The Prevention of Gestational Diabetes Mellitus With Antenatal Oral Inositol Supplementation: A Randomized Controlled Trial

Maria Farren, Niamh Daly, Aoife McKeating, Brendan Kinsley, Michael J. Turner, and Sean Daly

Diabetes Care 2017;40:759–763 | https://doi.org/10.2337/dc16-2449

OBJECTIVE

This study investigated if inositol in a combination of *myo*-inositol and *D*-chiro-inositol would prevent gestational diabetes mellitus (GDM) in women with a family history of diabetes.

RESEARCH DESIGN AND METHODS

This was a randomized controlled trial that examined whether inositol from the first antenatal visit prevents GDM. The trial was carried out in a single-center tertiary referral center. Women with a family history of diabetes were enrolled at the first antenatal visit. They were randomized to the intervention group, which received a combination of 1,100 mg *myo*-inositol, 27.6 mg *D*-chiro-inositol, and 400 μg folic acid, or to the control group, which received 400 μg folic acid only. All women had an oral glucose tolerance test between 24 and 28 weeks' gestation. The primary end point was the incidence of GDM. Statistical analysis was carried out using SPSS Statistical Package version 20.

RESULTS

Two hundred forty women, 120 in each arm, were recruited between January 2014 and July 2015. There were no differences in characteristics between the groups. The incidence of GDM was 23.3% (*n* = 28) in the intervention group compared with 18.3% (*n* = 22) in the control group (*P* = 0.34). The mean fasting plasma glucose at the glucose tolerance test was 81 mg/dL in both groups.

CONCLUSIONS

Commencing an inositol combination in early pregnancy did not prevent GDM in women with a family history of diabetes. Further studies are required to examine whether inositol supplements at varying doses may prevent GDM.

Gestational diabetes mellitus (GDM) may be defined as glucose intolerance with onset or first recognition during pregnancy (1). The prevalence of GDM varies widely depending, for example, on the diagnostic methodology, the population studied, and whether screening is universal or selective (2,3). GDM is associated with increased clinical risk for the woman and her offspring, including hypertensive disorders, cesarean section, fetal macrosomia, shoulder dystocia, and neonatal hypoglycemia (1). Following the Hyperglycemia and Adverse Outcomes (HAPO) Study, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommended new thresholds for the diagnosis of GDM (4). These were

Coombe Women & Infants University Hospital, Dublin, Ireland

Corresponding author: Maria Farren, mariafarren1983@gmail.com.

Received 19 November 2016 and accepted 23 February 2017.

Clinical trial reg. no. ISRCTN92466608, www.isrctn.org.

lower thresholds than those previously used and required only one, not two, abnormal glucose reading. As a result, the number of new cases of GDM diagnosed has increased dramatically (5).

Inositol (also known as inositol, hexahydroxycyclohexane, or *cis*-1,2,3,5-*trans*-4,6-cyclo-hexanehexol) is a cyclic polyol that is a precursor for phosphoinositides, which are involved in cell signal transduction and other secondary messengers that exert an insulin-like effect on metabolic enzymes, including those involved in glucose metabolism (6,7). Inositol is a collective term that refers to nine possible stereoisomers, of which *myo*-inositol (MI) is the most common. Inositol was once thought to be a B vitamin but because of its prevalence in the diet, it is now considered a pseudovitamin. A pseudovitamin implies that it is neither an essential vitamin nor a mineral but is of physiological importance. An analysis of the American diet in the 1980s estimated that a typical 2,500 kcal diet contained 900 mg inositol (8). Inositol is found in a variety of foods including whole grains, seeds, legumes, and citrus fruits (8).

