increase perinatal mortality in infants of mothers who chronically ingested salicylates throughout pregnancy. Conversely (Shapiro et al (1976)) using the collaborative perinatal project previously described by (Slone et al (1976)) could find no evidence that the prenatal aspirin is a cause of still birth, neonatal death or reduce birth weight.

### Clinical studies

(Goodlin et al 1978) was one of the first groups to report a beneficial effect of

Series	Pre-eclampsia				IUGR			
	Placebo		Aspirin		Placebo		Aspirin	
	No	%	No	%	No	%	No	%
Beaufils et al	6	13	0	0	13	29	4	8
Schiff et al	8	35	0	0	9	39	4	19
Benigni et al	0	0	0	0	6	38	2	12
Mcparland et al	10	19	1	2	7	14	7	14
Uzan et al	8	11	5	3	19	26	20	13
Azar and Turpin	4	9	1	2	--	--	--	--
Elmahishi et al	23	6.6	19	3.5	3	--	0	0
this study	10	12.5	192	4.1	-	-	-	-

Randomized Trail of Low dose Aspirin to Prevent Pre-eclampsia

aspirin in pregnancy. Aspirin 1800mg /day from 22 weeks resulted in correction of thrombocytopenia in a patient with recurrent pre-eclampsia and resulted in a successful pregnancy. The first prospective trial comprised 102 multipara at risk developing pre-eclampsia on the basis of their previous obstetric history (Beaufils et al 1985). Another study by (Wallenberg et al (1986)) using aspirin 60mg versus placebo. (Schiff et al 1989) - A total of 79. High-risk women were screened with use of the rollover test between 28 and 29 weeks. All of the above studies, though relatively small in terms of patient numbers, demonstrate a consistent beneficial effect of aspirin in high-risk pregnancies particularly in reducing the incidence and severity of PIH and additional enhancing of PIH fetal growth.

The dosage of Aspirin necessary to inhibit TXA2 synthesis without affecting prostacyclin synthesis is very low, many studies reported platelet cyclooxygenase inhibition with a single dose of 3.5 mg/kg, of body weight (or about 300 mg) with minimal inhibition of prostacyclin production.

Another study we designed is to determine the efficacy and safety of aspirin in healthy, nulliparous pregnant women. 1000 women were included, 500 women had been taking Aspirin. The incidence of pre-eclampsia was significantly lower in Aspirin group ( $p < 0.05$ ) there was a significantly higher birth weight in Aspirin group ( $P < 0.01$ ) and there was no intrauterine growth retar-

ation or intrauterine. Fetal death in Aspirin group compared to three intrauterine growth retardation and six intrauterine fetal deaths in control group (Elmahishi. M.S, Elmegrab.H. M FIGO 2000.)

### Conclusion

In this study we found that the uses of low dose aspirin (150 mg) daily use in primigravida will prevent complication of pre-eclampsia, reduces maternal morbidity and improves the neonatal out come.

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