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To Determine Efficacy Aspirin 150 mg vs 75 mg in Prevention of Preeclampsia and its Associated Complications

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ABSTRACT

Background: Preeclampsia is a pregnancy-specific multisystem progressive disorder, characterized by a new onset of hypertension and proteinuria or significant end-organ dysfunction without proteinuria typically after 20 weeks. If not controlled, it can lead to adverse fetal outcomes. Aspirin a COX inhibitor can delay or prevent the onset of PE. Its effectiveness and safety in relatively higher doses (150mg) need to be investigated in the local population. To compare the two different low doses of aspirin 75mg vs. high dose of 150mg in moderate and high-risk women for prevention of preeclampsia and its associated complications.

Methods: A Parallel arm randomized control open-label study was conducted at the Department of Obstetrics and Gynaecology of Ziauddin University Hospital Kemari, Karachi. A sample of 156 women, age >18 years, with moderate and high risk of Preeclampsia was selected consecutively. Random allocation of 78 women each was done to group A (75mg) versus group B (150 gm) of Aspirin. Patients with multifetal gestation, major fetal anomaly, thrombocytopenia, peptic ulcer, or bleeding disorder were excluded from the study. Ethical approval was sought from the ERC of Ziauddin University. Descriptive and analytical results expressed through SPSS software.

Results: Both groups were comparable in terms of their basic demographics. The effectiveness of Aspirin 75mg was 53% compared to 70% of Aspirin 150mg in the prevention of pre-eclampsia among high-risk women. With 75mg Aspirin the incidence of PE decreased slightly with increasing age while with 150mg, it increased (P values = 0.141, 0.111 & 0.290 respectively. Higher rates of placental abruption (54.3%) accompanied by preeclampsia were seen in group A as compared to (21.7%; p value = 0.016) in group B. The incidence of pre-term delivery, miscarriage, NICU admission & superimposed eclampsia were higher with low-dose aspirin (P values = 0.779, NA, 0.210, 0.592, NA & 0.772 respectively).

Conclusion: Aspirin 150mg in moderate and high-risk pregnancies starting at 11-14 weeks is more effective and safer than 75mg Aspirin reducing the incidence of Preeclampsia.

Keywords: Preeclampsia, Aspirin, Placental abruption, BMI, High-risk, Pre-term delivery.

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INTRODUCTION

Preeclampsia is a multisystem disorder of pregnancy. It is defined as recording 140/90 mm Hg or higher blood pressure at two separate readings taken at least six hours apart at or after the 20th week of gestation along with the presence of proteinuria (>3 gm)[1,2]. If not prevented or controlled it may worsen to eclampsia and HELLP syndrome. Approximately 14 million pregnancies are affected annually with pre-eclampsia and eclampsia responsible for 10% to 15% of maternal deaths[3,4]. In Pakistan with an MMR of 186 per 100,000 live births (PDHS-2018) the burden is nearly 30%[5,6].

One of the major therapeutic interventions to prevent preeclampsia is the use of Aspirin (a COX-II inhibitor with anti-inflammatory and anti-thrombotic properties). Initiating low-dose aspirin (LDA) therapy in early pregnancy can prevent the onset of pre-eclampsia or delay it[7]. further; it also minimizes the risk of pre-term delivery, stillbirth, fetal growth retardation, first-trimester miscarriages, and other complications[8,9].

The 2014 USPSTF guideline concluded that there are 24% fewer cases of preeclampsia when aspirin is used (60-150mg/day) after analyzing 15 high-quality RCT trials[9,10,11]. The ACOG (2018) approves using low-dose aspirin in high-risk cases.7 But most of the studies have assessed the Aspirin 60-100mg[12,13]. Evidence on the effectiveness/ safety of >100mg aspirin is limited[14]. To our knowledge, no such study has been conducted on aspirin in our population at a 150mg dose.

Thus; the current study was carried out to compare the effectiveness of a smaller dose i.e.; 75mg of aspirin with a relatively higher dose150mg of aspirin in the prevention of preeclampsia and its associated complications among women with a higher risk of preeclampsia.

