OBSTETRICS

Randomized controlled trial of prepregnancy lifestyle intervention to reduce recurrence of gestational diabetes mellitus

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BACKGROUND: Preconception lifestyle intervention holds potential for reducing gestational diabetes mellitus, but clinical trial data are lacking.
OBJECTIVE: This study aimed to determine the effects of a prepregnancy weight loss intervention on gestational diabetes mellitus recurrence in women with overweight/obesity and previous gestational diabetes mellitus.
STUDY DESIGN: A 2-site, randomized controlled trial comparing a prepregnancy lifestyle intervention with educational control was conducted between December 2017 and February 2022. A total of 199 English- and Spanish-speaking adults with overweight/obesity and previous gestational diabetes mellitus were randomized to a 16-week prepregnancy lifestyle intervention with ongoing treatment until conception or educational control. The primary outcome was gestational diabetes mellitus recurrence. Analyses excluded 6 participants who conceived but did not have gestational diabetes mellitus ascertained by standard methods.
RESULTS: In the 63 (33%) women who conceived and had gestational diabetes mellitus ascertained (Ns=38/102 [37%] intervention vs 25/91 [28.0%] control; *P*=.17), those in the intervention group had significantly greater weight loss at 16 weeks compared with controls (4.8 [3.4−6.0] vs 0.7 [−0.9 to 2.3] kg; *P*=.001) and a greater proportion lost ≥5% of body weight (50.0% [17/34] vs 13.6% [3/22]; *P*=.005). There was no significant difference in the incidence of gestational diabetes mellitus recurrence between the intervention (57.9% [ns=23/38]) and the control group (44.0% [ns=11/25]; odds ratio, 1.8 [0.59−5.8]). Independent of group, greater prepregnancy weight loss predicted 21% lower odds of gestational diabetes mellitus recurrence (odds ratio, 0.79 [0.66−0.94]; *P*=.008). A ≥5% weight loss before conception reduced the odds of gestational diabetes mellitus recurrence by 82% (odds ratio, 0.18 [0.04−0.88]; *P*=.03).
CONCLUSION: Lifestyle intervention produced considerable prepregnancy weight loss but did not affect gestational diabetes mellitus rates. Given that the conception rate was 50% lower than expected, this study was underpowered.

Key words: gestational diabetes, lifestyle intervention, preconception weight loss, randomized controlled trial

Introduction

Gestational diabetes mellitus (GDM) affects an estimated 7.8% of pregnant persons in the United States and has increased by 30% since 2016.[1] Hispanic women are disproportionately affected and have a GDM prevalence of 8.5%.[1] Women with GDM have increased risks for pregnancy complications and later cardiometabolic disease.[2] Between 40% and 73% of women with previous GDM will experience GDM recurrence,[3] which increases by 3-fold the risks of adverse short- and long-term outcomes. Intrauterine exposure to maternal GDM conveys high risk of short- and long-term health problems in the offspring and may perpetuate a cycle of obesity.

Several researchers and government agencies have called for clinical trials evaluating interventions that occur before pregnancy with the specific aim of reducing GDM and related adverse outcomes.[4−13] Findings from observational studies have suggested that preconception weight loss and physical activity may decrease the risk for developing GDM.[14] However, randomized clinical trials are lacking. A prepregnancy lifestyle intervention specifically targeting women with previous GDM may increase study power because of their greater risk of GDM in subsequent pregnancy, and also capitalize on a "teachable moment" when women may be more motivated to engage in behavior changes to prevent GDM recurrence.

The primary goal of the Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional trial was to evaluate the efficacy of a preconception behavioral weight loss intervention to reduce GDM recurrence in people with overweight/obesity. The primary hypothesis was that the recurrence of GDM would be reduced among participants assigned to the prepregnancy lifestyle intervention vs educational control. Secondary hypotheses were that the prepregnancy lifestyle intervention (vs educational control) would lead to greater weight loss and improvements in maternal metabolic risk factors (fasting glucose, blood pressure) and weight control behaviors (ie, diet, physical activity, weight control strategies) assessed at baseline, after 16 weeks of intervention, and at 26 weeks' gestation, and would reduce perinatal complications for participants and offspring.

