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RESEARCH ARTICLE

Metformin and Aspirin Versus Only Aspirin for Prevention of Preeclampsia: A Randomized Controlled Trial

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Abstract

Background: Preeclampsia is a pregnancy specific multiorgan involved disease characterized by de novo development of hypertension, proteinuria and/or any other end organ failure after 20 weeks of gestation. Preeclampsia is associated with two stages model of the placental dysfunction. An important step in the pathogenesis of preeclampsia is poor placental invasion. Significant efforts have been devoted to developing clinically useful screening methods and prevention strategies for pre-eclampsia. Early prediction and additional interventions could boost the beneficial effects of aspirin. The objective of this Randomized Controlled Trial study was to find out whether Metformin along with Aspirin is associated with significant reduction of incidence of Preeclampsia.

Method: The RCT was carried out involving 80 women (40 in control group and 40 in experimental group) in early pregnancy (6-12 weeks) attending the Fetomaternal Medicine OPD during the period of January 2022 to December 2022. The control group has received tab Aspirin 150 mg at bedtime and the intervention group took 500mg Metformin twice daily along with Aspirin. Aspirin was discontinued at 36 weeks or before 24 hours if delivery was anticipated. Metformin was continued up to 36 weeks. They were monitored regularly up to delivery to observe the outcome (development of Preeclampsia). Then comparison was done between intervention and control group to see the efficacy of Metformin in the intervention group. Collected data were processed and analyzed using SPSS (Statistical Package for Social Sciences), version 25.

Result: Total 80 respondents were included in this study. In this study, among the patients with 18-25 years, 30.4% suffered from preeclampsia; whereas among the participants with 25-30 years, the proportion of Preeclampsia was 50%. In this study, more than 50% of the participants were overweight and 13.8% were obese. Only 1(1.3%) was underweight .The major risk factors or comorbidities among the study participants was Diabetes in Pregnancy (32.5%) followed by Chronic Hypertension (25.0%) and previous history of Preeclampsia (20.0%) and family history of Preeclampsia (15.0%).In the intervention group 37.5% patients suffered from preeclampsia and in the control group the proportion was 60%.In the intervention group, 86.7% patients suffered preeclampsia at ≤34 weeks of gestation, whereas in control group 91.7% patients experienced preeclampsia at ≤34 weeks In 62.5% cases, the intervention was able to prevent preeclampsia and on the other

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hand ,control was able to prevent 40.0% preeclampsia. Thus, this difference in preventing preeclampsia was significantly higher in the intervention group (p value: 0.044).

Conclusion: The result of this study indicated that pregnant women with high risk can be treated with both Metformin and Aspirin from the first trimester for prevention of Preeclampsia.

Keywords: Preeclampsia, Prevention, Aspirin, Metformin.

