



Myo-Inositol, Probiotics, and Micronutrient Supplementation From Preconception for Glycemia in Pregnancy: NiPPeR International Multicenter Double-Blind Randomized Controlled Trial

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OBJECTIVE

Better preconception metabolic and nutritional health are hypothesized to promote gestational normoglycemia and reduce preterm birth, but evidence supporting improved outcomes with nutritional supplementation starting preconception is limited.

RESEARCH DESIGN AND METHODS

This double-blind randomized controlled trial recruited from the community 1,729 U.K., Singapore, and New Zealand women aged 18–38 years planning conception. We investigated whether a nutritional formulation containing *myo*-inositol, probiotics, and multiple micronutrients (intervention), compared with a standard micronutrient supplement (control), taken preconception and throughout pregnancy could improve pregnancy outcomes. The primary outcome was combined fasting, 1-h, and 2-h postload glycemia (28 weeks' gestation oral glucose tolerance test).

RESULTS

Between 2015 and 2017, participants were randomized to control ($n = 859$) or intervention ($n = 870$); 585 conceived within 1 year and completed the primary outcome (295 intervention, 290 control). In an intention-to-treat analysis adjusting for site, ethnicity, and preconception glycemia with prespecified $P < 0.017$ for multiplicity, there were no differences in gestational fasting, 1-h, and 2-h glycemia between groups (β [95% CI] \log_e mmol/L intervention vs. control -0.004 [-0.018 to 0.011], 0.025 [-0.014 to 0.064], 0.040 [0.004 – 0.077], respectively). Between the intervention and control groups there were no significant differences in gestational diabetes mellitus (24.8% vs. 22.6%, adjusted risk ratio [aRR] 1.22 [0.92–1.62]), birth weight (adjusted $\beta = 0.05$ kg [-0.03 to 0.13]), or gestational age at birth (mean 39.3 vs. 39.2 weeks, adjusted $\beta = 0.20$ [-0.06 to 0.46]), but there were fewer preterm births (5.8% vs. 9.2%, aRR 0.43 [0.22–0.82]), adjusting for prespecified covariates.

CONCLUSIONS

Supplementation with *myo*-inositol, probiotics, and micronutrients preconception and in pregnancy did not lower gestational glycemia but did reduce preterm birth.

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Suboptimal metabolic and nutritional health around conception and during pregnancy have important implications for pregnancy outcomes, fetal growth, adiposity, and long-term offspring health (1). Adverse effects of higher maternal glucose concentrations increase across the continuum of maternal glycemia (2,3), and micronutrient insufficiency is highly prevalent in women. Interventions that optimize glycemia and nutritional status are thought to improve pregnancy and offspring outcomes, but supportive evidence from intervention studies is sparse.

Pregnancy is a state of relative maternal insulin resistance, promoting glucose transfer to the fetus (4). Physiological insulin resistance and impaired insulin secretion can be accentuated by individual genetic and environmental vulnerabilities and lead to gestational diabetes mellitus (GDM) (5). The global GDM incidence is rising, estimated at 14% (6). Following GDM diagnosis, lifestyle changes, oral hypoglycemic drugs, and insulin can improve some short-term obstetric outcomes (7) but cannot fully mitigate pregnancy and offspring adversity (8). Risk reduction strategies have thus shifted toward GDM prevention. However, population trials of dietary, physical activity, or combined lifestyle measures, mostly beginning in the first half of gestation, have had limited impact on preventing GDM (9,10). This has led to postulations that preconception interventions could be more effective and that alternative approaches are required.

Small clinical trials have suggested that supplementation with *myo*-inositol or probiotics from early pregnancy may be beneficial; *myo*-inositol is a naturally occurring six-carbon polyol with insulin sensitizing actions arising from functions relating to many second messenger signaling pathways and endogenous insulin-mimetic factors (11). Meta-analysis of women given *myo*-inositol supplementation from the end of the first trimester reported reductions in GDM, gestational glycemia, and preterm birth (12). Similarly, meta-analysis of studies of probiotics (*Lactobacillus* and/or *Bifidobacterium* species) from early pregnancy showed improved insulin sensitivity (13). One trial of probiotics taken from the first trimester reported improved glucose tolerance and

reduced GDM (14). Low intakes and insufficiencies of several micronutrients (vitamin B6, vitamin B12, riboflavin, zinc) are prevalent in pregnancy and have been linked with glucose intolerance and pregnancy outcomes (15–17), but there are few intervention studies (18). Vitamin D deficiency has also been linked with GDM and preterm birth (19), but a trial of vitamin D supplementation starting in early pregnancy showed no preventive effects on pregnancy complications (20). Another trial of a nutritional supplement (containing protein, polyunsaturated fatty acids, and micronutrients without inositols or probiotics) in low-resource settings showed improved birth length but no difference in preterm birth compared with no supplementation, with no difference between the group starting supplementation preconception and the group starting in early pregnancy; glycemia outcomes were, however, not reported (21).

