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Original Research Article

Effect of myo-inositol and di-chiro inositol plus vitamin D supplementation during pregnancy on prevention of gestational diabetes: a multi-centric, prospective, randomized, double-blind clinical trial

Hema Divakar[1], Sheetal Joshi[1], Vidya Thobbi[2], Shobha Bembalgi[3], Sanjay Gupte[4], Vidya V. Bhat[5], Rita Singh[1], Poorni Narayanan[1], Bhagyashree Kulkarni[1], Prachi Ahire[6]*, Divakar G. V.[1], Isaac Manyonda[7]

[1]Divakar Specialty Hospital, Bangalore, Karnataka, India
[2]Alameen Medical College, Vijayapur, Karnataka, India
[3]KIMS College, Hubli, Karnataka, India
[4]Gupte Hospital, Pune, Maharashtra, India
[5]Radhakrishna Multispeciality Hospital and IVF Center, Bangalore, Karnataka, India
[6]Shield Healthcare Pvt Ltd, India
[7]St Georges Healthcare NHS Trust, Croydon, United Kingdom

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***Correspondence:**
Dr. Prachi Ahire,
E-mail: drprachi.ahire@shieldhealthcare.co.in

ABSTRACT

Background: Aim of study was to evaluate the impact of myoinositol and D-chiro inositol plus vitamin D supplementation on the prevention of gestational diabetes mellitus (GDM) in pregnant women.
Methods: In the multi-centric, prospective, randomised, double-blind clinical trial, either vitamin D alone (group I) or myoinositol and D-chiro inositol plus Vitamin D (group II) were administered to pregnant women from 12 weeks of gestation. The administration was continued until delivery to primigravids who were normoglycemic at 12 weeks of gestation and consented. From October 2018 to December 2019. A total of 1250 women were enrolled, and randomly allocated to either of the groups: 630 women in Group I and 620 in Group II. The allocation was blinded. The primary outcome was the rate of GDM as assessed by oral glucose tolerance test (OGTT) recommended by diabetes in pregnancy Study Group India (DIPSI), International Federation of Gynecology and Obstetrics (FIGO) and the Government of India, at first antenatal visit followed by at weeks 24 to 28 in both the groups.
Results: The rate of GDM was found more in group I as compared to group II treated with myoinositol and D-chiro Inositol plus vitamin D, but the difference was not statistically significant (5.08% in group I and 3.22% in group II).
Conclusions: In conclusion, an improved trend has been noticed in the reduction of the rate of GDM with myoinositol and D-chiro inositol plus vitamin D as compared to vitamin D alone. Myoinositol and D-chiro inositol plus vitamin D supplementation may be a good option for pregnant women to prevent the GDM occurrence especially in women having positive risk factors for GDM.

Keywords: Gestational diabetes, GDM, Myoinositol and D-chiro inositol, Prevalence, Vitamin D

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as "Impaired Glucose Tolerance with onset or first recognition during pregnancy".[1,2] A recent population-based cohort study, conducted in 2022 reported the gestational diabetes prevalence from 7% to 16% in India. A study conducted in 2013 across India by the Federation of Obstetricians and Gynecologist Society of India (FOGSI) and Diabetes in Pregnancy Study Group India (DIPSI) reported diagnosis of GDM in 740 (8%) women out of 9282 pregnant women enrolled. In addition, 27% of these women diagnosed with GDM reported history of foetal loss in previous pregnancy.[2,4] Asians and Indians are at higher risk of developing diabetes mellitus, so pregnant women are also at higher risk of developing GDM.[5] In India, GDM is reported in a large number of pregnancies (around 4 million pregnancies in a year), exposing them to the risk of perinatal morbidity and mortality if not managed appropriately.[2]

Pregnant women with increased hyperglycemia exhibit an increased risk of adverse maternal, fetal and neonatal outcomes.[6] The maternal risks are pre-eclampsia, polyhydramnios, postpartum haemorrhage, uterine atony, prolonged/obstructed labour, progression of retinopathy and infection. The fetal risks include intra-uterine death, spontaneous abortion, congenital malformation, stillbirth, birth injuries, shoulder dystocia, infant respiratory distress syndrome and neonatal hypoglycemia. This emphasises the need for early diagnosis or prevention of GDM.

