OBSTETRICS

Impact of probiotics in women with gestational diabetes mellitus on metabolic health: a randomized controlled trial

Karen L. Lindsay, PhD; Lorraine Brennan, PhD; Maria A. Kennelly, MRCPI; Orla C. Maguire, MSc; Thomas Smith, PhD; Sinead Curran, BSc; Mary Coffey, MSc; Michael E. Foley, MD; Mensud Hatunic, MD; Fergus Shanahan, MD; Fionnuala M. McAuliffe, MD

OBJECTIVE: Probiotics are live microorganisms that may confer health benefits on the host. Recent trials of probiotic use among healthy pregnant women demonstrate potential for improved glycemic control. The aim of this study was to investigate the effects of a probiotic capsule intervention on maternal metabolic parameters and pregnancy outcome among women with gestational diabetes.

STUDY DESIGN: This double-blind placebo-controlled randomized trial recruited pregnant women with a new diagnosis of gestational diabetes or impaired glucose tolerance following a 3-hour 100-g glucose tolerance test. Women were randomized to a daily probiotic (*Lactobacillus salivarius* UCC118) or placebo capsule from diagnosis until delivery. Fasting blood samples were collected at baseline and 4-6 weeks after capsule commencement for analysis of glucose, insulin, c-peptide, and lipids. The primary outcome was difference in fasting glucose postintervention, first analyzed on an intention-to-treat basis and followed by per-protocol analysis that excluded women commenced on pharmacological therapy (insulin or metformin). Secondary outcomes were changes in insulin, c-peptide, homeostasis model assessment and lipids, requirement for pharmacological therapy, and neonatal anthropometry.

RESULTS: Of 149 women recruited and randomized, there were no differences between the probiotic and placebo groups in postintervention fasting glucose (4.65 ± 0.49 vs 4.65 ± 0.53 mmol/L; $P = 373$), requirement for pharmacological therapy (17% vs 14%; $P = .643$), or birthweight (3.57 ± 0.64 vs 3.60 ± 0.57 kg; $P = .845$). Among 100 women managed with diet and exercise alone, fasting plasma glucose decreased significantly within both the probiotic (4.76 ± 0.45 to 4.57 ± 0.42 mmol/L; $P < .001$) and placebo (4.85 ± 0.58 to 4.58 ± 0.45 mmol/L; $P < .001$) groups, but the levels between groups did not differ ($P = .316$). The late gestation-related rise in total and low-density lipoprotein (LDL) cholesterol was attenuated in the probiotic vs the placebo group (+0.27 ± 0.48 vs +0.50 ± 0.52 mmol/L total cholesterol, $P = .031$; +0.08 ± 0.51 vs +0.31 ± 0.45 mmol/L LDL cholesterol, $P = .011$). No differences were noted between groups in other metabolic parameters or pregnancy outcome.

CONCLUSION: A probiotic capsule intervention among women with abnormal glucose tolerance had no impact on glycemic control. The observed attenuation of the normal pregnancy-induced rise in total and LDL cholesterol following probiotic treatment requires further investigation, particularly in this obstetric group at risk of future metabolic syndrome.

Key words: gestational diabetes, glycemic control, low-density lipoprotein cholesterol, probiotics, total cholesterol

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From UCD Obstetrics and Gynecology, School of Medicine and Medical Science, and National Maternity Hospital (Drs Lindsay, Kennelly, Foley, and McAuliffe), and UCD Institute of Food and Health, School of Agriculture and Food Science (Dr Brennan), University College Dublin; Department of Clinical Chemistry, St. Vincent's University Hospital, Elm Park (Ms Maguire and Dr Smith); Department of Clinical Nutrition, National Maternity Hospital (Ms Curran); and Departments of Midwifery (Ms Coffey) and Endocrinology (Dr Hatunic), National Maternity Hospital, Dublin, and Department of Medicine, Alimentary and Pharmabiotic Center, University College Cork, Cork (Dr Shanahan), Ireland.

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Corresponding author: Fionnuala M. McAuliffe, MD. fionnuala.mcauliffe@ucd.ie

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Gestational diabetes mellitus (GDM) is one of the most frequent metabolic complications of pregnancy with an estimated prevalence of up to 12% in developed economies.[1] GDM rates are likely to continue to rise under the growing burden of maternal obesity and adoption of new diagnostic criteria in some centers, which would result in the diagnosis of women previously considered to have normal glucose tolerance.[2] Thus, effective delivery of dietary and lifestyle advice and medical management of women with GDM in centers with limited resources may prove difficult. Furthermore, obese pregnant women with GDM may be less amenable to adopting recommended lifestyle behavior changes due to poor motivation and self-efficacy.[3] Therefore, research into new therapies for glucose control, which may complement current diet, exercise, and pharmacological therapies, may be of significant benefit for the future of GDM management.