Dysglycemia and maternal micronutrient insufficiency preconception or in early pregnancy are common in the general population and thought to influence the risk of adverse pregnancy outcomes (1,5,17,22). We hypothesized that a *myo*-inositol, probiotic, and micronutrient nutritional supplement commencing before pregnancy could collectively lower maternal glycemia and improve pregnancy outcomes across the general population. We therefore undertook an international, multicenter, double-blind randomized controlled trial (the Nutritional Intervention Preconception and During Pregnancy to Maintain Healthy Glucose Metabolism and Offspring Health [NiPPeR] study [23]) to investigate whether intervention with a nutritional supplement containing *myo*-inositol, probiotics, and additional micronutrients (vitamins D, B6, and B12; riboflavin; and zinc), compared with a standard preconception micronutrient supplement, taken before and during pregnancy would promote improved maternal pregnancy glycemia and outcomes.

RESEARCH DESIGN AND METHODS

This international, multicenter, double-blind randomized controlled trial recruited women who were planning to conceive within the next 6 months.

Women were recruited in Singapore, Auckland (New Zealand), and Southampton (U.K.), primarily from the community (Fig. 1). Our trial was approved by the U.K., Singapore, and New Zealand research ethics services at each site (Southampton: Health Research Authority National Research Ethics Service Committee South Central Research Ethics Committee reference 15/SC/0142; the National Healthcare Group Domain Specific Review Board Singapore reference 2015/00205; and the Health and Disability Ethics Committee New Zealand reference 15/NTA/21), with confirmation from the relevant regulatory authorities that the formulation was not an investigational medicinal product. Trial oversight and monitoring were provided by an independent data and safety monitoring committee.

Participants

On the basis of our previous population-based Southampton Women's Survey our initial target was 1,800 recruits to have 600 established pregnancies to study. Recruitment was stopped at 1,729 women when it became clear that the projected number of pregnancies would exceed our target (final conceptions $n = 725$) (Fig. 1).

Women were eligible for trial enrollment if they were aged 18–38 years, were planning to conceive within 6 months, and had future maternity care at the recruiting centers. In Singapore, women had to be of homogeneous or mixed Chinese, Malay, or Indian ethnicity. A priori, women conceiving within 1 year were followed through pregnancy and beyond. Women were excluded if they were pregnant or lactating at recruitment; were undergoing assisted conception (apart from taking clomiphene or letrozole alone); had known serious food allergy or preexisting type 1 or type 2 diabetes; or were using oral, implanted, or intrauterine contraception or taking metformin, systemic steroids, anticonvulsants, or treatment for HIV or hepatitis B or C in the past month. Participants provided written informed consent.