India has a high prevalence of GDM by global standards, healthcare resources are insufficient, and the variations in sociodemographic characteristics impact the prevalence of GDM. The International Federation of Gynecology and Obstetrics (FIGO) has redefined GDM as hyperglycemia in pregnancy (HIP). The FIGO guidelines endorsed the guidelines of the Government of India (GOI), the Diabetes in Pregnancy Group in India (DIPSI), and the Federation of Obstetrics and Gynecological Societies of India (FOGSI) for low resource countries like India. They recommend GDM/ HIP testing of all pregnant women (universal testing) at the first initial antenatal contact and 24–28 weeks' gestation using the one-step 75-g OGTT procedure whether in a fasting or non-fasting state.[7-9]

The management of GDM involves an integrative approach with dietary modifications, physical activity along with psychosocial interventions.[10] When this approach does not work, insulin is required with or without the addition of an oral hypoglycemic agent.[11] There is a need for treatments including nutritional supplements which can prevent occurrence of gestational diabetes or hyperglycemia in pregnancy. The treatments must be effective, safe in pregnancy and do not cause any side effects. Additionally, nutritional supplements will improve patient compliance being oral supplements, unlike parenteral administration of insulin.

Myoinositol (MI) is a cyclic polyol linked to phospholipids and found naturally in plants and animals. It is converted into its isomer D-chiro-inositol (DCI) in the tissues that express the epimerase enzyme.[12] These isomers serve as second messengers of insulin in glycosyl-phosphatidylinositol and inositol phosphoglycans pathways.[13] Myoinositol is reported to be beneficial in GDM by improving insulin resistance.[14,15] In addition, MI stimulates the translocation of GLUT-4 to the plasma membrane of skeletal muscles, leading to increased glucose uptake in the cells.[16] One of the studies reported that MI supplementation during the first trimester in pregnant obese (BMI 30 or more) women reduced the incidence of GDM significantly.[17] Another study in pregnant women with a family history of diabetes has shown that supplementation of MI reduces the incidence of GDM significantly and delivery of macrosomia foetuses.[18] The Cochrane analysis also suggests that antenatal supplementation of MI during pregnancy is beneficial in reducing the incidence of GDM.[19] In addition, a recent study has suggested that supplementation of MI plus α-lactalbumin in pregnant women with GDM reduces insulin resistance as assessed by reduction in homeostasis assessment of insulin resistance (HOMA-IR) values and amount of insulin usage in these women. Authors also reported a decline in subcutaneous adipose tissue deposition and fetal abdominal circumference, along with a decrease in pre-term births.[20]

Thus, we carried out a randomised, double-blind clinical trial to assess the impact of MI + DCI + vitamin D3 (vitamin D) supplementation in preventing GDM occurrence in pregnant women.

METHODS

A multi-centric, prospective, randomised, double-blind study was carried out in primigravid pregnant women. Local ethics committee approvals were taken, and the trial was conducted according to the principles expressed in the Helsinki Declaration. All the participants gave written informed consent. The CONSORT Statement has been adhered to, and the trial was registered in Clinical Trials Registry-India (CTRI) (Registration No.: CTRI/2018/06/014477). The study was carried out at five centres, viz. Al Ameen Medical College (ALM), Bijapur; Divakar's Speciality Hospital (DSH), Bengaluru; Gupte Hospital (GHP), Pune; Karnataka Institute of Medical Sciences (KIMS), Hubali and Radha Krishna Hospital (RKH), Bangalore. ALM, KIMS and RKH are public hospitals, while DSH and GHP are private hospitals.

GDM testing

The participants ingested 75 g of glucose that had been dissolved in 300 ml water. After 2 h, the participants' venous blood glucose levels were measured. GDM was diagnosed if the blood glucose levels were >7.8 mmol/L or >140 mg/dL. GDM testing was carried out at the following time points: during the first antenatal visit in the first

trimester, and in the second trimester during weeks 24 to 28 weeks.

Inclusion criteria

The inclusion criteria were a) Pregnant women primigravida; b) Gestation between 11-14 weeks; c) First glucose values <140 mg/dl as determined using a single step OGTT procedure which DIPSI, International Federation of Gynecology and Obstetrics (FIGO) and Government of India─recommend d) Willingness to provide the informed consent; and e) Willingness and ability to follow the study procedures.[1,2]

Exclusion criteria

The exclusion criteria were a) Previous abortion; b) Multigravida; c) First glucose values >140 mg/dl; d) Subjects with a known history of diabetes, and e) Pregestational morbid obesity (BMI over 35).

A simple computer-generated random sampling method was used with an allocation of 1:1 in each group. Group I received only vitamin D (1000 IU), while group II was the treatment arm that received the combination of MI (2 gms) + DCI (50 mg) + Vit D (1000 IU) twice a day (GDMSafe®, Shield Healthcare Pvt Ltd). Lower levels of Vit D have been reported to be associated with a higher risk of GDM.[21] Further, vitamin D supplement effectively reduces GDM occurrence possibly by increasing insulin sensitivity.[22] The supplementation was started immediately post-enrollment according to the assigned groups and continued till delivery in all the women. The primary outcome was the rate of GDM in pregnant women as determined by the single-step OGTT. Each participant was given sachets, which were identical in appearance. The sponsor supplied the sealed and numbered sachets according to the computer-generated randomised sequence. The unblinding was done by the sponsor after the database lock.