1. Introduction

Preeclampsia is a pregnancy specific multiorgan involved disease characterized by de novo development of hypertension, proteinuria and/or any other end organ failure after 20 weeks of gestation [1]. About 2 to 8 % of total pregnancies are affected by it.[2] It is also a major cause of maternal, fetal and neonatal morbidity and mortality [3,4].The new ACOG Practice Bulletin stated that although hypertension and proteinuria are the classical criteria for diagnosis of preeclampsia, the presence of any of the severe features like-Thrombocytopenia(platelet count <100,000), impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes(to twice the upper limit of normal concentration), severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnosis, renal insufficiency(serum creatinine greater than 1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease), Pulmonary edema, new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnosis or with visual disturbances. In addition, it is recommended that women with gestational hypertension with severe range of BPs (systolic BP of 160 mm of Hg or higher, or diastolic BP of 110 mm of Hg or higher) should also be diagnosed as preeclampsia with severe features [1]. Preeclampsia threatens the life of pregnant women, fetuses and newborns and often give rise to multiple pregnancy complications such as Eclampsia, HELLP Syndrome, Abruptio placentae, Acute Renal Failure(ARF), Acute Respiratory Distress Syndrome(ARDS), Disseminated Intravascular Coagulopathy (DIC),Transient Ischemic Attack(TIA)/ Cerebro Vascular Accident(CVA) and also chance of recurrence in next pregnancy, development of persistent hypertension and fetal complications like Fetal Growth Restriction(FGR), prematurity, Intrauterine Fetal Death(IUFD) and adverse perinatal outcomes, along with increased perinatal mortality [5]. The precise pathophysiology of preeclampsia still remains elusive but it is believed to be multifactorial [6]. Preeclampsia is associated with a two stages model of the placental dysfunction [7]. An important step in the pathogenesis of preeclampsia is poor placental invasion [8]. Extravillous cytotrophoblast invasion of the uterine spiral arteries remains limited to the superficial decidua and does not reach the myometrium, leading to shallow implantation and hypoperfusion of the placenta in the first trimester [9]. In the second and third trimesters, hypoperfusion of the placenta results in placental hypoxia and ischemia and the maternal-fetal interface is subjected to relatively strong oxidative stress [10] Early prediction is quite important as Aspirin, the only proven preventative method for pre-eclampsia, acts by reducing thromboxane A2 and platelet aggregation, has a dose- and time-dependent effect [11]. Early prediction and additional interventions could boost the beneficial effects of Aspirin [12]. However, only 12% of all preeclampsia cases are early-onset and prediction models show poorer precision for late-onset disease [13,14]. Furthermore, Aspirin failed to show a clinically meaningful effect on the development of late-onset pre-eclampsia, in which the majority of the disease burden lies [15]. Similar concentrations of metformin in the umbilical artery and umbilical vein suggest negligible metformin metabolism by the fetus [16]. Several meta-analyses that studied the teratogenic effect of Metformin on embryonic development found that this drug carries no increased risk for congenital malformations [17,18] and is currently classified as category B in the United States and as category C in Australia [19,20]. Similarly, no excess fetal or neonatal complications could be demonstrated when the administration of Metformin [21]. In addition, a study that investigated the neurodevelopmental effect at two years of age could not identify a significant difference between children exposed in utero to Metformin [22]. Maternal side-effects reported with the use of Metformin are mainly gastro-intestinal, i.e., nausea and diarrhea [19]. The rate of hypoglycemia is lower [23]. In addition, rare side-effects such as mild erythema and decreased vitamin B_{12} absorption have been associated with long-term administration [24]. Metformin also decreased the expression of vascular cell adhesion molecule 1 (VCAM1), expressed by endothelial cells that are dysfunctional or have been stimulated by tumor necrosis factor alpha (TNF-α),

a cytokine increased in the circulation of patients with preeclampsia,It has also been suggested that Metformin may prevent preeclampsia by improving cardiovascular function and limiting gestational weight gain [22]. Therefore, a preventive method targeting both early and late onset preeclampsia is highly desirable. To get such an effect, Aspirin was given in both group and Metformin in the intervention group. As such study is still not been conducted in our country, this Randomized Controlled Trial study will be very helpful if we found that Metformin prevents preeclampsia more along with Aspirin than Aspirin alone. Thus we will be able to reduce prevalence of it and also maternal and perinatal mortality and morbidity.

2. Materials And Methods

Study design: Randomized Controlled Trial.

Study Place: Department of Obstetrics and Gynecology, Dhaka Medical College Hospital, Dhaka, Bangladesh.

Period of study: January 2022 to December 2022.

Study population: Pregnant women attending Obstetric OPD, DMCH at her 1st trimester (6 -12 weeks) with risk factors of preeclampsia.

Sample size: To conduct the study, the sample size is calculated by using the following statistical formula for randomized control trials.

$$N = 2\frac{(z\alpha+z\beta)2}{(d-d0)^2} \times p \times (1-p)$$

Final sample size, n = 31 standard group, 31 treatment group. But I will take 40 on both groups to exclude drop out patients.

