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Original Article

Obstetrics and Gynaecology Section

# Myoinositol and Metformin versus Only Metformin in the Management of Gestational Diabetes Mellitus: A Randomised Open-label Clinical Trial

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## ABSTRACT

**Introduction:** The incidence of Gestational Diabetes Mellitus (GDM) is rising globally with India no exception. The overall prevalence of GDM in our country is 16.55%. Insulin is the gold standard for the treatment of diabetes. Metformin, an Oral Hypoglycaemic Agent (OHA) is promisingly used in place of or along with Insulin. Myoinositol an insulin sensitiser may have some role in the treatment of GDM.

**Aim:** To assess whether myoinositol in addition to metformin provides any better glycaemic control in GDM patients than those receiving metformin only.

**Materials and Methods:** An open-label randomised clinical trial was conducted in the Department of Obstetrics and Gynaecology of Medical College and Hospital, Kolkata, West Bengal, India, in which mothers with a singleton pregnancy with 2-hour Postprandial Blood Sugar (PPBS) ≥140 mg/dL after 75 gm oral glucose {Diabetes in Pregnancy Study Group of India (DIPSI) criteria} were included and those with pregestational diabetes, on any form of antidiabetic treatment and with other co-morbidities like renal pathology, hypertension were excluded. A total of 150 patients with GDM were given Medical Nutrition Therapy (MNT) and after two weeks, 66 patients were selected and randomly allocated into two groups. Group 1 was given Myoinositol along with metformin (n=33) and group 2 was given metformin only (n=33). Dropouts were three in each group. So, a net of 30 patients from each group was taken for the final analysis. A p-value ≤0.05 was considered statistically significant.

**Results:** The mean change in fasting glucose levels in group 1 was 19.30±9.713 mg/dL whereas in group 2 was 20.76±13.70 mg/dL (p=0.6343). The mean change in postprandial blood glucose was 59.4667±16.8026 mg/dL in group 1 and 54.7667±18.8674 mg/dL in group 2. Both these results were statistically not significant. Two (6.7%) patients required insulin in group 1 and 5 (16.7%) patients had insulin added in group 2. Association was not statistically significant (p=0.2276).

**Conclusion:** Myoinositol supplementation with metformin achieves good glycaemic control through its insulin-sensitising action and reduces the complications of GDM to a certain extent but it does not provide any extra benefits over metformin alone.


**Keywords:** Fasting glucose, Glycaemic control, Insulin-sensitising action, Postprandial plasma glucose

## INTRODUCTION

Pregnancy problems in diabetic mothers have been dramatically impacted during the past nine decades. Before the availability of insulin in the early 1920s, maternal death was common, as high as 40%, and perinatal death was expected in about 50%, of women with diabetes who became pregnant [1]. There is an increase in the prevalence and incidence of type 2 diabetes in developing countries. The 1997, World Health Organisation (WHO) estimation of the prevalence of diabetes showed an expected total rise of >120% from 135 million in 1995 to 300 million in 2025 [2]. Of this, the greatest number of cases is expected to be in India and China.

The GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [3]. The pregnancy that occurs in a woman who already has diabetes is termed as pre-GDM. Both these situations are associated with increased maternal and foetal morbidity and rarely mortality. A 90-95% of pregnancies that are complicated by diabetes are due to GDM [4]. The overall prevalence of GDM in our country is 16.55% (by criteria of 2-hour plasma glucose ≥140 mg/dL) [5].

Various interventions are used to manage GDM. MNT and insulin are the gold standards for the treatment of diabetes. The use of OHA such as metformin, glibenclamide is a promising alternative to insulin therapy because of easy administration and patient satisfaction due to non invasive treatment. A newer drug, myoinositol, which is an insulin sensitiser is being widely used in the management of Polycystic Ovarian Syndrome (PCOS), as well as, in the prevention of GDM in high-risk cases. Myoinositol-based second messengers regulate glucose intake, increase the activity of glucose transport proteins [6,7]. Thus, myoinositol may have some role in the treatment as well as in prevention of GDM [8-11].

With this background, the study was done to see, whether myoinositol supplementation along with metformin provides any better glycaemic control in GDM patients than those receiving metformin only. Secondary objectives were to study whether myoinositol in addition with metformin has any advantage over metformin alone in reducing maternal complications, neonatal complications and also to compare the number of mothers requiring insulin supplementation.

