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Myoinositol for Prevention of Gestational Diabetes Mellitus in High Risk Pregnant Patients

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ABSTRACT

Background: Gestational diabetes mellitus is the most common metabolic complication of pregnancy. It is one of the leading causes of pregnancy-related maternal and perinatal morbidity and long-term adverse outcomes for women and their children. Myo-inositol, one of the intracellular mediators of the insulin signal, has been shown to correlate with insulin sensitivity in type 2 diabetes mellitus.

Objectives: This study was aimed to compare the myo-inositol (a dietary supplement) and control in frequency of prevention of gestational diabetes mellitus in high risk pregnant women.

Methods: This randomized control trial was undertaken at the Gynecology and Obstetrics Department, MCH Unit 1 PIMS Hospital, Islamabad during December 2020 to May 2021. A sample size of 122 pregnant women was considered in this study. After taking an informed consent, a detailed history was taken. A screening OGTT was performed. Each patient in the intervention group was given myo-inositol in a dose of 2 gram once daily for 3 months and women in control group were given standard management. Women were followed according to the usual schedule typically every 4 weeks. Pregnant women were undergoing to second OGTT at 24-28 weeks for the diagnosis of gestational diabetes mellitus.

Results: An overall mean age of subjects was 36.39±3.27 years. A total 35 (28.7%) patient presented with GDM in this study of which 14.75% were from Group A (lifestyle modification + myo-inositol) whereas 42.62% were from group B considering lifestyle modification only and chi-square test showed a significant difference (p-value = 0.001) considering a good effect of myo-inositol to avoid GDM. Of total 35 GDM, 28 (80.0%) were diagnosed at gestational age of 24-28 weeks of gestation.

Conclusion: Myo-inositol supplementation among high risk group of GDM, has been proved to have a significantly better ($p<0.0001$) effect in reducing the occurrence of GDM as only 9/61(14.75%) high risk women with prior history of GDM showed recurrence subsequently in comparison to 26/61 (42.62%), who were not using Myo-inositol supplementation.

Introduction

Gestational diabetes mellitus (GDM) represents the predominant metabolic challenge during pregnancy, characterized by carbohydrate intolerance emerging or being identified for the first time during gestation.[1] It stands as a primary contributor to maternal and perinatal morbidity during pregnancy and can lead to enduring adverse effects on both mothers and their offspring. Women affected by GDM face elevated risks of cesarean delivery, hypertensive disorders, and a heightened likelihood of developing type 2 diabetes in the future.[2] Concurrently, fetal complications, such

as congenital anomalies, excessive fetal growth, birth traumas, intrauterine demise, and subsequent neonatal complications like hypoglycemia, childhood obesity, and later onset of type 2 diabetes, underscore the gravity of GDM.[3]

In the South Asian region, GDM prevalence, estimated at 25% by the South Asian Federation of Endocrine Societies (SAFES), poses a significant concern. However, the precise prevalence in Pakistan remains undetermined. Recent studies report an 11.5% prevalence of GDM in Asia, with projections indicating a global escalation, particularly within Asian populations.[4] Consequently, there is a pressing need for safe, efficacious, and well-received interventions to mitigate the rising tide of GDM.

Research indicates that myo-inositol, an intracellular mediator of insulin signaling, exhibits a positive correlation with insulin sensitivity in type 2 diabetes and enhances insulin action in polycystic ovary syndrome. This suggests its potential therapeutic utility in preventing GDM. Myo-inositol, naturally occurring in various dietary sources like cereals, legumes, and nuts, is now recognized as a supplement by the US Food and Drug Administration (FDA), deemed generally safe for consumption.[5,6]

A meta-analysis of antenatal myo-inositol supplementation trials in Italy reveals promising results in reducing GDM incidence.[7] Myo-inositol operates akin to insulin, eliciting insulin-like effects through cell signal transduction pathways. Notably, a study showcased a marked decrease in GDM incidence, from 71% in the control group to 6% in the myo-inositol group, alongside improved secondary outcomes such as decreased premature births, neonatal hypoglycemia, and reduced need for insulin therapy.[8]