METHODS

This Parallel arm randomized control open-label experimental study was conducted at the Department of Obstetrics and Gynecology, Ziauddin University Hospital, Kemari, Karachi. The Ethical Review Committee of Ziauddin University approved it. Sample size as calculated by using the WHO calculator while estimating the difference between two population portions; Confidence interval of 95%, absolute precision required 0.10 of 0.17 (low dose group~1) while other population proportion of 0.065 (high dose group~2). This way the sample size calculated was 156 (i-e; 78 in each group A sample of 156 pregnant women who were at moderate and high risk of preeclampsia were included in the study. women with moderate risk factors had increased BMI of more than 35, a family history of hypertension, history of preeclampsia. Women with high-risk factors were chronic hypertension, chronic DM, chronic kidney diseases, immunologic disorders like APLA, etc. Our inclusion criteria were age >18 years, having a live single fetus (11 to 14 weeks gestation), and agreed regular follow-ups were included in the study. Patients with multifetal gestation, major fetal anomaly, thrombocytopenia, peptic ulcer, or bleeding disorder were excluded from the study. Verbal and written consent was taken from all participants. This parallel arm randomized controlled open-label study was done in the duration of one year.

Women were divided into two groups. Randomization was done by 1;1 Group A; prescribed a tablet of Aspirin 75mg HS while Group B prescribed 150mg of Aspirin 2 tablets of 75mg. The patients were allotted the groups randomly using the opaque envelope method. A thorough history was taken, medical and obstetrical examinations were done along with all baseline investigations. Women were counseled properly regarding the side effects of aspirin e.g., indigestion, epigastria pain, or bleeding and to rush to hospital in case of emergency.

Regular monthly follow-up in the antenatal clinic up to 28 weeks then fortnightly from 34 weeks up to 36 weeks called, if pregnancy was uneventful. Aspirin was stopped at 36 weeks. However, visits were individualized in patients with PE depending on fetomaternal condition. During each visit, BP, weight, symphysial-fundal height, and proteinuria on the dipstick were measured routinely.Women were monitored for the development of preeclampsia, preterm labor, intrauterine death, or any symptoms due to taking aspirin during antenatal visits. Compliance noted monitored by pill counting method. Aspirin was provided to those patients who were properly counseled and compliant. A personal contact number was provided to them and their contact was taken for a time-to-time reminder. Some patients were lost of follow-up too were excluded from the study. Anti-hypertensive treatment was offered to chronic hypertensive who were not taking treatment or who had gestational hypertension with sustained systolic BP of 140mmhg or higher and sustained diastolic BP of 90mmhg or higher. Labetalol and Aldomet were given as first-line therapy. Outpatients were advised to monitor blood pressure at home and bring records of blood pressure in OPD while women with symptoms and signs of severe preeclampsia, eclampsia, and hematologic, and biochemical abnormalities were admitted to the hospital. Fetal growth scans were individualized according to blood pressure control .fetal Doppler advised if suspected intrauterine growth retardation. Patients with preeclampsia were monitored strictly during labor.

BP was checked for 15-30 minutes. Magnesium

sulfate was started in case of eclampsia or severe preeclampsia. Continuous fetal monitoring was done with CTG.

The software used for data entry and analysis was SPSS version 21. Univariate descriptive analysis was done. Bivariate analysis for association was expressed with the comparison of categorical variables in both groups performed by the chi-square test. P value <0.05 was considered significant.

RESULTS

Both the groups were comparable and no difference was noted regarding their basic demographics. Mean age was 27.06 ± 4.79 (Range: 18 to 34) and 27.08 ± 4.32 (Range: 18 to 35) years in group A (75mg) & group B (150mg) respectively (Table: 1). Likewise; regarding their family history of hypertension, H/o preeclampsia or eclampsia and pregnancy-induced hypertension; the two groups were almost identical. Cases of other comorbidities were diabetes mellitus (11.5% vs 10.3%), any immunologic disorder (6.4% vs 9%), or renal disease (2.6% vs 1.3%) in groups A & B respectively.

The primary outcome i-e; the effectiveness of Aspirin 75mg was 53% compared to 70% with Aspirin 150mg in the prevention of pre-eclampsia among women of high risk. Thus; pre-eclampsia incidence was 47% (n = 35) in group A but 30% (n = 23) in group B (Figure: 1). The stratified analysis reveals that the incidence of pre-eclampsia decreased slightly with increasing age of group A however; in group B, it increased as the age increased. (P values = 0.141, 0.111 & 0.290 respectively- Table: 2).

With higher BMI the risk of pre-eclampsia increased steadily & unanimously in both groups however; the frequency of preeclampsia tripled among group A while it doubled in group B. (P values = 0.963, 0.007, 0.153 & 0.024 respectively- Table: 3). Multigravida women were at higher risk of pre-eclampsia compared to younger primigravida within both groups (P values = 0.130 & 0.038 respectively- Table: 5).