Statistical analysis

Statistical analysis was carried out with R software version 4.1.0. Data are expressed as n (%) for categorical variables and n, mean ± standard deviation (SD) for numerical variables. Inferential analysis was carried out using the two-sample t-test. A p-value of <0.05 was considered significant.

RESULTS

During the enrollment period from October 2018 to December 2019, a total of 1707 women were screened for eligibility. A total of 1250 women were enrolled in the study, and randomly allocated to either of the groups: 630 women in Group I and 620 in Group II. A total of 957 pregnant women were available for the second OGTT, 492 women from Group I, and 465 from Group II (Figure 1).

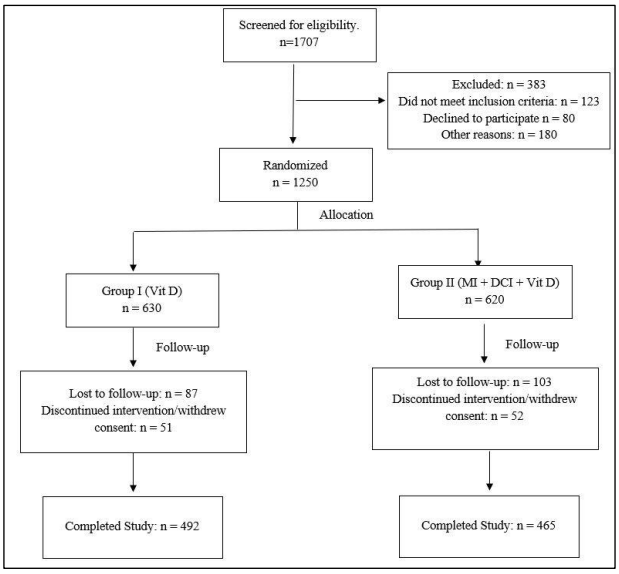

Figure 1: Flowchart of participants.

A total of 293 pregnant women were either lost to follow-up or discontinued the study or withdraw consent.

The maximum number of women were in the age group of 21 to 25 years. There were no significant differences between the groups with respect to mean age and BMI (Table 1). The mean glucose values for group I (received vitamin D) and Group II (treatment arm) at baseline were similar (Table 2).

Table 1: Age group distribution in pregnant women who completed the study.

Age group (years)	Group I (Vit D)	Group II (MI+ DCI+ Vit D)
18-20	147	137
21-25	193	163
26-30	124	121
31-35	24	37
35-40	04	07
Total	492	465

Table 2: Baseline characteristics.

Characteristic	Group I (Vit D)	Group II (MI+ DCI+ Vit D)	p value
Mean age±SD (years)	23.60±4.01	24.12±4.47	0.88
Mean BMI±SD	22.10±3.59	22.46±3.48	0.90
Mean glucose ± SD (mg/dl)	95.90±15.82	98.70±16.61	0.83

In group I, the overall rate was 5.08%, while in group II, the overall rate of GDM was 3.22%. There is a positive trend of reduction of GDM with MI plus DCI plus vitamin D supplementation but not statistically significant as compared to vitamin D alone. Two centres which were

public hospitals (KIMS and RKH) had no case of GDM. The rate of GDM in private and public hospitals was found to be 12.00% and 0.29%, respectively, in group I, while it was 7.04% and 0.38%, respectively, in group II treatment arm (Table 4). Adverse event was not reported during the study duration. A positive correlation was observed between glucose levels (week 24 to 28) and age and BMI, but it was not statistically significant (Table 5).

Table 3: Rate of GDM in group I and II at different study centres.

Centre	Group I (Vit D)			Group II (MI+ DCI+ Vit D)			
	Total participants (number)	GDM positive (number)	Rate Of GDM (%)	Total participants (number)	GDM positive (number)	Rate Of GDM (%)	p-value
ALM	189	1	0.5	161	01	0.6	0.89
DSH	176	21	11.93	174	12	6.89	0.11
GHP	24	3	12.5	25	02	8.0	0.61
KIMS	51	0	0	56	0	0	NA
RKH	52	0	0	49	0	0	NA
Total	492	25	5.08	465	15	3.22	0.15

Note: NA- Not assessable; ALM- Al Ameen Medical College (Bijapur); DSH- Divakar's Specialty Hospital (Bangalore); GHP- Gupte Hospital (Pune); KIMS- Karnataka Institute of Medical Sciences (Hubbali); RKH-Radha Krishna Hospital, (Bangalore)

Table 4: Rate of GDM in public and private hospitals.

