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ORIGINAL ARTICLE

Can Medical Nutrition Therapy Affect Feto-Maternal Outcomes in Gestational Glucose Intolerance: An Open-Label Pilot Randomized Control Trial in World's Diabetes Capital

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Abstract

Introduction Gestational diabetes is defined as the carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. Gestational glucose intolerance (GGI) is used to indicate pregnant women whose 2-h postprandial glucose is > 120 mg/dl and below 140 mg/dl (Diabetes in Pregnancy Study Group of India, DIPSI criteria).

Aim This study was planned to see whether intervention in GGI group helps to improve feto-maternal outcomes.

Methodology This open-label randomized control trial was conducted in Department of Obstetrics and Gynaecology of King George's Medical University, Lucknow. Inclusion criteria were all the antenatal women attending the antenatal clinic and diagnosed as GGI, and exclusion criteria were overt diabetes.

Results Total of 1866 antenatal women were screened, and among them, 220 (11.8%) women were diagnosed as gestational diabetes; 412 (22.1%) women were diagnosed as GGI. The mean fasting blood sugars in the women with GGI who had medical nutrition therapy were much lower than the women with GGI who did not have any intervention. The present study showed the women with GGI had higher complications like polyhydramnios, PPROM, foetal growth restriction, macrosomia, preeclampsia, preterm labour and vaginal candidiasis more in the women with GGI as compared to euglycaemic women.

Conclusion The present study of nutritional intervention in GGI group has shown trend towards lesser complication if we start medical nutrition therapy reflected by delayed development of GDM and less neonatal hypoglycaemia and hyperbilirubinemia.

Keywords GDM · GGI · Diabetes · Blood sugar · DIPSI · Medical nutrition therapy

Introduction

Diabetes in pregnancy is a great global concern and a potential emerging public health problem. Gestational diabetes mellitus is defined as the carbohydrate intolerance of variable severity with onset or first recognition during pregnancy [1], and it affects 9–25% of all pregnancies [2]. The prevalence of gestational diabetes varies between different geographical areas and so does the constraints in testing in terms of cost-effectiveness. Test method suggested by Diabetes in Pregnancy Study Group of India (DIPSI) has been considered as best-accepted testing method in Indian perspective and has also been accepted by the FIGO as a country-specific detection model. This is a single-step test measuring blood sugar 2 h after ingestion of 75 g oral glucose [3]. The threshold blood sugar level of ≥ 140 mg/dl is taken as cut-off for diagnosis of GDM. The term gestational glucose intolerance (GGI) is used to indicate pregnant women whose 2-h postprandial glucose is > 120 mg/dl and below 140 mg/dl. Unlike GDM, for gestational glucose intolerance, no intervention is stated by any of the available guidelines. It is important to recognize that the ideal fasting sugar should be less than 95 mg/dl and 2-h postmeal sugar has to be less than120 mg/dl and hence it is important to see whether gestational glucose intolerance might also need intervention [4, 5]. Prospective and retrospective studies have been done which substantiated the observation that the frequency of adverse foetal outcome increases with 2-h postprandial sugar > 120 mg/dl and taking care of these women had resulted in a better foetal outcome. However,

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whether any trivial intervention in form of medical nutrition therapy in GGI group can alter or improve feto-maternal outcome, needs a randomized control trial which has not been done ever. Enough evidence is available that timely diagnosis and management of GDM is having significant maternal and foetal health benefits. GGI appears to be a milder form of GDM and could be more amenable to simpler interventions. The pathophysiology of the disease appears to vary in different ethnic population, especially South Asian women. Novelty of the study is that present literature and available evidence are essentially lacking in any work or intervention in the GGI. This study was planned to see whether women with GGI have any increased feto-maternal complication compared to euglycaemics and whether any intervention in GGI group helps to improve feto-maternal outcomes in a tertiary care centre of North India.