Evaluating complications; the higher rates of placental abruption (54.3%) were noted in group A compared to (21.7%; p value = 0.016) group B. Likewise; incidence of pre-term delivery, miscarriage, NICU admission & superimposed eclampsia were higher with aspirin 75mg compared to aspirin 150mg. (P values = 0.779, NA, 0.210, 0.592, NA & 0.772 respectively- (Table: 6 & 7). There were no cases of IUGR and stillbirth in those treated with aspirin 150mg (group B).

Table 1. Baseline descriptive data of all women in both groups (n = 156)

Variable	Group	Minimum	Maximum	Mean	Std. Deviation
Age (Years)	**A**	18	34	27.06	4.79
Age (Years)	**B**	18	35	27.08	4.32
Number of children	**A**	0	4	1.42	1.02
Number of children	**B**	0	4	1.50	1.11
Gestational age at presentation	**A**	11	14	12.67	1.11
Gestational age at presentation	**B**	11	14	12.64	1.15
BMI (Kgs/m2)	**A**	18.21	34.76	26.20	4.10
BMI (Kgs/m2)	**B**	18.13	33.58	26.24	3.82
Labs (Platelets/ mm^3)	**A**	1,62,645	3,66,248	2,27,029.7	40,359.71
Labs (Platelets/ mm^3)	**B**	1,57,275	3,74,964	2,38,528.7	49,940.36

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Systolic BP in mmHg	**A**	140	200	169.82	15.89
Systolic BP in mmHg	**B**	145	195	166.49	16.57
Diastolic BP in mmHg	**A**	100	125	110.51	7.90
Diastolic BP in mmHg	**B**	95	130	115.05	7.67

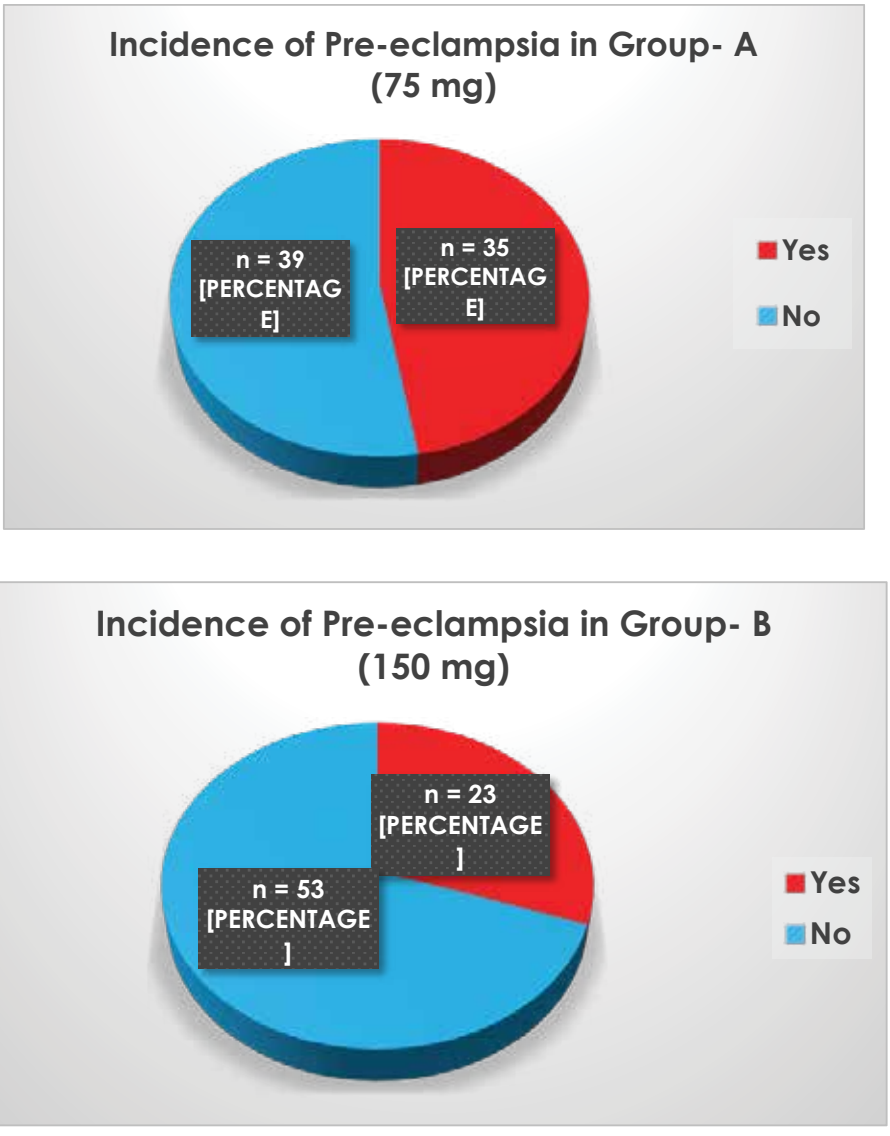

Figure: 1. Incidence of outcome i-e; Pre-eclampsia between the two groups [(Group- A= 74); (Group-B= 76)]