The Formulation

The intervention and control formulations were packaged as a powder in

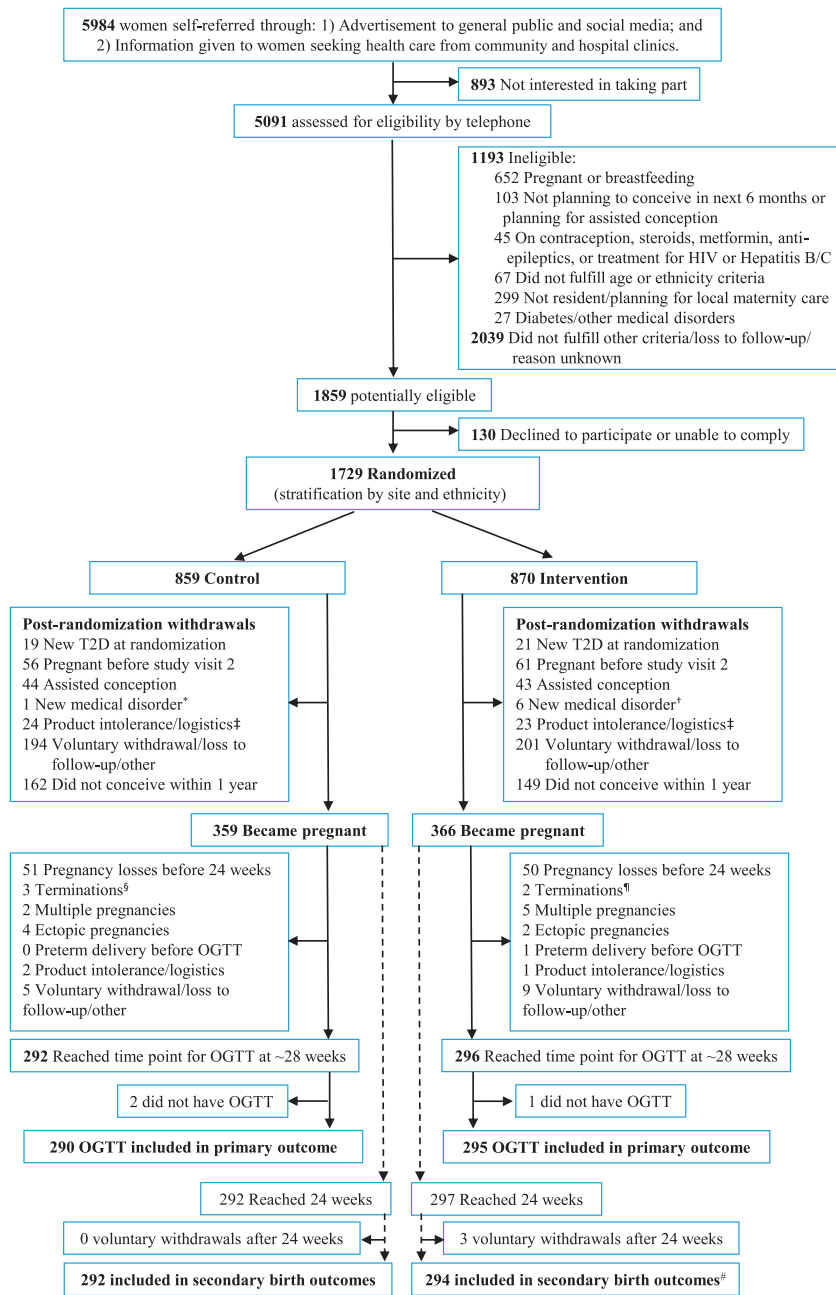


Figure 1—Consolidated Standards of Reporting Trials (CONSORT) diagram outlining participant flow. *Premature ovarian failure. †New-onset Graves disease, hemoglobinopathy with iron overload, prolactinoma, endometrial polyp, endometrial atypia, breast cancer. ‡Withdrew because product may contain animal remnants, no storage space in refrigerator, participant suspicion of product-related symptoms. §Includes two cases of trisomy 21, Klinefelter syndrome. ¶Includes hypoplastic left heart syndrome, unknown reason in private clinic. #Includes one still-birth and one neonatal death. T2D, type 2 diabetes.

sachets and stored at 2–6°C until made up in water and taken twice daily, with similar sensory characteristics. Formulations were produced by S.I.I.T. (Milan, Italy). Ingredients common to control and intervention formulations were folic acid 400 µg/day, iron 12 mg/day, calcium 150 mg/day, iodine 150 µg/day, and β-carotene 720 µg/

day; the intervention additionally included *myo*-inositol 4 g/day, vitamin D 10 µg/day, riboflavin 1.8 mg/day, vitamin B6 2.6 mg/day, vitamin B12 5.2 µg/day, zinc 10 mg/day, and probiotics (*Lactobacillus rhamnosus* NCC 4007 [CGMCC 1.3724] and *Bifidobacterium animalis* subspecies *lactis* NCC 2818 [CNCM I-3446]); average survival

counts remained within target over the shelf life of the refrigerated product) (24). Quantities were either standard amounts on the basis of previous trials (*myo*-inositol, probiotics) (12,14), amounts enhanced above those available in over-the-counter products (vitamin B6, vitamin B12, riboflavin), U.K. recommended daily allowance amounts for pregnant women (vitamin D, zinc, folic acid, iodine), or minimal amounts for micronutrients linked with potential detrimental effects at higher doses (iron, β-carotene, calcium).

Randomization and Procedures

Participants were randomly assigned in a 1:1 ratio to the control or intervention groups through the electronic study database (23), with stratification by site and ethnicity to ensure balanced allocation to the groups. Throughout the trial, participants, investigators, clinicians, and fieldworkers were unaware of the trial group assignments.

Following a baseline 75-g oral glucose tolerance test (OGTT), anthropometric measurements, and questionnaire ascertainment of the women’s characteristics, trial formulations were initiated before conception and continued until the end of pregnancy. Participants were instructed to contact the trial team as soon as they had a positive urinary pregnancy test, which was then confirmed by an ultrasonographic examination at 6–8 weeks gestation. Once pregnant, the women were followed up with questionnaires, for resupply of trial formulations, with a 20-week fetal anomaly scan, and with a 28-week OGTT. Plasma glucose was collected in antiglycolytic buffered tubes and transported on an ice slurry to the laboratory within 30 min using standardized protocols across sites. Glucose measurements using the glucose oxidase method were undertaken by a single laboratory at each site, with uniform external quality assurance per the Royal College of Pathologists of Australasia Quality Assurance Program. Plasma 25-hydroxyvitamin D and serum insulin concentrations (fasting, 30 min, and 120 min at preconception baseline; fasting and 30, 60, 90, and 120 min at the 28-week OGTT) were batch analyzed by liquid chromatography-tandem mass spectrometry

(Bevital, Bergen, Norway) and an electrochemiluminescence immunoassay (cobas; Roche Diagnostics), respectively. The HOMA for insulin resistance (HOMA2-IR) (<http://www.OCDem.ox.ac.uk>) (25) and Matsuda index measure of insulin sensitivity (<http://mmatsuda.diabetes-smc.jp/xpoints.html>) (26) were calculated.

Antenatal, peripartum, and neonatal outcomes were ascertained from medical records. Adherence to the trial formulation was ascertained by sachet counting. Good adherence was defined a priori as at least 60% of the sachets taken.

