

MINIREVIEW

Prevention of Gestational Diabetes Mellitus. Minireview

Doi: 10.36129/jog.2022.28

Rosario D'Anna

Department of Human Pathology, University of Messina, Messina, Italy

ABSTRACT

Gestational Diabetes Mellitus (GDM) is associated with adverse maternal, fetal and neonatal outcomes and is increasing worldwide probably for the increasing rate of overweight and obesity, being the latter a major risk factor. To these women with well recognized risk factors some interventions to prevent GDM should be offered. In this way, possible interventions are diet and/or exercise, metformin and myo-inositol. Diet and exercise are considered first line for the prevention of GDM, but in particular kind of pregnant women like obese, who usually follow unhealthy life styles, this type of intervention may fail. Metformin is usually used for the treatment of Diabetes Mellitus type 2 and recently also for hyperinsulinemic infertile women affected by polycystic ovary syndrome with the aim to restore ovarian cycle and ovulation. In these women, metformin was given off-label throughout pregnancy, but in prospective, randomized trials, especially when obese women are involved, metformin failed to prevent GDM. On the other hand, a supplement, myo-inositol demonstrated to reduce GDM rate when it was given since first trimester. This review analyses the effect of these three interventions for preventing GDM with the help of the most recent literature.

KEY WORDS

GDM, diet, exercise, life-style, metformin, myo-ionositol.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance that occurs for the first time or is first detected during pregnancy, but does not fulfil the criteria of overt diabetes (1). GDM is associated with adverse maternal, obstetrical and neonatal outcomes (2). In particular, women with GDM are more frequently affected by hypertensive syndromes and increased rate of caesarean section; furthermore, a future development of diabetes mellitus type 2 may occur. Fetuses of women with GDM are frequently large for gestational age with a higher rate of shoulder dystocia. In the newborns, hyperglycemia may be frequent and sometimes serious, and in the childhood an increased metabolic risk has been shown, such as obesity and higher blood pressure (3). Prevalence of GDM is increasing worldwide, principally for the increasing rate of overweight and obese pregnant women; furthermore, it may depend on different methods of diagnosis too. However, a recent meta-analysis (4) evidenced a GDM prevalence of about 11% in Europe and the same rate was in Italy too. Other risk factors are family history for diabetes type 2, ethnicity and advanced maternal age. In these recognized women at high risk for GDM, adequate interventions may prevent an unhealthy lifestyle like hypercaloric diet, inactivity, and excessive gestational weight gain. Among interventions for preventing GDM, at least three are considered of possible benefit: changes in lifestyle like diet and exercise, myo-inositol, and metformin, even if further high-quality studies are needed to make more robust data until now achieved (5).

DIET AND/OR EXERCISE

In a recent meta-analysis, comparing with standard care, a 23% reduction in the risk of GDM was shown as overall effect of intervention like only diet, or only exercise or mixed, showing no significant difference between these 3 types of interventions (6). This study demonstrated that one of the most important variable that may heavily influence GDM diagnosis was the excessive weight gain through pregnancy in accordance with Institute of Medicine guidelines (7). Furthermore, it was shown that the preventive effect of the interventions were more successful when the baseline risk of GDM was higher, like in the obese women (6), and that it was maximum when the intervention began early in pregnancy; in fact, it has been shown that pre-pregnancy physical activity may reduce GDM rate of 55% (8). Aerobic exercise should go on for a minimum of 15 minutes, at least 3 times a week and should be increased during the second trimester up to a maximum of 30 minutes, 4 times to week (9). A limitation of these type of GDM prevention was the adherence to the intervention, which is usually poor as reported by and Italian study (10). It's very difficult for an obese woman with an unhealthy lifestyle, to change it during pregnancy, thus the compliance of these high risk women for these types of interventions (diet and/or exercise) is often poor. This is why a lot of them prefer assuming drug or supplement than sacrifice themselves with strict diet or deep changes in their lifestyle.

