Time-to-conception and clinical pregnancy rate with a myo-inositol, probiotics, and micronutrient supplement: secondary outcomes of the NiPPeR randomized trial

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Objective: To determine whether a combined myo-inositol, probiotics and micronutrient nutritional supplement impacts time-to-natural-conception and clinical pregnancy rates.
Design: Secondary outcomes of a double-blind randomized controlled trial.
Setting: Community recruitment.
Patients: Women aged 18 to 38 years planning to conceive in the United Kingdom, Singapore, and New Zealand, excluding those with diabetes mellitus or receiving fertility treatment.
Intervention: A standard (control) supplement (folic acid, iron, calcium, iodine, β-carotene), compared with an intervention additionally containing myo-inositol, probiotics, and other micronutrients (vitamins B2, B6, B12, D, zinc).
Main Outcome Measures: Number of days between randomization and estimated date of natural conception of a clinical pregnancy, as well as cumulative pregnancy rates at 3, 6, and 12 months.

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Results: Of 1729 women randomized, 1437 (83%; intervention, n=736; control, n=701) provided data. Kaplan-Meier curves of conception were similar between intervention and control groups; the time at which 20% achieved natural conception was 90.5 days (95% confidence interval: 80.7, 103.5) in the intervention group compared with 92.0 days (76.0, 105.1) in the control group. Cox's proportional hazard ratios (HRs) comparing intervention against control for cumulative achievement of pregnancy (adjusted for site, ethnicity, age, body mass index, and gravidity) were similar at 3, 6, and 12 months. Among both study groups combined, overall time-to-conception lengthened with higher preconception body mass index, and was longer in non-White than in White women. Among women who were overweight the intervention shortened time-to-conception compared with control regardless of ethnicity (12-month HR=1.47 [1.07, 2.02], *P*=.016; 20% conceived by 84.5 vs. 117.0 days) and improved it to that comparable to nonoverweight/nonobese women (20% conceived by 82.1 days). In contrast, among women with obesity, time-to-conception was lengthened with intervention compared with control (12-month HR=0.69 [0.47, 1.00]; *P*=.053; 20% conceived by 132.7 vs. 108.5 days); an effect predominantly observed in non-White women with obesity.

Conclusions: Time-to-natural-conception and clinical pregnancy rates within a year were overall similar in women receiving the intervention supplement compared with control. Overweight women had a longer time-to-conception but there was suggestion that the supplement may shorten their time-to-conception to that comparable to the nonoverweight/nonobese women. Further studies are required to confirm this.

Clinical Trial Registration Number: clinicaltrials.gov (NCT02509988) (Fertil Steril® 2023;119:1031-42. ©2023 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: preconception, nutritional supplement, fertility, fecundability, NiPPeR trial

Fertility rates are declining globally, especially in high-income settings, with a concurrent increase in women reporting subfertility (1). Rising obesity rates accompanied by metabolic dysregulation and upward trends in diets rich in fat and sugar, but low in minerals and vitamins (2–4), are likely contributors. Increasing glycemia associates with reduced fecundability, even across the normal glycemic range (5). Additionally, several micronutrient insufficiencies have been linked with altered ovarian function and subfertility (6). Thus, a nutritional supplement aimed at improving metabolic health and micronutrient status could potentially enhance reproductive potential in young women (7, 8).

A particular nutrient of interest is inositol, an endogenously produced 6-carbon polyol, also derived from the diet (9). Myo-inositol, the most abundant inositol (10), is a component of phospholipids governing membrane functions such as calcium fluxes and second messenger signaling of hormones, including insulin and gonadotropins (11, 12). In a meta-analysis of trials in anovulatory polycystic ovary syndrome (PCOS) (13), inositol supplementation improved ovulation rate (relative risk: 2.3), menstrual cycle regularity (relative risk: 3.2), and glycemia/insulin parameters, but there was no impact on pregnancy rates. However, inositol's efficacy in promoting spontaneous conception in the general population is unclear (14).

Optimizing micronutrient status may directly improve both ovarian function and oocyte quality, and indirectly promote fertility through the promotion of insulin sensitivity and glucose metabolism, which suppresses hyperinsulinemia and hyperandrogenism that impair ovarian function (15). Vitamin D insufficiency is implicated in insulin resistance, metabolic syndrome, and PCOS, as well as associates with poor assisted reproductive technology (ART) outcomes and miscarriage (16, 17). Vitamins B6 and B12 are involved in homocysteine metabolism and DNA synthesis, vital for oocyte maturation, and insufficiency may compromise fertility (18, 19). In animal models, zinc insufficiency is linked to a low sex drive, anovulation, and irregular menstrual cycles, but its role in human reproduction remains inconclusive (20).

Positive effects of probiotics on fertility have been reported (21, 22). Gut microbiome dysbiosis is associated with PCOS in rodents (23, 24) and can trigger chronic inflammatory responses that exacerbate insulin resistance (25), resulting in hyperinsulinemia that interferes with follicular development and impairs oocyte function (26, 27). A meta-analysis of studies of probiotic supplements containing lactobacillus and bifidobacteria showed improved metabolic, hormonal, and inflammatory profiles in women with PCOS (28). Furthermore, oral *Lactobacillus rhamnosus* promotes a vaginal microbiome that favors sperm function (29, 30).

Previously, a trial of a multivitamin supplement without myo-inositol or probiotics reported a 5% shortening in time-to-conception (31). Now the *Nutritional Intervention Preconception and During Pregnancy to Maintain Healthy Glucose Metabolism and Offspring Health* (NiPPeR) trial (32) provides an opportunity to assess, as a secondary outcome, the influence of a combined myo-inositol, probiotic, and micronutrient supplement in further improving fertility in women planning to conceive, recruited outside the assisted reproduction setting. With the postulation of additive or synergistic effects between the supplement components, we hypothesized that women in the intervention arm would have a shorter time to spontaneous conception and a higher clinical pregnancy rate than those in the control arm.