Sample selection:

2.1 Inclusion Criteria

Pregnant women at first trimester (6-12 weeks) of pregnancy attending in obstetric OPD, DMCH who will agree to participate will be recruited in the study.

- Gestosis scoring

2.2 Exclusion Criteria

- H/O taking Alcohol and some drugs that interacts with metformin (phenytoin, Phenobarbital, cimetidine, rifampicin)
- Fetal abnormalities, as the possibility that those patients might have an option for a pregnancy termination existed and data collection would thus be incomplete.
- Pregnant ladies with no Gestosis score.
- Patient to disagreed to take part in study.

Study procedure: Pregnant women, attending the outpatient department of Fetomaternal Medicine Unit, DMCH for routine ANC at her 6-12 weeks and who will fulfill the mentioned selection criteria, were selected for study. The purpose and procedure of the study were discussed with them individually. After obtaining informed consent, the women were interviewed by the researcher herself for the purpose of collection of data. Single blinding (participants did not know about the type of drug which they had taken) was done. Data regarding demographic profile, medical and family history (history of chronic hypertension, diabetes mellitus, GDM, autoimmune disease, CKD, previous history of preeclampsia) were recorded. Obstetric history regarding gravity, parity, past obstetric history were documented. Then a complete physical examination of the subjects was carried out by the researcher. The blood pressure level was taken with an appropriate procedure like-

- Automated machines not recommended (unless calibrated against a mercury sphygmomanometer in the individual patient)
- Appropriate sized cuff
- Seated for 2-3 minutes with foot supported.
- Both arms first visit
- Palpate systolic and go 20 mm higher
- Deflate slowly 2 mm every seconds
- Use Korotkoff 5(or 4 if 5 absent) for diastolic
- Repeated measures may be required.

Period of the gestation were confirmed by recording CRL in early USG. Then the patients were randomly selected either as experimental or control group and drug were given according to grouping. The control group was received tab Aspirin 150 mg at bedtime and intervention group took 500mg Metformin twice daily along with Aspirin. They were counseled to take these drugs regularly after meal and also to come immediately if any adverse effects like vomiting, stomach upset, diarrhea etc occur, warned about warning symptoms of preeclampsia. If preeclampsia developed according to operational definition, then patients were followed up and treatment was given accordingly. Aspirin was discontinued at 36 weeks or before 24 hours or if delivery was anticipated. Metformin was continued up to 36 weeks. They were monitored

- 4 weekly up to 20 weeks, then
- 2 weekly up to 28 weeks and

- weekly up to delivery to observe the outcome (development of Preeclampsia).
- During each visit, detailed history was taken about any symptoms of Preeclampsia, thorough Physical examinations like- pulse, blood pressure weight, SFH, fetal movement, FSH were done and investigations were given as necessary
- Then comparison was done between intervention and control groups to see the efficacy of Metformin in the intervention group.

Data analysis: Collected data were kept in a master sheet followed by entry for back up support in excel, after initial editing & cleaning the furnished data were transferred for statistical analysis into SPSS for Windows (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.) software. For analyses, results were presented as mean ± standard deviation (SD) for quantitative variables and as absolute frequencies and percentages for categorical variables. Comparison was done by Chi-Square (X^2) test, a Fisher's exact test, Mann Whitney u test and Binary logistic regression test -where necessary.

3. Results

In the current study 80 pregnant women (40 in the control group and 40 in the experimental group), at their first trimester (6-12 weeks) were included, but during follow up, 1 patient was died in intervention group at 34 weeks' gestation due to Preeclampsia with severe features followed by Myocardial Infarction after delivery.