Outcomes

The primary outcome was fasting and/or 1-h and/or 2-h plasma glucose concentrations following a 75-g OGTT at 28 weeks' gestation (a priori specification included all conducted between 24 and 32 weeks). On the basis of prior systematic reviews, principal prespecified secondary outcomes were GDM (defined by International Association of Diabetes and Pregnancy Study Groups criteria [27]), large for gestational age at birth (using sex- and gestational age-specific Royal College of Paediatrics and Child Health 2009 U.K.-World Health Organization growth charts [28]), and preterm birth; other secondary outcomes are shown in Table 3 and Supplementary Table 2. Gestational age was determined using a prespecified algorithm (29) using menstrual data (date of last menstrual period [LMP], self-reported cycle regularity, mean cycle lengths in past 3 months), with first trimester fetal ultrasonographic crown-rump length measurement used if >7 days discrepancy between LMP and scan dates, uncertain LMP date, irregular cycles, or hormonal contraception use within past 3 months.

Statistical Analysis

Considering the composite multiple end point primary outcome of plasma glucose at three 75-g OGTT time points, the prespecified level of statistical significance was set as $P < 0.017$ (i.e., 0.05 divided by 3). With a sample size of 600 (300 in each group), a two-sided test with $\alpha = 0.017$, and 80% power, the detectable differences in fasting, 1-h, and 2-h glucose concentrations

between groups were 0.12, 0.45, and 0.34 mmol/L, respectively (each with a standardized effect size of 0.265 SDs using values reported in the Hyperglycemia and Adverse Pregnancy Outcome [HAPO] study [30]). Such magnitudes of glycemic change are expected to have clinically appreciable effects on neonatal size and adiposity and long-term offspring health (2,3).

Glucose values were \log_e transformed to achieve approximately normal distributions before using these values for analysis. Analysis of the primary outcome used linear regression on the intention-to-treat data set (all randomized participants who provided an OGTT at 24–32 weeks). Group (control or intervention) was included as a predictor and regressions adjusted for site, ethnicity, and corresponding preconception glycemia to account for potential imbalance between treatment arms among pregnancies that reached 24–32 weeks' gestation. Subsequent regression models were additionally adjusted for prespecified factors thought to be important predictors of outcomes and for other factors not balanced across control and intervention groups and believed to be prognostic; these are listed in the relevant tables of results. Likewise, HOMA2-IR and Matsuda indices were \log_e transformed, and comparisons at 28 weeks were similarly adjusted but with corresponding preconception values instead of preconception glycemia. Estimates of differences (β) between the groups are presented with 95% CIs; t tests on \log_e glucose were also conducted. Group comparisons were performed in two prespecified special interest subgroups: women who were overweight or obese (defined using ethnic-specific thresholds of BMI >23 kg/m² for Asians, including Chinese, Indians, Pakistani, Bangladeshi, Malay, and mixed Asian, and >25 kg/m² for non-Asians, including White Caucasian, Polynesian, Black, and mixed Asian-non-Asian) and women with documented evidence of dysglycemia before conception (defined as at least one of the following: GDM in a previous pregnancy or preconception baseline first visit raised HbA_{1c} [$\geq 5.7\%$ (39 mmol/mol)], impaired fasting glucose [5.6–6.9 mmol/L], or impaired glucose tolerance [2-h glucose 7.8–11.0 mmol/L]) (31).

The statistical analysis plan did not include correction for multiple comparisons for secondary or other outcomes; therefore, results for these outcomes are reported as point estimates and 95% CIs and should not be used to infer definitive treatment effects. Analyses were performed using Stata 15.1 software (StataCorp, College Station, TX).

RESULTS

Between 3 August 2015 and 12 May 2017, 1,729 women were recruited and randomly assigned to either the control ($n = 859$) or the intervention ($n = 870$) group. Pregnancies fulfilling the study criteria and reaching 28 weeks' gestation were achieved in 588 women, 292 (34%) of 859 and 296 (34%) of 870 in the control and intervention groups, respectively (Fig. 1); 585 (99.5%) of 588 had an OGTT and provided the primary outcome of glycemia at 28 weeks' gestation (median [interquartile range] 27.7 weeks [27.2–28.3]). Median BMI and other baseline characteristics were similar in the two study groups providing the primary outcome, except fewer women in the intervention group were obese, nulliparous, or had a family history of diabetes (Table 1).

Comparisons of unadjusted plasma glucose values at the three OGTT time points between the control and intervention groups were not significantly different (Table 2). In the primary outcome intention-to-treat analysis adjusting for site, ethnicity, and matched preconception glucose values (where available), plasma glucose values did not differ between study groups at each of the three time points ($P > 0.017$) (Table 2). Full adjustment as prespecified provided similar results (Table 2). The incidence of GDM was similar between study groups (Table 3). Sensitivity analyses excluding 32 participants who were subsequently found not to fulfill the eligibility criteria or did not have good adherence gave similar results (Supplementary Table 1).

