ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

METFORMIN IN PREVENTION OF PREGNANCY INDUCED HYPERTENSION IN MOTHERS AT RISK: A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL

KEY WORDS: preeclampsia , pregnancy induced hypertension , metformin

Dr Ayesha Khatun MBBS,MS Obstetrics And Gynaecology Ipgmer And Sskm Hospital , Kolkata

ABSTRACT

DISCUSSION: Pregnancy induced hypertension is one of the most dreaded complications of pregnancy causing significant morbidity and mortality to mother and fetus. There is a derth of therapeutic interventions which can be done in mothers at risk to prevent the onset of pregnancy induced hypertension.The search for a prophylactic drug to prevent onset of pregnancy induced hypertension but doesnot hinder normal placental trophoblastic invasion is the need of the hour. It is thought that placental hypoxia causes release of soluble factors which causes widespread endothelial dysfunction that manifests as pregnancy induced hypertension and associated multi-organ damage.Metformin has shown to inhibit soluble fms factors and is safe in pregnancy.Therefore metformin is an excellent candidate to prevent onset of pregnancy induced hypertension in mothers at risk. **AIM:** The primary aim of this study was to observe the efficacy of metformin to prevent onset of pregnancy induced hypertension in mothers at risk , the study also studies the relation between metformin use and APGAR score at 1 minute and 5 min, the study also compares need for NICU admission between metformin and placebo groups. **METHODS:** A double-blind, randomised, placebo-controlled trial was performed among the mothers satisfying the inclusion criteria.301 patients were enrolled ,they were randomly assorted by computer generated random numerical table.mothers were folllowed up until post delivery.statistical analysis was done by SPSS software. **RESULTS:**In metformin group 25% developed preganancy induced hypertension and 9.2% newborn needed NICU admission,metformin had no favourable effect on APGAR score. **CONCLUSIONS:** Metformin was not effective in preventing onset of pregnancy induced hypertension,metformin had no effect on APGAR score at 1 minute and 5 minutes and metformin did not reduce need for NICU admission in newborn.

INTRODUCTION

Pregnancy induced hypertension is a leading cause of maternal morbidity and mortality, studies have shown that it is possible to predict the development of early onset pre-eclampsia with good precision using a combination of maternal factors and biomarkers in the first trimester of pregnancy(Kalafat E 2018).Pregnancy induced hypertension is the result of placental hypoxia due to improper trophoblastic invasion,chronic placental hypoxia causes release of sFlt-1 and soluble endoglin(landau,2005) which diffuse into maternal circulation causing widespread maternal endothelial dysfunction leading to multi-organ injury which clinically manifests as pre-eclampsia and eclampsia(brownfoot fc,2016).Metformin a proven safe drug in pregnancy,has shown to reduce sFlt-1 levels ,endoglins and produces a anti-inflammatory effect owing to which metformin prevents endothelial dysfunction.

Objectives:

Primary objective : To observe the efficacy of metformin to prevent pregnancy induced hypertension in mothers at risk.
Secondary objective: To observe the effect of metformin on APGAR score at 1 min and 5 min after delivery.

To compare incidence of NICU admission between metformin and placebo group.

Materials and methods: A double-blind, randomized, placebo-controlled trial was performed from 1 st january 2021 to 31 st august 2022, among pregnant women at 13-15 completed weeks,comimg for antenatal checkup at obstetric OPD at IPGME&R AND SSKM hospital, Among the patients those high risk mothers satisfying the inclusion criteria were selected Inclusion criteria: Pregnant woman with 1) Previous history of pre-eclampsia 2) Primigravida 3) Obesity ,BMI >35 4) Patient of diabetes 5) Pregnancy interval of more than 10 years 6) Family history of pre-eclampsia 7) Multi-fetal pregnancy 8) Elderly Mothers (age >35 years)at presentation 9) Previous history of pre-eclampsia or gestational hypertension 10) Pre-existing vascular disease Pre-existing kidney disease.(including chronic kidney patient with GFR above 50 ml/min) Exclusion criteria 1)Patients already on metformin 2)Patients of CKD stage 3 or above 3)Patients taking metformin for treatment of pcos 4)Patients of chronic hypertension 5)Known hypersensitivity to metformin The study was approved by the departmental ethics committee and by the corresponding institutional ethics committee.Sample size was calculated via epiinfo software which came to 300 subjects, 320 subjects were enrolled,19 subjects were lost to follow up or discontinued.A computer-generated random numerical table was used by an independent statistician to prepare sealed opaque envelopes containing a group assignment. Two groups of envelopes corresponding to two study groups—were given to a third party (a nurse), who was unaware of the contents and distributed envelopes to patients randomly. Group I (metformin)- These patients received metformin 500 mg thrice daily 13-15 weeks onwards Group II (Placebo)- These patients were given similarly looking placebo thrice daily .Data were collected in subsequent visits and tabulated in excel sheets,the patient was followed up till delivery to look if patient develops pre-eclampsia.APGAR scores were noted at 1 and 5 minutes,NICU admission if needed was noted.