Table 1. *Distribution of the participants according to demographic characteristics*

		Intervention group (n1=40)	Control group (n2=40)	Total	P value
Age (years)	>18-<25	12 (30.0%)	11 (27.5%)	23 (28.8%)	0.953
	25-30	19 (47.5%)	19 (47.5%)	38 (47.5%)	
	>30	9 (22.5%)	10 (25.0%)	19 (23.8%)	
	Mean ± SD	27.68±5.85	27.40±4.49	24.54±5.19	[b]0.809
	Median (IQR)	26 (18-40)	27 (19-41)	26.5 (18-41)	
Religion	Muslim	39 (97.5%)	40 (100.0%)	79 (98.8%)	[a]>0.99
	Hindu	1 (2.5%)	0 (0.0%)	1 (1.2%)	
Socio economic condition	Lower	15 (37.5%)	19 (47.5%)	34 (42.5%)	0.366
	Middle	25 (62.5%)	21 (52.5%)	46 (57.%)	
Education	Illiterate	2(95.0%)	0 (0.0%)	2 (2.5%)	0.325
	Primary education	7 (17.5%)	9 (22.5%)	16 (20.0%)	
	Secondary education and above	31 (77.5%)	31 (77.5%)	62 (77.5%)	
Occupation	Housewife	31 (77.5%)	35 (87.5%)	66 (82.5%)	0.239
	Working	9 (22.5%)	5 (12.5%)	14 (17.5%)	

Chi-square test was done, [a] Fisher's exact test, [b] Mann Whitney u test S=significant, ns=non-significant Data were presented as frequency, percentage, Mean ± SD, Median (range)

Table 1 is showing the demographic characteristics of the participants. Majority (47.5%) of the participants were from 25-30 years of age followed by >18-<25 years (28.8%) and the mean age of the participants was 24.54±5.19 years. Almost 60% of the participants belonged to the middle class and more than 75% participants had completed secondary education and above. More than 80% of the participants were housewives. The participants in the intervention and control group were demographically and statistically indifferent (p value:>0.05).

Table 2. *Menstrual and obstetrical history of the study participants*

Obstetrical history		Intervention group (n1=40)	Control group (n2=40)	Total	P value
Gravida	Mean ± SD	2.90±1.51	2.38±1.33	2.65±1.50	0.087
	Median (range)	3(1-8)	2(1-6)	2 (1-8)	
Parity	Mean ± SD	2.00± 1.61	1.39+1.37	1.66±1.51	0.087
	Median (range)	2 (0-7)	1 (0-5)	1 (0-7)	

Menstrual history	Regular	34 (85.0)	33 (82.5)	67 (83.8)	[a]0.762
	Irregular	6 (15.0)	7 (17.5)	13 (16.2)	
Regular antenatal checkup	Yes	35 (87.5)	29 (72.5)	64 (80.0)	[a] 0.094
	No	5 (12.5)	11 (27.5)	16 (20.0)	

Mann Whitney u test, [a]Chi square test was done S=significant, ns=non-significant; Data were presented as frequency, percentage, Mean ± SD, Median (range). No significant difference in groups was observed in term of menstrual and obstetrical history of the study participants (p value: >0.05)

Table 3. *Distribution of risk factors/comorbidity among the participants*

Risk factors/comorbidity	Intervention group (n1=40)	Control group (n2=40)	Total	P value
Previous history of eclampsia	2 (5.0)	0 (0.0)	2 (2.5)	[a]0.494 [NS]
Previous history of pre-eclampsia	7 (17.5)	9 (22.5)	16 (20.0)	0.576 [NS]
Family history of pre-eclampsia	7 (17.5)	5 (12.5)	12 (15.0)	0.531 [NS]
CKD	2 (5.0)	2 (5.0)	4 (5.0)	[a]>0.99 [NS]
Hypertension	13 (32.5)	7 (17.5)	20 (25.0)	0.121 [NS]
Gestational diabetes mellitus	6 (15.0)	1 (2.5)	7 (8.8)	[a] 0.108 [NS]
obesity	2 (5.0)	1 (2.5)	3 (3.8)	[a]>0.99 [NS]
Diabetes in pregnancy	15 (37.5)	11 (27.5)	26 (32.5)	0.340 [NS]
Hypothyroidism	4 (10.0)	2 (5.0)	6 (7.5)	[a] 0.675 [NS]
Antiphospholipid antibody syndrome	1 (2.5)	2 (5.0)	3 (3.8)	[a]>0.99 [NS]
Systemiclupus erythematosus (SLE)	0 (0.0)	1 (2.5)	1 (1.2)	[a]>0.99 [NS]
Twin pregnancy	0 (0.0)	2 (5.0)	2 (2.5)	[a] 0.494 [NS]