## MATERIALS AND METHODS

The study was an open-label randomised clinical trial conducted in the Department of Obstetrics and Gynaecology of Medical College and Hospital, Kolkata, West Bengal, India, after getting approval from Institutional Ethics Committee (Ref. No. MC/KOL/IEC/Non Spon/458/12-2016) from May 2017 to April 2018. Sampling frame was all patients attending antenatal outdoor with GDM. A purposive sampling technique was used.

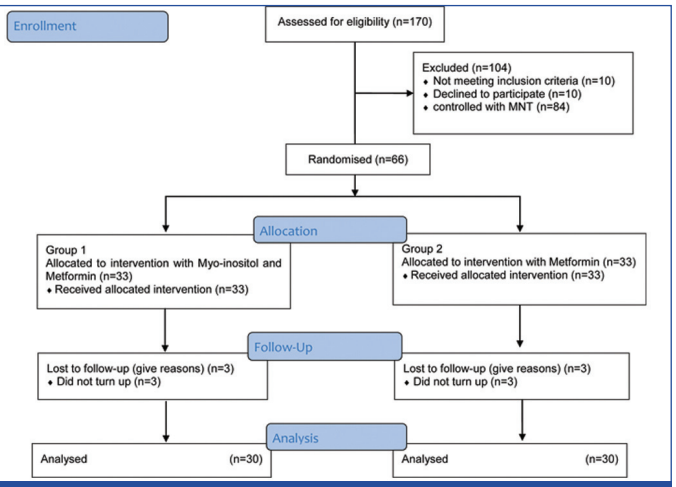
**Inclusion and Exclusion criteria:** Mothers with a singleton pregnancy with 2-hour PPBS ≥140 mg/dL after 75 gm oral glucose (DIPSI criteria) [12] were included in the study and those with pregestational

diabetes, on any form of antidiabetic treatment and with other co-morbidities like renal pathology, hypertension was excluded.

### Study Procedure

After counselling and proper consent, 150 patients were given MNT. After two weeks of MNT, 66 patients were selected for the study. This was a pilot study as no such similar study was available. According to current flat rules of thumb for an overall pilot trial sample size of a two-armed trial as per Sim and Lewis (n>=55, for small to medium effect sizes to minimise combined size) this sample size is justifiable [13].

They were randomly allocated into two groups of 33 each. Random allocation was generated by computer. One of the authors enrolled and assigned participants to interventions. Dropouts were three from each group. So, a net of 30 patients from each group was taken for the final analysis [Table/Fig-1].




**[Table/Fig-1]:** Consolidated Standards Of Reporting Trials (CONSORT) 2010 flow diagram.

Group 1 was given myoinositol along with metformin orally and group 2 was given oral metformin only. A combination of myoinositol 600 mg and metformin 500 mg was used twice daily initially in group 1. The dose was increased as indicated to achieve good glycaemic control. The maximum dose was two tablets twice daily i.e., myoinositol 2400 mg and metformin 2000 mg daily. For patients in group 2, the starting dose of metformin was 500 mg twice daily and the dose was increased as indicated to a maximum of 2000 mg daily.

During treatment, patients were monitored by measuring capillary blood glucose levels four times a day (fasting, two hours post-breakfast, two hours post lunch, 2-hour post dinner) till delivery, and the dose was modified twice weekly as necessary. The maternal and perinatal outcomes were studied.

Study variables were FBS, PPBS, gestational age at delivery, mode of delivery, birth weight, {Appearance, Pulse, Grimace, Activity and Respiration (APGAR)} score, and neonatal blood sugar level.

## STATISTICAL ANALYSIS

For statistical analysis, data were entered into a Microsoft excel spreadsheet and then analysed by Statistical Package for the Social Sciences (SPSS), version 24.0 and GraphPad Prism Version 5.0. Data had been summarised as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved Independent samples or unpaired samples. Unpaired proportions were compared by Chi-square test or Fischers-exact test, as appropriate. Once a t-value is determined, a p-value was found using a table of values from Student's t-distribution. The p-value ≤0.05 was considered statistically significant.

