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Treatment of Early Gestational Glucose Intolerance with Metformin reduces Primary neonatal outcomes in hospital-based Cohort

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Abstract

Background: Early detection of dyglycemia during I[st] Trimester specially during 8-10 weeks can help us to Prevent Gestational diabetes mellitus in later period of pregnancy. A 2-hour PPBG ≥110 mg/dL at week 8-10 weeks screening and early treatment with Medical Nutrition Therapy & Metformin may mitigate primary neonatal complications. ***Objective:*** To understand the efficacy of Medical Nutrition therapy with metformin on primary neonatal outcomes in early glucose intolerance (PPBG) ≥110 mg/dL at 8-10 Weeks of gestation; and to compare it with Medical Nutrition therapy only. The prevention of Gestational Diabetes Mellitus by 32 weeks in MNT and Metformin Group compare to MNT only. ***Method:*** A Cohort study based on pregnant women with Post Prandial Blood Glucose (PPBG) of ≥110 mg/dl during 8-10 weeks of gestational randomised in two group; one group received MNT and low does Metformin 250 mg two times a day and other group received MNT only which were followed till delivery. ***Results:*** The mean postprandial blood glucose (PPBG) levels were significantly lower in the Metformin MNT group compared to the MNT group at 16 weeks (110.74 vs. 118.23), 24 weeks (109.54 vs. 117.78), and 32 weeks (112.8 vs. 118.8), with P-values ≤0.001. Additionally, the primary adverse neonatal composite outcomes were significantly higher in the MNT group (55 cases, 52.3%) compared to the Metformin-MNT group (35 cases, 37.6%) with P ≤ 0.038. The MNT group also reported 20 spontaneous abortions (16%) and 12 stillbirths (9.6%), while the Metformin group reported none. ***Conclusion:*** It is our responsibility to prevent fetal hyperinsulinemia by ensuring that maternal 2-hour postprandial blood glucose (PPBG) levels are below 110 mg/dl by the 10th week of pregnancy. Fetal beta cells typically begin secreting insulin around the 11th week. This underscores the crucial role of maintaining good glycaemic control during pregnancy, not only for preventing gestational diabetes but also for ensuring the health of the fetus.

Categories: Endocrinology/Diabetes/Metabolism, Public Health, Health Policy

Keywords: ***Metformin, gestational diabetes mellitus (GDM), PPBG Post prandial blood glucose, MNT Medical Nutrition Therapy. OGCT Oral Glucose challenge Test, DIPSI diabetes in pregnancy study group India.***

Introduction

According to the IDF Atlas 10th edition, 537 million people have Diabetes by 2021, and this is likely to increase to 643 million and 783 million in 2030 and 2045, respectively. Additionally, 541 million people will have impaired glucose tolerance in 2021. It is also established that over 6.7 million people aged 20–79 will die from diabetes-related complications in 2021 [1].

The current threshold for normoglycemia during pregnancy needs to be reevaluated. Hernandez et al. conducted metanalysis analysis of 12 studies spanning 4 decades to examine glycemic patterns in normal pregnancies. Their findings suggest that the targets for managing hyperglycemia in pregnancy should be lower than those currently in use. They identified normal fasting blood glucose (FBG) levels to be 71 ± 8 mg/dl (3.9 ± 0.4 mmol/l) and postprandial blood glucose (PPBG) levels to be 99 ± 10 mg/dl (5.5 ± 0.6 mmol/l). The authors proposed therapeutic PPBG targets of less than 122 mg/dl (6.8 mmol/l) at one hour and less than 110 mg/dl (6.1 mmol/l) at two hours. These recommendations could potentially transform the management of hyperglycemia in pregnancy and significantly enhance maternal and fetal outcomes.

HbA1c values over 6.5% indicate pre-existing Diabetes or prediabetes, while 5.7% - 6.4% is considered prediabetic. Some studies suggest that an HbA1c level of 5.3% or higher in the first trimester may be linked to an increased risk of developing GDM [3]. However, its use for early GDM screening is still debated due to concerns about sensitivity and specificity compared to PPBG testing [4]. In a recent study conducted in India, the diagnostic sensitivity

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and specificity of PPBS and HbA1c were found to be high in groups with PPBG levels ≥110 mg/dl [5], but large and multicentric studies are needed to further strengthen the evidence.