Inositol is a precursor of inositol phosphoglycans (IPG) (7). These can be divided into two groups: the P-type, P-inositol phosphoglycans (P-IPG), and the A-type, A-inositol phosphoglycans (A-IPG), which are antagonistic of each other (9,10). In glycolysis, pyruvate dehydrogenase (PDH) phosphatases are activated by P-IPG (11). These in turn activate the complex enzyme PDH, an essential step in glycolysis. This process is suppressed by A-IPGs. In a state of insulin resistance, urinary inositol metabolites are increased. These are mainly of the P-IPG class and cause a ratio shift toward A-IPGs and a suppression of PDH (12). The premise of inositol supplementation is that this ratio distortion is normalized.

Recently, MI and the combination of MI with *D*-chiro-inositol (DCI) has been reported as reducing the incidence of GDM in at-risk groups such as obese women and women with polycystic ovary syndrome (PCOS) (13,14). However, no study to date has investigated whether MI and DCI in combination decreases the incidence of GDM in women who are at risk because of a family history of diabetes. There is also scant information on the effects of inositol on neonatal outcomes. The aim of our study was to determine if oral inositol in the combination of MI and DCI, started in early pregnancy, prevents GDM in women with a family history of diabetes.

RESEARCH DESIGN AND METHODS

We undertook a single-center, randomized controlled trial (RCT) between January 2014 and January 2016. The Health Products Regulatory Authority (formerly the Irish Medicines Board) was consulted in advance. As our product is not a drug, they were satisfied the product fulfilled the criteria of a pseudovitamin. Ethical approval was granted by the Hospital Research Ethics Committee in June 2013. The trial was registered with the ISRCTN registry and assigned the trial number ISRCTN92466608.

The study was powered statistically to demonstrate a reduction of 50% in GDM and thus required 240 women, 120 in the intervention arm and 120 in the control arm. The intervention arm received a combination of MI 1,100 mg, DCI 27.6 mg, and 400 μg folic acid per day (Inofolic Combi; Lo.Li. Pharma International, Rome, Italy), and the control arm received 400 μg folic acid per day (Clonfolic; Clonmel Healthcare). Women with a family history in a first-degree relative of diabetes, either type 1 or type 2, were eligible for inclusion. Exclusion criteria were: *1*) age younger than 18 years, *2*) multiple pregnancy, *3*) limited understanding of English, and *4*) any pre-existing liver or kidney disease or diabetes.

Women were recruited at their first visit between 10 and 16 weeks' gestation. The pregnancy was dated accurately by transabdominal ultrasound. After informed consent, women were randomized by the main researcher, using sealed envelopes, into either the intervention or control arm. Randomization was carried out by an independent statistician, and sealed envelopes were prepared independently. Compliance was assessed by pill counting with participants considered compliant if the supplement was taken 80% of the time. BMI was calculated by recording the weight and height of each participant at their first visit (15).

The primary outcome was the occurrence of GDM diagnosed with a 75-g oral glucose tolerance test (OGTT) performed between 24 and 28 weeks' gestation (5). GDM was diagnosed according to the recommendations of the IADPSG (4). Secondary outcomes included the development of preeclampsia or pregnancy-induced hypertension, induction of labor, the mode of delivery, perineal trauma, birth weight, shoulder dystocia, brachial plexus palsy, neonatal intensive care unit (NICU) admission, neonatal hypoglycemia, and respiratory distress syndrome.

The aim of the intervention was to show a 50% reduction in the incidence of GDM. When we considered the expected rate of GDM, it was calculated that 240 women were required to demonstrate a 50% GDM reduction with a statistical power of 80% ($P < 0.05$). Statistical analysis was carried out using SPSS Statistical Package version 20 (IBM, Chicago, IL). Data were expressed as means for continuous variables. All continuous variables were normally distributed and compared using a *t* test. For comparison of frequencies, the Pearson χ^2 test was used. A value of $P < 0.05$ was considered significant.