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AJOG at a Glance

Why was this study conducted?

The objective of Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional trial was to determine the effects of a prepregnancy lifestyle intervention on gestational diabetes mellitus recurrence in women with overweight/obesity and a history of gestational diabetes mellitus.

Key findings

The prepregnancy lifestyle intervention produced clinically meaningful weight loss but did not affect the rates of gestational diabetes mellitus.

What does this add to what is known?

Large scale, multicenter trials will be needed to determine whether improved prepregnancy weight prevents gestational diabetes mellitus and other perinatal morbidities.

Materials and Methods

Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional was a 2-site, parallel-group, randomized clinical trial in San Luis Obispo, California and Providence, Rhode Island. The protocol has been published previously.[15] Procedures were approved by the California Polytechnic State University, San Luis Obispo (#2017-019) and the Miriam Hospital (#2039-11) institutional review boards, and all participants provided written informed consent. Recruitment occurred between December 2017 and February 2022. Both sites recruited participants through direct methods, including placing clinic staff at recruitment clinics, and indirect methods, including social media, flyers, and community presentations. Administrative databases from healthcare settings were also used to identify and contact women with a history of GDM.

Eligibility was based on physician documentation of GDM during a previous pregnancy.[15–19] Furthermore, participants had to report plans for pregnancy within 1 to 3 years, responding with "≥1" to the question, "On a scale of 0 to 10, what are the chances of you becoming pregnant in the next 1 to 3 years?" (0=Not at all likely; 5=Somewhat likely; 10=Very likely). Other criteria were body mass index (BMI) ≥25 kg/m^2, age ≥18 years, ≥3 months postpartum, and being English- or Spanish-speaking. Exclusion criteria are shown in Figure 1. Participants who reported a semi-permanent form of birth control with no plans for removal were excluded from the trial, but birth control was not exclusionary otherwise. Eligible participants were randomized into the intervention or control group and stratified by site, prediabetes status (HbA1c <5.7 vs ≥5.7), and previous method of GDM diagnosis.[15]

Interventions

Standard care + education

Participants in this group were provided standard care by their usual providers before and during pregnancy. In addition, during 2, 20-minute meetings with a study interventionist at study entry and at 16 weeks, they received general education about preconception health.[15]

Standard care + education + weight loss intervention

This group received all aspects of standard care plus education. In addition, they received a lifestyle modification program designed to produce a 10% weight loss over 16 weeks and weight loss maintenance until conception.[15] For the first 16 weeks, participants met with the lifestyle interventionist weekly for ~30 minutes. Thereafter, participants met biweekly to maintain weight loss until conception. After conception, intervention contacts were discontinued. Participants were instructed to follow a standard calorie-restricted, nutritionally balanced diet (35% fat, 20% protein, 45% carbohydrate) and to increase their physical activity to at least 150 minutes per week.[15] Intervention visits (~30 min/each) with lifestyle interventionists were held in person, on the phone, or via video conferences, and occurred weekly for the first 16 weeks, then every 2 weeks until conception.[15]

