

# Can a Dietary Supplement Prevent Gestational Diabetes Mellitus?

**G**estational diabetes mellitus (GDM), glucose intolerance with onset or first recognition during pregnancy, has been increasing (1) and will increase further with widespread adoption of new diagnostic criteria recommended by the American Diabetes Association (ADA) (2). GDM, even at the milder end of the diagnostic spectrum, is associated with fetal macrosomia, neonatal adiposity, pre-eclampsia, and cesarean section (3), which can be reduced by diagnosis and treatment (4,5). Such treatment is not without cost (6), and an effective, relatively simple, inexpensive approach to prevention could result in significant savings to the health care system, not to mention decreasing morbidity. In this issue of *Diabetes Care*, D'Anna et al. (7) describe a randomized controlled trial (RCT) of such a potential prevention strategy.

Insulin resistance is characteristic of human pregnancy and may have evolved to ensure the fetus a continued supply of nutrients even in times of famine. Most gravidas increase insulin release and maintain euglycemia, while those with GDM are unable to do so adequately. While metformin, an insulin-sensitizing drug, initially appeared to prevent GDM in nonrandomized cohort studies, a double-blind RCT did not demonstrate efficacy (8). Inositol, present in many foods, is a component of inositolphosphoglycans, a second messenger for insulin action (9) (Fig. 1), and two of its nine isoforms, *myo*-inositol and *chiro*-inositol, have been used as insulin-sensitizing agents to treat insulin-resistant states such as polycystic ovary syndrome (PCOS) in doses ranging from 200 mg/day to 4 g/day (10–12). The authors of the current study have also demonstrated in an RCT a beneficial effect of *myo*-inositol in treating the metabolic syndrome in postmenopausal women (13). These same authors (14) reported a lower incidence of GDM (17 vs. 54%) among 46 PCOS patients who conceived on *myo*-inositol (4 g/day) and continued this regimen throughout pregnancy compared with 37 PCOS patients who conceived on metformin and discontinued it once pregnancy was diagnosed. In a randomized trial they demonstrated a greater reduction in insulin resistance

in women with GDM treated with *myo*-inositol and folic acid than in control GDM subjects treated with folic acid alone (15).

In the open-label RCT published in this issue of *Diabetes Care* (7), 110 non-obese gravidas, whose only risk factor for GDM was a first-degree relative with diabetes, were given *myo*-inositol 2 g twice daily along with folic acid 400  $\mu$ g twice daily from the end of the first trimester throughout the remainder of the pregnancy. Control subjects were 110 similar gravidas randomized to receive only the 400  $\mu$ g of folic acid twice daily. GDM (ADA criteria [2]) occurred in 6% of *myo*-inositol treated subjects versus 15% of control subjects ( $P = 0.04$ ). Fetal macrosomia was also reduced (0 vs. 7%,  $P = 0.007$ ) and average birth weight was 162 g lower in the treated group. The authors conclude that this preliminary report is good news, although larger confirmatory studies are needed.

RCTs are the strongest level of evidence, although it would have been preferable if the study were double-blinded rather than open-label. While GDM and macrosomia were reduced by the intervention, some less frequent outcomes such as hypertensive disorders, cesarean section, and shoulder dystocia were not different between *myo*-inositol-treated subjects and control subjects. While the study was underpowered to assess an effect on these outcomes, larger trials should answer these open questions. In this study, as in the authors' previous report on gravidas with GDM (15), fasting plasma glucose was reduced with *myo*-inositol treatment, as was the 1-h value on the 75-g oral glucose tolerance test compared with control subjects. Much of the increase in GDM is thought to be attributable to population increases in obesity. Because obese subjects were excluded from this study—and even overweight subjects were probably not common since the average prepregnancy BMI was around 23 kg/m<sup>2</sup>—it remains to be seen whether *myo*-inositol would be similarly effective in overweight and obese subjects. In the analysis reported, BMI had an effect on the development of

GDM that was independent of *myo*-inositol supplementation.