Target blood glucose levels should ideally be around 99 ± 10 mg/dl. We aim to ensure that newborns have a healthy birth weight, typically between 2.5 and 3.5 kg, appropriate for their gestational age.

Metformin Use During Pregnancy

Metformin has recently been endorsed as the first oral anti-diabetic drug that can be used safely from conception to delivery [6]. This medication is effective in lowering the risk of pregnancy-induced hypertension and pre-eclampsia. A study published in *The Lancet Diabetes & Endocrinology* found no significant differences in the weight, height, head circumference, or waist circumference of children born to mothers treated with Metformin compared to those given a placebo [7]. The Italian Medicines Agency has updated the summary of characteristics for extended-release Metformin, indicating that its use during pregnancy and the periconceptional period can be considered as an alternative or in addition to insulin [8]. Furthermore, the National Institute for Health and Care Excellence (NICE) in the UK has recommended Metformin as a first-line treatment for gestational diabetes mellitus (GDM) [9].

Evidence for Early Screening and Management of GDM for Improved Maternal-Fetal Outcomes

A healthy pregnancy is crucial. Newborns with a birth weight less than 2.5 kg or greater than 3.5 kg are at a higher risk of developing obesity, diabetes, hypertension, and cardiovascular disease in adulthood [10]. A recently concluded TOGOGM study showed that immediate treatment of gestational diabetes before 20 weeks of gestation resulted in a modestly lower incidence of adverse neonatal outcomes compared to delayed treatment [11].

Methodology

Design of the Study

A randomized prospective cohort study was initiated in the Department of Obstetrics and Gynecology at GSVM Medical College Kanpur, running from April 2023 to June 2024. All pregnant women meeting the specified inclusion and exclusion criteria were included in the study.

Inclusion Criteria: The study included all pregnant women between 8 to 10 weeks of gestation, with singleton pregnancies and diagnosed with impaired glucose tolerance (IGT) or gestational diabetes mellitus (GDM), to reflect a real-world scenario for treatment in both groups (**Table 1**).

Exclusion Criteria: Women with known diabetes (Type 1 or Type 2), those on Metformin for polycystic ovary syndrome (PCOS) or any other reason, and women who were beyond 10 weeks of gestation were excluded from the study. All participants were tested for 2-hour postprandial blood glucose (PPBG) at 8 to 10 weeks of pregnancy. A cutoff of 110 mg/dl was established, allowing sufficient time before fetal insulin secretion begins at 11 weeks. If the PPBG was ≥ 110 mg/dl during this period, participants were randomly assigned to one of two groups: one group received medical nutrition therapy (MNT) and Metformin (250 mg twice daily) until the end of the pregnancy, while the other group received MNT only, with the aim of maintaining the 2-hour postprandial blood sugar levels around or below 110 mg/dl (99 +/- 10). At 14 and 16 weeks of gestation, a 75-gm oral glucose challenge test (OGCT) should be conducted to assess whether the participant has developed GDM. If the initial test is negative, it should be repeated at the 24th and 32nd weeks.

Sample Size: A two-stage sampling technique was employed to recruit pregnant mothers for the cohort, using systematic random sampling to fulfil the inclusion criteria.

Statistical Analysis and Sample Size Estimation: The research question posed was: "How effective are Medical Nutritional Therapy (MNT) and metformin in preventing Gestational Diabetes Mellitus (GDM) in at-risk mothers (with a postprandial blood sugar (PPBS) level ≥110 mg/dl) compared to those receiving MNT alone?"

The sample size was calculated based on the assumption that 30% of all pregnant women would be at risk of GDM (defined as a 2-hour PPBS ≥110 mg/dl). The prevalence of GDM among high-risk pregnant women was estimated to be 14% (rounded from 13.7%). To achieve sufficient power for the study, a total of 186 high-risk pregnant women (≥110 mg/dl) were required, divided into two groups: one receiving MNT and the other receiving both MNT and metformin.