Materials and Methods

The NiPPeR study protocol was approved by the *research ethics committees* at 3 study sites: Southampton (United Kingdom), Auckland (New Zealand), and Singapore (33). All participants provided written informed consent.

Study Design and Participants

Between August 2015 and May 2017, NiPPeR recruited from the community women aged 18 to 38 years who were planning to conceive (33). Women were excluded if they had any type of diabetes mellitus, a known serious allergy, were

pregnant/lactating, or in the past month had received oral, implanted, or intrauterine contraception, metformin, systemic steroids, anti-convulsant medication or treatment for HIV or Hepatitis B/C. Women taking clomiphene citrate or letrozole within the previous 3 months or undergoing ART were excluded for this substudy.

Women were randomly assigned to the control or intervention groups (1:1 ratio) through a study database, with stratification by site and ethnicity. Participants, study teams and health care staff were blinded to the trial-group assignments until database lock of the primary outcome of gestational glycemia at 28 weeks gestation, which showed no difference (33).

Formulations and Procedures

The control and intervention formulations were packaged as a powder in sachets to be mixed with water (200 mL) and consumed twice daily; folic acid (400 μg/d), iron (12 mg/d), calcium (150 mg/d), iodine (150 μg/d), and β-carotene (720 μg/d) were common to both arms, with the intervention additionally containing myo-inositol (4 g/d; i.e., 2 g twice daily), vitamin D (10 μg/d), riboflavin (1.8 mg/d), vitamin B6 (2.6 mg/d), vitamin B12 (5.2 μg/d), zinc (10 mg/d) and probiotics (*Lactobacillus rhamnosus* NCC4007 [CGMCC 1.3724; LPR] and *Bifidobacterium animalis* sp. lactis NCC2818 [CNCM I-3446; Bl818]) (33). Investigational products were blinded with "nonspeaking" three-character length alphanumeric codes (2 for each study arm to minimize the risk of inadvertent unblinding) and had similar sensory characteristics. They had comparable rates of perceived minor side-effects (8.3% control, 7.5% intervention). Adherence was determined by sachet counting. Women were advised not to consume other supplements throughout the trial period.

At enrolment, sociodemographic characteristics, menstrual, obstetric and health histories, lifestyle habits and psychological stress measures were collected via interviewer-administered questionnaires. Weight and height were measured to derive body mass index (BMI). A 75-g oral glucose tolerance test was conducted providing fasting and 2-hour plasma glucose and insulin levels alongside glycated hemoglobin (HbA1c) (measured by a single standardized laboratory at each site per the *Royal College of Pathologists of Australasia Quality Assurance Program*). Insulin, antimüllerian hormone (AMH) (Roche Diagnostics immunoassay), and C-reactive protein (CRP; MALDI-TOF, Bevital Platform G) were each batch-analyzed by one common laboratory. Women with newly diagnosed diabetes mellitus at recruitment were excluded from the analysis. The *homeostasis model assessment for insulin resistance* (HOMA2-IR) (34) and *Matsuda index* measure of insulin sensitivity (35) were calculated. PCOS-like phenotype was defined by an AMH >3.2 ng/mL (36) accompanied by self-reported irregular menstruation (variation of >5 days in menstrual cycle length in last 6 months) with an average cycle length of ≥35 days (37).

Participants with a positive urinary pregnancy test by the second preconception study visit (PCV2; mostly 23–30 days [range 21–42] after randomization, 7.3% and 7.6% in the control and intervention arms, respectively) (Fig. 1) were excluded from the main analysis as we had postulated *a priori* that conception occurring within this duration may not be influenced by the intervention. At PCV2, HbA1c and CRP were measured again.

With a positive pregnancy test, women were scheduled for an ultrasound scan at 6 to 8 weeks of amenorrhea, at which time information on menstrual and contraceptive histories over the 3 months before conception were collected again. Trial participation ended after one year for those who had not conceived.

Outcomes

Assessment of fertility rate was a prespecified secondary outcome.^ Spontaneously conceived clinical pregnancy was the event of interest, defined as ultrasonographic evidence of a viable intrauterine pregnancy with a fetal pole and cardiac activity detected after 6 weeks amenorrhea, including multiple pregnancies.

Time-to-conception of a clinical pregnancy was computed as the interval between the date of randomization at preconception and the estimated date of conception (EDC; 38 weeks before the expected date of delivery) using an algorithm (38). In 406 conceptions (66%), EDC was computed from the first day of the last menstrual period (LMP), as these women had self-reported regular cycles and were certain of their LMP date, also considering their usual cycle length (averaged over last 3 months before conception) assuming ovulation occurs 14 days before each anticipated menstruation. In the remaining 209 cases (34%), EDC was based on the first ultrasound scan (using crown-rump length measurement of a viable fetus (39) in 203 cases, and biparietal diameter/head circumference in 6 cases) since there was >7 days discrepancy between LMP and scan dates, uncertainty of LMP, cycle irregularity or recent stopping of hormonal contraception (within 3 months). An indicative time at which 20% of women achieved conception (predicted *a priori* to be in the middle of the steepest section of slope of conception rate) in each group is presented. Clinical pregnancy rates were defined as proportions of women achieving a clinical pregnancy by natural conception within 3, 6, and 12 months after randomization, and live birth rates were compared between the study groups.