Table: 2. Intergroup comparison of incidence of pre-eclampsia with age stratification of the two groups [(Group- A= 74); (Group-B= 76)]

Age of the Patient			Pre – Eclampsia		Total	P value
			Yes	No		
Up to 20 years	Group	A (75mg)	4	4	8	0.141
			50%	50%	100%	
		B (150mg)	1	7	8	
			12.5%	87.5%	100%	
	Total		5	11	16	
			31.3%	68.8%	100%	
21-30 years	Group	A (75mg)	21	26	47	0.111
			44.7%	55.3%	100%	
		B (150mg)	16	36	52	
			30.8%	69.2%	100%	
	Total		37	62	99	
			37.4%	62.6%	100%	
31-35 years	Group	A (75mg)	10	9	19	0.290
			52.6%	47.4%	100%	
		B (150mg)	6	10	16	
			37.5%	62.5%	100%	
	Total		16	19	35	
			45.7%	54.3%	100%	
Total	Group	A (75mg)	35	39	74	**0.024**
			47.3%	52.7%	100%	
		B (150mg)	23	53	76	
			30.3%	69.7%	100%	
	Total		58	92	150	
			38.7%	61.3%	100%	

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Table: 3. Intergroup comparison of incidence of pre-eclampsia with BMI stratification of the two groups [(Group- A= 74); (Group-B= 76)]

BMI (Kgs/m²)			Pre – Eclampsia		Total	Total
			Yes	No		
Underweight	Group	A (75mg)	1	1	2	NA
			50%	50%	100%	
		B (150mg)	1	1	2	
			50%	50%	100%	
	Total		2	2	4	
			50%	50%	100%	
Normal Weight	Group	A (75mg)	07	18	25	0.963
			28%	72%	100%	
		B (150mg)	8	20	28	
			28.57%	71.42%	100%	
	Total		15	30	53	
			43.4%	56.6%	100%	
Overweight	Group	A (75mg)	17	14	31	**0.007**
			54.83%	45.16%	100%	
		B (150mg)	7	25	32	
			21.87%	78.13%	100%	
	Total		24	39	63	
			38.09%	61.90%	100%	
Obese	Group	A (75mg)	11	5	16	0.153
			68.75%	31.25%	100%	
		B (150mg)	6	8	14	
			42.85%	57.14%	100%	
	Total		17	13	30	
			33.3%	66.7%	100%	
Total	Group	A (75mg)	35	39	74	**0.024**
			47.3%	52.7%	100%	
		B (150mg)	23	53	76	
			30.3%	69.7%	100%	
	Total		58	92	150	
			38.7%	61.3%	100%	

Table: 4. Intergroup comparison of incidence of pre-eclampsia with gravida grouping in the two groups [(Group- A= 74); (Group-B= 76)]

Gravida Grouping			Pre – Eclampsia		Total	P value
			Yes	No		
Younger Primigravida	Group	A (75mg)	7	9	16	**0.038**
			43.8%	56.3%	100%	
		B (150mg)	2	16	18	
			11.1%	88.9%	100%	
	Total		5	9	34	
			31.3%	26.5%	100%	
Multigravida	Group	A (75mg)	28	30	58	0.130
			48.3%	51.7%	100%	
		B (150mg)	21	37	58	
			36.2%	63.8%	100%	
	Total		37	49	116	
			37.4%	42.2%	100%	
Total	Group	A (75mg)	35	39	74	**0.024**
			47.3%	52.7%	100%	
		B (150mg)	23	53	76	
			30.3%	69.7%	100%	
	Total		58	92	150	
			38.7%	61.3%	100%	

Table: 5. Frequency of complications in those who developed pre-eclampsia [(Group- A= 35/74); (Group-B= 23/76)]