Ethical Issues: Approval was obtained from the GSVM Medical College Institutional Ethical Committee (Reference: EC/BMHR/2022/142, dated April 18, 2023). Additionally, written informed consent was secured from all participants.

Statistical Methods: We organized the data using Microsoft Excel and conducted a thorough analysis with SPSS version 21.0. For continuous data, we calculated the mean and standard deviation (SD), while categorical data were presented as percentages. To compare the means or medians of the two groups, we used either an unpaired t-test or a Mann-Whitney U test, depending on data distribution.

Results

450 pregnant women were involved in a study where Postprandial blood glucose levels were measured at 8-10 weeks of Gestation. Of these, 227 had a level of≥ 110 mg/dl, and 218 of them were followed up till delivery in both groups, with 9 lost to follow-up. The study focused on 218 pregnant women with PPBS ≥110mg/dl who were followed up in two intervention groups: 93 pregnant women with MNT and Metformin, and 125 women with MNT only in the control intervention group. The study design was a prospective cohort study, and the methodology included regular monitoring of blood glucose levels and other maternal outcomes (**Table 1**).

Table 1: Characteristics of the Two Intervention Groups at post prandial at 8-10 weeks of gestation, during pregnancy and after Gestation.

	N = 93 **PPBS at 8-10 wks. ≥110(mg/dl)** **(Mean ± SD) No (%)** MNT+ Metformin	**N = 125** **PPBS at 8-10 wks. ≥110 (mg/dl)** **(Mean ±S D) No (%)** MNT only	**P-value**
Age(years)	24.0 ± 4.5	24.6 ± 4.7	0.961
IUD/Spontaneous abortion 8-28 Weeks	0(0.0)	20 (16)	0.00005

Still birth > 28 weeks	0(0.0)	12(9.6)	0.0021
Gestational week birth			
<37	8(8.6)	12(12.9)	0.343
37+	8(8.6)	19(20.4)	0.022
38+	49(52.7)	28(30.1)	0.0017
39+	22(23.6)	27(29.1)	0.40
40	6(6.4)	7(7.5)	0.77
Gravida			
Primi	42(45.1)	57(45.6)	0.94
Multi	51(54.9)	68 (54.4)	0.94
GDM at 8-10th Week	15(16.1)	18(14.4)	0.72
Hist of GDM	12(12.9)	15(12.0)	0.84
Hist of PCOS	8(8.6)	9(7.2)	0.70
Fetal waste hist			0.132
present	32(34.4)	43(34.4)	0.10
Absent	61(65.6)	82 (65.6)	
Type of delivery			
NVD	61 (65.6)	63 (67.7)	0.75
LSCS	32 (34.4)	30 (32.3)	0.75
Term of delivery			1.000
Preterm	8(8.6)	12 (12.9)	0.34
Term	85(91.4)	81 (87.1)	
Family history of DM			0.75
YES	24(25.8)	30 (24.0)	
NO	69 (74.2)	95 (76.0)	
BMI kg/m2	24.9 ± 4.1	24.2 ± 3.4	0.18
BMI category			0.148
Normal (18.5-22.9)	23(24.7)	21(22.6)	
Over weight (23.0-24.9)	28(30.1)	30(32.3)	
Obese (25.0-29.9)	25(26.8)	23(24.7)	
Morbid obese (30-40)	17(18.2)	19(20.4)	

Table 2: Primary Neonatal outcomes in Medical Nutrition Therapy (MNT) + Metformin group; and MNT Group

