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Prevention of pre-eclampsia with low dose aspirin in primigravida

Abstract

Background: Pre-eclampsia affects up to 10% pregnancies worldwide and is one of the foremost causes of poor maternal & fetal outcome. The situation in Pakistan is even grave with high rate of maternal mortality due to pre-eclampsia. Though multiple risk factors are associated with pre-eclampsia, it is known that first pregnancy itself is a significant pre-eclamptic risk factor. Therefore, in this study we intent to gauge the effects of low dose aspirin among primigravida women in prevention of pre-eclampsia.

Methods:This randomized controlled study was conducted in Maternal Child Health Centre (MCH), Pakistan Institute of Medical Sciences. Total 156 patients were enrolled in this study. Primigravida women without any other pre-eclamptic risk factor consulting before the 16th week of amenorrhea were selected in the study. One group (78) was given 75mg aspirin orally from 8-16 weeks of gestation till 36 weeks of gestation while the other group received no aspirin. Both groups were followed for regular antenatal check up.

Results: The mean age of patients was 24.1 years and 24.9 years in the aspirin and control group, respectively. In aspirin group 2 (2.5%) while 9 (11.5 %) patients in control group developed pre-eclampsia (*p* 0.05). Moreover, we found pre-eclampsia in aspirin group was of lesser severity as compared to those in control group. Further, proportion wise the risk of pregnancy induced hypertension and eclampsia were also reduced with aspirin, however, these were not found statistically significant.

Conclusion: Low dose aspirin has significant effect on primigravida women in pregnancy in terms of prevention of pre-eclampsia.

Keywords: aspirin, pregnancy, prevention, preeclampsia

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Introduction

Pre-eclampsia is a multi-system disorder of pregnancy associated with hypertension and proteinuria. Its incidence varies between 2-10%, depending on the population studied. Moreover, it is the second leading cause of direct maternal and fetal deaths in Pakistan.[1] Although, there is obvious predisposition in certain people to develop pre-eclampsia, the risk is 5-7% among primigravida women.[2] Further, while the origin of the pre-eclampsia remains unclear, it is believed that pre-eclampsia is associated with the deep placentation disorders. The physiological change-over of uterine spiral arteries between 8-16weeks of gestation is the classical placental disorder associated with the pre-eclampsia.[3] Moreover; elevated platelet triggering is the set component of pathophysiology of pre-eclampsia. This may persuade to platelet utilization and ensuing the microvasculature's coagulation system set off, which sequentially leads to endothelial injury, vasospasm and end organ damage.

Biochemical studies also propose a pathological disparity between vasodilator & vasoconstrictor eicosanoid byproducts of the cyclo-oxygenase pathway. Concerning pre-eclampsia, the raised thromboxane A_2 (TXA_2) to prostaglandin I_2 (PGI_2) ratio is a core hallmark of pre-eclampsia biochemistry.[3] Various studies have reported the significance of prescribing aspirin during first trimester to prevent the development of any defect in the physiological process of trophoblastic invasion in to the spiral arteries and turning of the spiral vessels into low resistance arteries. This effect of aspirin is by suppressing the generation of prostaglandins & thromboxane due to its irretrievable squelching of the cyclo-oxygenase enzyme. Moreover, uncoupling oxidative phosphorylation in mitochondria, instigate NO-radicals origination, signal harmonization of pro-inflammatory Kinins and transcription elements are supplementary aspirin roles in prevention of pre-eclamsia.[4] Therefore, to attain the paramount benefit, it sounds convincing to begin aspirin therapy in early gestation.