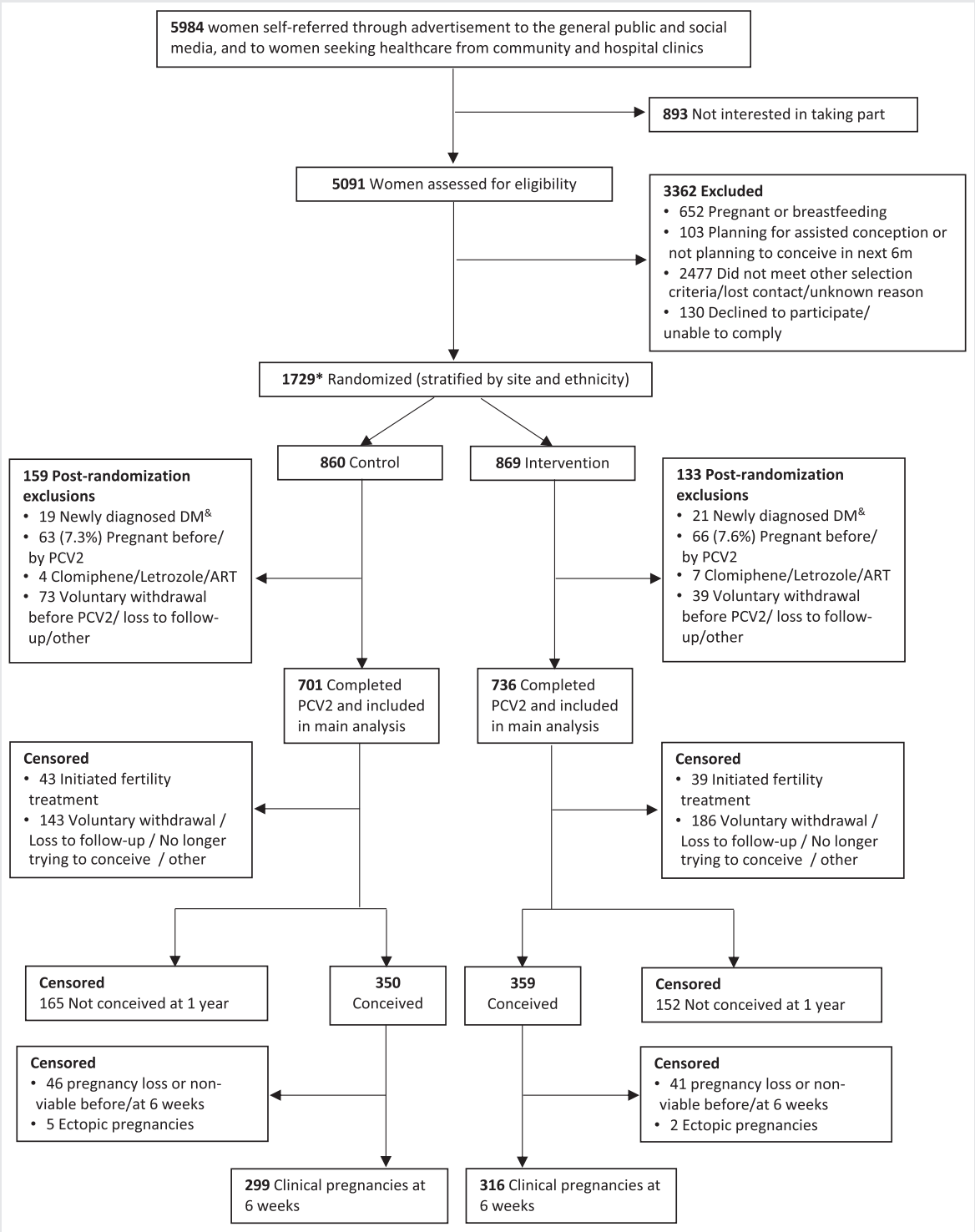
Statistical Analysis

All randomized participants remaining in the study at PCV2 were included in the analyses (Fig. 1). Time-to-conception for each group was estimated with the Kaplan-Meier method, with statistical significance assessed by log rank testing. Censoring was applied when a woman had not conceived after a year, was lost to follow-up, reported no longer trying to conceive, withdrew voluntarily or for a medical reason, subsequently initiated fertility or ART treatment including clomiphene citrate or letrozole or metformin, miscarried before a clinical pregnancy could be established or had an ectopic pregnancy (Fig. 1).

Cox proportional hazards modeling estimated the hazard ratio (HR with 95% confidence intervals [CI]) between control and intervention groups for achievement of a clinical

^ Fertility outcomes were prespecified at the outset in our internal protocol, however, we mistakenly omitted this information from the original trial registration in July 2015, and it was added in September 2018 (before completion of the 1 year follow-up allowed to achieve conception for all participants).

FIGURE 1



CONSORT: Flow of participants assigned to the control and intervention groups. *Our initial target was 1800 recruits to have 600 pregnancies to study the primary outcome of gestational glycemia; in the event pregnancy rates were higher and recruitment was stopped at 1729 women as the projected number of pregnancies would exceed our target. &DM diagnosed by fasting glycemia ≥7.0 mmol/L or 2-hour glycemia ≥11.1 mmol/L in a prepregnancy 75-g oral glucose tolerance test (51) at recruitment. ART = assisted reproductive technology, PCV2 = preconception visit 2 (mostly 23–30 days [range 21–42] after randomization), DM = diabetes mellitus.