Outcome assessments

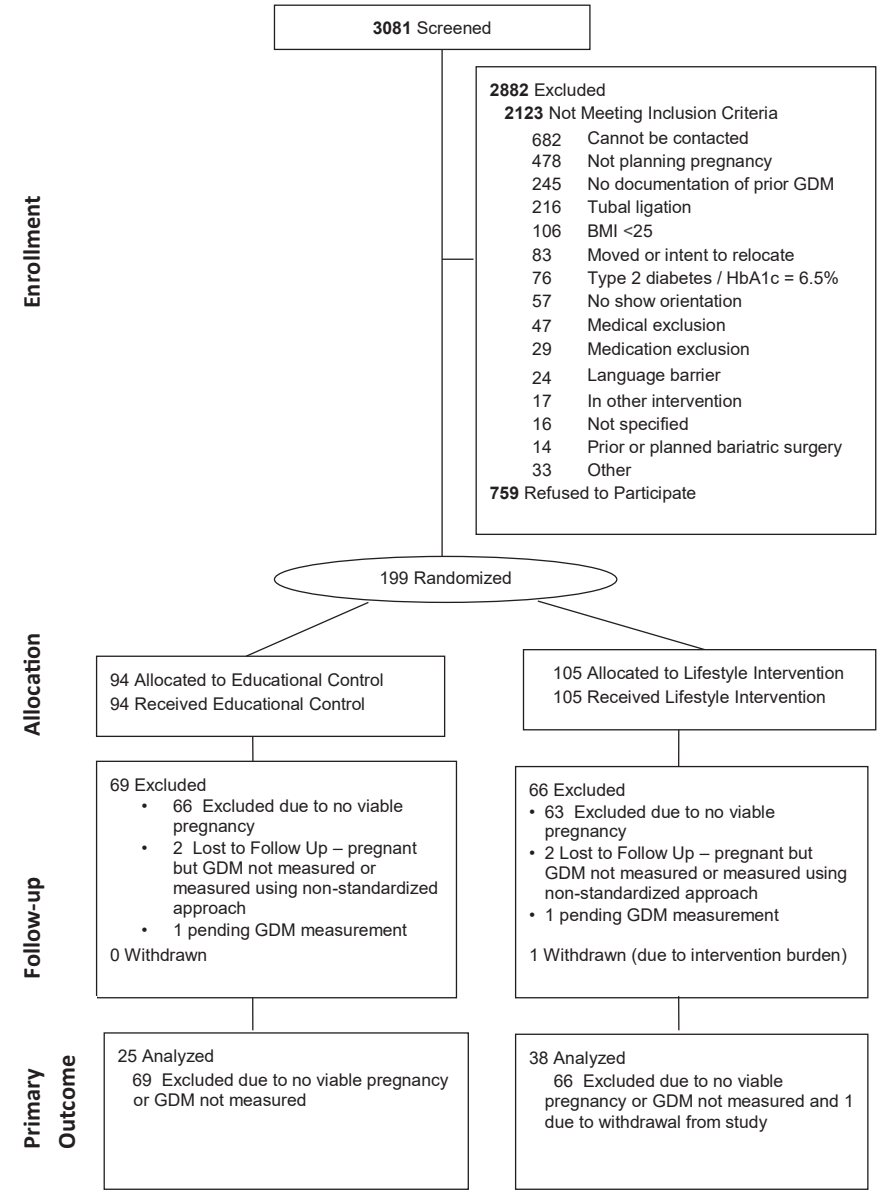
Core assessments were conducted at baseline, after 16 weeks, at 26 weeks' gestation, and at 6 weeks postpartum, and brief quarterly visits occurred until conception.[15] Participants received $25 for completing baseline, 16-week, and 6-week-postpartum visits, $50 for completing the 26 weeks' gestation visit, and $15 for quarterly brief assessments.

Assessment staff was masked to randomization. The study's primary outcome was GDM diagnosis in next pregnancy based on the Carpenter and Coustan criteria[20] and required 2 abnormal values on a study-measured 3-hour oral glucose tolerance test (OGTT). When possible, a study measure was conducted, but in most cases (N=48), the diagnosis of GDM was based on provider assessment with 2-hour OGTTs and other tests interpreted according to the study's a priori criteria.[15]

Secondary outcomes measured by trained staff included maternal weight, height, fasting glucose, systolic and diastolic blood pressure, HbA1c, and 6-week infant weight and length.[15]

Adherence to the intervention was measured through attendance at intervention sessions and number of daily self-monitoring records returned. In addition, dietary intake was measured using 24-hour recalls[15,21] and physical activity using the wrist-worn accelerometer.[22] Validated questionnaires measured weight control practices and psychosocial factors.[15] Maternal and perinatal complications were abstracted from medical charts. Composite measures of adverse[23] and serious perinatal

FIGURE 1
Participation in the Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional RCT



BMI, body mass index; *GDM*, gestational diabetes mellitus; *RCT*, randomized controlled trial.