However, the literature on myo-inositol supplementation for GDM prevention remains limited, particularly among high-risk pregnant women in Pakistan.[9] Given the multifactorial nature of GDM, influenced by environmental factors, dietary habits, ethnic disparities, and genetic variations, a nuanced approach to intervention management is imperative. Implementing simple, novel, and effective strategies with minimal adverse effects, alongside rigorous systematic sampling methods, can enhance the generalizability of study findings and optimize GDM prevention efforts. The aim of present study was to compare the myo-inositol (a dietary supplement) and control in frequency of prevention of gestational diabetes mellitus in high risk pregnant women.

Methods

This Randomized controlled trial was conducted at Gynecology and Obstetrics Department, MCH PIMS, Islamabad during December 2020 to May 2021. A sample size of 122 (61 in each group) patients was calculated by using a level of significance as 5%, power of test 90% and expected prevalence of GDM in study group as 6% and control group as 71%.[8]

A Non probability consecutive sampling was done and pregnant patients at high risk of GDM before 20 weeks along characteristics like BMI > 28, Age > 30 years, Family history (first degree relatives with DM), History of baby delivered >9lbs or LGA, Previous h/o GDM , H/O Polycystic ovaries were included in the study. Pregnant women with multiple pregnancy, known patients of type I or type II diabetes, Concomitant treatment with corticosteroids, Hypertension or renal or hepatic disease and Diabetes mellitus diagnosed at booking were excluded from this study.

Data Collection Procedure : The study was initiated after the approval of the institutional ethics committee. All patients presenting at MCH Unit 1 and fulfilling the inclusion criteria were recruited after informed verbal consent. Women were taken at booking antenatal visit at 16-20 weeks gestation. Detailed obstetric, menstrual and past medical history was taken from enrolled patients followed by general, systemic and obstetrical examination along with all routine investigations. A screening OGTT was performed with a 75-g, 2-h glucose tolerance test, with cutoff values of >92 mg/dL for time 0, >180 mg/dL after 1 h, and >153 mg/dL after 2 h; at least one of the three values over or equal to the cutoff for diagnosis of gestational diabetes mellitus.

After checking their eligibility and taking written informed consent, a lottery method was

used to divide the patients in intervention and control groups. Each patient in the intervention group was given myo-inositol in a dose of 2 gram once daily for 3 months and women in control group were given standard management (dietary modification). Women were followed according to the usual schedule typically every 4 weeks till 26 to 28 weeks of gestation every 2 to 3 weeks till delivery. The plasma glucose level of each patient in both of the study groups was measured at baseline and then monitored once at the end of 3 months of follow up each. Pregnant women were undergoing to second OGTT at 24-28 weeks for the diagnosis of gestational diabetes mellitus. The main outcome was measure the occurrence of gestational diabetes mellitus in both groups.

Primary Outcome: A comparison of occurrence of GDM among intervention and control groups was primary outcome of this study. Other related factors like mean gestational age, infant health etc. were secondary outcomes of this study. Relationship of age of women with onset of GDM among both groups may also be assessed as secondary outcome.

Data analysis procedure: Data was entered in SPSS version 26.0 for analysis. Descriptive statistics were calculated for both qualitative and quantitative values. Mean and standard deviations was calculated for quantitative variables like age and gestational age, weight, height, BMI and Blood glucose levels etc. Frequencies and percentages were calculated for qualitative variables like onset of GDM, previous histories, and both groups were compared for GDM using chi-square test. A p-value of <0.05 was considered as significant. Effect of confounders like age, gestational age, type of risk factor, and BMI were controlled by stratification. Post stratification Chi square test was applied and p-value of <0.05 was considered as significant.