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pregnancy daily/monthly or a live birth. The HR of clinical pregnancy achievement was first calculated from a multivariate Cox model that included the intervention as the exposure, adjusted for the stratification factors of site and ethnicity (basic model), followed by a fully-adjusted model including clinically important prognostic factors based on literature (age/BMI as continuous variables, gravidity as a dichotomous variable). Possible model fit improvement was examined by the addition of further covariates including cycle regularity and glycemia. Sensitivity analyses were conducted excluding those with a possible infertility issue unlikely to be addressed by maternal nutritional interventions, as reflected by subsequent ART post-recruitment or failure to conceive after a year. An additional *per protocol* analysis was performed including only participants with >80% adherence, and another including those who conceived before PCV2 but using assumed EDC because of missing LMP and scan data.

To examine whether the intervention had differential effects in subpopulations, prespecified subgroup analyses by metabolic, menstrual, and gravidity status were conducted. Additionally, interaction terms (intervention characteristic) were introduced into the basic models to uncover differential effects in subpopulations stratified by ethnicity, age, BMI (nonoverweight/nonobese, overweight, obese using ethnic-specific [Asian vs. non-Asian] thresholds (40)], household income, cardiometabolic health status (fasting/2-hour glycemia, HbA1c, HOMA2-IR, CRP), gravidity, menstrual cycle regularity, PCOS-like features, different ovarian reserve (AMH concentrations), and psychological stress (Table 1 and Supplementary Fig. 1, available online, for categorizations). Analyses were also performed to examine the influence of these factors on overall time-to-conception in the combined control/intervention group. Where intervention effects were found, exploratory analyses (with emphasis on effect sizes and 95% CI) were conducted to investigate the potential underlying mechanisms, including changes in cycle regularity, HbA1c, and CRP with the intervention.

Analyses were performed using Stata 15 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX:StataCorp LP). Statistical significance was considered when 2-tailed probability was <0.05. The power calculation for the primary outcome of gestational glycemia dictated a sample of 300 in each study arm to achieve 80% power (with α=0.017) to detect pre-defined clinically appreciable group differences in fasting, 1-hour and 2-hour glucose concentrations in a 28-week oral glucose tolerance test (33). Based on previous studies we had initially anticipated that 1800 would need to be recruited preconception to have 600 established pregnancies to study, but actual conception rates were higher and recruitment was stopped at 1729 when projected conceptions were estimated to exceed 600. There was no interim analysis during the trial.

RESULTS

Of 1729 women randomized, 1437 (intervention, n = 736 [85% of randomized]; control n = 701 [82% of randomized]) fulfilled the criteria for inclusion into this substudy (Fig. 1). At baseline, sociodemographic characteristics, gynecological history, lifestyle, and metabolic health parameters were similar between the 2 study groups (Table 1). Prepregnancy supplement adherence was similar in control and intervention groups, with 73.3% having >80% adherence, 19.8% at 60% to 80% adherence, 6.1% at 30% to 60% adherence and <1% with <30% adherence or missing data.

Overall time-to-conception was not different between the 2 study groups (Fig. 2). The time taken for 20% of women to achieve a natural conception was similar in the intervention and control groups (90.5 [95% CI, 80.7–103.5] vs. 92 [76.0–105.1] days). HRs comparing control against intervention groups for achievement of a clinical pregnancy at 3, 6, and 12 months indicated no differences between study groups, either with adjustment for site and ethnicity only, or with further adjustment for age, BMI, and gravidity. Addition of further covariates did not improve model fit. Findings were robust to sensitivity analyses: excluding those with a possible fertility issue not rectifiable by nutritional supplementation (n = 82 who subsequently received fertility treatment, n = 371 who did not conceive at 1 year; Supplementary Table 1, available online), *per protocol* analyses including only those with adherence >80% (n = 1054; HR: 0.99 [0.84–1.18]; P=.946), as well as analyses additionally including those who conceived before PCV2 (n = 1566; HR: 1.00 [0.86–1.15]; P=.980), showed similar results. Live birth rates were also not different between groups (HR: 0.94 [0.79–1.11]; P=.46).

Further analyses combining the control and intervention groups confirmed that participant characteristics associated with time-to-conception were as expected based on literature. Increased maternal age, high BMI, low household income, increased psychological stress, menstrual irregularity, no previous pregnancy, high fasting/2-hour glycemia, HbA1c, HOMA2-IR, and CRP characteristics were all associated with longer time-to-conception (Supplementary Fig. 1). Women in Singapore (20% conceived by 151.0 [95% CI: 115.5–174.0] days) conceived slower than women in the United Kingdom (74.0 [58.0–84.5] days; P=.005) or New Zealand (80.5 [69.8–99.5] days; P=.015). In the United Kingdom and New Zealand, White women (20% conceived by 73.0 [64.0–82.1] days) conceived more quickly than non-White women (102.4 [71.0–136.0] days; P=.003). As Singapore had an ethnic mix comprising only Asians, women were analyzed separately; compared with Chinese women (103.6 [79.9–131.5] days), South Asian women were not significantly different (185.0 days; P=.274) but Malay women took longer to conceive (284.5 days; P<.0001).

Prespecified subgroup analyses examined for differential effects of the intervention according to baseline characteristics. Intervention showed similar effects as control on time-to-conception in different ethnic, age, gravidity, income, psychological stress, metabolic health, and menstrual regularity groups, except for BMI categories; the intervention effect differed in overweight vs. nonoverweight/nonobese women (P-interaction = 0.014). Among obese women, intervention demonstrated a further interaction with White/non-White categories, and differed to its effect in nonoverweight/nonobese women (P-interaction = 0.049).