METFORMIN

Metformin is a biguanide derivative with insulin sensitizer effects. It's the most common oral drug used for the treatment of Diabetes Mellitus (DM). Metformin reduces plasma insulin concentration improving peripheral glucose uptake and reducing glucose production by the liver (gluconeogenesis). First use of metformin in non diabetic subjects was for infertile women affected by Polycystic Ovary Syndrome (PCOS), who are very often hyperinsulinemic and this may disturb ovarian cycle preventing ovulation. Thus metformin is currently used to improve ovulation rate in infertile women with PCOS, with beneficial effects compared to placebo (11). Since infertile hyperinsulinemic pregnant women with PCOS were at high risk for developing GDM and other adverse pregnancy outcomes, such as miscarriages or hypertensive syndromes, researchers were encouraged to continue metformin treatment throughout pregnancy although it was off label. Some prospective cohort studies (12,13) demonstrated a significant reduction of GDM when metformin was given from the first trimester of pregnancy. But the first randomized, double blind, controlled study didn't confirm a beneficial effect of metformin in preventing GDM (14). Other 2 large randomized, controlled studies carried out with obese women, with a dosage of 3 g per day, failed to demonstrate a reduced rate of GDM compared to placebo (15,16). Furthermore, a recent Cochrane Review confirms that the use of metformin didn't prevent GDM (5). Furthermore, gastrointestinal side effects are common when metformin is used determining sometimes a reduction of daily dosage (16). Safety for the fetus is still questionable even if no significant differences were reported between treated and not treated women in the two large recent studies regarding fetal and neonatal outcomes (15,16). A follow-up study with these children at 4-7 years old is still ongoing.

MYO-INOSITOL

Myo-inositol (MI) is a polyol and it is the most abundant of the nine isomeric forms of inositol, a ubiquitous substance in nature. MI is abundant in a lot of food like fruits and vegetables, but also in meat. Human body may produce MI from D-glucose, especially in the kidney (17). An epimerase may convert MI in another inositol isomer, D-chiro-inositol (DCI); the conversion rate of MI to DCI

in muscle and liver is almost 9% (18). Both are contained in inositol phosphoglycans, which act as insulin mediators (19). In particular, MI promotes glucose uptake in tissues that have high glucose utilization such as brain, heart and ovary (20), whereas DCI promotes glycogen synthesis in tissues specialized in glycogen storage, such as liver, muscle and fat (21). As matter of fact, MI may reduce circulating insulin with beneficial effects on Polycystic Ovary syndrome (PCOS) in which hyperinsulinemia affects ovarian cycle provoking anovulation and infertility. PCOS was the syndrome in which MI was firstly used, obtaining normal cycles and pregnancies in infertile women with amenorrhea and anovulation (22), and recently a reduction of miscarriages too (23). In our Unit, women affected by PCOS were treated with MI until they became pregnant, but also during whole the pregnancy (24). Our first study was a retrospective one carried out on the charts of PCOS women treated with MI, with the aim to find out which was the GDM rate (24). Although it was a limited number of women, the difference was statistically significant comparing GDM rate in PCOS women treated with MI (17%) and a control not treated PCOS group (54%) (24). This first study encouraged us to perform prospective studies in which MI might be used for the prevention of GDM. Thus, we began three prospective, randomized, controlled study involving women with 3 different risk factors for GDM: a family history with DM type 2 (25); obesity (26) and overweight (27) women. The rate of GDM in the control group of each study was obviously different, being 15%, 27% and 33% respectively, depending on the severity of the risk factor. On the other hand, in the treated group the reduction of GDM diagnosis rate was highly significant: 6%, 11% and 14% respectively. Interestingly the rate of reduction of GDM diagnosis was the same, about 2/3 in the group treated with MI (4 g/day). Furthermore, in the study carried out with the obese women a reduction in insulin resistance in the group treated with MI was demonstrated (26). A similar study (28), in which a lower dosage (1.2 g/die) of MI was used, failed to show the decrease of GDM rate in women treated with MI, suggesting that the successful result of MI is dose dependent. However, different meta-analysis demonstrated that MI may reduce GDM rate with a significant difference between groups (5,29). In a secondary analysis (30), databases of the 3 studies were considered all together with the aim of exploring whether MI was effective also in improving clinical outcomes of those women. Total number of women enrolled in the 3 studies was 660, which is underpowered in regard to clinical outcomes like hypertensive syndromes or pre-term birth for which the number should be double. However, some significant statistically differences were highlighted in this secondary analysis (30). In particular, pre-term birth and rate of macrosomic and large for gestational age fetuses were significantly decreased in the group treated with MI. A very recent experimental study (31) could support inositol use for the prevention of GDM; the Authors demonstrated that placental inositol content was 17% lower in women with GDM compared to controls. Fasting glycemia was associated with a reduced placental myo-inositol synthesis and with a reduced expression of inositol transporters. Furthermore, low placental inositol correlated positively with accelerated fetal growth (31). Another important issue is the safety profile of MI and 2 recent meta-analysis (5, 29) reported no maternal adverse events and no congenital malformations in newborns. On the contrary, it's remarkable that MI has been shown to be effective in the prevention of neural tube defects (32) Furthermore, American "Food and Drug Administration" includes MI in the list of compound considered generally safe (33).