Glycemia outcomes were examined in two special interest subgroups specified a priori where it was hypothesized that the intervention could have a greater effect. Among women who were overweight or obese before conception ($n = 258$), intervention did not alter fasting and 1-h glycemia; 2-h

Table 1—Baseline preconception characteristics of women who provided a primary outcome

	Control (n = 290)	Intervention (n = 295)
Age (years)	30.14 (3.30)	30.53 (3.40)
BMI (kg/m ²)	23.75 (21.34–27.5)	23.65 (21.16–26.23)
Overweight*	68 (23.5)	89 (30.3)
Obese*	61 (21.0)	40 (13.6)
Ethnic origin		
White Caucasian	167 (57.6)	180 (61.0)
Chinese	73 (25.2)	72 (24.4)
South Asian (Indian, Pakistani, Bangladeshi)	15 (5.2)	15 (5.1)
Malay	12 (4.1)	11 (3.7)
Other (mixed, Black, Polynesian)	23 (7.9)	17 (5.8)
Site		
New Zealand†	116 (40.0)	113 (38.3)
Singapore	82 (28.3)	84 (28.5)
U.K.‡	92 (31.7)	98 (33.2)
Nulliparous	200 (69.0)	171 (58.0)
Smoker	12 (4.2)	12 (4.1)
Family history of type 2 diabetes	79 (27.2)	56 (19.1)
Household income quintile		
5 (lowest)	5 (1.7)	2 (0.7)
4	20 (6.9)	24 (8.1)
3	69 (23.8)	54 (18.3)
2	95 (32.8)	109 (37.0)
1 (highest)	91 (31.4)	92 (31.2)
Not available	10 (3.5)	14 (4.8)
Preconception plasma glucose (OGTT) (mmol/L)		
Fasting	4.85 (4.52–5.18)	4.85 (4.63–5.18)
30 min	7.81 (6.71–8.90)	7.70 (6.60–9.01)
2 h	5.40 (4.41–6.38)	5.51 (4.63–6.27)

Data are mean (SD), median (interquartile range), or n (%). *Defined using ethnic-specific thresholds for overweight and obesity: BMI ≥23 to <27.5 and ≥27.5 kg/m², respectively, for Asians, including Chinese, Indians, Pakistani, Bangladeshi, Malay, mixed Asian; BMI ≥25 to <30 and ≥30 kg/m², respectively, for non-Asians, including White Caucasian, Polynesian, Black, mixed Asian–non-Asian. †72.9% White Caucasian, 16.6% any Asian, 10.5% other. ‡94.8% White Caucasian, 2.6% any Asian, 2.6% other.

glycemia was higher in the intervention group (adjusted β = 0.076 [95% CI 0.020–0.131] log_e mmol/L, equivalent to 0.53 mmol/L glucose) but with no increased risk of GDM (Supplementary

Table 1). In women with documented dysglycemia before conception (n = 94), glycemia at 28 weeks and GDM incidences were similar between study groups (Supplementary Table 1).

Interaction terms in the fully adjusted models including all women showed no evidence of differential effects on 28-week glycemia in response to the intervention among the three study sites and among ethnicities. As measures of insulin resistance and insulin sensitivity, respectively, HOMA2-IR (adjusted β = −0.022 [−0.090 to 0.046]) and Matsuda index (adjusted β = 0.001 [−0.068 to 0.070]) at 28 weeks were also similar between study groups.

Adjusting for covariates, there was a lower incidence of preterm birth (<37 weeks gestation) in the intervention group (adjusted risk ratio [aRR] 0.43 [95% CI 0.22–0.82]) (Table 3). There were similar trends in both spontaneous and iatrogenic preterm births. The effect of the intervention was principally observed for late preterm births (34–36 completed weeks' gestation, aRR 0.41 [0.20–0.85]) and preterm births associated with preterm prelabor rupture of membranes (PPROM) (aRR 0.21 [0.06–0.69]), with the incidence of PPRM itself also reduced (aRR 0.39 [0.16–0.97]) (Table 3). There were no differences in mean gestational age at delivery, neonatal unit admissions, and neonatal septicemia (Table 3).

The incidence of major postpartum hemorrhage (>1-L blood loss) was lower in the intervention group (aRR 0.44 [95% CI 0.20–0.94]); this reduction was not explained by cesarean section delivery rates or birth weight, which were similar between study groups (Table 3). There were no differences between groups for the secondary outcomes of miscarriage, congenital anomaly, severe

Table 2—Primary outcome of maternal OGTT plasma glucose values at 28 (24–32) weeks' gestation