Centre	Group I			Group II		
	Total participants	GDM positive	Rate of GDM (%)	Total participants	GDM positive	Rate of GDM (%)
Private hospitals	200	24	12.00	199	14	7.04
Public hospitals	292	1	0.34	266	1	0.38

Table 5: Correlation between glucose levels of positive cases of GDM in group I and II with age and BMI.

	Age	BMI
Glucose levels at 24 to 28 weeks for Group I	r = +0.11	r = +0.12
Glucose levels at 24 to 28 weeks for Group II	r = +0.26	r = +0.35

Two centres which are public hospitals had (KIMS and RKH) zero incidence of GDM and ALM centre the other public hospital had a 0.5% versus 0.6 % rate of GDM. The rate of GDM observed by these three centres is significantly less than the other two centres (DSH and GHP) which are private hospitals. We could not identify the cause for such a low rate of GDM in the three public hospitals

DISCUSSION

The current study proved that MI plus DCI plus vitamin D supplementation showed the trend of reducing the occurrence of GDM in pregnant women, but the reduction is not statistically significant compared to vitamin D alone. The previous studies reported that MI supplementation in pregnant women who were overweight or obese (BMI 30 or more) significantly reduced the incidence of GDM by lowering insulin resistance.[19] Similarly, women with elevated fasting glucose levels during the first or early second trimester, supplementation with MI decreased the incidence of GDM significantly along with improved secondary outcomes like insulin therapy, neonatal hypoglycaemia and polyhydramnios. To best of our knowledge, this was the first clinical study conducted in pregnant women in India to assess the benefit of MI plus DCI plus vitamin D supplementation in reducing the GDM occurrence. MI plus DCI plus vitamin D supplementation was well tolerated, without any adverse event reported in this study. By reducing the GDM occurrence, the subsequent benefit in reducing the adverse maternal, fetal and neonatal outcomes by MI plus DCI plus vitamin D supplementation must not be ignored.

The rate of GDM in the current study was 5.08% and 3.22% in group I and group II, respectively, which was definitely less than the reported studies in literature but the difference between the two arms was not statistically significant.

In our study, the rate of GDM in private and public hospitals was found to be 12.00% and 0.29%, respectively, in group I, while it was 7.04% and 0.38%, respectively, in group II treatment arm. The difference in the rate of GDM between private and public hospitals is difficult to rationalise. This suggests that more extensive studies are

needed with larger and equal sample sizes in private and public hospitals.

The current study is associated with certain limitations. Documented evidence has suggested that MI supplementation showed a significant reduction in GDM occurrence in women carrying risk factors for GDM. These risk factors include obese or overweight pregnant women, pregnant women with elevated fasting glucose levels at baseline, pregnant women with a family history of type II diabetes or women with advanced age.[19,22] However, in our study, all the pregnant primigravida women were enrolled without identifiable risk factors. Furthermore, several studies have reported that GDM occurrence increases with age and is higher in females aged 30 years or more.[23,24] Almost 90% of the pregnant women in our study were less than 30 years of age, and approximately 70% were in the age grope of 18 to 25 years.

This warrants a study in a larger population with equal distribution of pregnant women from all age groups and with associated risk factors. Studies recruiting women equally from both public and private hospitals will help identify the beneficial effects of MI in preventing GDM. In addition, we did not measure other clinical outcomes like gestational hypertension, macrosomia, or neonatal hypoglycaemia.

