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Original Article

Management of early gestational glucose intolerance to improve pregnancy outcomes

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Abstract. Diabetes during pregnancy detection does not mean prevention. A 2-hour postprandial blood glucose (PPBG) ≥110 mg/d at 8-10 weeks is crucial for predicting Gestational Diabetes Mellitus (GDM). Intervention should start at week 8 to prevent GDM as fetal beta cells start insulin secretion by 11th weeks. To Evaluate the efficacy of metformin in high-risk GDM pregnant women having postprandial blood glucose levels ≥110 mg/dL at 8-10 Weeks of gestation; Assess if Medical Nutrition Therapy (MNT) with or without metformin can prevent GDM in women with PPBG ≥110mg/dl at 8-10 weeks and Evaluate complications and outcomes in pregnant women and neonatal morbidities in Early Gestational Glucose Intolerance (EGGI) in intervention groups. A Prospective cohort study included pregnant women at 8 to 10 weeks of gestation, divided into two groups based on their blood sugar levels of ≥110 mg/dl. Those with higher levels ≥110 mg/dl received two different interventions: metformin MNT and MNT only. Follow-up outcomes were done until delivery. The mean 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. Neonatal morbidity was significantly lower in the metformin-MNT group (48 cases, 51.6%) compared to the MNT group (80 cases, 76.2%), with P < 0.001. These findings highlight the superior effectiveness of the MNT-metformin intervention. In conclusion, it is essential to keep maternal 2-hour PPBG levels below 110 mg/dl by the 10th week of pregnancy to prevent fetal hyperinsulinemia. Fetal beta cells typically begin secreting insulin around 11th week. Maintaining good glycemic control during pregnancy is crucial for preventing gestational diabetes and ensuring the health of the fetus.

Keywords: Metformin, gestational diabetes mellitus, primordial prevention, post prandial blood sugar, medical nutrition therapy, oral glucose challenge test.

Introduction

According to the International Diabetes Federation (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].

In 2001, the American Institution Centre for Disease Control (CDC) and Prevention formulated a press document stating that the "Co-epidemics of diabetes-obesity is dangerous to the health of Americans, which is based on the finding of the "Diabetes Prevention Program (DPP), which states that diabetes could be prevented by promoting healthy lifestyles. However, in 2001, 6.1% of the US population had been suffering from Diabetes [2]. Currently, IDF Atlas states the prevalence of Diabetes has increased to about 10.5%, which signifies less impact of the DPP Program on diabetes prevention [3].

The ovum contains many mitochondria, but the sperm comprises only a few, and even those are left over after penetrating the ovum; at fertilization, only the spermatozoa's nucleus enters the ovum, and mitochondria and cytoplasm are derived from the maternal side, each islet cell work as endocrine tissue and differentiate by 10-11 weeks [4] of gestation, and if maternal glucose is slightly increased during this period it stimulates Foetal B cells to secrete more insulin, leading to fetal hyperinsulinemia "Foetal Origin of Adult Disease" as

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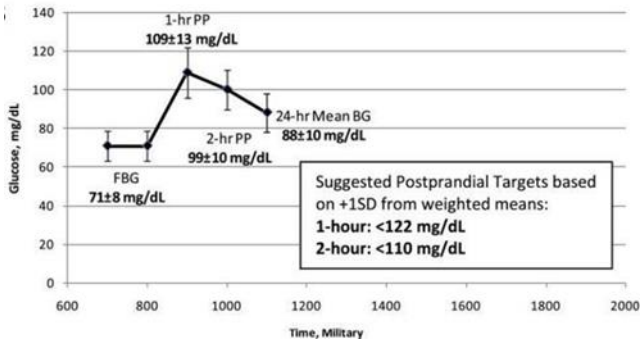

Figure 1 Patterns of glycemia in normal pregnancy. Mean pattern of glycemia across 12 studies [8]. Credit: Hernandez TL

hypothesized by David Barker [5,6]. The major developmental events in the natural history of non-communicable diseases (NCDs) start while the fetus is in the womb. Therefore, all the studies establish that the Intra-uterine environment impacts an inherited Destiny. Maternal and placental stress can induce changes in the fetal epigenome, profoundly impacting fetal development and potentially leading to lasting phenotypic alterations and disease [7].

