Original Article

Role of Myo-inositol Supplementation in Prevention of Gestational Diabetes Mellitus in Parturient Women at Risk

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Abstract

Objective: To assess the frequency of gestational diabetes mellitus in parturient women at risk after supplementation of Myo-Inositol as compared to placebo.

Methodology: This randomized controlled trial was conducted in the Outpatient Department of Obstetrics and Gynecology, PIMS, Islamabad from July 2020 to January 2021. A total of 120 pregnant women, irrespective of parity in the first trimester, who had 1 or more first-degree relative diagnosed with diabetes mellitus, and were overweight (BMI >25 kg/m2) or obese (BMI >30 kg/m2) at their first antenatal visit were selected. Women with already diagnosed with diabetes mellitus were excluded. Starting from the end of the first trimester or the start of the second trimester (12-15 weeks of gestation) the intervention group was supplemented with 2g Myo-Inositol and 200 mcg Folic acid twice daily as compared to placebo which was given only 200 mcg Folic acid twice daily. Between 24-48 weeks, they were tested for 75gm 2 hour OGTT.

Results: The mean age of women in interventional group was 27.78 ± 4.07 years and in the placebo group was 28.88 ± 4.19 years. The mean gestational age was 9.33 ± 1.90 weeks in intervention group and 9.52 ± 1.85 weeks in the placebo group. In this study, the frequency of gestational diabetes mellitus in parturient women at risk after supplementation of Myo-Inositol was 16.67% as compared to 36.67% in placebo (p-value, 0.01).

Conclusion: Myo-Inositol supplementation reduces the rate of development of GDM in pregnant women having known risk factors.

Keywords: Gestational diabetes, Myo-Inositol supplementation, Obese, Prevention.

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Introduction

Currently, gestational diabetes mellitus (GDM) is a serious global public health problem.[1] Its prevalence is on the rise, ranging up to 16.5%, thus, posing a great health challenge.[2] Gestational diabetes mellitus is a complex disorder with a number of risk factors, including advanced age (>35 years), pre-pregnancy obesity or overweight, excessive gestational weight gain, excessive central body fat deposition, family history of diabetes, short stature (1.50 m), excessive foetal growth, polyhydramnios, hypertension, or preeclampsia in the current pregnancy, history of recurrent miscarriage, offspring malformation.[3]

GDM has its potential effects on fetus (preterm birth, stillbirth, macrosomia) neonate (neonatal hypoglycemia, shoulder dystocia, NICU admission) and maternal health (hypertensive disorders, increased rate of operative delivery).[4] Therefore, the importance of pre-conceptional evaluation and counseling of women with pre-gestational diabetes mellitus cannot be overstated. Poor glycemic management later in pregnancy increases the chance of macrosomia and its consequences by two to four times.[4]

Additionally, perinatal mortality rates (stillbirths and first-week neonatal deaths) among women who are diabetic remain approximately two to four times higher than those

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observed in the non-diabetic population, and perinatal morbidity (neonatal hypoglycemia, macrosomia, LGA, birth asphyxia) is higher as well.[5]

Globally, there are many guidelines with recommendations for suitable management strategies for GDM when lifestyle modifications have failed to achieve the control. Insulin, metformin, and glibendine are the treatment options that are used to maintain blood glucose levels within reference range. Since the investigations by Langer et al. and Rowan et al. confirmed that glyburide (glibenclamide) and metformin are effective substitute for insulin, oral hypoglycemic medications for the treatment of gestational diabetes mellitus (GDM) have become more frequently used.[4,5] Due to their accessibility and lower rate compared to insulin, oral hypoglycemic medications are a suitable option that improves patient compliance.[6]

Several inositol isomers and in particular myo-inositol (MI) which is an insulin sensitizing substance, is shown to be efficient in lowering post-prandial blood glucose.[5] Myo-inositol is produced by the human body from D-glucose, but it is present in all living cells as membrane phospholipids. It can be found in pulses, nuts and fruits (in particular citrus fruits). Initial evidence shows reduction in gestational diabetes by up to 60% as the effect of myo-inositol supplementation.[6] In one study that was conducted in Italy it was seen that Myo-inositol supplementation reduced the rate of gestational diabetes mellitus by 14% as compared to controls (33.6%) when prescribed to women who were obese.[7] In another study, it was concluded that it also reduced GDM rate in women who had family history of type 2 diabetes as compared to controls (6% vs 15.3%).[8]

There is scarcity of data in our part of the world regarding the efficacy of Myo-inositol in prevention of GDM, therefore, we conducted this study to assess the use of Myo-inositol in our settings to prevent the development of GDM in pregnancy, thereby decreasing maternal and neonatal morbidity.