Among nonoverweight/nonobese women, time-to-conception was similar in the control and intervention groups

TABLE 1

Baseline characteristics of preconception women by nutritional supplement allocation

Characteristics	Control (n=701)	Intervention (n=736)
Sociodemographic		
Study site		
UK	174 (24.8%)	195 (26.5%)
Singapore	279 (39.8%)	292 (39.7%)
New Zealand	248 (35.4%)	249 (33.8%)
Age, (y)		
mean (SD)	30.70 (3.56)	30.64 (3.69)
Ethnicity		
White	321 (45.8%)	346 (47.0%)
Chinese	193 (27.5%)	213 (28.9%)
South Asian	46 (6.6%)	47 (6.4%)
Malay	72 (10.3%)	67 (9.1%)
Other	69 (9.8%)	63 (8.6%)
Household income[a]		
Low income	59 (9.0%)	59 (8.6%)
Middle income	291 (44.2%)	296 (43.4%)
High income	308 (46.8%)	327 (48.0%)
Gynecological		
Gravidity		
Never pregnant	378 (53.9%)	376 (51.1%)
Pregnant before	323 (46.1%)	360 (48.9%)
Parity		
Nulliparous	492 (70.2%)	487 (66.2%)
Parous	209 (29.8%)	249 (33.8%)
Cycle length, (d)		
mean (SD)	30.70 (6.27)	30.44 (5.9)
Cycle regularity		
Regular	450 (65.0%)	466 (64.5%)
Irregular[b]	242 (35.0%)	257 (35.5%)
Possible PCOS[c]		
Not PCOS-like	633 (93.1%)	675 (94.0%)
PCOS-like	47 (6.9%)	43 (6.0%)
AMH concentrations (ng/mL)		
median (IQR)	2.7 (1.7, 4.5)	3.1 (1.7, 4.7)
Lifestyle		
Alcohol intake (per week)		
None	212 (30.2%)	227 (30.8%)
>0 and ≤2.5 units	260 (37.1%)	265 (36.0%)
>2.5 units	229 (32.7%)	244 (33.2%)
Smoking status		
Never	558 (79.8%)	565 (77.0%)
Previous	100 (14.3%)	114 (15.6%)
Active	41 (5.9%)	54 (7.4%)
Instances of moderate/ vigorous physical activity in past 7 days		
Number of instances	3 (2, 5)	3 (1, 5)
Psychological Stress and Pressure[d]		
None	170 (24.2%)	168 (22.8%)
Slightly	339 (48.4%)	379 (51.5%)
Moderately to extremely	192 (27.4%)	189 (25.7%)
Metabolic health		
BMI, kg/m^2		
median (IQR)	24.1 (21.3, 28.8)	23.9 (21.3, 28.4)
Fasting glucose, mmol/L		
median (IQR)	4.96 (4.63, 5.18)	4.85 (4.63, 5.18)

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TABLE 1

Continued.

Characteristics	Control (n=701)	Intervention (n=736)
2-hour post glucose[e], mmol/L		
median (IQR)	5.62 (4.63, 6.82)	5.62 (4.63, 6.60)
HbA1c, mmol/mol		
median (IQR)	34 (32, 36)	34 (31, 36)
HOMA2-IR		
median (IQR)	0.96 (0.67, 1.54)	0.95 (0.63, 1.40)
Matsuda index		
median (IQR)	4.38 (2.74, 6.42)	4.62 (3.00, 6.59)
C-reactive protein, μg/mL		
median (IQR)	0.71 (0.24, 2.28)	0.67 (0.24, 1.93)

Data presented as number (%) unless otherwise stated. Sample sizes do not always equal to 701 for control group and 736 for intervention group because of missing values.
AMH = antimüllerian hormone, BMI = body mass index (calculated as weight in kilograms divided by height in meters squared), HbA1c = glycated hemoglobin, HOMA2-IR = updated homeostasis model assessment for insulin resistance, IQR = interquartile range, PCOS = polycystic ovary syndrome, Matsuda index = marker of insulin sensitivity, SD = standard deviation.
[a] Low: 1st-3rd decile, Middle: 4th-7th decile, High: 8th-10th decile
[b] Self-reported menstrual cycle lengths that varied by more than 5 days in past 6 months.
[c] PCOS-like defined as those with AMH >3.2 ng/ml and self-reported menstrual irregularities (defined as a variation of >5 days in menstrual cycle length in last 6 months and an average cycle length of greater than 35 days).
[d] Responses to the question "In general, how much stress or pressure have you experience in your daily living in the last 4 weeks?" based on the 12-Item Short-Form Health Survey (SF-12v2) and is a good measure of mental health functioning (52).
[e] As evaluated in a 75g oral glucose tolerance test.

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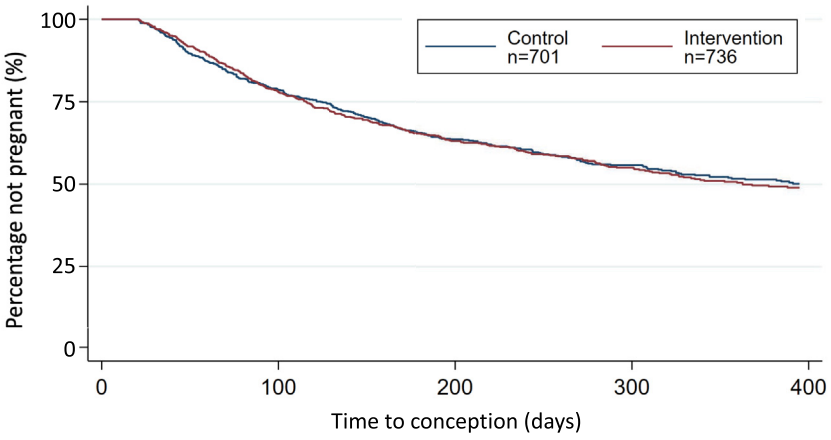
(Fig. 3A). Compared with control, the intervention shortened time-to-conception among overweight women toward that of nonoverweight/nonobese women (Fig. 3A). This effect was observed in White and non-White women (Fig. 3B). However, women with obesity showed longer time-to-conception with intervention than control (Fig. 3A). This effect was only observed in non-White women (Fig. 3C). Within the obese category, baseline characteristics of the control and intervention groups were similar (Supplementary Table 2, available online), so our results cannot be attributed to imbalances in these potential confounders. Furthermore, among non-White women with obesity additional adjustment for household income and psychological stress did not alter the intervention effect (HR: 0.35; P=.003).