Results

A total of 122 pregnant women were recruited in this study with an overall mean age of 36.39±3.27 years of age with a minute difference in mean ages of both study groups. Separation of age groups showed that most of the 47.5% patients were in age range of 36-40 years followed by 41.0% in age range of 38-35 years and rest of 11.5% women were in age group of > 40 years. Further segregation of women with reference to age groups amongst group A and Group B are also presented in Table 1.

General gynecological characteristics of the pregnant women were also noted which include gravidity, parity, number of alive births and miscarriages which ranged 2-6, 2-4, 2-4, and 1-2 respectively. History of miscarriage was present among 21/122 (17.2%) pregnant women and frequency of each category is presented in Table 2. Mean ± standard deviation of these variables were also calculate to stratify the data and an insignificant difference regarding gravidity, parity, alive births, miscarriage, and baseline gestational age with p-values 0.081, 0.693, 0.960, 0.320, 0.183 respectively showing an equal distribution to control confounding factors.

Baseline anthropometric, fasting blood sugar and OGTT were also obtained and stratified for normal distribution among both groups and again an insignificant difference was observed with p-values remained for weight (0.621), height (0.685), BMI (0.661), fasting blood sugar (0.641), OGTT at 1 hour (0.795) and 2 hour (0.205). Segregation of baseline data is present among both groups is presented in Table 3.

Fasting blood sugar and OGTT were performed at the gestational age of 24-28 weeks and differences in mean values of all parameters among both groups were observed. Mean values obtained in Group A, considering lifestyle modification with additional daily intake of 2g myo-inositol were remained lower towards normal as compared to group B which considered lifestyle modification only. Fasting blood sugar although obtained lower mean values in Group A as compared to Group B but an insignificant difference was observed (p-value = 0.216) however both readings of OGTT showed a significant difference (p-value < 0.0001) among both groups.

Fasting blood sugar and 2 hour post prandial sugar tests were obtained from pregnant women at 34-36 weeks of gestation and a significant difference of lower mean values (p value <0.0001) were observed in Group A as compared to Group B indicating a better effect of addition of myo-inositol with lifestyle modification as shown in Table 5.

Table 1: Distribution of Age Groups in Study Groups

Age Group (Years)	Group				Total	
	Group A (Lifestyle Modification + Myo-inositol)		Group B (Life Style Modification)			
	n	%	N	%	n	%
31-35	25	41.0	25	41.0	50	41.0
36-40	30	49.2	28	45.9	58	47.5
>40	6	9.8	8	13.1	14	11.5

Table 2: Characteristics of Study Subjects

Characteristics		Group				Total	
		Group A		Group B			
		n	%	n	%	n	%
Gravidity	**2**	12	19.7	19	31.1	31	25.4
	3	25	41.0	18	29.5	43	35.2
	4	20	32.8	17	27.9	37	30.3
	5	4	6.6	6	9.8	10	8.2
	6	0	0.0	1	1.6	1	0.8
Parity	**2**	14	23.0	19	31.1	33	27.0
	3	27	44.3	28	45.9	55	45.1
	4	20	32.8	14	23.0	34	27.9
Alive Birth	**2**	14	23.0	19	31.1	33	27.0
	3	33	54.1	36	59.0	69	56.6
	4	14	23.0	6	9.8	20	16.4
Miscarriage	**0**	53	86.9	48	78.7	101	82.8
	1	6	9.8	11	18.0	17	13.9
	2	2	3.3	2	3.3	4	3.3

Table 3: Segregation of Baseline Finding

Baseline Findings	Group				Overall	
	Group A		Group B			
	Mean	Stand. Dev.	Mean	Stand. Dev.	Mean	Stand. Dev.
Weight	75.08	5.56	76.41	4.86	75.75	5.24
Height	154.79	2.58	153.93	2.61	154.36	2.62
BMI	31.29	1.37	32.20	1.27	31.75	1.39
Fasting Blood Sugar	89.48	9.03	91.54	9.05	90.51	9.06
OGTT (1Hr with 75gm)	169.48	9.88	168.49	10.06	168.98	9.94
OGTT (2Hr with 75 gm)	139.00	20.51	129.44	22.38	134.22	21.91