RESULTS

From January 2014 to July 2015, 442 women were screened for eligibility. Ninety-three women did not meet the study criteria. Of these, 27% ($n = 25$) did not know adequate English to consent to participation, whereas 38% ($n = 35$) were >16 weeks' gestation at recruitment. The remainder were excluded because of maternal medical problems (11%), fetal issues including miscarriage (24%), and age younger than 18 years (1%). One hundred nine women declined to participate. Therefore, 240 women were randomized: 120 in the intervention group and 120 in the control group. There was no difference in the characteristics between the two groups (Table 1). The study population was representative of our hospital population in that the mean age was 31.3 years (range 18–45 years), the mean BMI was 26.1 kg/m^2 (range 15.7–46.7 kg/m^2), 16% were obese, and 33% were nulliparous (16).

All women were analyzed by intention to treat. There were no side effects reported from taking either the intervention or control supplement. The time spent within the study was similar between the groups. The average gestation at enrollment in the intervention group was 12.5 weeks compared with 12.6 weeks in the control ($P = 0.45$). Those in the intervention group spent a mean of 183.6 days in the study compared with

Table 1—Characteristics of the study population

	Inositol plus folate (n = 120)	Folate alone (n = 120)	P value
Age, years	31.1 ± 5.1	31.5 ± 5.0	0.77
BMI, kg/m^2	26.0 ± 5.3	26.2 ± 5.5	0.30
Obese	19 (16)	19 (16)	1.00
Nulliparous	40 (33)	38 (32)	0.78
Smokers	8 (7)	7 (6)	0.14
Irish-born	89 (74)	83 (69)	0.39
History of GDM	10 (8)	15 (13)	0.29
Gestation at recruitment, weeks	12.5 ± 1.6	12.6 ± 1.5	0.45

Data are n (%) or mean ± SD.

181.2 in the control group (P = 0.56). There was no difference in compliance between the two groups, with 72% (n = 86) compliance in the intervention compared with 73% (n = 87) compliance in the control group (P = 0.89). Women underwent a GTT between 24 and 28 weeks' gestation.

In the inositol group, the rate of GDM was 23% (n = 28) compared with 18% (n = 22) in control group (P = 0.34). There was also no difference in the incidence of GDM by BMI category (Table 2). In those with a normal BMI, the incidence of GDM was 10.0% in the intervention compared with 13% in the control group (P = 0.66). In the overweight and obese category, the incidence of GDM was 35% in the intervention group compared with 24% in the control group (P = 0.17).

We analyzed the impact of inositol on the fasting, 1-h, and 2-h glucose levels taken at the OGTT (Table 2). There was no difference between the groups for each time point. The mean fasting plasma glucose level for the OGTT was 81 mg/dL in both the intervention and control group (P = 1.0). The mean glucose in the intervention group for the 1-h sample was 138.6 mg/dL compared with 133.2 mg/dL in the control group (P = 0.42), and in the 2-h sample, the mean glucose value in the intervention group was 102.6 mg/dL compared with 97.2 mg/dL in the control group (P = 0.07).

For analysis of secondary outcomes, there were 117 women in each arm (Table 3). There were three women in each arm that could not be included for analysis because of pregnancy loss or delivery elsewhere. There was no difference in mean birth weight between the two groups. The mean birth weight in the intervention group was 3,467 ± 562.2 g compared with 3,323 ± 519.6 g in the control group (P = 0.52). There was no difference in the incidence of macrosomia when defined as either ≥4.0 or ≥4.5 kg. The incidence of babies born weighing >4.5 kg was 3% (n = 3) in the intervention group compared with 2% (n = 2) in the control group (P = 0.65). There was also no difference in the number of babies born with a birth weight less than the 10th centile, with 6% incidence in the intervention group (n = 7) compared with 3% (n = 3) in the control group (n = 0.19). The rate of cesarean delivery was 32% in the intervention (n = 37) compared with 35% (n = 41) in the control group (P = 0.58). There were no incidence of shoulder dystocia or brachial plexus injury in either group. There was also no difference between the groups for perineal trauma (3% in the intervention compared with 1% in the control; P = 0.17) or primary postpartum hemorrhage (9% in the intervention compared with 14% in the control; P = 0.21).