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complications[24] were computed. Other adverse events and sociodemographics were measured by self-report.

Sample size

Based on previous research,[15,25–27] assumptions were that ≥70% of participants would conceive during the study (the other 30% would be lost to follow-up or not become pregnant) and GDM would recur in 60% of the pregnancies. A target sample size of 252 was projected to yield 176 pregnant participants (≥88 in each group) and provide adequate statistical power (≥81.98%) to detect a minimum effect size (odds ratio [OR]) of 0.43 (intervention 38% vs control 60%) on the proportions developing recurrent GDM, taking into account estimations of site-specific clustering effects and effect modifiers (ie, weight status, ethnicity, parity) of GDM recurrence.

Analysis plan

All participants with confirmed pregnancy and valid GDM outcome measure were included in the primary analysis. A multiple logistic regression analysis was used to examine the effect of treatment group on the proportion of women who developed GDM. The a priori model included site and covariates to adjust for baseline parity, age, education, income, smoking, race/ethnicity, BMI, and time since last pregnancy with GDM. Sensitivity analyses were done to confirm the robustness of the primary outcome results. The effects of the intervention on secondary outcomes were examined using linear mixed-effects models with fixed effects for treatment condition, time (baseline, 16 weeks, 26 weeks' gestation), site, baseline value, and covariates. General linear models and logistic regression analyses were performed to address the effects of the intervention on perinatal outcomes, including the same covariates. Similar logistic regression analyses with the same covariates examined prepregnancy predictors of GDM.

Results

Figure 1 summarizes participant flow into the trial. Of the 3081 screened, 199 were randomized, including 105 in the intervention and 94 in the control group; randomization was stratified by site, prediabetes status and previous method of GDM diagnosis, which resulted in unequal group sizes.[28] Of the 199 participants, those who did not become pregnant (n=129), withdrew (n=1), were pregnant but study ended before GDM measure (n=2), or had GDM not measured or measured using non-standardized approach in clinic setting (n=4) were excluded; this left an analytic sample of 63 (33%) participants (Ns=38/102 [37%] intervention vs 25/91 [28.0%] control; *P*=.17). The demographic characteristics (ie, parity, age, education, income, smoking, race/ethnicity, BMI, and time since last pregnancy with GDM) and group

assignment did not significantly differ between participants who became pregnant and had GDM ascertained and those who did not become pregnant. Participants who became and who did not become pregnant during the trial also had similar preconception weight losses (2.4 [5.6] vs 2.5 [6.3] kg, respectively; P=.56; includes both intervention and control group).

Comparing baseline ratings (1−10) of perceived likelihood of becoming pregnant during the trial, those who subsequently became pregnant had higher baseline scores than those who did not become pregnant (8.0 [2.4] vs 6.7 [2.9], respectively; P=.001). A point-biserial correlation suggested that higher baseline ratings correlated with higher pregnancy incidence (r=0.25; P=.001).

Pregnancy occurred on average 49.8 (standard deviation [SD], 40.0) weeks after randomization, and time until pregnancy did not significantly differ between the intervention and the control group (53.0 [44.3] vs 44.7 [32.1] weeks, respectively; P=.36); 27% of participants (n=17) became pregnant between study entry and 16 weeks (n=8 during the first 8 weeks and n=9 during the second 8 weeks); 31.8% (n=20) between 16 and 52 weeks; 33.3% (n=21) between 52 and 104 weeks; and 7.9% (n=5) between 2 and 3 years. Attendance rates at core measurement visits were 88.9% (56/63) at 16 weeks, 88% (56/63) at 26 weeks' gestation, and 85.5% (52/63) at 6 weeks postpartum (no significant differences by randomized group). Participant characteristics were well-balanced by randomized group (Table 1).