Chi-Square test and [a]Fisher's exact test was done S=significant, ns=non-significant Data were presented as frequency, percentage

The major risk factors or comorbidity among the study participants was diabetes in pregnancy (32.5%) followed by hypertension (25.0%) and previous history of preeclampsia (20.0%) and family history of preeclampsia (15.0%). No significant difference in risk factors or comorbidities among groups was found (p value: >0.05)

Table 4. *Physical parameters of the study participants at booking*

Physical parameters		Intervention group (n1=40)	Control group (n2=40)	Total	P value
Pulse (per minutes)	Mean ± SD	92.10±5.16	90.90±4.79	91.82±4.747	0.230 [NS]
	Median (range)	96 (84-100)	88 (80-96)	92 (80-100)	
Systolic blood pressure (SBP) [mm of Hg]	Mean ± SD	120.88±11.20	119.87±10.88	119.25±10.94	0.605 [NS]
	Median (range)	120 (100-140)	120 (100-150)	120 (100-150)	
Diastolic Blood Pressure (DBP) [mm of Hg]	Mean ± SD	79.63±9.89	77.75±10.37	77.61 ±10.05	0.285 [NS]
	Median (range)	80 (60-95)	80 (60-100)	80 (60-100)	
Body mass index (BMI) [Kg/m^2]	Mean ± SD	27.43±4.25	25.71±3.24	27.11±4.17	0.090[NS]
	Median (range)	27.45 (20.50-38.5)	26 (18.20-36.00)	27 (18.20-38.50)	

Mann Whitney U test was done S=significant, ns=non-significant, Data were presented as Mean ± SD, Median (range)

The mean± SD of the SBP in the intervention group was 120.88±11.20 mm of Hg and in the control group it was 119.87±10.88 mm of Hg. The mean± SD of the DBP in the intervention group was 79.63±9.89 mm of Hg and in the control group it was 77.75±10.37 mm of Hg. The mean± SD of the BMI in the intervention group was 27.43±4.25 Kg/m^2 and in the control group it was 25.71±3.24 Kg/m^2. No significant difference in physical parameters among groups was found (p value: >0.05)

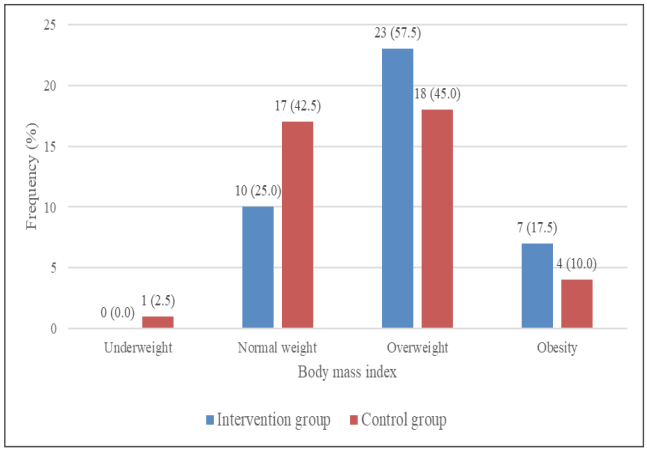

Figure 1. *Distribution of the study participants according to different category of body mass index (BMI)*

Figure 1 is showing that more than 7 (17.5%) participants in the intervention group were obese and 4 (10%) participants of the control group were obese. Only 1(1.3%) was underweight and she was in the control group. No significant difference in BMI was observed between groups (p value: 0.180).