The rate of preterm delivery was 7% in the control (n = 8) compared with 2% in the intervention (n = 2; P = 0.11). In the control group, five of the cases of preterm delivery had a previous history making them higher risk of preterm delivery in this pregnancy. The other three cases in the control group were primiparous. In the intervention group, both cases occurred in primiparous women.

There were four admissions to NICU in the intervention group and six in the control group (P = 0.51). The rate of neonatal hypoglycemia was 8% in the intervention group (n = 9) compared with 1% in the control group (n = 1; P = 0.01). There was no difference in the rates of neonatal jaundice or respiratory distress syndrome between the two groups (Table 3).

Table 2—Primary outcome and results of OGTT carried out between 24 and 28 weeks' gestation

	Inositol plus folate (n = 120)	Folate alone (n = 120)	P value
Incidence of GDM	28 (23)	22 (18)	0.34
Incidence of GDM in women with BMI <25 kg/m^2	6/58 (10)	8/62 (13)	0.66
Incidence of GDM in women with BMI >25 kg/m^2	22/62 (35)	14/58 (24)	0.17
Fasting glucose OGTT, mg/dL	81.0 ± 14.3	81.0 ± 10.9	1.00
1-h glucose OGTT, mg/dL	138.4 ± 49.9	133.2 ± 35.0	0.42
2-h glucose OGTT, mg/dL	102.6 ± 30.2	97.2 ± 24.8	0.07

Data are n (%) or mean ± SD.

CONCLUSIONS

This was the first study that used the combination of MI/DCI in pregnancy to prevent GDM. Contrary to previous RCTs, we found that inositol did not reduce the incidence of GDM in women with a family history of diabetes. There was no difference in outcomes when we compared groups by BMI categories, and there was no difference when we analyzed the effect of inositol on the fasting, 1-h, and 2-h glucose samples at the time of the OGTT. We found that the incidence of neonatal hypoglycemia was greater in the intervention arm compared with the control. However, for this to be a clinically significant finding, all neonates in the study would require blood glucose sampling, which did not occur. Within the intervention arm, there was a greater number of women with GDM, making it more likely that their babies would be tested. Therefore, we cannot conclude that the intervention resulted in more cases of hypoglycemia, but in future studies, all babies should have their blood glucose recorded.

A strength of this study is that this is the first time that inositol has been used in pregnancy in a combination that reflects the physiological ratio of inositol in the body (17). Previous studies have

Table 3—Secondary outcomes

Outcome	Inositol plus folate (n = 117)	Folate alone (n = 117)	P value
Time in study, days	183.6 ± 30.5	181.2 ± 31.9	0.56
Gestation at delivery, weeks	39.5 ± 1.3	39.1 ± 1.8	0.07
Birth weight, g	3,467.0 ± 562.2	3,323.0 ± 519.6	0.52
Macrosomia (>4.5 kg)	3 (3)	2 (2)	0.65
Weight >4.0 kg	14 (12)	9 (8)	0.27
>90th centile	14 (12)	10 (9)	0.38
<10th centile	7 (6)	3 (3)	0.19
Cesarean delivery	37 (32)	41 (35)	0.58
PIH/PET	2 (2)	8 (7)	0.11
Preterm delivery	2 (2)	8 (7)	0.11
Shoulder dystocia	0	0	
Brachial plexus injury	0	0	
Third-degree perineal tear	4 (3)	1 (1)	0.17
Primary postpartum hemorrhage	10 (9)	15 (14)	0.21
NICU admissions	4 (3)	6 (5)	0.51
Hypoglycemia	9 (8)	1 (1)	0.01
Neonatal jaundice	2 (2)	8 (7)	0.05
Respiratory distress	2 (2)	1 (1)	0.56

Data are n (%) or mean ± SD. PET, preeclampsia toxemia; PIH, pregnancy-induced hypertension.