Exploratory analyses suggest that a potential underlying mechanism for shortening time-to-conception could be suppression of inflammation by the intervention during the preconception period; this is supported by a lower CRP trend seen in the overweight intervention group compared with overweight controls (mean difference -0.12 [-0.26, 0.01] SDs accounting for baseline CRP values, site and ethnicity, P=.078), but no study arm difference was observed among the obese group (CRP -0.032 [-0.14, 0.07] SDs; P=.55; with no effect of White ethnicity within this model, P=.914). There were no changes in menstrual cycle regularity or preconception HbA1c with the intervention in women with overweight or obesity.

DISCUSSION

This randomized controlled trial demonstrated that a combined myo-inositol, probiotic, and micronutrient supplement

FIGURE 2



Outcome	Control (n=701)	Intervention (n=736)	Hazard ratio (95% CI)†	p	Adjusted HR (95% CI)^	p
20th centile of time-to-conception (95% CI), days	92.0 (76.0, 105.1)	90.5 (80.7, 103.5)	-	-	-	-
Clinical pregnancy rate daily over 3 m	0.23%	0.25%	1.05 (0.85, 1.28)	0.68	1.01 (0.82, 1.25)	0.90
Clinical pregnancy rate daily over 6 m	0.22%	0.22%	0.99 (0.83, 1.19)	0.95	0.97 (0.81, 1.15)	0.70
Clinical pregnancy rate daily over 12 m	0.20%	0.20%	1.00 (0.86, 1.18)	0.97	0.98 (0.83, 1.15)	0.77
Clinical pregnancy rate monthly (100 person-months) over 12 m	5.95%	6.11%	-	-	-	-

Time-to-conception and clinical pregnancy rates in control and intervention groups. Kaplan-Meier plot with over-time-censoring of withdrawn cases, including initiation of fertility treatment and very early pregnancy losses. Hazard ratios by Cox proportional hazards modeling between the intervention and the control groups †adjusted for the stratification factors of site and ethnicity (5 groups), and ^further adjusted for age, body mass index, and gravidity. CI = confidence interval, HR = hazard ratio, m = number of months after randomization.

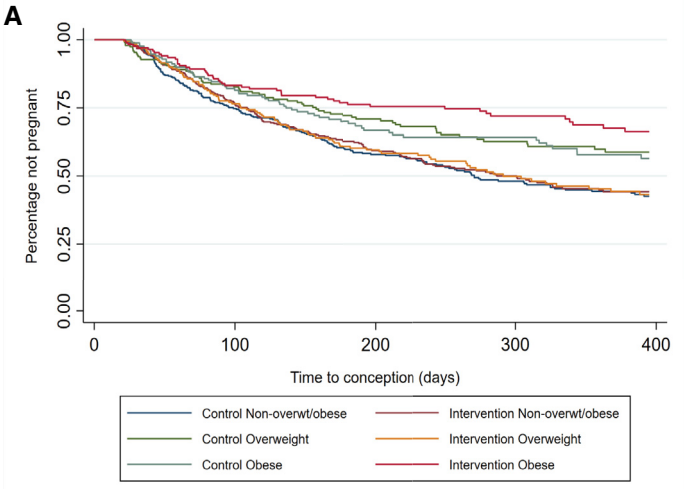
Chan. Nutritional supplement and conception. Fertil Steril 2023.

in women planning conception did not change the overall time-to-natural-conception or clinical pregnancy rates up to one year, nor the live birth rates. However, the intervention shortened time-to-conception among overweight women. The chance of conceiving in the overweight intervention group was 1.47 times that of the overweight control group by the end of a year, becoming equivalent to that of nonoverweight/nonobese women. This effect may be mediated by an improved regulation of inflammatory factors, represented by a lower CRP level. Among women with obesity the intervention lengthened the time-to-conception, an effect confined to non-White women with obesity, where the chance of conceiving in the intervention group was lowered to less than half ($2/5^{th}$) of that of the control group by one year.

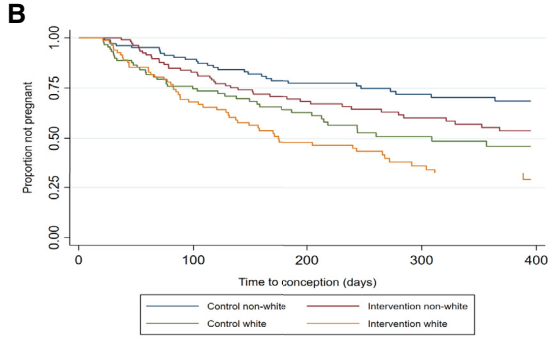
The overall longer time-to-conception in older, obese, and metabolically less healthy women provides internal validation that our trial population behaved as expected based on current understanding. This suggests that recruitment and eligibility methods did not result in a population unrepresentative of women planning conception. A novel finding is the variation in time-to-conception between ethnic groups, with a shorter time-to-conception in White than in non-White women and in Chinese than in Malay women among Asian ethnicities. This accords with an observational study in Singapore (41) which showed lower conception rates in Malay than in Chinese women (39% vs. 46%) over one year. Most non-White participants were recruited in Singapore, and in agreement with our findings, the 2017 Global Burden of Disease Study also reported a lower total fertility rate in Singapore than that in the United Kingdom and New Zealand (42). Ethnic differences may be explained by genetic variations, diet, culture, unmeasured lifestyle, and sexual practices, which remain poorly characterized. Nonetheless, these factors could not be addressed by the intervention because there were no clear ethnic differences in the overall response to the NiPPeR supplement, accepting that there were relatively modest numbers of participants in each non-White ethnicity.