Previously various studies published with aspirin use in pre-eclampsia prevention reported contradictory results. Those studies were heterogeneous in view of aspirin dosage, and gestational age at recruitment and the risk of pre-eclampsia. This divergence is presumably the chief reason for the presence of conflicting results in numerous aspirin studies administered during pregnancy. Further, a meta-analysis reported that aspirin prescription at low-set doses ahead of 16weeks of gestation in a high-risk pregnant women results reduction in a relative risk of pre-eclampsia.[5,6] In disparity, the change is insignificant when the aspirin is started afterwards 16th week. One of the study also reported 17% depletion in the chance of pre-eclampsia among high risk pregnant women using low dose aspirin.[7] Moreover, another study reported the improved after effects of gestational hypertensive disorders with the administration of aspirin to low risk nulliparous women, at an earlier gestational (8–10)weeks of their first pregnancy.[8]

Currently, recommendation is to give low dose aspirin as early as 12-16weeks of gestation to high risk pregnant women. However, first pregnancy itself is significant risk factor for pre-eclampsia development. Therefore, in our study we assessed the effects of low dose aspirin in preventing pre-eclampsia among primigravida women when given in early weeks of gestation (8-16weeks). This study may add up to enhance the evidence based on most advantageous timing of aspirin as well as use of aspirin as preventive medication among primigravida women.

Methods

This randomized controlled study was conducted from January 2018 to March 2019 in Maternal Child Health center, Pakistan Institute of Medical Sciences. Primigravida consulting before the 16th week of gestation and without previous vascular or renal pathology were included in the study. All patients already taking aspirin for any other medical reason, with chronic hypertension, diabetes, and nephropathy or with auto-immune disorder / thrombophilia were not included in the study. Also, those having family history of pregnancy induced hypertension/pre-eclampsia were excluded from study.

Approvals from hospital ethical and research committee were taken to conduct the study. The purpose and benefits of the study were explained to the patients and a written informed consent was obtained. Total 156 patients were analyzed in this study after randomization by lottery method in to two groups; Aspirin (75mg once daily) was prescribed to one group starting from 8-16weeks of gestation till 36weeks of gestation while the other group (78) was not given aspirin. This was followed by baseline investigations at booking, with additional biochemical profile: serum glutamic oxalo acetic transaminase (SGOT), serum uric acid, urine albumin. Routine antenatal care was provided and on each visit their vitals including weight, height, blood pressure was documented. All the details; name, age, gravidity, parity was noted in a pre-designed proformas. Exclusion criteria was strictly followed to control confounders & biased results. The data was scrutinized using SPSS (ver 21). Chi-square test used to compare incidence of pre-eclampsia in both groups, p value < 0.05 - significant.

Results

Total 156 primigravida women were recruited and randomly allocated to aspirin group and control groups equally. The mean age of patients was 24.1years in aspirin & 24.9years in the control group. Most of the women in both-groups were found between 21 and 25years. The mean BMI was 22.2±5.6 in aspirin group and it was 24.5±4.7 in the control group. No difference was noted in occupation and almost two third (58.3%) of them were not doing any job or were housewives. And a similar proportion belonged to low monthly income class (62.8%). No difference in other sociodemographic characteristics & anthropometric parameters noted (Table 1). In this study majority of the patients 45 (57.6%) presented between 13 to 16 weeks of gestation whereas 33 (42.4%) of the patients presented before 12 weeks of gestation. (Figure 1)

Table 1 Socio-demographic and anthropometric details in the two study groups

	Aspirin group(n=78)	Control group(n=78)	p-value
Age (years)			
Up to 20	13(16.6%)	10(12.8%)	
21 to 25	44(56.4%)	40(51.2%)	
26 to 30	18(23.1%)	25(32.0%)	0.28
31 or above	5(6.4%)	3(3.8%)	
Mean±SD	24.1±4.3	24.9±2.7	0.16
BMI			
Mean±SD	22.2±5.6	24.5±4.7	0.06
Occupation			
No job/house wife	43(55.1%)	49(62.8%)	
Light job	14(17.9%)	10(12.8%)	0.41
Stressful	21(26.9%)	19(24.3%)	
Education			
Illiterate/Primary	32(41.0%)	40(51.2%)	
Secondary	27(34.6%)	22(28.2%)	0.26
Higher	19(24.3%)	16(20.5%)	
Monthly income			
Low	50(64.1%)	48(61.5%)	
Satisfactory	28(35.8%)	30(38.4%)	0.86
High	0(0.0%)	0(0.0%)	