used inositol, but only in the MI form, but the combination of MI/DCI in a 40:1 ratio is a novel approach to trying to mirror what occurs in vivo (13,17). The study randomization process was successful. Our study population reflected the diverse population of our hospital. The study had a single researcher who had frequent contact with all participants. All women were provided with 24-h telephone access to the main researcher. This ensured a high level of continuity with good compliance throughout the study. A weakness was that this was an open-label study. This was a requirement of The Health Products Regulatory Authority (formerly the Irish Medicines Board). Therefore, there was a potential for bias as investigators were aware of which supplement was dispensed, and women were aware of which supplement they were taking. However, clinicians responsible for managing the pregnancy and delivery were blinded to which arm women were in.

Previous studies have focused on MI alone, in which there has been limited work with regard to MI/DCI in combination. It is possible that MI supplementation alone is more effective in glucose metabolism compared with MI/DCI in combination. Previous reports have reported on small numbers. Indeed, this has been highlighted as a potential limitation in a recent Cochrane review of antenatal supplementation with MI for the prevention of GDM (18).

MI has been shown to reduce the incidence of GDM in several different groups at risk for developing GDM. Previous trials have found that MI reduces the rate of GDM in women with PCOS, obesity, and a family history of GDM (13,14,19). In an RCT of 98 women with PCOS, the incidence of GDM in the intervention group was 17% (n = 7) compared with 54% (n = 20) in the control group (P = 0.001) (14). They concluded that the risk of GDM in the control group was double that compared with the MI group with an odds ratio of 2.4 (95% CI 1.3–4.4). A large RCT of 220 women in 2013 showed that the incidence of GDM in women with a family history of diabetes who took MI was 6.0% (n = 6) compared with 15.3% (n = 15) in those who did not (19). A third study from the same Italian group investigated the effect of MI in the prevention of GDM in women who were obese (13). This study showed that the incidence of GDM in the intervention group was 14.0% compared with 33.6% in the control group (P = 0.01).

The only study that used the combination of MI/DCI occurred outside of pregnancy. This was a study of 50 women that examined the effect of MI/DCI in the reduction of metabolic syndrome in women with PCOS (20). This study reported an improvement in the metabolic parameters of participants when given either MI alone or MI/DCI in combination. There was no difference between the two groups at the end of treatment, which lasted for 6 months. However, the combination of MI/DCI improved metabolic parameters sooner, with a statistical difference between the two groups observed after 3 months of treatment.

Previous studies used MI alone at a dose of 2–4 g/day (7,13,14). This is compared with 1,100 mg taken daily by the women in our study. The premise was that this dose in combination with DCI 27.6 mg/day may be effective in preventing GDM. The dosing regimen for combined MI/DCI in our study was extrapolated from the above study that gave MI/DCI to women who were not pregnant and had PCOS (20). However, we have found that this dose does not prevent the development of GDM, and we therefore believe it to be inadequate. We know from previous studies that inositol is safe at higher doses, so it would be of value for future research to focus on higher doses of MI/DCI when used in combination.

Contrary to previous research, our RCT found MI/DCI in combination did not reduce the incidence of GDM in those at risk because of a family history of DM. Therefore, MI/DCI at this dose should not be considered in routine antenatal supplementation. Indeed, we recommend that companies that manufacture antenatal supplements should not add inositol to their products, as there is not enough known regarding its efficacy. Similar to views held in previous reports, larger studies with varying doses of inositol are required to evaluate clinical effectiveness of inositol during pregnancy (18,21). For a future study to potentially show a reduction in GDM of 30%, 540 women would be required in each arm. However, a challenge with many of these women is defining their background risk as many have multiple risk factors for GDM.