Table 4: Distribution of Findings at 24-28 Weeks of Gestation

24-28 weeks of Gestation	Group				Total	
	Group A		Group B			
	Mean	Stand. Dev.	Mean	Stand. Dev.	Mean	Stand. Dev.
Fasting Blood Sugar	89.43	9.33	91.87	10.17	90.65	9.80
OGTT (1 Hr)	172.13	16.97	189.30	33.55	180.71	27.84
OGTT (2 Hr)	117.16	18.76	137.70	34.53	127.43	29.53

Table 5: Distribution of Findings at 34-36 Weeks of Gestation

34-36 weeks of gestation	Group				Total	
	Group A		Group B			
	Mean	Stand. Dev.	Mean	Stand. Dev.	Mean	Stand. Dev.
Fasting Blood Sugar	104.20	13.57	116.13	21.57	110.16	18.92
2 hr post prandial	160.46	32.42	189.46	47.48	174.96	43.021

Figure 1: Distribution of GDM among Both Groups

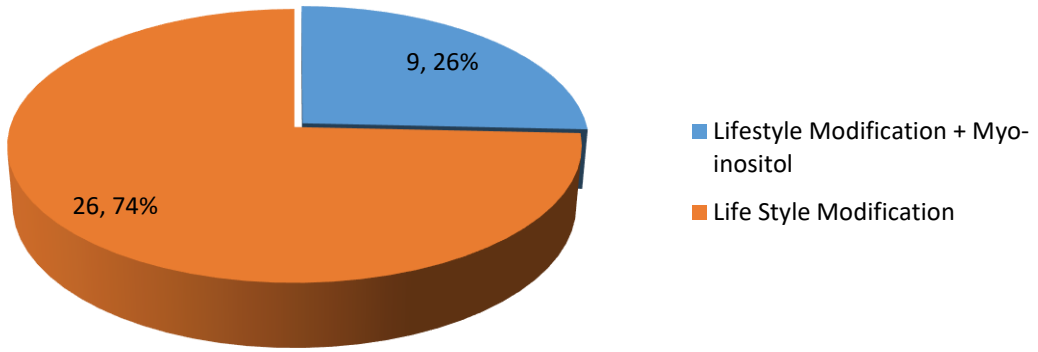

Table 6: Outcomes of GDM Regarding Age Groups

Outcome		Age Group (Years)					
		31-35		36-40		>40	
		n	%	n	%	n	%
Group A	GDM	4	16.0	4	13.3	1	16.7
	Normal	21	84.0	26	86.7	5	83.3
	Total	25	100	30	100	6	100
Group B	GDM	7	28.0	16	57.1	3	37.5
	Normal	18	72.0	12	42.9	5	62.5
	Total	25	100	28	100	8	100

Table 7: Stratification of Occurrence of GDM in Age Groups

Chi-Square Tests	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2.045[a]	2	0.360
Likelihood Ratio	2.071	2	0.355
Linear-by-Linear Association	1.006	1	0.316
N of Valid Cases	122		
a. 1 cells (16.7%) have expected count less than 5. The minimum expected count is 4.02.			

Table 8: Group-wise Stratification of Onset of GDM by Gestational Age

Counts					Pearson Chi-Square	p-value
Factor		Onset of GDM		Total		
		Group A	Group B			
Gestational Age at onset of GDM (Weeks)	24.00	0	3	3	3.635	0.603
	25.00	0	4	4		
	26.00	3	8	11		
	27.00	3	4	7		
	28.00	1	2	3		
	35.00	2	5	7		

A total 35 (28.7%) patient presented with GDM in this study of which 9/61 (14.75%) were from Group A (lifestyle modification + myo-inositol) whereas 26/61 (42.62%) were from group B considering lifestyle modification only and chi-square test showed a significant difference (p-value = 0.001) considering a good effect of myo-inositol to avoid GDM. An overall distribution of GDM patients remained to be 26% from group A and 74 % from group B as depicted in figure 1.