## RESULTS

The pretreatment mean Fasting Blood Sugar (FBS) and PPBS in both groups were more or less similar. Both the groups were comparable in terms of mean age, Body Mass Index (BMI), and Gestational Age (GA) at the onset of treatment [Table/Fig-2]. The mean change in FBS and PPBS after treatment in both the groups was statistically not significant [Table/Fig-3,4]. But the difference in mean weight gain in group 1 vs group 2 was statistically significant [Table/Fig-5].

Maximum patients delivered at 36-38 weeks (23 in group 1 and 24 in group 2). Four in group 1 and three in group 2 delivered before 36 weeks. Rest three patients in each group 1 and group 2 were delivered at 39 weeks. Only one baby was born with a birth weight of more than 4 kg, which was in group 2. The difference in mean birth weight vs group was not statistically significant (p=0.5143). The difference in mean APGAR and the difference in mean newborn blood glucose vs group was not statistically significant [Table/Fig-6]. Association between neonatal and maternal complications vs group was not significant [Table/Fig-7,8].

A total of 2 (6.7%) patients required insulin in group 1 and in group 2, 5 (16.7%) patients had insulin added. Association was not statistically significant (p=0.2276). In group 1, 23 (76.7%) patients were delivered by LSCS and 7 (23.3%) patients had vaginal delivery. In group 2, 23 (76.7%) patients had {Lower (uterine) Segment Caesarean Section (LSCS)} and 7 (23.3%) patients had vaginal delivery. Association of delivery vs group was not statistically significant (p=1.00).

| Variables | Groups | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| Age | Group 1 | 30 | 27.0333 | 4.6571 | 19.00 | 35.00 | 27.00 | 0.4921 |
| | Group 2 | 30 | 26.2000 | 4.6786 | 19.00 | 38.00 | 26.50 | |
| BMI | Group 1 | 30 | 23.0200 | 2.7621 | 16.00 | 29.00 | 23.00 | 0.7051 |
| | Group 1 | 30 | 23.3000 | 2.9379 | 18.00 | 33.00 | 24.00 | |
| GA entry | Group 1 | 30 | 28.4000 | 2.2376 | 23.00 | 32.00 | 29.00 | 0.1878 |
| | Group 1 | 30 | 27.5000 | 2.9449 | 22.00 | 33.00 | 28.00 | |

**[Table/Fig-2]:** Distribution according to Age (years), BMI (kg/m$^2$) and mean gestational age at entry (weeks).
Unpaired t-test used to calculate the p-value

| Variables | Groups | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| FBS 1 | Group 1 | 30 | 105.4667 | 12.4089 | 77.00 | 128.00 | 105.00 | 0.5065 |
| | Group 2 | 30 | 108.1667 | 18.3173 | 80.00 | 148.00 | 108.00 | |
| FBS 2 | Group 1 | 30 | 86.3333 | 7.2497 | 72.00 | 101.00 | 86.00 | 0.6139 |
| | Group 2 | 30 | 88.9333 | 8.2779 | 72.00 | 105.00 | 90.00 | |
| FBS change | Group 1 | 30 | 19.3000 | 9.7137 | 4.00 | 43.00 | 19.00 | 0.6343 |
| | Group 2 | 30 | 20.7667 | 13.7030 | 2.00 | 55.00 | 18.00 | |

**[Table/Fig-3]:** Distribution of mean Fasting Blood Sugar before treatment (FBS 1), after treatment (FBS 2) and mean FBS change in mg/dL.
Unpaired t-test used to calculate the p-value

| Variables | Groups | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| PPBS 1 | Group 1 | 30 | 180.3667 | 16.3211 | 152.00 | 220.00 | 179.00 | 0.9877 |
| | Group 2 | 30 | 180.3000 | 17.0863 | 156.00 | 220.00 | 179.00 | |
| PPBS 2 | Group 1 | 30 | 120.9000 | 8.3226 | 108.00 | 147.00 | 122.00 | 0.0925 |
| | Group 2 | 30 | 125.5333 | 12.2832 | 96.00 | 146.00 | 125.50 | |
| PPBS change | Group 1 | 30 | 59.4667 | 16.8026 | 33.00 | 98.00 | 56.00 | 0.3125 |
| | Group 2 | 30 | 54.7667 | 18.8674 | 25.00 | 109.00 | 50.00 | |