Methodology

This randomized controlled trial was conducted in the outpatient department of obstetrics and gynaecology at PIMS, Islamabad from July 2020 to January 2021. A total of 120 pregnant women, irrespective of parity, in the first trimester who had 1 or more first-degree relatives diagnosed with diabetes mellitus, and were overweight (BMI >25 kg/m^2) or obese (BMI >30 kg/m^2) at their first antenatal visit were selected. Women with type 1 or type 2 diabetes, a history of glycosuria or deranged sugars in a previous pregnancy, or who had been diagnosed with GDM in previous pregnancies were excluded. Starting from the end of the first trimester or the start of the second trimester (12-15 weeks of gestation), the intervention group was supplemented with 2g Myo-Inositol and 200 mcg Folic acid twice daily as compared to placebo group which was given only 200 mcg Folic acid twice daily between 24-48 weeks, they were tested for 75gm 2 hour OGTT.

The American Diabetes Association (ADA) defines GDM as "any degree of glucose intolerance with onset or first recognition during pregnancy". The oral glucose tolerance test (OGTT) is a screening test for GDM that is performed in pregnant women with identified risk factors such as a strong family history at 24-28 weeks of gestation. Patients are labeled to be diagnosed case of GDM as defined by National Institute of Clinical excellence, if any of the values exceed these reference values; fasting blood glucose more than or equal to 5.6 mmol/liter, 2-hour postprandial blood glucose more than or equal to 7.8 mmol/liter.

Women who have a first-degree relative with Type 2 diabetes mellitus or who are overweight or obese are considered at-risk parturients.(BMI>25 kg/m^2 or >30 kg/m^2 respectively).

The sample size of sixty patients in each group was calculated using the WHO calculator, by taking the level of significance of 5%, power of test of 80%, anticipated population proportion with GDM in Myo-Inositol group of 14% and in placebo 33.6%.[7] The ethical letter has been taken from Institutional review board (SZAMBU) and written informed consent was taken from the patients.

Women were recruited if they met the inclusion criteria. Patients were assigned to either the intervention group or placebo group randomly, and, proforma was filled at their first visit in first trimester. Then they were advised to follow up at 24-28 weeks for OGTT. Adherence to the treatment was checked through phone calls and reminders were given to them in each antenatal visit.

Starting from the end of first trimester or start of second trimester (12-15 weeks of gestation) the intervention group was supplemented with 2g Myo-Inositol and 200mcg Folic acid twice daily as compared to placebo group which was given only 200mcg Folic acid twice daily. After that they were tested for 75gm 2 hour OGTT between 24-28 weeks. In this test, patients were called with an overnight fasting status (of around 8 hours), fasting blood glucose levels are checked in venous

sample, patients are then given 75g of glucose dissolved in 250 ml water at the same time.

Again venous sample was tested for blood glucose levels after 2 hours to see the degree of glucose intolerance.

Data was analyzed in SPSS version 22. The numeric data (age, parity and gestational age) was expressed as mean+/-standard deviation, and the categorical variables (GDM, risk factors) will be expressed as count and percentage. The chi square test was used to compare the frequency of GDM between the two groups. A p-value < 0.05 was considered statistically significant.