Table 5. *Distribution of preeclampsia according to mean gestation weeks among study groups after intervention*

Preeclampsia		Mean ±SD	P value
Weeks of gestation	Intervention group (n1=15)	30.73±3.47	0.720^{NS}
	Control group (n2=24)	30.29±3.85	

Independent sample t test was done, s=significant, ns=non-significant, Data were presented as mean ±SD

Table 5 is showing that in the intervention group the mean± SD weeks of gestation at which the patients was diagnosed as preeclampsia was 30.73±3.47 weeks and for the control group it was 30.29±3.85 weeks. No significant difference in the mean weeks of gestation for development of preeclampsia was found (p value: 0.720).

Table 6. *Distribution of preeclampsia according to weeks of gestation among study groups after intervention*

Groups	Preeclampsia (Weeks of gestation)		Total	P value
	≤34	>34		
Intervention group (n1=15)	13 (86.7)	2 (13.3)	15 (100.0)	0.631^{NS}
Control group (n2=24)	22 (91.7)	2 (8.3)	24 (100.0)	
Total	35 (89.7)	4 (10.3)	39 (100.0)	

Fisher's exact test was done, S=significant, ns=non-significant, Data were presented as frequency, percentage

In total 39 patients suffered from preeclampsia. In 35 (89.7) cases preeclampsia occurred ≤34 weeks of gestation. In the intervention group, 86.7% patients suffered from/ experienced preeclampsia at ≤34 weeks of gestation, whereas in control group 91.7% patients experienced preeclampsia at ≤34 weeks. No significant difference in the weeks of gestation of experiencing preeclampsia in between groups was found (p value: 0.631).

Table 7. *Distribution of preeclampsia according to study groups after intervention*

		Pre-eclampsia		Total	P value
		Yes	No		
Intervention	Intervention group	15 (37.5)	25 (62.5)	40 (100.0)	0.044^{S}
	Control group	24 (60.0)	16 (40.0)	40 (100.0)	
Total		39 (48.8)	41(51.2)	80 (100.0)	

Chi-Square test was done, S=significant, ns=non-significant, Data were presented as frequency, percentage

Table 7 and Figure 2 is showing that, in the intervention group 37.5% patients suffered from preeclampsia and in the control group the proportion was 60%. In 62.5% cases the intervention was able to prevent preeclampsia and conventional/or placebo was able to prevent 40.0% preeclampsia. And this difference in preventing preeclampsia was significantly higher in the intervention group (p value: 0.044). Metformin reduced occurrence of Preeclampsia in 22.5% in this study.

Table 8. *Risk ratio analysis for determining the impact of giving intervention (Aspirin and metformin) in study participants*

	Risk Ratio	95% Confidence interval	P value
Control group (Aspirin) (reference category)			
Intervention (Aspirin and metformin)	0.625	0.389-1.003	0.05^{NS}

Risk ratio analysis was done, NS=significant, Data was presented as risk ratio, 95% Confidence interval

Table 8 is showing that, giving Aspirin and metformin as intervention than aspirin alone decreases the risk of developing preeclampsia as P value is 0.05. As the Risk Ratio (RR) is 0.625, so intervention group is a protective factor but 95% CI of Risk Ratio is (0.389-1.003) which is not statistically significant as it includes 1.