Lifestyle intervention effects on weight

The lifestyle intervention was effective in producing weight loss, with an average weight loss in the intervention group of 4.8 (3.5−6.0) kg (5.7% weight loss) at the end of the 16 weeks, as opposed to the 0.7 (−0.9 to 2.3) kg (0.7% weight loss) loss in the control group (P=.001; 4.1 [2.0−6.2] kg difference; N=56). At the final preconception visit (49.7 [SD, 39.9] weeks after randomization), intervention participants had greater weight loss than controls, but the difference was not statistically significant (2.8 [−0.7 to 6.3] kg difference; N=58) (Figure 2, A). A greater proportion of intervention (vs control) participants achieved ≥5% weight loss after 16 weeks (50.0% [17/34] vs 13.6% [3/22], respectively; OR, 10.4 [2.0−53.0]) and at the final preconception visit (42.9% [15/35] vs 17.4% [4/23]; OR, 6.9 [1.4−33.8]) (Figure 2, B). Proportions of intervention and control participants losing ≥10% were low at 16 weeks (14.7% [5/34] and 0% [0/22], respectively; P=.07) and the final preconception visit (20.0% [7/35] and 3.5% [2/23], respectively; P=.22). Proportions of intervention and control participants who moved down BMI categories at the final visit were 26.5 % (9/34) and 10.0% (1/23), respectively (P=.09).

Primary outcome: incidence of gestational diabetes mellitus

Although the intervention increased weight loss before pregnancy, it had no significant effect on GDM recurrence rate relative to the control (57.9% vs 44.0%, respectively; OR [95% confidence interval], 1.84 [0.59−5.8]). In a priori analyses that adjusted for baseline covariates, there was no significant effect of randomized group on incidence of GDM (Figure 3). Similar results were found in sensitivity analyses that included only participants whose recurrent GDM was diagnosed with 2-step OGTT (Figure 3); 86.8% (33/38) of intervention and 88% (22/25) of control participants received the 2-step OGTT (P=.70). None of the covariates in the model were significantly related to GDM recurrence, and no significant group×sociodemographic variable interactions on GDM recurrence were observed. Additional analyses, adjusting for other covariates, such as baseline fasting glucose or HbA1c levels, GDM ascertainment methods (previous pregnancy and current), weeks of gestation for GDM ascertainment, and diabetes mellitus medications, duration until pregnancy, or timing of GDM screening, or excluding women who became pregnant during the intervention, did not alter these findings.

Secondary outcomes: glucose, blood pressure, and behavior changes

No significant group×time (baseline, 16 weeks, 26 weeks' gestation) interaction was found for glucose (P=.14) (Supplemental Table 1). For diastolic blood pressure, a group×time interaction (P=.04) was observed, and post hoc tests suggested a 7.1 (−13.0 to −1.3) mm Hg greater improvement in the intervention (vs control) group after 16 weeks (P=.02). There was no significant effect of the intervention on systolic blood pressure (Supplemental Table 1). The intervention significantly improved weight control practices and cognitive restraint and reduced depressive symptoms over 16 weeks and had no significant group effects on changes in dietary intake or physical activity (Supplemental Table 1).

Examining attendance during the 4-month program within the intervention group, participants attended a mean (SD) of 9.5 (5.2) visits (59.2 [32.9]%). Intervention participants tracked dietary intake for 43.5 (34.2) days (36.3 [28.5]%) on average during the 4-month program. Both higher attendance (r=0.47; P=.001) and greater number of food records completed (r=0.53; P=.001) were positively correlated with weight loss.