Outcome	**PPBS≥110mg/dl, Fetal-maternal outcomes Metformin & MNT Intervention Mean ± SD, N= 93 (%)**	**PPBS≥110 mg/dl Fetal-maternal outcomes & MNT Intervention Mean ± SD, N=125 (%)**	**P-value**
Primary pregnancy outcomes			
PPBS– 8 weeks	122.76 ± 6.7	123.26 ±5.2	0.55
PPBS- 12 weeks	115.48± 5.6	116.37 ± 10.7	0.43
OGCT – 16 weeks	110.74 ± 10.2	118.23 ± 12.8	0.001
OGCT – 24 weeks	109.54 ± 9.6	117.78 ±10.7	0.001
OGCT – 32 weeks	112.8 ± 9.8	118.8 ± 11.8	0.001
PPBS Post-Partum	106.29± 8.4	109.29± 9.5	0.023
Glycated Haemoglobin % (24-32 Weeks)	5.44±0.31	5.63±.58	**0.006**
Adverse-neonatal outcomes*[a,b,c,d,e]	**35 (37.6)**	**55 (52.3)**	**0.038**
Secondary outcome			
Birth weight (kg.)	2.92 ± 0.4	3.04 ± 0.4	**0.042**
IUD/Spontaneous abortion	0(0.0)	32(25.6)	0.001
≥28 Weeks Still birth	0(0.0)	12(12.9)	0.002
<2.5 kg Birth weight	10(10.8)	18(19.3)	**0.0003**
2.5 – 2.99	35(37.6)	34(36.6)	0.87
3.0 – 3.49	39(41.9)	27(29.0)	0.07
≥3.45[a]	9(9.6)	14(15.1)	0.26
Neonatal morbidity	**48**	**80**	**0.001**
Still-birth[b]	0(0.0)	12(12.9)	0.0001
Phototherapy[c]	14(15.1)	12(12.9)	0.67
Hyperbilirubinemia	14(15.1)	12(12.9)	0.38
Hypoglycemia	4(4.3)	12(12.9)	0.036

RDS[d]	4(4.3)	5(7.5)	0.73
Preterm Birth <37th week Gestation[e]	**8(8.6)**	**12(12.9)**	**0.34**
LGA	6(6.5)	9(9.7)	0.42
NICU	12(12.9)	18(19.4)	0.23
GDM in 32 weeks ≥140 mg/dl	2(2.1)	10(10.7)	0.017

*Adverse neonatal outcomes (composite|) includes: [a] Macrosomia: newborn weight more than 3.45 kg, [b] still birth >28 weeks of Pregnancy, [c] newborn received phototherapy or any trauma to newborn during delivery, [d] RDS (respiratory distress in newborn), [e] Pre-term delivery less than 37 weeks.

The Primary Outcomes: The adverse neonatal composite outcomes in the two groups were statistically significant, with results of 35 (37.6%) in the MNT-Metformin group compared to 55 (52.3%) in the MNT group (P ≤0.038), (**Table 2**)

Gestational diabetes mellitus (GDM) was observed in 2.1% of participants by 32 weeks of gestation versus 10.7% in the MNT-Metformin and MNT groups, respectively, which is highly significant (P 0.017)

Hypoglycemia in neonates was significantly higher in the MNT group, with 12 cases (12.9%), compared to 4 cases (4.3%) in the Metformin MNT group (**Table 2**).

Discussion & Conclusion

Our study is an initial step towards creating evidence that early detection and treatment could potentially prevent the conversion to GDM in pregnancy, leading to significantly improved Primary Neonatal outcomes, while our present study shows promising results, as this is one center study during early Pregnancy so study has its own limitations, therefore large sample size and multicentric study are needed to further validate our findings.

Taking preventive action by managing maternal postprandial blood glucose levels effectively from the 8th-10 week onwards is key to following a regimen of medical nutrition therapy (MNT) and continuing with Metformin throughout pregnancy, taking positive steps to support mother-fetal development. The crucial development of fetal beta cells around the 11th week emphasizes the importance of sustained efforts to prevent fetal hyperinsulinemia.

Disclosures

Consent to Participate in Study

All human subjects provided written informed consent with guarantees of confidentiality. Institutional Ethics Committee, GSVM Medical College, Kanpur, issued approval No (DHR).EC/BMHR/2022/142. Institutional Ethical Committee, Medical College, Kanpur approved this Study on 18.04.2023 at the meeting organized by Medical College with No. 103 via Number EC/BMHR/2022/142. The principles of the Helsinki Declaration were followed. All the authors approved the final manuscript for publication.

Animal subjects

All authors have confirmed that this Study did not involve animal subjects or tissue.

Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Conflicts of interest

None

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Availability of data and materials

Data and materials were available for all the authors.

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