The current threshold for normoglycemic need to be challenged, Hernandez et al. studied the pattern of glycemia in normal pregnancy by pooling analysis of 12 studies involving 45 years of data. They indicated that the glycaemic targets in managing hyperglycaemia in pregnancy must be lower than the currently used ones. They detected the normal levels of fasting blood glucose (FBG) to be 71±8 mg/dl (3.9±0.4 mmol/l) and postprandial blood glucose (PPBG) to be 99±10 mg/dl (5.5±0.6 mmol/l). They have suggested therapeutic PPBG targets of <122 mg/dl (6.8 mmol/l) at one hour and <110 mg/dl (6.1 mmol/l) at two hours (Figure 1) [8], which could potentially revolutionize the management of hyperglycaemia in pregnancy and significantly improve maternal and fetal outcomes

Materials and Methods

Design of the study

A randomized Prospective Cohort study started in the Department of Obstetrics and Gynaecology, GSVM Medical College Kanpur, from April 2023 to June 2024. All pregnant women with inclusion and exclusion criteria were studied.

Procedure

As for inclusion criteria, all pregnant women within 8 to 10 weeks of pregnancy, singleton pregnancies, and IGT/GDM were included to match a real-world scenario with the Intention to treat in both Groups. Exclusion criteria were known diabetic (Type 1 or Type 2), any women on metformin for Polycystic ovary syndrome (PCOS) or any reason, and women beyond 10 weeks of pregnancy.

All pregnant women are being tested for 2hr PPBG at the 8^{th}-10^{th} week of pregnancy. A 110 mg/dl cut-off means enough time is available before fetal insulin secretion starts in the 11th week. If PPBG is ≥110 mg/dl in the 8^{th}-10^{th}

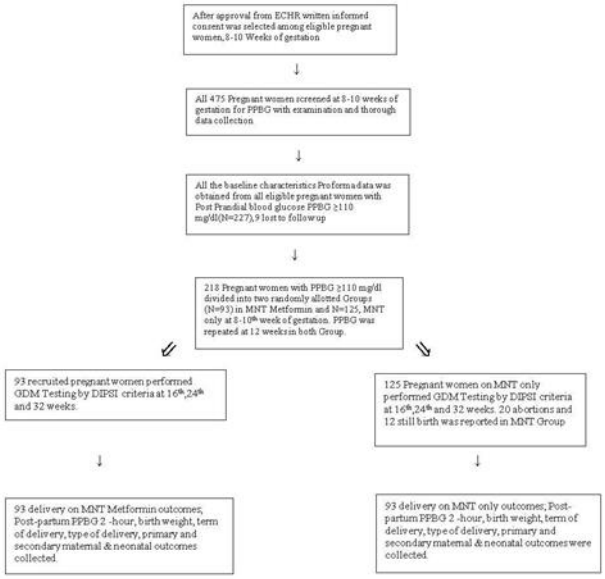

Figure 2 Pregnant women Flow Chart

week, they were treated with MNT and metformin 250 mg twice daily till the end of the pregnancy, and other group with MNT only till the end of the pregnancy in randomly allotted two groups to 2-hour PPBS to be maintained around or less than the 110mg/dl (99 +/- 10). At the 14, 16 weeks a 75gm Oral Glucose Challenge Test (OGCT) (DIPSI Test) should be done to determine whether she developed Gestational Diabetes Mellitus (GDM) and, if negative, test be repeated at the 24th and 32nd weeks.

The study focused on all pregnant women who met specific inclusion and exclusion criteria. The women were randomly assigned to these two groups to maintain their 2-hour PPBG levels around or below 110 mg/dl (99 +/- 10) during the 8th-10th week of pregnancy; all pregnant women were tested for 2-hour PPBG with a cutoff of 110 mg/dl was used to determine if there was sufficient time before fetal insulin secretion begins at the 11th week. If the PPBG level was found to be ≥110 mg/dl in the 8th-10th week, two groups were randomly allocated as per the random number table selected. One group were treated with MNT and metformin 250 mg twice daily until the end of the pregnancy, and another control group received only MNT until the end of the pregnancy. Additionally, at the 14th and 16th weeks, a 75g OGCT, also known as the DIPSI Test, was performed to determine if the women had developed GDM. The test should be repeated at the 24th and 32nd weeks if the result is negative (Figure 2)

After obtaining approval from the Ethics Committee of the Medical College, pregnant women with gestation periods between 8 and 10 weeks were enrolled in the study in two groups by random sampling.

All eligible women were recruited after written informed consent. A thorough history and complete physical examination were done as per standard protocol. The gestation period was estimated based on the last menstrual period or USG findings. All women were undergone 2 hours of postprandial blood glucose after breakfast during 8-10 weeks of gestation. The blood

TABLE 1
CHARACTERISTICS OF THE TWO INTERVENTION GROUPS AT POST PRANDIAL AT 8-10 WEEKS OF GESTATION, DURING PREGNANCY AND AFTER GESTATION.