Material and Methods

This open-label randomized control trial was conducted in Department of Obstetrics and Gynaecology of King George's Medical University, Lucknow, in outpatient clinic. Inclusion criteria were all the pregnant women coming to antenatal clinic and diagnosed as GGI by DIPSI criteria. Exclusion criteria were all women with gestational diabetes (DIPSI sugar level ≥ 140 mg/dl) or overt diabetes, twin pregnancy or not willing for participation. The study was conducted over a period of one year. Ethical clearance was taken from Institutional Ethical Committee (89th ECMII B/ thesis/P 60). Trial was registered with www.ctri.gov.in REF/2017/10/15732 on 28.10.2017. Block randomization (2:2) was done according to computer-generated random number table into two groups A (medical intervention), B (no intervention). Group C included euglycaemic women as control. Allocation concealment was done by sequentially numbered opaque sealed envelopes (SNOSE).

Sample size: As it was a pilot study, at least 100 pregnant women (50 in each group) were planned to be recruited. $n = z2p(1-p)/d2$, $z = 1.962*0.4*0.6/0.22 = 50$.

When $z = 1.96$ at 95% confidence & 80% power, P = prevalence of targeted characteristics 40% or 0.4400 or 50% (for exploratory study $p = 0.5$) $D = 20\%$ (error allowance). Thus, calculated sample size was 50 in each group.

All women with GGI were randomized in group A (GGI with intervention group) or group B (GGI with nonintervention group). Patients with 2-h blood sugar values below 120 mg/dl were registered as group C (euglycaemic group). Written informed consent to participate in the study was taken from each patient. After a detailed history, examination and investigations, group A received maternal nutrition plan in women with GGI consisted of 50–60% calories from carbohydrate, 25–30% from fat, 10–20% from protein. Saturated fat intake was less than 10% of the total calories, and dietary cholesterol was less than 300 mg/dl. A detailed diet plan was made for each woman, and it was explained to them taking care of their meal preferences.

Medical nutrition therapy (MNT) was given to pregnant women in group A for a period of 4 weeks and was followed with fasting and 2-h postprandial (lunch) blood sugars. No intervention was done in group B, but these women were also followed up with monthly blood sugars fasting and two-hour postprandial (lunch). In both groups of GGI group, DIPSI sugar testing was repeated between 24 and 28 weeks and again between 32 and 34 weeks. If the blood glucose levels were found to be ≥ 140 mg/dl at any time, these women were diagnosed as having gestational diabetes and were noted. In group A (intervention group), MNT was continued even if repeat DIPSI sugar level at 24–28 week or 32–36 week was less than 120 mg/dl. Feto-maternal outcomes in all the three groups were noted. Figure 1 shows the consort chart.

Results

Total of 1866 antenatal women were screened by blood sugar testing as per DIPSI criteria for gestational glucose intolerance at their first visit. Among these 220 (11.8%) women were diagnosed as GDM, 412 (22.1%) women were diagnosed as GGI and 1265 (67.8%) women were having blood sugar value of < 120 mg/dl. A total of 148 women with GGI were registered in this study after fulfilling the inclusion criteria. Incidence of GGI in present study was 22.1%.

Study group consists of 148 women in GGI category. Out of this, total of 73 women belonged to group A and were given intervention (medical nutrition therapy). In group B, total of 75 women were registered; no intervention was done in this group. The third group C was taken as control, and 73 euglycaemic women were registered. The subjects of these three groups were matched and comparable, and there was no significant difference among them.

Mean period gestation of women with GGI at which they converted to GDM in group A and B was 31.50 ± 3.30 week and 30.88 ± 4.66 weeks, respectively, with no statistically significant difference ($p = 0.680$). Fourteen out of 73 women in the intervention group and 17 out of 75 women in the control group converted to GDM. Although statistically not significant, a greater number of women converted into GDM in nonintervention group (B) as compared to intervention group (A). Since these women converted to GDM and were managed with insulin or oral hypoglycaemic agent, they are excluded from the final analysis of women with GGI.