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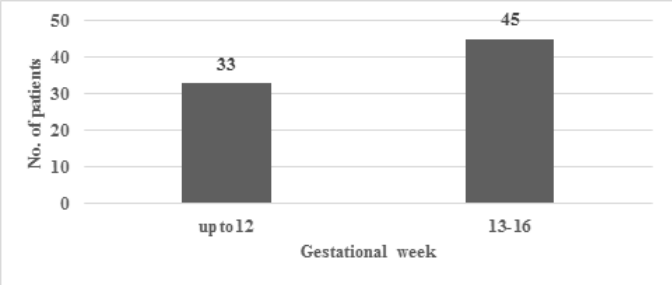

Figure 1 No. of primigravida initiating aspirin at ≤12 weeks of gestation and between 13 to 16 weeks of gestation. (n=78).

The average blood pressure was compared between aspirin group and control-group. The average systolic BP was 116.5mmHg in aspirin group & 122.5 mmHg in the control group. Though mean blood pressure of both groups was in normal range but this distinction in the two means was statistically significant *(p*-value, 0.01). Similarly, the mean diastolic BP was 75.9mmHg in aspirin group and 75.3mmHg in control group and this difference in two means was also found statistically-significant (*p* value, 0.04) (Table 2).

Table 2 Comparison of average blood pressure between the two study groups

	Aspirin group(n=78)	Control group(n=78)	p-value
Systolic BP (mmHg)			
Mean±SD	116.5	122.5	0.01
Diastolic BP (mmHg)			
Mean±SD	75.9	75.3	0.04

The laboratory parameters like uric acid, urinary albumin and SGOT were also compared among the two study groups. In aspirin group, the mean uric acid was 3.6 ± 0.9 mg/dl whereas it was sufficiently greater 4.2±1.2mg/dl in control group (p value, 0.001). The mean urinary albumin also found significantly greater in the control group 0.25±0.65 while in aspirin group 0.01±0.11. This distinction was found statistically significant (*p* value, 0.002). The mean SGOT was found comparable in both study groups (*p*-value, 0.21) (Table 3).

Table 3 Comparison of laboratory findings of patients in the two study groups

	Aspirin group(n=78)	Control group(n=78)	p-value
Serum uric acid (mg/dl)			
Mean ± SD	3.6±0.9	4.2±1.2	0.001
Urinary albumin			
Mean ± SD	0.01±0.11	0.25±0.65	0.002
SGOT			
Mean ± SD	25.7±4.4	26.6±4.9	0.21

Further, we found pre-eclampsia in aspirin group was of lesser severity as compared to those in control group. In the aspirin group, systolic BP and diastolic BP ranged from 150–160 / 90-100 compared to 140-190/ 90-120 in the control group, respectively. Details of individual cases with gestational hypertension in both study groups can be seen in (Table 4).

Table 4 Clinical and pathological details of gestational hypertension patients in the study

	No.	Gestational hypertension	Uric acid	Systolic BP	Diastolic BP	Urine albumin	SGOT	Platelet
Aspirin	1	PIH	6	150	100	nil	32	normal
	2	Pre-eclampsia	7	160	90	1	41	normal
	3	Pre-eclampsia	6	160	90	1	36	normal
Control	1	PIH	6	150	100	nil	32	normal
	2	PIH	7	140	90	nil	41	normal
	3	Pre-eclampsia	6	160	90	1	36	normal
	4	Pre-eclampsia	8	170	120	3	56	normal
	5	Pre-eclampsia	7	160	100	2	44	normal
	6	Pre-eclampsia	8	190	110	1	66	normal
	7	Pre-eclampsia	7	160	110	2	35	normal
	8	Pre-eclampsia	7	150	100	1	68	normal
	9	Pre-eclampsia	7	160	90	2	35	normal
	10	Pre-eclampsia	7	150	90	3	39	normal
	11	Pre-eclampsia	6	170	100	2	48	normal
	12	Eclampsia	8	190	120	3	62	normal