In conclusion, lifestyle changes should be the first line of intervention for GDM prevention, but difference with no intervention is still not so clear probably for a poor compliance of the women, in particular for overweight and obese. Metformin, the most used in DM treatment is not so effective in GDM and women complain several side effects. MI seems to be effective and safe with a good compliance in pregnant women, it could be a promising supplement for GDM prevention

REFERENCES

[1] American Diabetes Association. Classification and diagnosis of diabetes. Standard of medical care in diabetes. Diabetes Care 2020; 43(suppl 1), S14–S31.

- [2] The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New Engl J Med* 2008; 358:1991-2002.
- [3] Tam WH, Ma RCW, Ozaki R, Li AM, Chan MHM, Yuen LY, Lao TTH, Yang X, Ho CS, Tutino GE, Chan JCN. In Utero Exposure to Maternal Hyperglycemia Increases Childhood Cardiometabolic Risk in Offspring. *Diabetes Care* 2017; 40:679-86.
- [4] Paulo MS, Abdo NM, Bettencourt-Silva R, Al-Rifai RH. Gestational Diabetes Mellitus in Europe: Systematic Review and Meta-analysis of prevalence studies. *Front Endocrinol (Lausanne)* 2021; 12 :691033)
- [5] Griffith RJ, Alsweiler J, Moore AE, Brown S, Middleton P, Shepherd E, Crowther CA. Interventions to prevent women from developing gestational diabetes mellitus: an overview of Cochrane Reviews. *Cochrane Database Syst Rev* 2020; Jun 11;6(6):CD012394.doi: 10.1002/14651858.CD012394.pub3.
- [6] Guo X-Y, Shu J, Fu X-H, Chen X-P, Zhang L, Ji M-X, Liu X-M, Yu T-T, Sheng J-Z, Huang H-F. Improving the effectiveness of lifestyle interventions for gestational diabetes prevention: a meta-analysis and meta-regression. *BJOG* 2019; 126:311-20.
- [7] Rasmussen K, Yaktine AL, eds; Institute of Medicine; National Research Council. *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, DC: National Academies Press; 2009.
- [8] Tobias DK, Zhang C, van Dam RB, Bowers K, Hu FB. Physical activity before and during pregnancy and risk of gestational diabetes mellitus: a meta-analysis. *Diabetes Care* 2011; 34:223-9.
- [9] Bianchi C, Aragona M, Bertolotto A, Bottone P, Calabrese, Cuccuru I, et al. Improving prescription of physical exercise in prophylaxis/therapy of gestational diabetes: a survey from evidence to current recommendations. *Italian Journal of Gynecology and Obstetrics* 2016; 28: 15-22.
- [10] Bruno R, Petrella E, Bertarini V, Pedrielli G, Neri I, Facchinetti F. Adherence to a lifestyle programme in overweight/obese pregnant women and effect on gestational diabetes mellitus: a randomized controlled trial. *Matern Child Nutr* 2017; Jul;13(3):e12333 doi: 10.1111/mcn.12333. Epub 2016 Sep 19.
- [11] Sharpe A, Morley LC, Tang T, Norman RJ, Balen AH. Metformin for ovulation induction (excluding gonadotrophins) in women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2019, Dec 17;12(12):CD013505.
- [12] Katthab S, Mohsen IA, Aboul Foutouh I, Ashmawi HS, Mohsen MN, van Wely M, van der Veen F, Youssef MA. Can metformin reduce the incidence of gestational diabetes mellitus in pregnant women with polycystic ovary syndrome? Prospective cohort study. *Gynecol Endocrinol* 2011; 27:789-93.
- [13] De Leo V, Musacchio MC, Piomboni P, Di Sabatino A, Morgante G. The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications. *Eur J Obstet Gynecol Reprod Biol* 2011; 157:63-6.
- [14] Vanky E, Stridsklev S, Heinstad R, Romunstad P, Skogoi K, Kleggetveit O, Hjelle S, von Brandis P, Eikeland T, Flo K, Berg KF, Bunford G, Lund A, Bjerke C, Almas I, Berg AK, Danielson A, Lahmami G, Carlsen SM. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab* 2010; 95:E448-55.