On comparison mean fasting blood sugar showed statistically significant difference ($p = 0.036$) between two groups. Though both were within the desired range, intervention

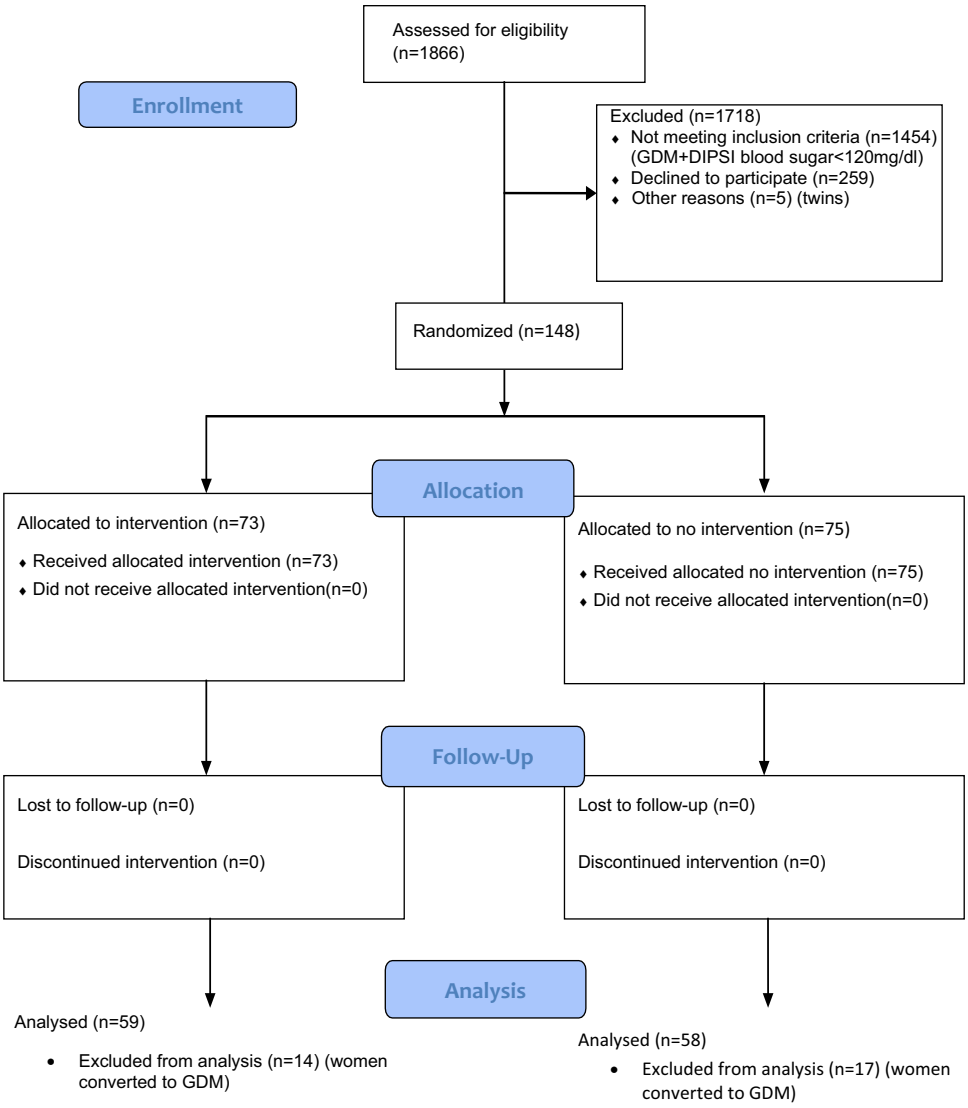

Fig. 1 Flowchart for randomization

group with MNT in GGI is showing trend towards lowering the fasting blood sugar values (Table 1).

Table 2 shows distribution of maternal complication during antenatal period in study ($n = 117$) and control group. The mode of delivery in all the three groups did not show any significant difference between rates of normal delivery, operative vaginal delivery and caesarean section. The mean ($\pm$ SD) birth weight of baby in group A was 2.77 ± 0.60 and B was 2.54 ± 0.71 kg, respectively, while control group was 2.62 ± 0.60 which was statistically nonsignificant (F/X^2 value 2.015, p value 0.136). Various maternal complications were compared between the three groups as shown in Table 3. Foetal and neonatal complications were compared between the three groups as shown in Table 4.