OGTT time point	Control		Intervention		β (95% CI) for log _e glucose (log _e mmol/L)	
	n	Plasma glucose (mmol/L)	n	Plasma glucose (mmol/L)	Adjusted*	Fully adjusted†
Fasting	290	4.41 (4.08–4.63)	295	4.30 (4.08–4.63)	−0.004 (−0.018 to 0.011)	0.0002 (−0.014 to 0.014)
P value		—		0.55	0.63	0.98
1 h	283	8.02 (6.60–9.23)	294	8.24 (6.93–9.45)	0.025 (−0.014 to 0.064)	0.036 (−0.003 to 0.074)
P value		—		0.26	0.22	0.07
2 h	287	6.49 (5.51–7.70)	295	6.60 (5.84–8.02)	0.040 (0.004–0.077)	0.043 (0.006–0.081)
P value		—		0.03	0.03	0.02

Data are median (interquartile range [unadjusted]) unless otherwise indicated. All P values (t tests on log_e-transformed glucose and linear regressions) were not significant ≥0.017 (a priori statistical significance is P < 0.017). *Log_e glucose at 24–32 weeks adjusted for site, ethnicity, and baseline log_e glucose (for fasting and 2-h only; baseline 1-h glucose not available); n = 584 and 578 for fasting and 2-h glucose, respectively, as a result of missing values for corresponding preconception glucose. †Log_e glucose at 24–32 weeks adjusted for site, ethnicity, maternal age, prepregnancy BMI, preconception smoking, parity, family history of diabetes, and baseline log_e glucose (for fasting and 2-h only; baseline 1-h glucose not available); n = 581, 574, and 575 for fasting, 1-h, and 2-h glucose, respectively, as a result of missing data.

Table 3—Secondary outcomes of pregnancy complications, delivery events, and neonatal outcomes with the NiPPeR intervention compared with control

	Control	Intervention	Effect of intervention
Pregnancy complications			
GDM* (denominator: all those who completed OGTT at 24–32 weeks)	64/283 (22.6)	73/294 (24.8)	RR (95% CI) [†] 1.22 (0.92–1.62) (n = 545)
Miscarriages <24 weeks' gestation (denominator: all those who became pregnant after the second preconception visit)	51/359 (14.2)	50/366 (13.7)	0.91 (0.62–1.33) (n = 688)
Congenital abnormalities‡ (denominator: all reaching 7 weeks)	16/314 (5.1)	15/330 (4.5)	0.83 (0.35–1.96) (n = 557)
Severe nausea and vomiting of pregnancy§ (denominator: all reaching 7 weeks)	51/305 (16.7)	43/322 (13.4)	0.86 (0.57–1.30) (n = 553)
Hypertensive disorders of pregnancy, both preeclampsia and pregnancy-induced hypertension¶ (denominator: all pregnancies reaching ≥24 weeks)	14/292 (4.8)	12/294 (4.1)	1.19 (0.55–2.59) (n = 557)
Delivery outcomes (denominator: all live births ≥24 weeks unless otherwise stated)			
Gestational age at birth in decimal weeks	39.2 (1.74)	39.3 (1.78)	Mean difference (95% CI) [#] or RR (95% CI) [#] 0.20 (–0.06 to 0.46) (n = 553)
All preterm deliveries (<37 weeks) (spontaneous labor onset: iatrogenic, n:n)	27/292 (9.2) (12:15) ^{††}	17/293 (5.8) (8:9) ^{‡‡}	0.43 (0.22–0.82) (n = 553)
Late preterm deliveries (34 weeks ^{+0 days} to 36 weeks ^{+6 days}) (spontaneous labor onset: iatrogenic, n:n)	22/292 (7.5) (11:11)	13/293 (4.4) (6:7)	0.41 (0.20–0.85) (n = 553)
PPROM	19/280 (6.8)	8/277 (2.9)	0.39 (0.16–0.97) (n = 526)
Preterm deliveries associated with PPRM (spontaneous labor onset: iatrogenic, n:n)	17/280 (6.1) (8:9)	5/277 (1.8) (2:3)	0.21 (0.06–0.69) (n = 526)
Cesarean section delivery (elective: emergency, n:n)	85/292 (29.1) (41:44)	84/293 (28.7) (34:50)	0.99 (0.76–1.28) (n = 553)
Major postpartum hemorrhage (>1-L blood loss, denominator: all pregnancies reaching ≥24 weeks)	24/292 (8.2)	9/294 (3.1)	0.44 (0.20–0.94) (n = 554)
Neonatal outcomes (denominator: all live births ≥24 weeks)			
Mean difference (95% CI) [#] or RR (95% CI) [#]			
Birth weight (kg)	3.30 (0.54)	3.33 (0.55)	0.05 (–0.03 to 0.13) (n = 553)
Large for gestational age (>90th centile adjusted for sex and gestational age ^{**})	22/292 (7.5)	21/293 (7.2)	0.94 (0.54–1.63) (n = 555)
Small for gestational age (<10th centile adjusted for sex and gestational age ^{**})	21/292 (7.2)	24/293 (8.2)	1.34 (0.79–2.29) (n = 555)
Admission to neonatal unit	19/290 (6.6)	24/293 (8.2)	1.11 (0.57–2.17) (n = 550)
Neonatal hypoglycemia requiring dextrose treatment	24/292 (8.2)	19/293 (6.5)	0.79 (0.43–1.48) (n = 553)
Neonatal septicemia (positive blood culture)	0/287 (0)	2/288 (0.7)	Insufficient to analyze