**[Table/Fig-4]:** Distribution of mean Postprandial Blood Glucose (PPBS) before. treatment (PPBS 1), after treatment (PPBS 2) and mean PPBS change in mg/dL.
Unpaired t-test used to calculate the p-value

| Variable | Groups | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| Wt gain (kg) | Group 1 | 30 | 11.2367 | 0.7185 | 10.00 | 13.00 | 11.20 | 0.0463 |
| | Group 2 | 30 | 11.6600 | 0.8834 | 10.20 | 14.20 | 11.45 | |

**[Table/Fig-5]:** Distribution of mean weight gain (kg) during pregnancy.
Unpaired t-test used to calculate the p-value

| Variables | Groups | Number | Mean | SD | Minimum | Maximum | Median | p-value |
|---|---|---|---|---|---|---|---|---|
| GA at delivery (weeks) | Group 1 | 30 | 36.9667 | 1.3515 | 34.00 | 39.00 | 37.00 | 0.6290 |
| | Group 2 | 30 | 37.1333 | 1.3060 | 33.00 | 39.00 | 37.00 | |
| Birth weight (kg) | Group 1 | 30 | 2.9650 | .3754 | 2.10 | 3.70 | 2.90 | 0.5143 |
| | Group 2 | 30 | 3.0417 | .5183 | 2.00 | 4.25 | 3.00 | |
| APGAR | Group 1 | 30 | 8.5667 | .7739 | 7.00 | 10.00 | 9.00 | 0.3068 |
| | Group 2 | 30 | 8.7667 | .7279 | 7.00 | 10.00 | 9.00 | |
| New born blood glucose | Group 1 | 30 | 75.1333 | 16.5503 | 45.00 | 107.00 | 76.00 | 0.9878 |
| | Group 2 | 30 | 75.0667 | 17.1885 | 40.00 | 102.00 | 74.00 | |

**[Table/Fig-6]:** Distribution of mean Gestational Age (GA) at delivery in weeks, mean birth weight (kg), mean APGAR score and mean newborn Blood Glucose (mg/dL).
Unpaired t-test used to calculate the p-value

| Neonatal complications | Group 1 | Group 2 | p-value |
|---|---|---|---|
| Large for gestational age[b] | 6 (20.0%) | 7 (23.0%) | 0.754001 |
| Hyperbilirubinemia[b] | 1 (3.3%) | 1 (3.3%) | 1.0 |
| Hypoglycaemia[b] | 1 (3.3%) | 3 (10.0%) | 0.604773 |
| Preterm[b] | 4 (13.3%) | 3 (10.0%) | 0.687573 |
| SNCU admission[c] | 0 | 2 (6.6%) | 0.4915 |
| Respiratory distress syndrome[c] | 0 | 1 (3.3%) | 1.0 |
| Septicaemia[c] | 0 | 1 (3.3%) | 1.0 |
| No[b] | 22 (73.3%) | 17 (56.6%) | 0.278958 |

**[Table/Fig-7]:** Association of neonatal complications.
b=Chi-square test, c=Fischers-exact test

| Maternal complications | Group 1 | Group 2 | p-value |
|---|---|---|---|
| Candidiasis[b] | 2 (6.7%) | 2 (6.7%) | 1.0 |
| Hypothyroid[b] | 3 (10.0%) | 1 (3.3%) | 0.604773 |
| APH[b] | 1 (3.3%) | 1 (3.3%) | 1.0 |
| PIH[b] | 3 (10.0%) | 5 (16.7%) | 0.704111 |
| UTI[b] | 3 (10.0%) | 2 (6.7%) | 0.640429 |
| Polyhydramnios[c] | 0 | 1 (3.3%) | 1.0 |
| No[b] | 20 (66.7%) | 20 (66.7%) | 1.0 |

**[Table/Fig-8]:** Association of maternal complications.
b=Chi-square test, c=Fischers-exact test; APH: Antepartum haemorrhage; PIH: Pregnancy induced hypertension; UTI: Urinary tract infection; SNCU: Special newborn care unit

## DISCUSSION

During the study period, 150 patients with GDM and treated with MNT. After two weeks of MNT, 66 patients (44%) did not achieve adequate glycaemic control (2-hour plasma glucose >120 mg/dL). This corroborates with the findings of Langer O that approximately 30-50% of women with GDM require pharmacological therapy when diet therapy alone fails to achieve glycaemic control [14].