Discussion

The presence of gestational glucose intolerance can be considered as borderline diabetes mellitus in pregnancy. The targets of blood sugar are suggested to be < 90 mg/dl for fasting and < 120 mg/dl for 2-h postprandial value. Therefore, blood sugar value > 120 mg/dl 2 h after meal or after taking glucose can be considered abnormal. It is recommended that women who have GDM and if 2-h postprandial blood sugar values are > 120 mg/dl, medical nutrition therapy should be initiated. Same principle was applied in this study, where all the women whose post 2-h blood sugar value was $\geq$ 120 mg/dl, after 75 g glucose (considered as GGI) was started on medical nutrition therapy. The mean fasting blood sugars in the women with GGI who had medical nutrition therapy were much lower than the women with GGI who did not have any intervention. The difference in these values was statistically significant ($p = 0.036$). This concept has

Table 1 Demographic characteristics (mean ± SD) of study and control group

Variable (mean ± SD)	Group A (GGI with intervention) ($n=73$) (%)	Group B (GGI without intervention) ($n=75$) (%)	Group C (control group) ($n=75$) (%)	F/X^2 Value	p value
Age (years) (mean)	28.64 ± 4.57	27.80 ± 4.79	29.09 ± 4.30	1.56	0.213
Weight (prepregnancy in kg) (mean)	58.92 ± 9.37	57.20 ± 7.72	58.51 ± 7.27	0.91	0.406
Height (cm) (mean)	151.90 ± 4.45	152.24 ± 4.60	152.43 ± 3.72	0.28	0.753
BMI (kg/m^2) (mean)	25.55 ± 4.01	24.68 ± 3.11	25.17 ± 2.92	1.23	0.295
Period of gestation in weeks at diagnosis of GGI (mean ± SD)	19.84 ± 9.62	20.36 ± 9.32		0.34	0.737

Table 2 Distribution of antenatal complication during antenatal period in study (n = 117) and control group

Complications	Group A (intervention group) ($n=59$) (%)	Group B (nonintervention group) ($n=58$) (%)	Between A and B		Study group (A + B) ($n=117$) (%)	Group C (control group) ($n=75$) (%)	Between study and control group	
			X^2	p			X^2	p value
Abortion	2 (3.4)	3 (5.2)	0.23	0.634	5 (4.3)	0 (0.0)	3.29	0.070
Polyhydramnios	5 (8.5)	8 (13.8)	0.84	0.360	13 (11.1)	5 (6.7)	1.06	0.303
Foetal growth restriction	8 (13.7)	11 (19.0)	0.63	0.428	19 (16.2)	9 (12.0)	0.66	0.417
Macrosomia	1 (1.6)	4 (6.9)	1.93	1.640	5 (4.3)	1 (1.3)	1.31	0.253
Preeclampsia and partial HELLP	7 (11.9)	15 (25.9)	3.42	0.065	22 (18.8)	10 (13.3)	0.98	0.321
PPROM	11 (18.6)	14 (24.1)	0.39	0.530	25 (21.4)	3 (4.0)	11.07	< .001
Preterm labour	9 (15.3)	10 (17.2)	0.04	0.834	19 (16.2)	6 (8.0)	2.74	0.098
Vaginal candidiasis	7 (11.9)	11 (19.0)	0.97	0.324	18 (15.4)	6 (8.0)	2.28	0.131
Intrauterine demise	1 (1.7)	2 (3.4)	0.32	0.569	3 (2.6)	3 (4.0)	0.31	0.677
Women with no complication	22 (37.3)	27 (46.6)	0.74	0.391	49 (41.9)	33 (44.0)	0.08	0.772

Table 3 Distribution of maternal complications during intrapartum and postpartum period in study (n = 112) and control group