Predictors of gestational diabetes mellitus

Independent of group, increasing weight loss between study entry and last weight measured before pregnancy predicted 21% lower odds of GDM recurrence (OR, 0.79 [0.66−0.94]; P=.008); for every 1 kg lost before pregnancy, GDM recurrence was reduced by 24%. A ≥5% weight loss before conception reduced the odds of GDM recurrence by 82% (OR, 0.18 [0.04−0.88]; P=.03). A shift down in BMI category (obese to overweight or overweight to normal weight) reduced the odds of GDM recurrence by 97% (OR, 0.03 [0.002−0.38]; P=.007). Greater weight regain from 16 weeks to last weight before pregnancy trended (P=.051) toward higher odds of GDM (OR, 1.2 [0.9−1.5]). Higher baseline levels of fasting glucose (OR, 1.1

TABLE 1
Baseline characteristics of participants in the analytic sample by condition

Characteristic	Total n=63	Control n=25	Intervention n=38
Age, y, mean (SD)	32.7 (4.5)	32.9 (5.1)	32.4 (4.2)
Hispanic/Latino, n (%)	35 (55.6)	13 (52.0)	22 (57.9)
Heritage, n (%) (participants could select multiple)			
American Indian or Alaskan Native	1 (1.6)	1 (4.0)	0 (0)
Asian	1 (1.6)	1 (4.0)	0 (0)
Black or African American	2 (3.2)	0 (0)	2 (5.3)
Native Hawaiian or Pacific Islander	2 (3.2)	1 (4.0)	1 (4.0)
White	27 (42.9)	12 (48.0)	15 (39.5)
Other	9 (14.3)	2 (8.0)	7 (18.4)
Married or living with sig. other; n (%)	50 (79.4)	20 (80.0)	30 (60.0)
Annual household income, n (%)			
<$50,000	30 (47.6)	12 (48.0)	18 (47.6)
≥$50,000	33 (52.4)	13 (52.0)	20 (52.6)
Education, n (%)			
High school or less	27 (42.9)	10 (40.0)	17 (4.7)
Some college/college or more	36 (57.1)	15 (60.0)	21 (55.3)
Employment, n (%)			
Employed full time (≥35 h/wk)	29 (46.0)	9 (36.0)	20 (52.6)
Employed part time (<35 h/wk)	10 (15.9)	5 (20.0)	5 (13.2)
Unemployed	24 (38.1)	11 (44.0)	13 (24.2)
Previous pregnancies, mean (SD)	2.5 (1.5)	2.4 (1.5)	2.6 (1.4)
Years since previous GDM, mean (SD)	1.7 (1.5)	1.4 (1.2)	1.9 (1.7)
Previous GDM diagnostic method			
75-g OGTT	15 (23.8)	7 (28.0)	8 (21.1)
100-g OGTT	34 (54.0)	15 (60.0)	19 (50.0)
Other	14 (22.2)	3 (12.0)	11 (28.9)
Weight, kg, at study entry, mean (SD)	83.6 (19.9)	81.7 (18.1)	84.9 (21.0)
BMI, kg/m^2, at study entry, mean (SD)	32.9 (6.5)	32.1 (5.8)	33.4 (6.7)
Site, n (%)			
Cal Poly	34 (54.0)	14 (41.2)	20 (58.8)
Brown University	29 (46.0)	11 (37.9)	18 (62.1)
Prediabetes, n (%)	10 (15.9)	3 (12.0)	7 (18.0)
HbA1c, mean (SD)	5.4 (0.3)	5.3 (0.3)	5.4 (0.1)
Weight status			
Overweight, n (%)	25 (39.7)	12 (48.0)	13 (34.2)
Obese, n (%)	38 (60.3)	13 (52.0)	25 (65.8)

BMI calculated as weight in kilograms divided by the square of height in meters.

BMI, body mass index; *Cal Poly*, California Polytechnic State University, San Luis Obispo; *GDM*, gestational diabetes mellitus; *OGTT*, oral glucose tolerance test; *SD*, standard deviation.