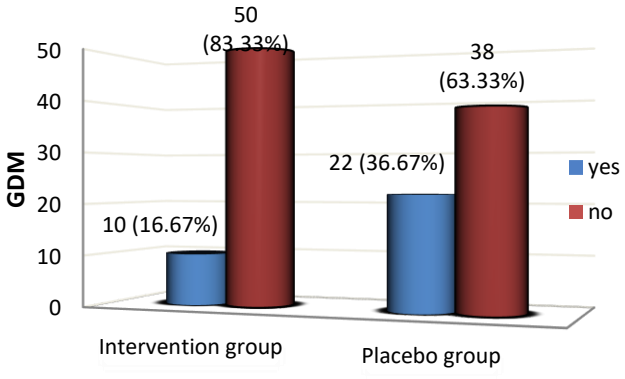
Results

The mean age of women in the interventional group was 27.78 ± 4.07 years and in placebo group was 28.88 ± 4.19 years. According to Table I, 73 of the patients (60.83%) were between the ages of 18 and 30. The mean gestational age of women in interventional group was 9.33 ± 1.90 weeks and in placebo group was 9.52 ± 1.85 weeks. In most of the cases in both groups gestational age was between 8-12 weeks, 49 (81.6%) in intervention and 52 (86.6%) in placebo group. Similarly, two-third of the study cases had parity of 1-2, with 40 (66.6%) in the intervention group and 34 (56.6%) in the placebo group (p-value, 0.199). There were 36 (60.0%) overweight women in the intervention group and 38 (63.3%) in the placebo group; the remaining cases in both groups were obese (p-value, 0.707). (Table I)

As per the primary outcome of the study, the frequency of GDM was compared between the study groups. In the intervention (Myo-Inositol) group, there were 10 (16.6%) women who developed GDM compared to 22 (36.6%) women in the placebo group. And this difference was statistically significant between the two groups, thus, clearly proving the preventive role of Myo-Inositol supplementation for GDM in pregnancy. (Figure I)

Table I: Distribution of baseline characteristics of patients in the two groups (n=120)

	Intervention group (n=60)	Placebo group (n=60)
	N (%)	N (%)
Age (years)		
18-30	40 (66.6%)	33 (55.0%)
31-40	20 (33.3%)	27 (45.0%)
Gestational age (weeks)		
≤7	11 (18.3%)	08 (13.3%)
8-12	49 (81.6%)	52 (86.6%)
Parity		
1-2	40 (66.6%)	34 (56.6%)
>2	20 (33.3%)	26 (43.3%)
BMI		
Overweight	36 (60.0%)	38 (63.3%)
Obese	24 (40.0%)	22 (36.6%)



P-value = 0.013 which is statistically significant

Figure I: Comparison of GDM between supplementation of Myo-Inositol and placebo.

Further analysis was done to find out factors related to the prevention of GDM by the intervention group. Younger women, ages 18 to 30, were less likely to

Table II: Comparison of GDM in the two groups with respect to stratification of baseline characteristics.

	Gestational Diabetes Mellitus				
	Intervention group (n=60)		Placebo group (n=60)		P-value
	Yes (n=10)	No (n=50)	Yes (n=22)	No (n=38)	
Age (years)					
18-30	6 (60.0%)	34 (68.0%)	16 (72.7%)	17 (44.7%)	0.002
31-40	4 (40.0%)	16 (32.0%)	6 (27.3%)	21 (53.3%)	0.854
Gestational age (weeks)					
≤7	4 (40.0%)	7 (14.0%)	1 (4.5%)	07 (18.4%)	0.243
8-12	6 (60.0%)	43 (86.0%)	21 (95.5%)	31 (81.6%)	0.001
Parity					
1-2	4 (40.0%)	22 (44.0%)	13 (59.1%)	07 (18.4%)	0.001
3-4	6 (60.0%)	28 (56.0%)	9 (40.9%)	31 (81.6%)	0.605
Other risk factors					
Overweight	3 (30.0%)	15 (30.0%)	8 (36.3%)	15 (39.4%)	0.194
Obese	7 (70.0%)	28 (560%)	10 (45.0%)	19 (50.0%)	0.192
First-degree relative	1 (10.0%)	17 (34.0%)	7 (31.8%)	10 (26.3%)	0.012

develop GDM after intervention compared to placebo (p-value, 0.002). Similarly, gestational age of 8 to 12 weeks was less likely to develop GDM after intervention with Myo-Inositol supplementation compared to placebo (60.0% vs 95.5%, p-value 0.001). Moreover, primiparous and para 2 women were more likely to get prevented with intervention of Myo-Inositol supplementation (p-value, 0.001). No difference in the occurrence of GDM was witnessed in overweight and obese women in both study groups (p-value, 0.194). However, even in first-degree relative cases there was a significant preventive role of Myo-Inositol supplementation in the development of GDM (p-value, 0.012). (Table II)