Probiotics, defined as live microorganisms that may confer a health benefit on the host,[4] potentially represent a new and novel mechanism for influencing metabolic health during pregnancy.[5] Probiotics may safely and effectively manipulate the human gut microbial composition and function, to reduce the adverse metabolic effects associated with pathogenic microbial communities.[6,7] On this basis, the use of probiotics in pregnancy for improving maternal metabolic and pregnancy outcomes has been the topic of recent reviews.[8-11] However, there have been only 3 published randomized controlled trials (RCT) to date that have directly investigated the glycemic effects of probiotics in pregnancy, either among healthy pregnant women[12,13] or women at risk of GDM.[14] These studies report a mix of positive and null outcomes. However, the positive glycemic effects of probiotics reported among nonpregnant individuals with diabetes[7] raises the question as to whether probiotics could aid the treatment of women with GDM.

The objective of the Probiotics in Pregnancy Study was to investigate the effect of a daily probiotic supplement vs placebo on fasting glucose, other metabolic parameters and pregnancy outcome among women with a new diagnosis of either impaired glucose tolerance (IGT) or GDM not treated with pharmacological therapy.

Materials and Methods

Study design and setting

This was a single-center, double-blind, placebo-controlled, randomized trial with maternal written consent, conducted in accordance with the standards of the National Maternity Hospital (NMH) Ethics Committee, which granted full ethical approval for the trial in November 2011. The trial is registered on Current Controlled Trials (ISRCTN97241163 Part B).

Patient selection and recruitment

The Probiotics in Pregnancy Study population was a presenting sample of pregnant women attending the NMH who were newly diagnosed with either IGT (1 raised value) or GDM (≥2 raised values) following a 3-hour 100-g oral glucose tolerance test[15] in the current pregnancy. Routine clinical care for diagnosed women attending the hospital includes advice on a low glycemic index diet, self-monitoring blood glucose levels using glucometers, and fortnightly attendance at the diabetes clinic for monitoring of glucose control. At follow-up clinic visits, if a patient has a fasting plasma glucose >5 mmol/L (90 mg/dL) and/or 1-hour postprandial plasma glucose >7 mmol/L (126 mg/dL) following a standard breakfast, and the patient is considered to be compliant to the low glycemic index diet at home, dietary control of glucose is deemed inadequate and treatment with metformin or insulin is commenced.

Women were approached by the research dietitian during the dietary and lifestyle education class, which is run weekly in the NMH for women with IGT or GDM. Information sheets were provided and written consent was obtained from eligible and willing participants. Inclusion criteria were a new diagnosis of IGT or GDM in the current pregnancy, age >18 years, <34 weeks' gestation, singleton pregnancy and adequate English to enable full understanding of the study. Women were excluded if they had pregestational diabetes, were aged <18 years, were ≥34 weeks' gestation, had a multiple pregnancy or fetal anomaly, were commenced on insulin or metformin therapy immediately after diagnosis, or had a poor understanding of the English language.

Blinding, masking, and randomization

The probiotic and placebo capsules were produced and supplied by Alimentary Health Ltd, Cork, Ireland, and anonymously labeled as "A" or "B." Each active probiotic capsule contained 100 mg of *Lactobacillus salivarius* UCC118 at a target dose of 10^9 colony-forming units. Further details of the probiotic and placebo capsule contents and packaging have been previously described.[14]

Allocation to either one of the capsules was conducted by an independent researcher using a computer-generated simple randomization process in a ratio of 1:1. No stratification factors were applied. The allocation sequence was concealed from the research dietitian enrolling and assessing the participants in sequentially numbered, sealed, opaque envelopes. After written informed consent was obtained and baseline assessments were completed, the envelope corresponding to each participant study identification number was opened to reveal the allocation to capsule A or B. Although, the research dietitian was then aware that all participants allocated to one of the capsules were all in the same treatment arm, the identity of the treatment arm remained unknown. To minimize risk of bias, all clinical and laboratory staff who were involved with care of study participants or analysis of samples remained blinded to the allocation sequence.

Data collection, intervention, and trial management

On recruitment, the research dietitian provided each participant with an information sheet outlining fermented and probiotic-containing foods and supplements to avoid throughout the remainder of their pregnancy to minimize the risk of confounding from the