Variable	PPBS at 8-10 wks. ≥110(mg/dl) MNT+ Metformin (Mean ± SD) N = 93 (%)	PPBS at 8-10 wks. ≥110 (mg/dl) MNT only (Mean ±S D) N = 125 (%)	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)	

glucose was measured using a plasma-calibrated glucometer after noting the exact time of the meal. They were followed up in the antenatal clinic and underwent GDM screening with DIPSI test per Technical and operational Guidelines for hyperglycaemia, Ministry of Health and Family Welfare, India [13], GDM is diagnosed by a non-fasting, blood glucose ≥ 140mg/dl after 2 hours of 75gm glucose challenge. GDM screening was done at 14-16 weeks, 24-28 weeks, and between 32-34 weeks.

All recruited women were followed up closely till delivery. At delivery, the baby's weight and other morbidities and any postnatal complications in the mother were noted (Table 1).

Sample size

A two-stage sampling technique was used to encourage pregnant mothers and admit them to the cohort; the inclusion criteria were fulfilled using systematic random sampling.

Statistical analysis

Sample size estimation

The research question is, "how efficacious are MNT and metformin in preventing GDM in at-risk mothers (PPBS ≥110mg/dl) compared to those receiving MN alone?" The sample size was calculated based on the

TABLE 2
PRIMARY AND SECONDARY PREGNANCY OUTCOMES.

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**
<2.5 kg	8(8.6)	18(19.3)	0.035
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
Indication of LSCS			0.55
No indication	61	63	
CPD	6	6	
FD	6	5	
MSL	6	6	
MSFD	2	2	
PROM	4	3	
Breech	3	3	
Previous LSCS	5	5	
Neonatal morbidity	**48**	**80**	**0.001**
Still birth[b]	0(0.0)	12	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
Maternal morbidity	**30(32.3)**	**40(32)**	**0.96**
+Pregnancy related hypertension	9(9.6)	10(10.7)	0.80
GHTN[a]	7(7.5)	7(7.5)	0.5
Severe Pre-eclampsia[b]	2(2.1)	3(3.2)	0.65
Hypothyroid	4(4.3)	6(6.4)	0.52
GDM status change			
GDM at Diagnosis 8-10 weeks	15(16.1)	18(14.4)	0.72
GDM in 32 weeks ≥140 mg/dl	2(2.1)	10(10.7)	0.017
Post-Partum IGT 140-199mg/dl	2(2.1)	6(6.5)	0.142

*****Adverse neonatal outcomes (composite|) includes; preterm delivery less than 37 weeks, Still birth >28 weeks of Pregnancy, (LGA) Large for gestational age, Macrosomia: newborn weight more than 3.45 kg, newborn received phototherapy or any trauma to newborn during delivery or RDS(respiratory distress in newborn); +Pregnancy related hypertension includes composite of gestational hypertension(GHTN), preeclampsia and eclampsia; MSL(Meconium stain liquor);Hypoglycemia includes blood sugar <40 during 4 hour of birth; FD(Fetal distress);PROM (Premature rupture of membrane); CPD (Cephalic Pelvic Disproportionate);OGCT(Oral Glucose challenge Test).

assumption that 30% of all pregnant women would be at risk of GDM (at 2-hour PPBS ≥110% mg/dl), and the prevalence of GDM among high-risk (≥110 mg/dl) Pregnant Women (PW) was 14.0% (13.7% was rounded to 14%). Together, 186 high-risk PW (≥110 mg/dl) were needed for the study in two groups with MNT and MNT with Metformin.

Ethical issues

Clearance from the ethical committee, GSVM Medical college, Institutional ethical committee was taken via EC/BMHR/2022/142, dated 18.04.2023, adhered to the International Council for Harmonization (ICH) - Good Clinical Practice (GCP) (ICH-GCP) guidelines, the objective and procedure of the study were explained to the participants, and written informed consent was taken from all the participants. Confidentiality is ensured at all stages of the study, and afterward, the option to opt-out is open without any clause; if the woman is found to have GDM, she will be managed as per the standard clinical protocol of

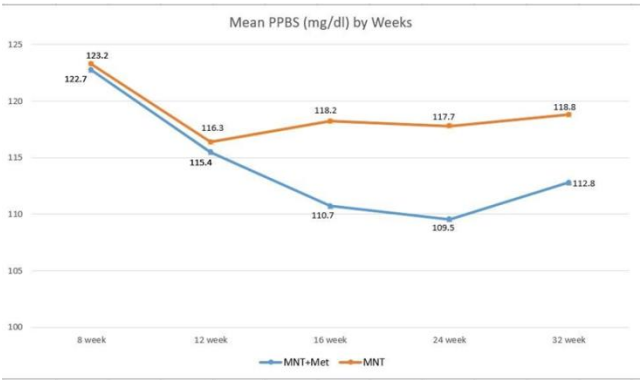

Figure 3 Mean Glycemic level (mg/dl) by weeks in the MNT+ Metformin and MNT groups.

the department. Due to this study, there is no extra risk involved to the patient, and the patient does not bear any financial burden by participating.