When a treatment is proposed for use in pregnancy, special consideration must be given to safety for the mother and the fetus. *myo*-Inositol is present in many foods, particularly fresh fruits and vegetables, beans, grains, and nuts. It is not considered a drug but rather a dietary supplement and is thus not subject to the jurisdiction of the U.S. Food and Drug Administration. It is widely available online and in health food stores, but the advertised composition of such supplements must be interpreted with caution given the lack of regulation and monitoring. When the *myo*-inositol content of various foods was analyzed, an average 2,500 kcal American diet was estimated to contain approximately 900 mg of inositol (16). A review of data from 12 clinical trials in which *myo*-inositol was used for treatment of PCOS, erectile dysfunction, depression, and other psychiatric disorders found that mild gastrointestinal side effects were reported only with doses of 12 g/day or more (17). The dosage used in the RCT reported herein was 4 g/day. Fetal effects, if any, should be proportional to the ease with which a substance crosses the placenta. Metformin, for example, is concentrated on the fetal side of the placenta (18), and it is unclear whether fetal effects are harmful, beneficial, or neutral. Measurements of fetal levels of maternally infused stable isotope-labeled *myo*-inositol in normal pregnancies at term demonstrated that less than 10% of fetal inositol was maternally derived, suggesting little placental transport in late pregnancy (19).

A review of exogenous use of inositol (20) recommended caution in its use during pregnancy, citing two studies suggesting that inositol may stimulate uterine contractions. The cited studies demonstrated that oxytocin induced the formation of inositol triphosphate in cultured myometrial cells, suggesting that inositol triphosphate may act as a second messenger for oxytocin (21), and that inositol triphosphate can stimulate isolated rat uterine muscle segment contractions



- Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009;361:1339–1348
6. Moss JR, Crowther CA, Hiller JE, Willson KJ, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women Group. Costs and consequences of treatment for mild gestational diabetes mellitus—evaluation from the ACHOIS randomised trial. *BMC Pregnancy Childbirth* 2007;7:27–34
  7. 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
  8. Vanky E, Stridsklev S, Heimstad R, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab* 2010;95:E448–E455
  9. Saltiel AR. Second messengers of insulin action. *Diabetes Care* 1990;13:244–256
  10. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. *N Engl J Med* 1999;340:1314–1320
  11. Gerli S, Mignosa M, Di Renzo GC. Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double blind placebo-controlled trial. *Eur Rev Med Pharmacol Sci* 2003;7:151–159
  12. Unfer V, Carlomagno G, Dante G, Facchinetti F. Effects of *myo*-inositol in women with PCOS: a systematic review of randomized controlled trials. *Gynecol Endocrinol* 2012;28:509–515
  13. Santamaria A, Giordano D, Corrado F, et al. One-year effects of *myo*-inositol supplementation in postmenopausal women with metabolic syndrome. *Climacteric* 2012;15:490–495
  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. Corrado F, D'Anna R, Di Vieste G, et al. The effect of *myo*inositol supplementation on insulin resistance in patients with gestational diabetes. *Diabet Med* 2011;28:972–975
  16. 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
  17. Carlomagno G, Unfer V. Inositol safety: clinical evidences. *Eur Rev Med Pharmacol Sci* 2011;15:931–936
  18. Vanky E, Zahlens K, Spigset O, Carlsen SM. Placental passage of metformin in women with polycystic ovary syndrome. *Fertil Steril* 2005;83:1575–1578
  19. Staat BC, Galan HL, Harwood JEF, et al. Transplacental supply of mannose and inositol in uncomplicated pregnancies using stable isotopes. *J Clin Endocrinol Metab* 2012;97:2497–2502
  20. Colodny L, Hoffman RL. Inositol—clinical applications for exogenous use. *Altern Med Rev* 1998;3:432–447
  21. Phaneuf S, Europe-Finner GN, Carrasco MP, Hamilton CH, López Bernal A. Oxytocin signalling in human myometrium. *Adv Exp Med Biol* 1995;395:453–467
  22. Chien EK, Saunders T, Phillippe M. The mechanisms underlying Bay K 8644-stimulated phasic myometrial contractions. *J Soc Gynecol Investig* 1996;3:106–112
  23. Dessì A, Atzori L, Noto A, et al. Metabolomics in newborns with intrauterine growth retardation (IUGR): urine reveals markers of metabolic syndrome. *J Matern Fetal Neonatal Med* 2011;24(Suppl. 2):35–39
  24. Scioscia M, Kunjara S, Gumaa K, McLean P, Rodeck CH, Rademacher TW. Urinary excretion of inositol phosphoglycan P-type in gestational diabetes mellitus. *Diabet Med* 2007;24:1300–1304