Funding. This study was supported by Coombe Women & Infants University Hospital. The food supplement was provided at no cost from Lo.Li. Pharma.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.F. contributed to the conception and design of the study, performed the study, analyzed the data, and wrote and edited the manuscript. N.D. and A.M. collected data, analyzed data, and contributed to the writing and editing of the manuscript. B.K., M.J.T., and S.D. contributed to the conception and design of the study, analysis of data, and writing and editing of the manuscript. M.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Preliminary findings of this study were presented at the Annual Academic Meeting of the Royal College of Obstetricians & Gynaecologists, London, U.K., 3–4 March 2016.

References

1. Metzger BE, Coustan DR. Proceedings of the 4th International Workshop-Conference on Gestational Diabetes Mellitus. Chicago, Illinois, USA. 14-16 March 1997. Diabetes Care 1998; 21(Suppl. 2):B1–B167
2. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. Ann Intern Med 2013;159:123–129
3. Buckley BS, Harreiter J, Damm P, et al.; DALI Core Investigator Group. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabet Med 2012;29:844–854
4. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–682
5. Ali FM, Farah N, O'Dwyer V, O'Connor C, Kennelly MM, Turner MJ. The impact of new national guidelines on screening for gestational diabetes mellitus. Ir Med J 2013;106:57–59
6. Michell RH. The multiplying roles of inositol lipids and phosphates in cell control processes. Essays Biochem 1997;32:31–47
7. Saltiel AR. Second messengers of insulin action. Diabetes Care 1990;13:244–256
8. Clements RS Jr, Darnell B. Myo-inositol content of common foods: development of a high-myo-inositol diet. Am J Clin Nutr 1980;33: 1954–1967
9. Caro HN, Kunjara S, Rademacher TW, et al. Isolation and partial characterisation of insulin-mimetic inositol phosphoglycans from human liver. Biochem Mol Med 1997;61:214–228
10. McLean P, Kunjara S, Greenbaum AL, et al. Reciprocal control of pyruvate dehydrogenase kinase and phosphatase by inositol phosphoglycans. Dynamic state set by "push-pull" system. J Biol Chem 2008;283:33428–33436
11. Roche TE, Baker JC, Yan X, et al. Distinct regulatory properties of pyruvate dehydrogenase kinase and phosphatase isoforms. Prog Nucleic Acid Res Mol Biol 2001;70:33–75
12. Kunjara S, Wang DY, Greenbaum AL, McLean P, Kurtz A, Rademacher TW. Inositol phosphoglycans in diabetes and obesity: urinary levels of IPG A-type and IPG P-type, and relationship to pathophysiological changes. Mol Genet Metab 1999;68:488–502
13. D'Anna R, Di Benedetto A, Scilipoti A, et al. Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women: a randomized controlled trial. Obstet Gynecol 2015;126:310–315
14. D'Anna R, Di Benedetto V, Rizzo P, et al. Myo-inositol may prevent gestational diabetes in PCOS women. Gynecol Endocrinol 2012;28: 440–442
15. Fattah C, Farah N, Barry SC, O'Connor N, Stuart B, Turner MJ. Maternal weight and body composition in the first trimester of pregnancy. Acta Obstet Gynecol Scand 2010;89:952–955
16. Coombe Women & Infants University Hospital. Annual clinical report [Internet], 2014. Dublin, Ireland, Coombe Women & Infants University Hospital. Available from http://www.coombe.ie/download.php?downloadId=1224. Accessed 8 March 2017
17. Unfer V, Porcaro G. Updates on the myo-inositol plus D-chiro-inositol combined therapy in polycystic ovary syndrome. Expert Rev Clin Pharmacol 2014;7:623–631
18. Crawford TJ, Crowther CA, Alsweiler J, Brown J. Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes. Cochrane Database Syst Rev 2015;12:CD011507
19. D'Anna R, Scilipoti A, Giordano D, 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;36:854–857
20. Nordio M, Proietti E. The combined therapy with myo-inositol and D-chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone. Eur Rev Med Pharmacol Sci 2012;16:575–581
21. Coustan DR. Can a dietary supplement prevent gestational diabetes mellitus? Diabetes Care 2013;36:777–779