The mean weight gain for women in group 1 was 11.2367±.7185 kg and that for group 2 was 11.6600±.8834 kg, with a p-value of 0.0463. This result was statistically significant. Thus, we can say that myoinositol helps in checking the excessive weight gain during pregnancy in a GDM mother. This result is similar to that found by DI Biase N et al., [15]. They studied the effectiveness of D-Chiro-Inositol (DCI) in gestational diabetes compared with the control group not getting DCI. They found that median weight gain in the control group was 11.5 kg whereas in the DCI group it was 9 kg. The difference between the two groups was statistically significant (p-value=0.048). The authors conclude that myoinositol may increase insulin sensitivity by checking weight gain and thus, may have a role in treatment of GDM.

When existing literature on the concerned topic was sought, no exactly similar study was found. The studies which have been published are either those using myoinositol for the prevention of GDM or, more recently, a few have worked on using myoinositol and D-chiro inositol in the treatment of gestational diabetes and compared the results with placebo.

Matarrelli B et al., studied effect of myoinositol on singleton pregnant women who were non obese but with elevated fasting blood glucose detected in first or early second trimester and followed them till delivery. The incidence of GDM was significantly reduced (p=0.001) in those who received myoinositol compared to those who received placebo (relative risk=0.127). In myoinositol group insulin requirement was less and pregnancy could be continued longer, newborn birth weight was significantly less and these babies had fewer episodes of hypoglycaemia [16]. According to Dell'Edera D et al., supplementation with DCI and D-myoinositol gives good control of maternal glycaemic status and good perinatal outcomes [17].

Kulshrestha V et al., conducted a pilot study to compare the efficacy of myoinositol, given at a dose of 1 gm twice daily as an adjuvant to dietary modification for the treatment of GDM in Asian Indian women compared to controls, who did not receive myoinositol. Approximately 90% of women with GDM became normoglycaemic with myoinositol and this was significant, when compared to controls. They concluded that oral supplementation with myoinositol in a dose of 1gm twice daily when started soon after the diagnosis of GDM, is effective in achieving glycaemic control and decreasing the need for additional pharmacological therapy in Asian Indian women [18].

Guarnotta V et al., showed that women with GDM treated with myoinositol showed improved glycaemic control in the 3rd trimester of pregnancy and a lower insulin requirement, compared to controls. In addition, they showed lower preterm birth weight and neonatal hypoglycaemia, compared to women not supplemented with myoinositol [19]. In the present study, both metformin myoinositol combination and only metformin showed equally good glycaemic controls and comparable maternal and perinatal outcomes. But due to lack of exactly similar type of study, it was not possible for authors to corroborate their findings with the existing literature.

Only 23.3% of cases had successful vaginal delivery in each group and the rest 76.7% of cases in each group underwent caesarean section for maternal, foetal, or obstetric complications. This rate of caesarean delivery is much higher than the ideal caesarean section rates (10-15%) considered by the international healthcare community [20,21].

The number of newborns who were Large for Gestational Age (LGA) was 6 (20%) in group 1 and 7 (23.33%) in group 2. There were no reported adverse effects of the drugs by the study population which led to discontinuation of therapy. In addition, further trials of myoinositol for the treatment of GDM should explore the optimal dose, frequency, and timing of supplementation, report on adverse effects, and assess the long-term effects of this intervention.

### Limitation(s)

As the present study lacks a good sample size, an accurate comparison of the neonatal and maternal complications between the two groups by a proper statistical analysis was inconclusive. Blinding was not done. Participants of varying ethnicities and with varying risk factors for GDM were not included.

## CONCLUSION(S)

Myoinositol supplementation with metformin not only achieves good glycaemic control, but also alleviates the complications of GDM to a certain extent by its insulin-sensitising action, but it does not provide much extra benefits over metformin alone. Future trials may throw some light on the objectives stated in the present study and whether myoinositol supplementation with metformin will provide any extra benefit or not.

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