Out of total 35 GDM pregnant women 28 (80.0%) were diagnosed at gestational age of 24-28 weeks while only 7 (20.0%) were diagnosed afterwards showing most probable time of diagnosis of GDM lies in 24th to 28th weeks of gestation.

Occurrence of GDM in various age groups were also observed and it was revealed that most of 20/58 (34.48%) GDM was presented in age group of 36-40 years 11/50 (22.0%) was presented in age group of 31-35 years and 4/14 (28.6%) in age group of >40 years however chi-square test showed an insignificant difference remained (p-value 0.360). Further group-wise segregation of GDM outcomes with reference to the age groups is presented in Table 6.

Comparison of occurrence of GDM in various age groups was observed by applying Pearson chi-square test, likelihood ratio and linear-by-linear association and insignificant difference (p>0.05) was noted as presented in Table 7.

Group-wise stratification of onset of GDM by gestational age showed an insignificant difference (p>0.05) as shown in Table 8.

Discussion

In the current study, 28.7% of patients developed gestational diabetes mellitus (GDM). Among them, 14.75% belonged to the group receiving lifestyle modification plus myo-inositol, while 42.62% were from the group undergoing lifestyle modification alone. A significant difference was observed through a chi-square test (p-value = 0.001), suggesting a favorable effect of myo-inositol in preventing GDM. These findings align with previous research indicating a reduction in GDM incidence among women administered myo-inositol compared to placebo, with a relative risk of 0.127.[8] Similarly, a study involving 220 pregnant women randomized to myo-inositol or placebo reported significantly lower GDM rates in the myo-inositol group (11.6% vs. 27.4%, p = 0.004), translating to a 67% risk reduction.[10] This underscores the efficacy of myo-inositol supplementation, particularly in overweight non-obese women.

In another randomized trial involving obese pregnant women, myo-inositol supplementation significantly reduced the incidence of GDM compared to the control

group (14.0% vs. 33.6%, P=.001), with additional benefits observed in insulin resistance reduction.[11] Moreover, a review of various investigations highlighted that while physical activity alone did not significantly impact GDM frequency, it notably reduced GDM occurrence when considering insulin resistance. However, there was no significant difference in GDM rates between moderate-intensity exercise intervention and standard prenatal care.[12]

Regarding age, the present study found no significant association with GDM occurrence, consistent with a meta-analysis showing a linear relationship between maternal age and GDM risk. However, the study's choice to include pregnant women over 30 years old might explain this deviation from previous findings, suggesting that maternal age ≥25 years should be considered a risk factor for GDM development.[13] Notably, various risk factors such as obesity, pre-diabetes, familial diabetes history, and polycystic syndrome were included in the present study's criteria, with no discernible impact on myo-inositol treatment outcomes.

Furthermore, studies from Peru and among Asian populations highlighted the prevalence of GDM and associated risk factors such as maternal obesity and family history of diabetes.[14] Intervention programs targeting early diagnosis and management should account for these factors. Additionally, Asian women with a history of previous GDM, congenital anomalies, or macrosomia may require special attention as high-risk cases for GDM during pregnancy, necessitating further exploration.[15,16]

Conclusion

Myo-inositol supplementation among high risk group of GDM, has been proved to have a Significantly better ($p<0.0001$) effect in reducing the occurrence of GDM as only 9/61(14.75%) high risk women with prior history of GDM showed recurrence subsequently in comparison to 26/61 (42.62%), who were not using Myo-inositol supplementation. All high risk patients with histories of obesity, GDM in prior pregnancy, diabetes in 1st degree relative, and polycystic syndrome etc. were included and efficacy of myo-inositol showed promising effects in terms of final outcomes by reducing the onset of GDM.

Conflict of Interest: The authors have no competing interests.

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