4. Discussion

This RCT was done to find out whether Metformin along with Aspirin from the first trimester can reduce Preeclampsia significantly or not. A total number of 80 (40 in control group and 40 in experimental/ interventional group) patients were included in this study by block randomization, from obstetrics and Fetomaternal medicine outpatient department of Dhaka medical college hospital, Dhaka during the period of January 2022 to December, 2022. The sociodemographic characteristics of the study subjects in relation to Intervention and Control group is shown in table 1. Here, age, religion, socioeconomic status, education and occupation of both group was compared and participants were demographically and statistically different. Majority (47.5%) of the participants are from 25-30 years which is similar with the study of U.S. National Library of Medicine [25]. In this study, no significant differences were observed in menstrual and obstetrical history of the participants between intervention and control group. In this study, among the patients with 18-25 years, 30.4% suffered from preeclampsia; whereas among the participants with 25-30 years, the proportion of Preeclampsia was 50.0%. The proportion gradually increased along with the increased age category and the proportion of preeclampsia was highest (68.4%) among the patients with age>30 years which is almost similar with the study of Bej Puny and Sultana R [26,27]. But another study of Parmar M T showed that teenage pregnancy was the risk factors [28]. In this study, this difference in proportion of preeclampsia in different age group was statistically significant (p value: 0.048).It is because in our study, the number of teenage pregnancy is negligible in control and experimental group. The major risk factors or comorbidities among the study participants was Diabetes in Pregnancy (32.5%) followed by Chronic Hypertension (25.0%) and previous history of Preeclampsia (20.0%) and family history of Preeclampsia (15.0%). Similar results observed in a study by Parmar M T and S Ganesh Kumar [29] most of the cases were having family H/O Preeclampsia, such results shown by Ferdousi Begum, TA Chowdhury, Konar H [28-31]. However in this study, no significant difference in risk factors or comorbidities among groups was found (p value: >0.05) as this was taken by matching during randomization. In this study, more than 50% of the participants were overweight and 13.8% were obese. Only 1(1.3%) was underweight which is also similar with the study of Ferdousi Begum, A Chawdhury [32]. In our RCT, Metformin 1 gm along with Aspirin was given in the intervention group and only Aspirin was given in the control group and in the intervention group 37.5% patients suffered from preeclampsia and in the control group the proportion was 60%. In 62.5% cases, the intervention was able to prevent preeclampsia and on the other hand, control was able to prevent 40.0% preeclampsia. Thus, this difference in preventing preeclampsia was significantly higher in the intervention group (p value: 0.044). Giving Aspirin and Metformin as intervention rather than Aspirin alone decreases the risk of developing preeclampsia. As the Risk Ratio (RR) is 0.625, so the intervention group is a protective factor for our study but 95% CI of Risk Ratio is (0.389-1.003) which is not statistically significant as it includes 1. In this study, both Aspirin and Metformin in the intervention group and Aspirin in the control group was given from the first trimester, then regular followed up with measurement of blood pressure, proteinuria and other relevant investigations. In the control group, with the use of Aspirin ,40% Preeclampsia was prevented whereas 15% and 16 % of preventing Preeclampsia was found in the study of Ferdousi Begum, TA