Data are mean (SD) or n (%) unless otherwise indicated. RR, risk ratio. *According to International Association of Diabetes and Pregnancy Study Groups criteria (fasting glucose ≥5.1 mmol/L or 1-h glucose ≥10.0 mmol/L or 2-h glucose ≥8.5 mmol/L) (24); includes only women with complete OGTT data at all three time points. †Adjusted for site, ethnicity, maternal age, preconception BMI, household income level, parity, preconception smoking, preconception baseline fasting glucose, family history of diabetes, and offspring's sex (not applicable for miscarriages). ‡Includes anomalies in the following categories: in the control group, four cases of karyotypic/multiple anomalies, two cardiovascular, six genitourinary, two respiratory, two musculoskeletal; in the intervention group, five cases of karyotypic/multiple anomalies, three cardiovascular, four genitourinary, three musculoskeletal. §Requiring admission to the hospital for intravenous rehydration with or without significantly deranged biochemistry or weight loss. ||Preeclampsia defined as hypertension in pregnancy associated with significant proteinuria or evidence of multisystem disorder; there were no differences in incidence between study groups. ¶Pregnancy-induced hypertension defined as isolated nonproteinuric hypertension in a previously normotensive woman or aggravation of hypertension during pregnancy; there were no differences in incidence between study groups. #Adjusted for site, ethnicity, maternal age, preconception BMI, household income level, parity, smoking during pregnancy, offspring sex (except for large and small for gestational age), and (where data were available) 28 weeks' gestation fasting glucose. **By Royal College of Paediatrics and Child Health 2009 U.K.-World Health Organization growth charts (25). Use of respective local population charts, Fenton growth charts, and World Health Organization INTERGROWTH-21st charts did not materially alter results. ††Iatrogenic preterm births include cases of induction of labor and nonlabor cesarean section. Indications for iatrogenic delivery in the control group were as follows: five for PPRM alone, four for PPRM plus another indication (previous cesarean section, vasa previa, breech presentation, maternal medical condition), five for placental-associated conditions (intrauterine growth restriction with or without preeclampsia or placental abruption), and one maternal medical condition. ‡‡Indications for iatrogenic delivery in the intervention group were as follows: three for PPRM alone, four for placental-associated conditions (intrauterine growth restriction with or without preeclampsia or placental abruption), one maternal medical condition, and one fetal anomaly with breech presentation.

nausea and vomiting of pregnancy, hypertensive disorders of pregnancy, intrauterine death, neonatal death, neonatal hypoglycemia, and other neonatal complications (Table 3 and Supplementary Table 2).

Among women who provided the primary and birth outcomes, overall supplement adherence was good, with 80.7% having 80–100% adherence, 15.9% having 60–80% adherence, and only 3.4% having <60% adherence averaged from recruitment to delivery. Adherence was similar in the control and intervention groups. As a further indication of good adherence, 25-hydroxyvitamin D concentrations in the intervention and control groups were similar at the preconception baseline but higher in the intervention compared with the control group at the 28-week OGTT (median 92.8 vs. 63.0 nmol/L). Among all randomized women, withdrawals because of perceived minor side effects from the supplement were similar in both groups (8.3% control, 7.5% intervention), as were other serious adverse events (2.3% control, 2.8% intervention) (Supplementary Table 3).

CONCLUSIONS

In this international, multicenter, randomized controlled trial, nutritional formulation enriched with *myo*-inositol, probiotics, and multiple micronutrients, commenced preconception and continued throughout pregnancy, did not result in lowered maternal glycemia at 28 weeks' gestation. There were no significant effects on the incidence of GDM and large-for-gestational-age infants. Intervention reduced preterm birth, affirming findings from previous *myo*-inositol trials. We also found a reduction in the incidence of major postpartum hemorrhage.

Three previous trials of open-label *myo*-inositol taken from early pregnancy to prevent GDM in women in Italy focused on discrete high-risk groups for dysglycemia, namely those who were overweight or obese or with a family history of type 2 diabetes (32). All showed a similar reduction in GDM, with an overall odds ratio (OR) of 0.34, as well as lower fasting, 1-h, and 2-h glycemia in a 24–28-week OGTT (32). A further small trial among women with impaired fasting glycemia in early

pregnancy reported a large reduction in GDM risk (relative risk 0.127) alongside lower fasting and 1-h glycemia (33). These observations contrast with the finding of no difference in glycemia at 28 weeks' gestation with our intervention. However, our study intervention was administered double-blinded over two important periods—preconception and pregnancy—in a general population of women planning pregnancy across multiple centers and ethnicities, excluding those with existing or newly diagnosed type 1 or 2 diabetes preconception. Subgroup analysis of overweight and obese women or those with documented dysglycemia did not show any benefit of our intervention on glycemia, although the trial was not powered to do so. Our results, however, are consistent with an Irish trial of a lower dose of *myo*-inositol combined with *D*-chiro-inositol in women with a family history of type 1 or 2 diabetes, which showed no impact on glycemia (34).