- [15] Chiswick C, Reynolds RM, Denison F, Drake AJ, Forbes S, Newby DE, Walker BR, Quenby S, Wray S, Weeks A, Lashen H, Rodriguez A, Murray G, Whyte S, Norman JE. Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2015; 3:778-86.
- [16] Syngelaki A, Nicolaidis KH, Balani J, Hyer S, Akolekar R, Kotecha R, Pastides A, Shehata H. Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus. *NEJM* 2016; 374:534-43.
- [17] Beemster P, Groenen P, Steegers-Theunissen R. Involvement of inositol in reproduction. *Nutr Rev* 2002; 60:80-7.
- [18] Pak Y, Huang LC, Lilley KJ, Larner J. In vivo conversion of [3H]myo-inositol to [3H] D-chiro-inositol in rat tissues. *J Biol Chem* 267:16904-10.
- [19] Di Paolo G, De Camilli P. Phosphoinositides in cell regulation and membrane dynamics. *Nature*. 2006;443:651-7.
- [20] Nestler JE, Unfer V. Reflections on inositol(s) for PCOS therapy: steps toward success. *Gynecol Endocrinol* 2015;31:501-5.
- [21] Croze ML, Soulage CO. Potential role and therapeutic interests of myo-inositol in metabolic diseases. *Biochimie* 2013;95:1811-27.
- [22] Facchinetti F, Bizzarri M, Benvenga S, D'Anna R, Lanzone A, Soulage C, Di Renzo GC, Hod M, Cavalli P, Chiu TT, Kamenov ZA, Bevilacqua A, Carlomagno G, Gerli S, Montanino Oliva M, Devroey P. Results from the International Consensus Conference on Myo-inositol and D-chiro-inositol in Obstetrics and Gynecology: the link between metabolic syndrome and PCOS. *Eur J Obstet Gynecol Reprod Biol* 2015; 195:72-6.
- [23] Soufizadeh N, Farhadifar F, Seydoshohadaei F, Rezaei M, Rasouli MA, Ebrahimpour K. The effect of inofolic supplementation on women with polycystic ovarian syndrome (PCOS): a Randomized Clinical Trial study. *Italian Journal of Gynecology and Obstetrics* 2021; 33:256-62.
- [24] D'Anna R, Benedetto V, Rizzo P, Raffone E, Interdonato ML, Corrado F, Di Benedetto A. Myo-inositol may prevent gestational diabetes in PCOS women. *Gynecol Endocrinol* 2012; 28:440-2.
- [25] D'Anna R, Scilipoti A, Giordano D, Caruso C, Cannata ML, Interdonato ML, Corrado F, Di Benedetto A. Myo-Inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes. *Diabetes Care* 2013; 36:854-7.
- [26] D'Anna R, Di Benedetto A, Scilipoti A, Santamaria A, Interdonato ML, Petrella E, Neri I, Pintaudi B, Corrado F, Facchinetti F. Myo-inositol Supplementation for Prevention of Gestational Diabetes in Obese Pregnant Women: A Randomized Controlled Trial. *Obstet Gynecol* 2015;126:310-5.

[27] Santamaria A, Di Benedetto A, Petrella E, Pintaudi B, Corrado F, D'Anna R, Neri I, Facchinetti F. Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial. *J Matern Fetal Neonatal Med* 2016; 29:3234-7.

[28] Farren M, Daly N, McKeating A, Kinsley B, Turner MJ, Daly S. The prevention of gestational diabetes mellitus with antenatal oral inositol supplementation. A randomized, controlled trial. *Diabetes Care* 2017;40:759-63.

[29] Vitagliano A, Saccone G, Cosmi E, Visentin S, Dessole F, Ambrosini G, Berghella V. Inositol for the prevention of gestational diabetes: a systematic review and meta-analysis of randomized, controlled studies. *Arch Gynecol Obstet* 2019; 299:55-68.

[30] Santamaria A, Alibrandi A, Di Benedetto A, Pintaudi B, Corrado F, Facchinetti F, D'Anna R. Clinical and metabolic outcomes in pregnant women at risk for gestational diabetes mellitus supplemented with myo-inositol: a secondary analysis from 3 RCTs. *Am J Obstet Gynecol.* 2018; 219:300e1–300e6.

[31] Pillai RA, Islam MO, Selvam P, Sharma N, Chu AHY, Oliver C et al. Placental inositol reduced in Gestational diabetes as glucose alters inositol transporters and IMPA1 enzyme expression. *J Clin Endocrinol Metab* 2021; 106:e875-e890.

[32] Gambioli R, Forte G, Buzzaccarini G, Unfer V, Laganà AS. Myo-Inositol as a Key Supporter of Fertility and Physiological Gestation. *Pharmaceuticals (Basel)* 2021; 14:504.

[33] Facchinetti F, Cavalli P, Copp AJ, D'Anna R, Kandarakis E, Greene NDE, Unfer V; Experts Group on Inositol in Basic and Clinical Research. An update on the use of inositols in preventing gestational diabetes mellitus (GDM) and neural tube defects (NTDs). *Expert Opin Drug Metab Toxicol* 2020;16:1187-1198.