Statistical analysis and results:Total 301 patients were enrolled in this study,which were randomly assorted to either metformin or placebo at 13-15 weeks ofgestation. The mean age of our study population was 26.41 years. Most of our population belonged to lower middle class(27.9%), o. In our study 248 had normal blood pressure throughout pregnancy while 53 had pregnancy induced hypertension.Among primigravida 28 patients (13.3%) developed PIH while 183(86.7%) had normal blood pressure among multigravida 25(27.8%)has PIH while 65(72.2%) had normal blood pressure .38 patients on metformin developed PIH(25%) while 30 patients on placebo developed PIH(16.8%).there was no significant statistical difference between preeclampsia onset in the two groups(p=0.255).

TABLE 1 TABLE COMPARING OUTCOME OF PREGNANCY BETWEEN METFORMIN AND PLACEBO

PREECLAMPSIA	METFORMIN	PLACEBO
YES	38	25
NO	114	124
TOTAL	152	149

In metformin group the APGAR score at1min had the following distribution 5:0% , 6:37%, 7:55.7%, 8:50%, 9:40% In

placebo group the APGAR score at 1min had the following distribution 6:2.7% , 7: 46.9% 8:49.0% 9:1.4% The relation between metformin and apgar scoreat1 min was not significant p =[0.351]. In metformin group the APGAR SCORE at 5min were 6:0.7% 7:9.35 8:40% 9:46.7% 10:3.3% There was no significant relation between metformin and APGAR score at 5 min(p=0.530) The relation between metformin and APGAR score at 5 minute was not significant p =[0.351].

TABLE 2 TABLE COMPARING APGAR SCORE AT 1 MIN BETWEEN GROUPS OF INTERVENTION

APGAR score at 1 min	METFORMIN	PLACEBO
6	23	4
7	46	69
8	80	70
9	3	2
TOTAL	152	145

TABLE 3 TABLE COMPARING APGAR SCORE AT 5 MIN BETWEEN GROUPS OF INTERVENTION

APGAR score at 5 min	METFORMIN	PLACEBO
6	1	1
7	14	3
8	60	42
9	70	88
10	5	9
TOTAL	150	151

Among subjects with metformin ,14 (9.2%) needed NICU admission while among placebo 17 (11.4%) needed NICU admission.The proportion of subjects who took metformin vs placebo did not differ by proportion of NICU admission, p= [0.651].

TABLE 4
TABLE COMPARING NICU ADMISSION BETWEEN THE GROUPS OF INTERVENTION

NICU ADMISSION	METFORMIN	PLACEBO
YES	14	17
NO	138	132
TOTAL	152	149

Discussion:

This parallel group double blind randomised control trial was conducted at department of Obstetrics &Gynaecology of IPGME&R AND SSKM Hospital from january 2021- august 2022.

Total 301 patients were enrolled in this study,which were randomly assorted to either metformin or placebo at 13-15 weeks of gestation

The mean age of our study population was 26.41 years,maximum age recorded was 39 years while minimum age recorded was 17 years.The enrolled patients 211(70.1%) were primigravida and 90(29.9%) were multigravida.In our study 248 had normal course of pregnancy while 53 had pregnancy induced hypertension.among primigravida 28 patients (13.3%) developed PIH while 183(86.7%) had normal pregnancy,among multigravida 25(27.8%)has PIH while 65(72.2%) had normal pregnancy.The birthweight in metformin group and placebo group was compared, there was no statistical significance between metformin and birthweight(p=0.864).In metformin group the APGAR score at 1 min had following distribution 5:0(0%) 6:10(37%) 7: 64(55.7%) 8:74(50%) 9:2(40%) In placebo group the APGAR score at 1 min had following distribution 5:1(100%) 6:17(63%) 7:51(44.3%) 8:74(50%) 9:3(60%) The relation between metformin and apgar score at 1 min was not significant p = [0.351].

In metformin group the APGAR SCORE at 5 min were 6: 1 (0.7%) 7: 14 (9.35) 8: 60(40%) 9: 70 (46.7%) 10:5(3.3%) There was no significant relation between metformin and APGAR score at 5 min(p=0.530)

The relation between metformin and apgar score at 1 min was not significant p = [0.351].

Among subjects with metformin,14 (9.2%) needed NICU admission while among placebo 17 (11.4%) needed NICU admission.The proportion of subjects who took metformin vs placebo did not differ by proportion of nicu admission, p = [0.651]. 38 patients on metformin developed PIH(25%) while 30 patients on placebo developed PIH(16.8%).there was no significant statistical difference between preeclampsia onset in both groups(p=0.255)

Conclusion:Preeclampsia affects 10% of pregnancy worldwide as per WHO data, if pre-eclampsia can be prevented from developing,it will lead to reduction of morbidity and mortality of expectant mothers, metformin dubbed as aspirin of 21st century(Romereo) is used in our study to evaluate its efficacy in preventing preeclampsia .

As evident in our study:

Metformin did not protect from onset of preeclampsia in mothers at risk.

Metformin doesn't influence APGAR scores at 1 minute and 5 minutes.

Metformin doesn't reduce NICU admissions in newborn.

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Conflict of interest: None declared

Ethical approval: Approved by the institutional ethics committee.

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