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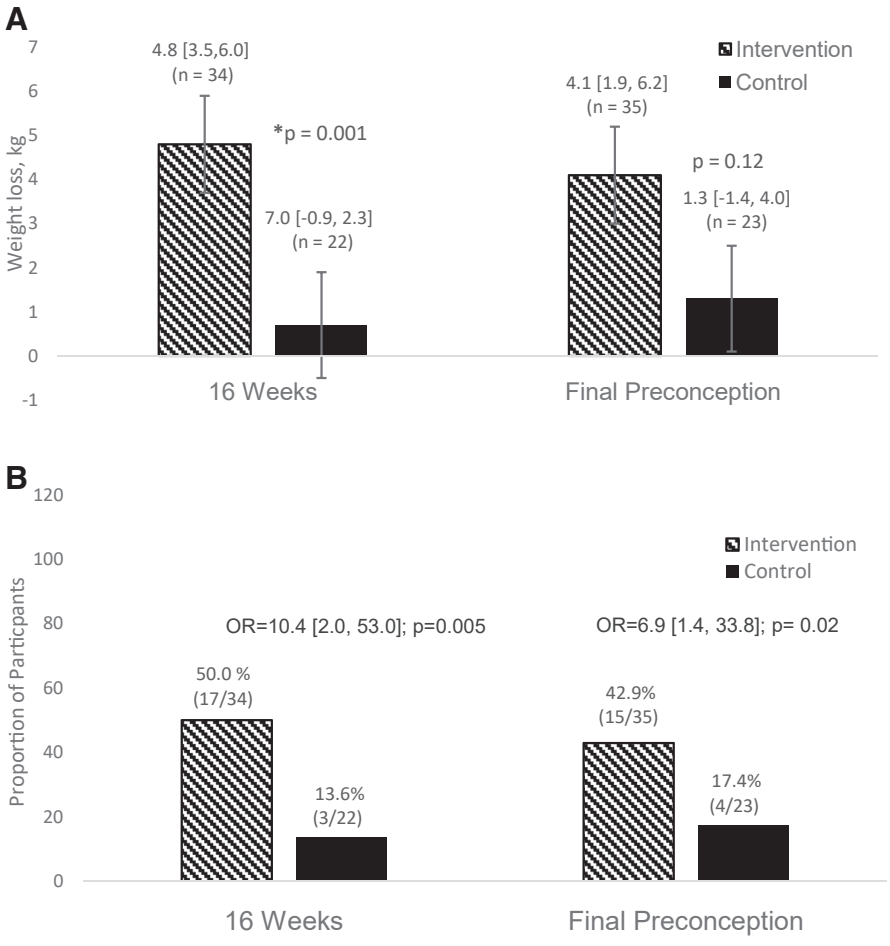
FIGURE 2
Weight Loss in Kilograms in Intervention and Control Participants Before Pregnancy



A, Weight loss in kilograms in intervention and control participants before pregnancy. Figure shows results from general linear models, including adjusted means and confidence intervals and standard error bars. The a priori model included all participants, including the 17 who became pregnant before 16 weeks' gestation, and the following covariates: site, parity, age, education, income, smoking, race/ethnicity, BMI, and time since last pregnancy with gestational diabetes mellitus. **B,** Proportion of intervention and control participants losing ≥5% of initial body weight before pregnancy. Figure shows results from logistic regression analysis. The model included site and the following a priori covariates: parity, age, education, income, smoking, race/ethnicity, BMI, and time since last pregnancy with gestational diabetes mellitus.

BMI, body mass index; *OR*, odds ratio.

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[1.1−1.2]; *P*=.01) predicted greater odds of GDM recurrence, but subsequent changes in glucose and baseline and changes in behavioral and psychosocial factors did not significantly relate to GDM recurrence.