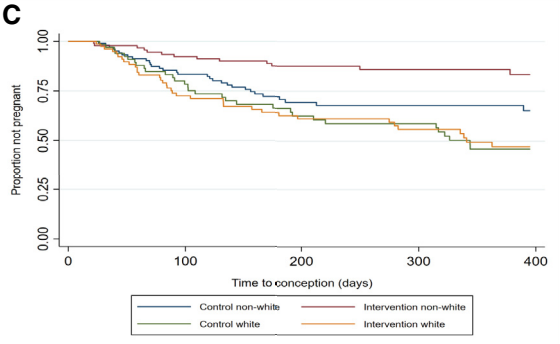
Not finding an improved conception rate nor changes in cycle regularity with an intervention containing myo-inositol contrasts with smaller trials in women with PCOS or fertility issues (13, 43). Possible reasons for these discrepancies include the generally healthier population in our trial, with

FIGURE 3



	Control		Intervention		HR (95% CI)	p
	N	20% TTC (days; 95% CI)	N	20% TTC (days; 95% CI)	control vs. intervention at 12m	
Non-overwt /obese	339	76.0 (60.4, 93.8)	375	87.5 (72.1, 100.4)	0.94 (0.76,1.16)	0.537
Overweight	193	117.0 (76.0, 159.0)	189	84.5 (65.8, 108.0)	1.47 (1.07, 2.02)	0.016
Obese	169	108.5 (78.0, 143.9)	170	132.7 (84.5, 275.0)	0.69 (0.47, 1.00)	0.053





	Control		Intervention		HR
	N	20% TTC (days; 95% CI)	N	20% TTC (days; 95% CI)	control vs. intervention at 12m
White	89	68.0 (46.0, 127.0)	82	74.0 (38.5, 88.0)	NSDNM
Non-White	104	163.0 (103.6, 308.5)	107	115.5 (70.0, 151.7)	NSDNM

	Control		Intervention		HR
	N	20% TTC (days; 95% CI)	N	20% TTC (days; 95% CI)	control vs. intervention at 12m
White	66	99.5 (57.0, 134.5)	78	80.7 (52.1, 104.5)	NSDNM
Non-White	103	131.0 (71.0, 181.5)	92	Only 14.1% conceived	0.38 (0.20, 0.72); p=0.003

Effect of intervention stratified by body mass index (BMI) groupings (defined using ethnic-specific thresholds for overweight and obesity: BMI ≥23 to <27·5 and ≥27·5 kg/m^2, respectively, for Asians including Chinese, Indians, Pakistani, Bangladeshi, Malay, mixed Asian; BMI ≥25 to <30 and ≥30 kg/m^2, respectively, for non-Asians including White Caucasian, Polynesian, Black, mixed Asian-non-Asian) (40). Hazard ratios by Cox proportional hazards modeling between the intervention and the control groups in **(A)** all 3 BMI categories stratified by intervention group †adjusted for the stratification factors of site and White/non-White; **(B)** overweight women stratified by ethnicity and intervention group; **(C)** obese women stratified by ethnicity and intervention group. BMI = body mass index. CI = confidence interval, HR = hazard ratio, non-overwt/obese = nonoverweight/nonobese, NSDNM = not significantly different from the null model, TTC = time-to-conception.

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only 6.4% having PCOS-like features, the more diverse ethnic mix, and the possibility of potential interactions with other intervention components. The PCOS-like subgroup was, however, underpowered for separate assessment of intervention efficacy. Our findings also differ from the multivitamin (without myo-inositol or probiotics) trial conducted in Hungary that reported a marginally shorter time-to-conception with supplementation (31), which could also be because of population differences. Young women at our respective study sites are known to show low to moderate prevalence of micronutrient insufficiencies (44–47). With randomization, baseline micronutrient levels are expected to be similar between groups; however, we cannot discount the possibility that anticipated increases in the intervention group may not have risen to a level capable of improving fertility or reducing miscarriage (48).

Promisingly, our trial suggests that a nutritional supplement might optimize time-to-conception among overweight women to that of nonoverweight/nonobese women, with similar effects in White and non-White women; caution is nonetheless needed in drawing a definitive conclusion given that this is a secondary trial outcome with more limited statistical power in this subgroup. Exploratory analyses suggest a generally less proinflammatory environment, represented by lower plasma CRP approximately a month after starting the intervention, could be a possible underlying mechanism. Lower CRP has previously been associated with better fertility (49), with improved ovulatory function and endometrial receptivity, hence the chances of conception and successful implantation.