Complication	Group A (intervention group) ($n=57$) (%)	Group B (nonintervention group) (n = 55) (%)	Between A and B group		Study group (A + B) ($n=112$) (%)	Group C (control group) ($n=75$) (%)	Between study and control group	
			X^2	p value			X^2	p value
Vaginal and perineal tears	6 (10.5)	5 (9.1)	0.065	0.799	11 (9.4)	3 (4.0)	2.2	0.138
Puerperal sepsis	0 (0.0)	2 (3.6)	2.11	0.146	2 (1.8)	0 (0.0)	1.35	0.245
Postpartum haemorrhage	4 (7)	5 (9.1)	0.16	0.687	9 (8)	8 (10.7)	0.376	0.540
Surgical site infection	0 (0.0)	3 (5.5)	3.195	0.074	3 (2.7)	2 (2.7)	0	0.996

its beginning long back in 1998; a similar observation was noted by Bonomo et al. [6] in 1998 who enrolled women with borderline gestational glucose intolerance (taken as elevated 50 g glucose challenge test followed by normal oral glucose tolerance test using Carpenter and Coustan criteria). The women in this study who received dietary treatment had improved fasting and 2-h postprandial glucose levels.

Table 4 Distribution of foetal and neonatal complications among the study (n = 112) and control group

Complication	Group A (intervention group) (n = 57) (%)	Group B (nonintervention group) (n = 55) (%)	Between A and B group		Study group (A + B) (n = 112) (%)	Group C (Control group) (n = 75) (%)	Between study and control group	
			X^2	*p* value			X^2	*p* value
Congenital anomalies	1 (1.8)	3 (5.5)	1.11	0.291	4 (3.6)	3 (4.0)	0.023	0.880
Birth injury	2 (3.5)	2 (3.6)	0.001	0.971	4 (3.6)	0.(0.0)	2.737	0.098
Hypoglycaemia	8 (14)	12 (21.8)	1.156	0.282	20 (17.9)	2 (2.7)	9.985	0.002
Respiratory distress syndrome	5 (8.8)	6 (10.9)	0.144	0.704	11 (9.8)	4 (5.3)	1.226	0.268
Transient tachypnoea of new born	2 (3.5)	1 (1.8)	0.307	0.580	3 (2.6)	1 (1.3)	0.388	0.533
Neonatal Sepsis	6 (10.5)	4 (7.3)	0.364	0.546	10 (8.9)	3 (4)	1.687	0.194
Birth asphyxia	3 (5.3)	2 (3.6)	0.174	0.677	5 (4.5)	0 (0.0)	3.44	0.064
Hyperbilirubinemia	2 (3.5)	6 (10.9)	2.311	0.128	8 (7.1)	5 (6.7)	0.016	0.900
Neonatal mortality	1 (1.7)	0 (0.0)	0.974	0.324	1 (0.8)	0 (0.0)	0.673	0.412

The present study showed the women with GGI had higher antenatal complications like polyhydramnios, foetal growth restriction as well as macrosomia. Preeclampsia, preterm labour and vaginal candidiasis were also more in the women with GGI as compared to euglycaemic women. These antenatal complications, however, were more in GGI group; the difference was not statistically significant. PPROM was however much higher in women with GGI, as compared to euglycaemic women, and this difference was statistically significant ($p < 0.001$). Out of 148 women registered in GGI group, 5 (3.4%) women had abortions. Among them, 2 (2.7%) women were in group A (intervention group) and 3 (4%) were in group B (nonintervention group). Yang et al. [7] in 2002 conducted this study on diabetes in pregnancy in six urban districts of Tianjin and screened pregnant women for diabetes using WHO cut-off (2-h postprandial blood glucose between 140 and 200 mg/dl). Women with IGT had significantly higher blood pressure. Preterm rupture of membranes and preterm labour were also much higher in women with IGT. Higher incidence of preterm delivery was also noted among women with increasing values of blood sugar levels 2 h after 75 g glucose. In this study, one woman (1.7%) in group A (intervention group) and 2 women (3.4%) in group B (nonintervention group), had intrauterine foetal demise.