Chwaudhury [32] and Coomarasamy A [33]. This may be because they used the protocol of 75 mg of Aspirin and in this study, 150 mg Aspirin was used at bed time. In a study by Bujold, Aspirin treatment started before 16 weeks was also linked with a significant reduction in the incidence of severe Preeclampsia (RR 0.10; 95% CI 0.01 to 0.74) [34]. Another more recent meta-analysis was done by Roberge S and low-dose aspirin started at 16 weeks or earlier also was associated with a reduction in severe Preeclampsia (RR 0.09, 95% CI 0.02–0.37, 0.7% treated compared with 15.0% control) [35] which are almost similar with the current study as Binary logistic regression shown that the RR 0.625 but 95% CI (0.389-1.003) which is not similar as our sample is less. Another study by Feng Y showed that the posterior probabilities of metformin having a beneficial effect on the prevention of pre-eclampsia were 92.7% (RR, 0.72; 95% CI, 0.42–1.16) [36] which is also similar to this study by reducing preeclampsia with the use of both Metformin and Aspirin by 62.5% as the RR (0.625) and also the 95% CI (0.389-1.003) which includes 1. Another five randomized controlled trials were done comparing metformin treatment (n = 611) with placebo/control (n = 609), no difference in the risk of pre-eclampsia was found [37] which is also not similar with our study as the p value of our study is 0.046 and thus the difference of preventing Preeclampsia is significantly higher in the intervention group than the control group. This dissimilarity may be due to that Metformin may not be able to prevent Preeclampsia when used without Aspirin. In another related interesting study by Syngelaki A showed the use of Metformin in obese pregnant women without diabetes mellitus. There were 225 women in each group. The treated women benefited in the incidence of preeclampsia (3.0% vs 11.3%), both of which were lower in the metformin group in comparison with placebo with a remarkable 76% reduction in rates of preeclampsia (P<.001) [38] which is also similar with our study. In this nationwide population-based cohort study based in Swedish population, all singleton births (n = 1,016,805) from 686,847 women since 2006 up to 2016 were included. Multivariable logistic and Cox regression modeling with RR and hazard ratios (HR) and 95% confidence intervals were used to study the association between the exposure of maternal PCOS, metformin during pregnancy and Pregnancy outcomes preeclampsia. PCOS in women without Metformin use during pregnancy was associated with higher risks of preeclampsia (RR = 1.09, 1.02–1.17). Metformin use during pregnancy (in women without PCOS) was associated with a 29% lower risks of preeclampsia (RR = 0.71, 0.51–0.97) [38] which is also similar with this study as in this study, we have found that 22.5% more reduction of risk of Preeclampsia in Intervention group. In the ASPIRE trial, in women with singleton pregnancy who were identified by means of first-trimester combined screening as being at high risk for preterm Preeclampsia, the administration of Aspirin at a dose of 150 mg per day from 11–14 weeks until 36 weeks' gestation reduces the incidence of preterm Preeclampsia by >60% [39]. In this study, in the intervention group, 86.7% patients suffered from preeclampsia at ≤34 weeks of gestation, whereas in the control group 91.7% patients experienced preeclampsia at ≤34 weeks. No significant difference in the weeks of gestation of experiencing preeclampsia in between groups was found (p value: 0.631). In our study, Aspirin reduced risk of Preeclampsia in 40% cases. More recently, an open label, randomized control trial (RCT) in which high risk for preeclampsia pregnant subjects were randomly assigned to either an intervention group (Metformin 1 gm twice daily plus Aspirin 100 mg per day and standard of care) versus control group (Aspirin 100 mg per day and standard of care) that was administered between 11 to 13 weeks of gestation until delivery. Only women at high risk of pre-eclampsia as defined by the ACOG practice bulletin will be included. Patient assignment was blinded as control group will not be given a placebo; Enrolled subjects will be followed throughout pregnancy and up to 30 days post-delivery (as per hospital practice). But results is a waiting for publish [40].

5. Conclusion

The result of this study indicated that pregnant women with high risk for developing Preeclampsia can be treated with both Metformin and Aspirin from the first trimester as Preeclampsia was prevented in 62.5% cases in contrast of 40% by control group. Reduction of Preeclampsia was found 22.5% more with use of Metformin along with Aspirin.

5.1 Limitations

Like other studies the present study was also not flawless. Although optimum care has been tried by the researcher in every step of this study, some limitations still exist:

- Limited sample size was a major limitation.
- The data of the study collected from DMCH only; therefore, there might be an issue of generalization of the study findings. The result of the study might not be reflecting the exact picture of the country.

- The present study was conducted at a very short period of time.
- Due to financial burden and time limitation, MAP and Uterine Artery PI were not done as risk scoring.

5.2 Recommendation

As still now scarcity of study regarding this preventive method of Preeclampsia, more study with large sample size will be needed Further studies on a large scale are recommended for the well establishment of the fact that Metformin can be used as a preventive method for Preeclampsia along with Aspirin. So that, Preeclampsia and its complications will be reduced significantly and thus maternal and perinatal mortality will also be reduced. Awareness should be developed among obstetricians towards prediction and preventive methods for Preeclampsia from the first trimester of pregnancy.

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