Similar to our findings, differential metabolic responses to myo-inositol supplements in the morbidly obese compared with the less obese/overweight have previously been reported among women experiencing oligomenorrhoea and PCOS, with benefit reported only in the latter group and not the former (50), suggesting that supplementation effect is influenced by the degree of BMI elevation. As expected, our study found higher baseline CRP, HbA1c, and HOMA2-IR with increasing BMI categories (Supplementary Table 3, available online). We speculate that metabolic dysregulation in women with obesity could be too extreme to be amenable to sufficient improvement with a nutritional supplement alone. Further, the lengthened time-to-conception in non-White women with obesity was not accompanied by detrimental changes in menstrual cycle regularity, inflammation, or HbA1c, nor explained by variations in household income or psychological stress. We previously reported that the NiPPeR intervention slightly increased post-prandial glycemia at 28 weeks of gestation in women with a high preconception BMI (33), and higher glycemia could also be occurring preconception. Given that the non-White obese subgroup started off with the highest HbA1c at baseline, partly reflecting increased glycemia over the previous 3 months that may impair fertility, just a further slight increase in preconception glycemia could result in discernable deterioration in fertility that may be less obvious in White women with obesity who started with a lower baseline HbA1c. However, our trial design did not allow us to examine this postulation further because HbA1c was the only available marker of glycemia measured after intervention and preconception, and its assessment a month after intervention would not be long enough to permit discernment of an intervention effect on glycemia.

Strengths of our study are its multi-centered, multi-ethnic, double-blind nature that decrease bias and improve generalizability, the relatively large sample size for a community-recruited preconception trial as opposed to a subfertile population seeking assisted conception, and the over 70% follow-up rate at 1 year. Randomization resulting in similar baseline characteristics in the 2 study groups would have largely mitigated the effects of any unmeasured confounding. By design, participants were confined to those planning conception, which would be the main scenario where a woman could choose to commence a nutritional supplement, so the lack of application to unplanned pregnancies is not relevant. Recruited women were mostly healthy, highly educated with high socioeconomic status, so the efficacy of a nutritional supplement in more deprived, less healthy women, who may arguably derive more benefit, remains uncertain. However, our study showed no differential effects of the intervention in different household income groups. Further limitations were predominantly because of fecundability being a secondary outcome, and concerns regarding subject burden, so participants were not clinically assessed for PCOS using international consensus criteria, other causes of female/male subfertility, nor time trying to conceive before trial participation, but these would likely be balanced between randomized groups. The possibility that antagonistic effects between components of the intervention have masked the potential beneficial effects of some of its ingredients requires further examination.

CONCLUSIONS

Overall, compared with a standard micronutrient supplement, women taking the combined myo-inositol, probiotics, and micronutrient supplement showed similar time-to-natural-conception and clinical pregnancy rates within a year. Although supplementation may have the potential to shorten time-to-conception in overweight women to that comparable with nonoverweight/nonobese women, it may exacerbate the already suboptimal fertility in women with obesity, particularly those of non-White ethnicity. Further investigation is required to confirm these effects and better understand the underlying mechanisms.

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Tiempo de concepción y tasa de gestación clínica con un suplemento de mioinositol, probióticos, y micronutrientes: resultados secundarios del ensayo aleatorizado NiPPeR

Objetivo: Determinar si un suplemento nutricional combinado de mioinositol, probióticos y micronutrientes impacta en el tiempo de concepción natural y tasas de gestación clínica.

Diseño: Resultados secundarios de un ensayo controlado aleatorizado doble ciego.

Lugar: Reclutamiento comunitario.

Pacientes: Mujeres de 18 a 38 años planificando concebir en el Reino Unido, Singapur, y Nueva Zelanda, excluyendo aquellas con diabetes mellitus o que recibieron tratamiento de fertilidad.

Intervención: Un suplemento estándar (control) (ácido fólico, hierro, calcio, yodo, β-caroteno), comparado con una intervención adicional conteniendo mioinositol, probióticos, y otros micronutrientes (vitaminas B2, B6, B12, D, zinc).

Medidas de resultado principal: Número de días entre la aleatorización y la fecha estimada de concepción natural de un embarazo clínico, así como también tasas de embarazo acumulativas a 3, 6, y 12 meses.

Resultados: De 1729 mujeres aleatorizadas, 1437 (83%; intervención, n=736; control, n=701) proporcionaron datos. Las curvas de concepción de Kaplan-Meier fueron similares entre los grupos de intervención y control; el tiempo en el que el 20% logró la concepción natural fue 90.5 días (intervalo de confianza 95%: 80.7, 103.5) en el grupo de intervención comparado con 92.0 días (76.0, 105.1) en el grupo control. Las razones de riesgo proporcional de Cox (HRs) comparando intervención contra control para el logro acumulativo de embarazo (ajustado por lugar, etnia, edad, índice de masa corporal, y paridad) fueron similares a los 3, 6, y 12 meses. Entre ambos grupos de estudio combinados, el tiempo total para la concepción se alargó con mayor índice de masa corporal preconcepcional, y fue mayor en mujeres no blancas que en blancas. Entre las mujeres con sobrepeso la intervención acortó el tiempo a la concepción comparado con los controles independientemente de la etnia (12 meses HR = 1.47 [1.07, 2.02], P=.016; 20% concebido en 84.5 vs 117.0 días) y lo mejoró comparable a mujeres sin sobrepeso/ no obesas (20% concebido en 82.1 días). En cambio, entre mujeres con obesidad, el tiempo a la concepción se alargó con intervención en comparación con controles (12 meses HR = 0.69 [0.47, 1.00], P=.053; 20% concebido en 132.7 vs 108.5 días); un efecto predominantemente observado en mujeres no blancas con obesidad.

Conclusiones: El tiempo de concepción natural y las tasas de gestación clínica dentro del año fueron en general similares en mujeres recibiendo el suplemento de intervención comparado con el control. Las mujeres con sobrepeso tuvieron un tiempo más largo para la concepción pero hubo cierta tendencia a que el suplemento pudiese acortar el tiempo de concepción, comparable al de las mujeres sin sobrepeso/ no obesas. Se requieren más estudios para confirmar esto.