CONCLUSION

In conclusion, an improved trend has been noticed in the reduction of the rate of GDM with MI + DCI + Vit D as compared to Vit D alone. However, the role of MI + DCI + Vit D in reducing GDM occurrence and subsequently reducing adverse maternal, fetal, and neonatal outcomes must not be ignored. The authors opine that MI + DCI + Vit D supplementation may be a good option for the prevention of GDM in pregnant women with positive risk factors.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Ministry of Health and Family Welfare, New Concept Information Systems. Maternal and health division, diagnosis and management of gestational diabetes mellitus: technical and operational guidelines. 2018. Available at: https://nhm.gov.in/New_Updates_2018/NHM_Components/RMNCH_MH_Guidelines/GestationalDiabetes-Mellitus.pdf. Accessed on 20 May 2023.
2. (DIPSI) DiPsGI. Diagnosis and management of gestational diabetes mellitus, 2021. Available at: https://icogonline.org/wp-content/uploads/pdf/gcpr/gdm-dipsi-guidline.pdf. Accessed on 20 May 2023.
3. Bahl S, Dhabhai N, Taneja S, Mittal P, Dewan R, Kaur J, et al. Burden, risk factors and outcomes associated with gestational diabetes in a population-based cohort of pregnant women from North India. BMC Preg Childb. 2022;22(1):1-6.
4. Veeraswamy S, Divakar H, Gupte S, Datta M, Kapur A, Vijayam B. Need for testing glucose tolerance in the early weeks of pregnancy. Indian J Endocrinol Metab. 2016;20(1):43-6.
5. (FOGSI) FoOaGSoI. Gestational diabetes. newsletter of endocrinology committee FOGSI. 2021;17.
6. Thanawala U, Divakar H, Jain R, Agarwal MM. Negotiating gestational diabetes mellitus in india: a national approach. Medicina (Kaunas). 2021;57(9).
7. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Available at: http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf. Accessed on 20 May 2023.
8. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676-82.
9. Gilbert L, Gross J, Lanzi S, Quansah DY, Puder J, Horsch A. How diet, physical activity and psychosocial well-being interact in women with gestational diabetes mellitus: an integrative review. BMC Preg Childbirth. 2019;19(1):60.
10. Mpondo BC, Ernest A, Dee HE. Gestational diabetes mellitus: challenges in diagnosis and management. J Diabetes Metab Disord. 2015;14:42.
11. Heimark D, McAllister J, Larner J. Decreased myo-inositol to chiro-inositol (M/C) ratios and increased M/C epimerase activity in PCOS theca cells demonstrate increased insulin sensitivity compared to controls. Endocr J. 2014;61(2):111-7.
12. Larner J, Brautigan DL, Thorner MO. D-chiro-inositol glycans in insulin signaling and insulin resistance. Mol Med. 2010;16(11-12):543-52.
13. Corrado F, D'Anna R, Di Vieste G, Giordano D, Pintaudi B, Santamaria A, et al. The effect of myoinositol supplementation on insulin resistance in patients with gestational diabetes. Diab Medi: J Brit Diabet Associa. 2011;28(8):972-5.
14. Vitagliano A, Saccone G, Cosmi E, Visentin S, Dessole F, Ambrosini G, et al. Inositol for the prevention of gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. Arch Gynecol Obstet. 2019;299(1):55-68.
15. Sobota-Grzeszyk A, Kuzmicki M, Szamatowicz J. Myoinositol in the prevention of gestational diabetes mellitus: is it sensible? J Diabet Res. 2019;2019:3915253.
16. D'Anna R, Di Benedetto A, Scilipoti A, Santamaria A, Interdonato ML, Petrella E, et al. Myo-inositol

supplementation for prevention of gestational diabetes in obese pregnant women: a randomized controlled trial. Obstet Gynecol. 2015;126(2):310-5.
17. D'Anna R, Scilipoti A, Giordano D, Caruso C, Cannata ML, Interdonato ML, et al. myo-Inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: a prospective, randomized, placebo-controlled study. Diabetes Care. 2013;36(4):854-7.
18. Crawford TJ, Crowther CA, Alsweiler J, Brown J. Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. Coch Data Syst Rev. 2015(12):CD011507.
19. D'Anna R, Corrado F, Loddo S, Gullo G, Giunta L, Di Benedetto A. Myoinositol plus alpha-lactalbumin supplementation, insulin resistance and birth outcomes in women with gestational diabetes mellitus: a randomized, controlled study. Sci Rep. 2021;11(1):8866.
20. Dwarkanath P, Vinotha P, Thomas T, Joseph S, Thomas A, Shirley G, et al. Relationship of early vitamin D concentrations and gestational diabetes mellitus in Indian pregnant women. Front Nutr. 2019;6:116.
21. Rudnicki PM, Molsted-Pedersen L. Effect of 1,25-dihydroxycholecalciferol on glucose metabolism in gestational diabetes mellitus. Diabetologia. 1997;40(1):40-4.
22. Palacios C, Trak-Fellermeier MA, Martinez RX, Lopez-Perez L, Lips P, Salisi JA, et al. Regimens of vitamin D supplementation for women during pregnancy. Coch Data Syst Rev. 2019;10:CD013446.
23. Karcaaltincaba D, Calis P, Ocal N, Ozek A, Altug Inan M, Bayram M. Prevalence of gestational diabetes mellitus evaluated by universal screening with a 75-g, 2-hour oral glucose tolerance test and IADPSG criteria. 2017;138(2):148-51.\

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