We did not find any difference in mode of delivery in women with GGI as compared to women with euglycaemia. Macrosomia was found to be higher in women with GGI as compared to women with euglycaemia, but it was not statistically significant. In concordance with it, macrosomia occurred more frequently in women with impaired glucose tolerance group in a study done by Yang et al. also.

There was no difference in maternal mortality between the GGI or control group. Neonates of mother with GGI had significantly higher incidence of hypoglycaemia as compared to mothers with normal blood sugar levels, implying that the graded increase in blood sugar levels in mothers even when not in the range of diabetes, leads to similar neonatal complications. Incidence of respiratory distress syndrome, birth asphyxia and neonatal sepsis which are seen higher in neonates of GDM mothers were also high in women with GGI, though not statistically significant. There was no difference in hyperbilirubinemia in neonates of mother with GGI. On the contrary, Yang et al. found similar rates of hypoglycaemia and birth asphyxia irrespective of blood sugars (impaired glucose tolerance or normal glucose levels). No significant association of neonatal hypoglycaemia or neonatal morbidity was seen with maternal blood sugar values 2 h after 75 g glucose in study by Jensen et al. [8].

Mean period of gestation at diagnosis of GGI was 19–20 weeks in this study. This allowed 15–20 weeks of duration of medical nutrition therapy to understand whether there was any difference in feto-maternal outcomes. There were fewer women with GGI with medical nutrition therapy who converted to GDM over the study period as compared to women who did not receive any intervention. Mean fasting and postprandial blood sugar levels were also much lower in women who received intervention. In a similar study by Bonomo et al., women with borderline glucose intolerance were randomized to receive dietary treatment or none. It was seen that women who received dietary management had significantly lower fasting glycaemia similar to our study. Fewer LGA babies were born to these mothers who received dietary management. The authors suggested that even mild alterations in glucose tolerance can result in excessive or disharmonious foetal growth, which can be prevented by simple noninvasive therapeutic measures. In another dietary intervention study by Mirzamoradi et al. [9], two groups were compared. One group had abnormal value after 75 g glucose as per IADPSG criteria, and the other group had

two-step approach with two abnormal values as per ACOG criteria; preterm labour and neonatal hyperbilirubinemia were more in two-step approach. The study concluded that no difference existed between the treatment based on two screening methods in terms of feto-maternal outcome except neonatal hyperbilirubinemia. Hence, treatment of mild gestational diabetes was justified to improve neonatal outcome. The present study highlights the high prevalence of GGI in studied population. It also suggested that GDM testing protocol should be done in first trimester to allow early diagnosis and treatment.

Although the present study of nutritional intervention in GGI group has not shown statistically significant changes in general as compared to no intervention, it has shown trend towards lesser complication in intervention group and delayed development of GDM and less neonatal hypoglycaemia and hyperbilirubinemia in intervention group. There is a need of multiple large interventional multi-centric studies to have better understanding of carbohydrate intolerance during pregnancy and its effect on maternal, foetal and neonatal complications.

Conclusion

The present study of nutritional intervention in GGI group did show benefits, chiefly a delayed development of GDM and lesser neonatal hypoglycaemia and hyperbilirubinemia in intervention group. There is definitely a need of multiple large interventional multi-centric studies to have better understanding of carbohydrate intolerance during pregnancy and its effect on maternal, foetal and neonatal complications. We realize that in this part of the world diabetes needs a lower threshold to be picked up and intervention should be started in prediabetic state to prevent the development of the frank disease. One of the long-term consequences of GDM is development of type 2 diabetes in future, and that is why, prevention right at the onset of first threat in form of gestational glucose intolerance (GGI), can be rightly said as a golden opportunity and a ray of hope to prevent the global diabetic burden.

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Author Contributions VD laid down the hypothesis and concept of the study. AS and NK carried out the recruitment and study documentation. AA helped in literature search. SA helped in follow-up of patients, and AP helped in data analysis.

Declarations

Conflict of interest There is no conflict of interest among the authors. There is no financial relationship with any organizations.

Ethical Approval All procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent Informed consent was obtained from all patients for being included in the study.

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