Group	Placenta Abruption		Total	Statistics
	Yes	**No**		
A (75mg)	19 (54.3%)	16 (45.7%)	35 (100%)	Chi-Square = 6.061
B (150mg)	5 (21.7%)	18 (78.3%)	23 (100%)	***P value <0.016***
Total	24 (41.4%)	34 (58.6%)	58 (100%)	
Group	**Pre-term Delivery**		**Total**	**Statistics**
	Yes	**No**		
A (75mg)	13 (37.1%)	22 (62.9%)	35 (100%)	Chi-Square = 0.276
B (150mg)	7 (30.4%)	16 (69.6%)	23 (100%)	P value = 0.779
Total	20 (34.5%)	38 (65.5%)	58 (100%)	

Group	Miscarriage		Total	Statistics
	Yes	No		
A (75mg)	5 (14.3%)	30 (85.7%)	35 (100%)	NA
B (150mg)	0 (00%)	76 (100%)	23 (100%)	
Total	5 (8.6%)	53 (91.4%)	58 (100%)	
Group	**IUGR**		**Total**	**Statistics**
	Yes	**No**		
A (75mg)	10 (28.6%)	25 (71.4%)	35 (100%)	Chi-Square = 1.924
B (150mg)	3 (13%)	20 (87%)	23 (100%)	
Total	13 (22.4%)	45 (77.6%)	58 (100%)	P value = 0.210
Group	**NICU admission**		**Total**	**Statistics**
	Yes	**No**		
A (75mg)	19 (54.3%)	16 (45.7%)	35 (100%)	Chi-Square = 0.648
B (150mg)	10 (43.5%)	13 (56.5%)	23 (100%)	P value = 0.592
Total	29 (50%)	29 (50%)	58 (100%)	
Group	**Stillbirth**		**Total**	**Statistics**
	Yes	**No**		
A (75mg)	5 (14.3%)	30 (85.7%)	35 (100%)	NA
B (150mg)	0 (0%)	23 (100%)	23 (100%)	
Total	5 (8.6%)	53 (91.4%)	58 (100%)	
Group	**Superimposed eclampsia**		**Total**	**Statistics**
	Yes	**No**		
A (75mg)	11 (31.4%)	24 (68.6%)	35 (100%)	Chi-Square = 0.191
B (150mg)	6 (26.1%)	17 (73.9%)	23 (100%)	P value = 0.772

DISCUSSION

Preeclampsia (PE), is a pregnancy-specific multisystem disorder affecting 2 to 15% of pregnancies globally and controllable with the use of prophylactic aspirin in high-risk women[15]. Delivery is the only definite treatment of PE. Many studies evaluated low doses of Aspirin 60-80mg showing a 10%–50% reduction in the incidence of preeclampsia, while a few studies also evaluated the efficacy of a 150mg dose[9,13]. Keeping abreast of the variability of responses to different doses of the same medicine; this study compared low dose Aspirin (75mg) with higher dose (150mg). To our knowledge, this is among very few studies to investigate the effectiveness of relatively higher doses of aspirin in the Pakistani population.

The current study noted as much as 17% fewer cases of PE as the incidence was 47% (n = 35) in group A (75mg) while 30% (n = 23) in group B (150mg) in the current trial; overall reduction in PE incidence was 37%. The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) a landmark trial study also noted a significant reduction of 62% for preterm PE at 11-14 weeks of gestation with aspirin (RR = 0.38; 95% CI: 0.20–0.72; P = 0.011) found that PE occurred in 15 out of 87 participants (17%) who received 75mg of aspirin, while in the group that received 150mg of aspirin, it occurred in 6 out of 91 participants (6.5%)[12,16].

Use of daily aspirin of 150mg from 11 to 14 weeks of gestation until 36 weeks of gestation brought a reduction in preterm PE in women at high risk for Pre eclampsia[17]. While a lesser dose of 100mg of aspirin started at 12–20 weeks of gestation to 34 weeks of gestation in high-risk groups of PE did not reduce it[18]. Wang Y and other studies found similar results[19, 20, 21].

While looking at other doses,(data based on One large study in U.S. and U.K. each and 13 smaller trials with additional six randomized, controlled trials (RCTs)) reported that Aspirin (60 to 150mg) reduced the 10-24% risk of PE. According to Bujold found decreased rates of fetal growth restriction (8% vs. 2%; P = 0.20); PE (12% vs. 15%; P = 0.78), preterm preeclampsia (4% vs. 2%; P = 0.56), and early-onset PE (0% vs. 2%; P = 0.52) with 80mg and 160mg of aspirin[22]. In the Roberge's article a dose-response relationship of up to 150mg of aspirin was identified in the prevention of preeclampsia before early onset, however, no cases of gastritis or other side effects[23]. In the current study, 4 women from group A and 2 from group B did not follow up however; no serious side effects were noted.