In another small trial, dietary counseling and probiotics in pregnant women improved glycemia (OR for elevated glucose 0.31) and insulin sensitivity (14); these findings are discordant with ours despite using the same probiotic combination. However, a meta-analysis of 10 trials of probiotic supplementation in pregnancy found no difference in fasting glycemia (despite a reduction in HOMA-IR) (13), and a recently completed trial showed no difference in GDM rates, with slightly higher fasting glycemia (35). Inconsistent findings may be attributable to different populations and concurrent use of different combinations of prenatal supplements.

Meta-analysis of the group of three Italian *myo*-inositol studies found a reduction in fetal macrosomia (OR 0.38) and large for gestational age (OR 0.52) (32) in contrast to the finding of no difference with our intervention. The same meta-analysis also found a reduction in preterm birth (OR 0.44) (32), with the separate Irish inositol trial of a lower *myo*-inositol dose observing a nonstatistically significant trend of fewer preterm births in the intervention group (2% vs. 7%, $P = 0.11$) (34). Another meta-analysis of trials of multiple micronutrient supplements concluded that the supplements probably also lead to a slight reduction in preterm birth (aRR 0.95 [95% CI 0.90–1.01]) (36). In contrast, none of

the probiotic trials reported a change in preterm birth rates. Nonetheless, findings of a meta-analysis of *myo*-inositol trials (12) are consistent with our demonstration of a reduction in preterm birth. Furthermore, our finding of a reduction particularly in PPRM and PPRM-associated preterm births in the intervention group indicates that this is the likely explanation for reduced prematurity. Approximately 30% of preterm births are preceded by PPRM, of which 60–70% occur late preterm after 34 weeks' gestation (37). PPRM is postulated to break down the barrier to ascending pathogens, resulting in intrauterine infection, increased inflammation, and the triggering of preterm labor. In our trial, there was only a reduction in preterm births with intervention without any associated difference in clinically detectable infections between study groups. Potential mechanisms for a preventive effect on PPRM-associated preterm births in our study may include anti-inflammatory effects of *myo*-inositol (38) and a contribution from the potential synergistic effect of micronutrients, including zinc and vitamin D (39). Our results of specifically a reduction in late preterm births is still clinically significant since prematurity survivors in this group constitute the majority of cases of neurodevelopmental disability associated with preterm delivery (40); thus, the supplement could potentially be impactful.

Our observation that intervention was associated with a reduction in major postpartum hemorrhage is novel and has not previously been reported with *myo*-inositol, probiotics, or the micronutrients enriched in the supplement used. Since this observation is not explained by differences in cesarean section rates, parity, or birth size, this effect may be mediated by other factors, such as length of labor, myometrial contractility, or blood coagulation, which remain to be examined. Of note, our study found no difference in hypertensive disorders of pregnancy, which is in contrast to a probiotic trial reporting an increased trend of preeclampsia (35) possibly because of counteraction by other components in our intervention. However, our result of a lack of effect on hypertensive disorders is consistent with the *myo*-inositol trials and a

vitamin D trial (20) that also reported no difference.

Collectively available data suggest that further studies are required to determine whether there are subpopulations, dose regimens, or intervention commencement time points when *myo*-inositol and probiotics may lower maternal glycemia. Conversely, there appears to be a potential benefit of *myo*-inositol-containing supplements in reducing preterm birth. Whether the other components of our intervention could play an additive role in preterm birth reduction is unclear. Assessment of longitudinal changes in levels of *myo*-inositol and the other components may shed further light on potential pathways of effect, which may pave the way for the design of more definitive trials in the future.

In contrast to most previously published *myo*-inositol and probiotic trials, major strengths of our study are its double-blind design and inclusion of multi-ethnic women from three different continents. Nevertheless, generalizability is limited by the lack of Latina and Native American Indians and only a few Black and Polynesian participants, by less than half of participants being overweight/obese unlike typical U.S. and Western populations, and by our trial being conducted in high-resource settings. Microbiome data were not available to confirm viability of the probiotic in participant samples, and sachet counts provide a limited measure of adherence to the intervention; good adherence is, however, suggested by higher plasma 25-hydroxyvitamin D concentrations in the intervention group at 28 weeks' gestation. Another limitation is that we studied a combination of *myo*-inositol and probiotics with micronutrients. Previous studies have generally examined these individually or as a less complex formulation (e.g., *myo*-inositol with vitamin D) (12). We cannot exclude the possibility that constituents of the supplement may have moderated individual effects in lowering maternal glycemia or that intervening in the general population (vs. a high-risk population) or commencing intervention preconception (vs. early pregnancy) altered the impact on gestational glycemia. In conclusion, our trial showed that supplementation with *myo*-inositol, probiotics, and multiple micronutrients

preconception and in pregnancy did not lower gestational glycemia but did reduce preterm birth.

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