Discussion

There are many strategies for the management of GDM. Insulin is the most well-known therapy, however, it causes various side effects. Insulin is a challenging and debatable treatment option due to its cumbersome administration procedure and high risk of side effects like hypoglycemia and weight gain. Now Inositol (1,2,3,4,5,6-hexahydroxycyclohexane) is gaining popularity, which is an emerging novel intervention for GDM. It is a cyclic polyol found naturally in plants and animals and mediates cell-signal transduction along with expressing insulin-like effects.[9,10]

This study highlights a significant preventive role of Inositol supplementation in GDM. In this study, the frequency of gestational diabetes mellitus in parturient women at risk after supplementation of Myo-Inositol was 16.67% as compared to the placebo, which was 36.67%, this difference was statistically significant (p-value, 0.013). Comparatively, in a study that was conducted in Italy, it was seen that Myo-inositol supplementation reduced the rate of gestational diabetes mellitus by 14% as compared to controls (33.6%) when prescribed to women who were obese.[7] In another study, it was concluded that it also reduced GDM rate in women who had a family history of type 2 diabetes as compared to controls (6% vs 15.3%).[8]

In one prospective, double-blind, randomized controlled pilot study of women with an elevated fasting blood glucose of ≥92 mg/dL in their first or early second trimesters, the incidence of GDM was remarkably reduced and found to be only 6% in the group treated with myo-Ins when compared to the placebo group, which had a GDM-incidence rate of 71%. Others reported this evidence as well.[11,12]

Santamaria et al found that the incidence of GDM was remarkably reduced (11.6%) in those treated with Myo-Ins when compared to the placebo group, which had a GDM-incidence rate of 27.4%. Evidently, Myo-Ins supplementation initiated from early pregnancy was associated with a 67% reduced risk of developing GDM in overweight women.[13]

The current study's findings and other comparative evidence support the hypothesis that myo-inositol supplementation may benefit overweight or obese women in lowering their risk of GDM. Many other authors agree that starting myo-inositol supplementation early in pregnancy reduces the risk of GDM in overweight women.[14] D'Anna et al treated 99 Caucasian pregnant women who had a parent with type 2 diabetes. They were given 2 g of myo-Ins plus 200 µg of folic acid BD while a placebo group of another 98 women was given only 200 µg of folic acid BD from the first trimester till delivery. When compared to the placebo group, the incidence of GDM in the myo-Ins group was found to be 6%, indicating a 65% reduction in risk for GDM.[15] Furthermore, a significant decrease in foetal macrosomia and birth weight was observed in the intervention group.[15]

In current medical practice, the recommended first step of GDM management includes lifestyle and dietary modifications and, if non-pharmacological intervention proves insufficient, administering oral antihyperglycemic agents or insulin.[16] Inositol serves as a precursor to two crucial compounds: myo-inositol (myo-Ins) and D-chiro-inositol (D-chiro-Ins), collectively known as inositolphosphoglycans (IPGs), which play an important role in the pathogenesis of diabetes.[17]

Normally, insulin binds to its receptors on the cell membrane to form the insulin-receptor substrate (IRS), which in turn increases the glucose transporter type 4 (GLUT-4) translocation via the phosphatidylinositide 3-kinase (PI3K) pathway, thereby mediating glucose uptake. Myo-Ins contributes to glucose homeostasis at the cellular level by activating the PI3K pathway.[18] It has been observed that conditions resulting in insulin resistance are characterized by a high level of urinary inositol metabolites, pointing to their efficacy as insulin mediators.[9]

Keeping the above evidence and discussion in view, it can be argued that Myo-Inositol supplementation is a significant preventer of GDM with high effectiveness when compared with placebo. Younger age, advanced gestational age, low parity, and first-degree relative

marriage were all significant factors associated with prevention.

This study has many advantages, firstly it was an interventional study for GDM which is a very serious and frequent condition in local settings as well as internationally. Secondly, the proven effectiveness of the intervention suggests benefits for overweight/obese pregnant women who are at risk of developing GDM.

Conclusion

Myo-Inositol supplementation reduces the rate of development of GDM in pregnant women having known risk factors. It is recommended that Myo-Inositol supplementation should be used as routinely in pregnant women having known risk factors in order to reduce gestational diabetes mellitus and its resultant complications.

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