The mean age was 27.06 ± 4.79 years in group A (75mg) while in group B was 27.08 ± 4.32 years; there were no significant differences found concerning parity, gestational age at presentation, BMI (Kgs/m2), systolic & diastolic blood pressure and laboratory findings as platelets count. Further analysis showed that the incidence of pre-eclampsia decreased slightly with increasing age among women treated with 75mg of Aspirin but was inverse 150mg Aspirin (P values = 0.141 & 0.111 respectively). On the other hand, the higher the BMI, the higher the risk of pre-eclampsia (P values = 0.963, 0.007, 0.153 & 0.024 respectively).

The studies as well as other studies, found an effect of age on the incidence of PE in high-risk women[13,24]. There was a maximum 30% reduction in risk of all gestational age preeclampsia at all aspirin doses.[21] Henderson reported in their research that Aspirin (60 to 150mg) reduced IUGR up to 20% and 14% preterm birth among women at elevated risk of PE. Also, there was no effect on perinatal mortality and no overall effect of low-dose aspirin on maternal health.

The current study found that among those who developed PE, the occurrence of Placental abruption (PA) was higher (54.3%) within group A compared to group B [i-e; (21.7%); P value = 0.016]. The incidence of PA in a study conducted by Kumar N. was 2 (2.1%) in (150mg group) versus 4 (4.5%) in (75mg group). Thus; PA can be curtailed to half if PE is controlled with higher doses of Aspirin.

Incidence of pre-term delivery, miscarriage, IUGR, NICU admission, stillbirth & superimposed eclampsia were lower among group A compared to those treated with aspirin group B[20,21].
We have found similar results i-e; PE declined by 18%, and 9% reduction in the RR for preterm births, 14% reduction in fetal deaths, neonatal deaths or death before hospital discharge. Contrary to that it was found that these agents probably slightly increase postpartum hemorrhage >500 mL. The study concluded that doses of aspirin less than 75mg appear to be safe however; higher doses might be better in effectiveness.

Among women with chronic hypertension, low-dose aspirin prophylaxis did not significantly reduce the odds of superimposed preeclampsia in the randomized controlled trials (OR = 0.83; 95% confidence interval)[25]. While; in our study, we found no significant difference between the groups. The ASPRE trial suggests a 68% reduction in length of stay in the neonatal intensive care unit (NICU) mainly due to a reduction in early-onset PE and a reduction in the total number of small-for-gestational-age (SGA) infants[22, 24].In the current study, there were no cases of IUGR and stillbirth in those treated with aspirin 150mg.

US Preventive Services Task Force Recommendation Statement recommends the use of low-dose aspirin (81mg/d) as preventive medication for preeclampsia after 12 weeks of gestation having a high risk for preeclampsia further stating that effective dosages of low-dose aspirin range from 60 to 150mg/d[7, 9, 10].

As opposed to providing aspirin prophylactically to the entire population, it is advisable to administer it to women who are identified through screening as being at a high risk of developing preeclampsia as was done in the current study. The dose of 150mg of aspirin per day was selected on the basis of previous evidence of a dose-dependent benefit to therapy-[10,13,17,19,20]. Concerns regarding premature closure of the fetal arterial duct have never been confirmed & there is a lack of data regarding such possible side effects.

The current study has generated robust evidence that Aspirin in a dose of 150mg is more effective and safer compared to the lower dose of 75mg for the prevention of preeclampsia among high-risk pregnancies. The limitation was its small sample; the sampling was consecutive and there was no control arm. Overall; the current study based on its findings, recommends Aspirin use in high PE-risk cases in a local population

CONCLUSION

The current study found that using Aspirin prophylactically at a dose of 150mg among high-risk pregnancies starting at 11-14 weeks is more effective and safer than 75mg in reducing the PE incidence. Thus; this study recommends its use in the local population.

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CONFLICT OF INTEREST
Nil.

ETHICS APPROVAL
Approved by EC of ZMU Reference Code: 6101022SBGYN

PATIENT CONSENT
Nil

AUTHORS' CONTRIBUTIONS
SA brought the idea, design of study and Manuscript writing, literature search, proposal writing data analysis. **RK** helped in the literature search and data collection. **AS** contributed to Proposal writing, entered data, and primary data analysis. **HS** Manuscript writing and final data analysis. **UM** contributed to data collection and results generation.

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