Statistical method

We meticulously organized the data in MS Excel and conducted a comprehensive analysis using SPSS 21.0. We calculated the mean and standard deviation (SD) when dealing with continuous data, while categorical data was skilfully presented as percentages. Comparing the means or medians of the two groups, we opted for the precision of either an unpaired t-test or a Mann-Whitney U test. We harnessed the power of the Chi-square or Fisher exact test to delve into the association of categorical variables. Our approach to expressing discrete variables as percentages and continuous variables as mean and standard deviation was clear and effective. Utilizing the independent t-test, we rigorously assessed if there was a significant difference in mean value between groups. Every test was conducted with a two-tailed method and a P-value of <0.05 was the threshold for statistical significance.

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. It is observed that the mean age SD (24.0 ± 4.5) and (24.6 ± 4.7), mean birth PPBS at 8-10 weeks (122.76 ± 6.7) and 123.26 ±5.2 were non-significant in respective intervention groups (Table 2, Figure 3) and others maternal outcomes e. g; Gestational week birth, Gravida, GDM at 8-10th Week, Hist of GDM, hist of PCOS, Fetal waste hist, Type of delivery, Term of delivery, Family history of DM, GDM status, BMI kg/m2, Indication of LSCS, Preterm Birth <37th week between the groups are statistically non-significant (P>0.05, indicating these characteristics are similar in both the groups (Table 1, Table 2).

Regarding the primary outcomes, the difference in the mean PPBS values between the groups in the initial week from 8 to 12 weeks is Non- significant (Table 2); a gradual decrease in mean PPBS value was observed in the intervention group Metformin MNT group, and an almost similar PPBS value non-significant was noticed in MNT group from 8th week (122.76 ± 6.7 Vs. 123.26 ±5.2) till 12thweek (115.48± 5.6 Vs. 116.37 ± 10.7); but subsequently later a significant difference in mean ±SD PPBG were observed in 16 weeks (110.74 ± 10.2 Vs. 118.23 ± 12.8), 24 weeks (109.54 ± 9.6 Vs. 117.78 ±10.7), and 32 weeks (112.8 ± 9.8 Vs 118.8 ± 11.8), the difference in the mean value of OGCT value is significant (P≤0.001) between the group. The mean ± SD OGCT value remained significant till 32 weeks in the two groups, indicating that the intervention significantly impacted the glycemia level in the intervention group compared to the control MNT group (Figure 3)

As for the other 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). However, the primary maternal hypertension composite outcomes were not statistically significant, with instances of 9 (9.6%) in the MNT group versus 10 (10.7%) in the Metformin MNT group (P = 0.80) (Table 2).

The incidence of spontaneous abortion and stillbirths was 20 (16%) and 12 (9.6%) in the MNT group compared to none in the MNT-Metformin intervention group, which is highly significant. 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. This reflects a relative risk reduction of 86.9% and 25.6%, both of which are significant. Additionally, a significant reduction in postpartum impaired glucose tolerance (IGT) was observed between the MNT-Metformin and MNT groups, with rates of 2.1% and 6.5%, respectively (Table 2). The mean glycated haemoglobin levels were 5.44 ± 0.31 in the MNT-Metformin group and 5.63 ± 0.58 in the MNT group, which was statistically (P = 0.006).

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. The percentage of neonatal morbidity was significantly lower in the Metformin MNT intervention group, with 48 cases (51.6%), compared to 80 cases (76.2%) in the MNT intervention group (P < 0.001) (Table 2).

Regarding the secondary outcome of maternal morbidity, observations in both groups were similar, with 30 cases (32.3%) in the MNT-Metformin group compared to 40 cases (32.0%) in the MNT group. The difference was non-significant, with P value 0.96 (Table 2).

Discussion

As hypothesized by Seshiah et al., the 10th week of gestation's post prandial blood glucose 2 hours predicts

GDM. 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 maternal-fetal outcomes especially 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.

Pre-pregnancy planning is crucial for ensuring the best possible outcomes for your baby. Taking proactive steps to improve metabolic control in the early stages of pregnancy can significantly impact the well-being of both mother and child. By closely monitoring blood glucose levels, particularly with a 2-hour PPBG110 mg/dl reading in the 10th week, one can predict and address the risk of gestational diabetes. Taking preventive action by managing maternal postprandial blood glucose levels effectively from the 8^{th}-10 week onwards is a key to following a regimen of 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. The concept of early prevention of diabetes, once established, may be achievable, providing a strong foundation for a healthy pregnancy.

Conflict of interest

The authors declare no conflicts of interest.

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