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In the control group, one patient developed pregnancy induced hypertension (PIH) between 28 and 36weeks of gestation. Six women developed pre-eclampsia in control group between 28 and 36 weeks compared to none (0.0%) in aspirin. Proportion wise the risk of early pre-eclampsia was reduced with aspirin. However, it could not be proven significant statistically RR (95% CI), 0.08 (0.004 – 1.34), *p*-0.08 (Figure 2)

As per study objective, pre-eclampsia & other hypertensive disorders in pregnancy were compared between the two groups. In aspirin group only two (2.5%) patients had pre-eclampsia whereas in the control group nine (11.5%) patients developed pre-eclampsia with RR (95% CI), 0.22(0.05 – 0.99). This difference was statistically significant (*p* 0.05). The remaining 75 (96.2%) cases in aspirin and 64 (82.1%) in the control group were found to be normal. Further, there was significant overall risk reduction of gestational hypertension with aspirin was RR (95% CI), 0.24 (0.07–0.81), *p* 0.03. Proportion wise the risk of PIH and eclampsia were also reduced with aspirin, however, these were not found statistically-significant (Table 5). This can be due to all patients were diagnosed timely and managed accordingly.

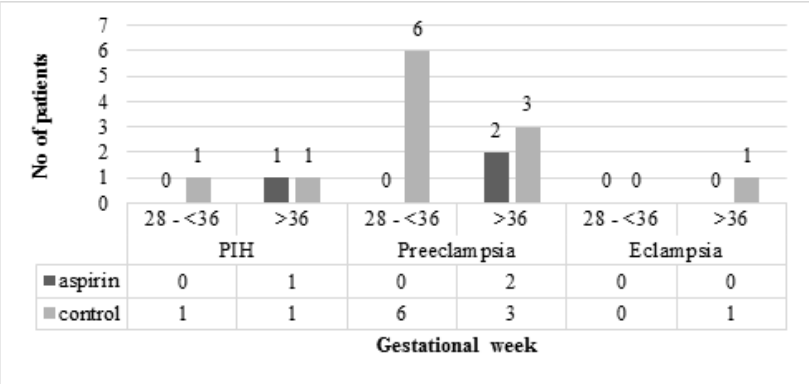

Figure 2 Graphical presentation of number of primigravida women developing hypertensive complication of pregnancy over gestational weeks.

Risk reduction of PIH early on (28 to 36 weeks) with aspirin:

RR (95% CI) 0.33 (0.01–8.0), *p* 0.5

Risk reduction of pre-eclampsia early on (28 to 36 weeks) with aspirin:

RR (95% CI) 0.08 (0.004 –1.34), *p* 0.08

Table 5 Comparison of gestational hypertension between the two study groups

	Aspirin group(n=78)	Control group(n=78)	Relative risk reduction(95%CI)		p-value
Normal	75 (96.2%)	64 (82.1%)			
Gestational hypertension	3 (3.8%)	12 (14.9%)	0.24	(0.07–0.81)	0.03
PIH	1 (1.3%)	2 (2.5%)	0.5	(0.04–5.4)	0.5
Pre-eclampsia	2 (2.5%)	9 (11.5%)	0.22	(0.05 – 0.99)	0.05
Eclampsia	0 (0.0%)	1 (1.3%)	0.33	(0.01 – 8.05)	0.5

Discussion

Pre-eclampsia is a fatal complication of pregnancy associated with the serious outcomes for mother and fetus. The risk prone groups are primigravida women, increasing age, family history of pre-eclampsia/ hypertension and pre-existing hypertension, multiple pregnancy and diabetic pregnancy. Although many treatment strategies are in place to prevent pre-eclampsia, but most of them are targeted towards high risk individuals only. Being primigravida is its self a risk factor for pre-eclampsia but there is no current recommendation for any preventive measures to be taken for this risk factor alone. Here, we assessed the effect of aspirin from early pregnancy as a preventive measure for pre-eclampsia.

The age of women presenting with pregnancy varies according to social background and geographical region, otherwise there is not much difference in their presentation. In this study, patient's mean age was 24.5±3.9 years and majority (80.0%) were between 21 and 30years of age. Comparative evidence regarding age of presentation have been reported by various investigators.[8,9]. Further, in the current study most of the women were house wives, and had low monthly income. The relationship of low socioeconomic status and less influential social background has a significance in the development of hypertension in general patients, as far as pregnancy induced hypertension is concerned there is a need to work on this type of associations.

Further, investigators have reported that when aspirin is given early on in the pregnancy it reduces the risk of pre-eclampsia with greater impact and intensity.[5,8] Most of the current study women presented between 13 and 16 weeks of gestation, whereas some presented earlier. In the present study, women in the control group had significantly higher levels of systolic and diastolic blood pressure than those in aspirin group. Moreover, only 2.5% cases in the aspirin

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group while 11% in the control-group developed pre-eclampsia. Previous studies reported that if aspirin is administered at an early gestation point (<16weeks), it dampens the risk of developing a hypertensive gestational disorder by three times and prolongs the time of delivery about 2 weeks.[5,8] Moreover, Park et al witnessed that aspirin administration early in the pregnancy significantly reduced pre-eclampsia, they reported that among women with pre-eclampsia delivering before 37weeks of gestation, in the observation arm there were 0.83% cases with pre-eclampsia compared to only 0.37% in the interventional arm.[9]

The value of aspirin is accepted by a number of national and international institutions who recommend prescription to high risk groups. Further analysis suggests that it is early intervention (<16weeks gestation) that is of most benefit, resulting in a 50% reduction (RR 0.47, 95% CI, 0.34–0.65) in pre-eclampsia at all gestations.[10] In the current study aspirin significantly reduced the risk of pre-eclampsia compared to control group (RR 0.24; 95% CI, 0.07 -0.81). Many others have also witnessed a similar trend of prior aspirin treatment which shows a positive effect, with a relative risk ranging from 0.07 to 0.63 for pre-eclampsia & from 0.20 to 1 for intrauterine growth retardation.[11]

Although the exact mechanism regarding the initiation of hypertensive disorders of pregnancy remains enigmatic, vascular disorder characterized by generalized endothelial damage and vasospasm is a well-known pathology resulting in systemic complications during pregnancy[12]. Apart from the pathogenesis, there is also uncertainty in its natural course.[13] Moreover, the classical course of illness (characterized by a progressive edema, mild to severe hypertension and the onset of severe symptoms, which is followed by the occurrence of convulsion or coma) may not be seen in several women. This might self-explain the reason that in our study % of women developing PIH and pre-eclampsia are not comparable even in same study groups. Further, derangement of other renal and pathological parameters has also shown a protective response of aspirin in the current study. It was noticed that serum uric acid and serum albumin were significantly raised in the control arm than aspirin group. This shows that low dose aspirin when given early in pregnancy has multiple controls and not only the onset of pre-eclampsia is averted, the glycemic and renal function is also kept normal thus, giving ample chance to the mother and fetus to live and grow healthy. This data supports the early initiation of aspirin among primigravida women in preventing pre-eclampsia development.

Conclusion

In our study, low dose aspirin has significant effect on primigravida women in terms of prevention of pre-eclampsia. Moreover, the glycemic & renal parameters in terms of blood pressure, urinary albumin and uric acid also remained within normal range in aspirin group when compared with those not given aspirin (controls). Therefore, we recommend that aspirin should be considered in the prophylaxis of pre-eclampsia in primigravida women. Further, we recommend large-scale studies on prevention of pre-eclampsia in primigravida using aspirin multinational level so that the results of this study can be validated and could then be generalized.

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None.

Conflicts of interest

The author declares that there are no conflicts of interest.

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