Perinatal outcomes and safety

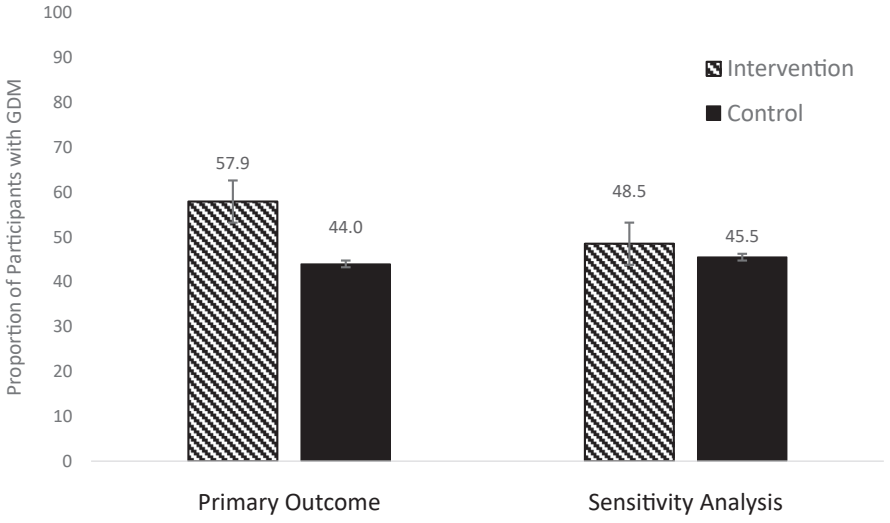
On the basis of final measured weight before pregnancy, no significant intervention vs control group differences were observed in gestational weight gain (GWG) at 26 weeks' gestation, GWG at end of pregnancy, proportions gaining above National Academy of Sciences guidelines during pregnancy, or magnitude of postpartum weight retention at 6 weeks postpartum (Table 2). The incidences of miscarriages (N=12 overall) and other adverse events were similar in both groups (Supplemental Table 2). The groups did not significantly differ in incidence of receiving metformin, insulin, or other medications (data not shown) during pregnancy.

Comment

This study was a randomized controlled trial examining the effects of a prepregnancy weight loss intervention on GDM in women with overweight/obesity and previous GDM. Women in the intervention arm lost 5.7% of their initial body weight over 4 months before pregnancy, and 50.0% lost a clinically meaningful significant ≥5%. Despite promoting clinically meaningful weight loss, the intervention (vs educational control) had no effect on GDM recurrence. Collapsing across groups, preconception weight loss reduced odds of GDM recurrence by 21%, and weight loss ≥5% of initial body weight reduced odds of GDM recurrence by 82%.

The study was underpowered to determine effects on GDM recurrence. Sample size during pregnancy was much lower than expected (n=63 instead of 176), due in large part to a lower-than-anticipated pregnancy rate (35% vs 70%). Based on original projections, post hoc power calculations showed that the achieved sample size of 63 provided only 29.4% power to detect the medium effect size of 0.43 that was projected. Reasons for lower-than-expected conception rates in the study were unclear. Conception rates in previous preconception trials have been higher at 42%,[30] 52%,[31] and 63%.[32] This study took place during the COVID-19 pandemic, when national pregnancy rates were known to decline.[33] Our eligibility criteria included people who endorsed any likelihood of pregnancy (≥1 on a 0-to-10−point scale), which may have increased potential generalizability of the study's findings given that >40% of pregnancies are unplanned,[34] but could have reduced conception rates. Six of the participants who became pregnant (8%) had GDM ascertained in a nonstandardized manner and were removed from the analyses. Future research may consider enrolling people with higher baseline ratings of perceived likelihood of getting pregnant. Trials

FIGURE 3
Proportions with recurrent GDM in prepregnancy intervention and control groups



Intervention (n/n, %)	22/38 (57.9%)	16/33 (48.5%)
Control (n/n, %)	11/25 (44.0%)	10/22 (45.5%)
OR [95% CI]	1.84 [0.59, 5.8]	1.2 [0.36, 4.0]
Unstandardized beta (SE)	0.61 [0.58]	0.18 (0.62)

Sensitivity analysis reflects participants with the same GDM diagnostic method (2-step oral glucose tolerance test). The model included site and the following a priori covariates: parity, age, education, income, smoking, race/ethnicity, body mass index, and time since last pregnancy with GDM.

CI, confidence interval; *GDM*, gestational diabetes mellitus; *OR*, odds ratio; *SE*, standard error.

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requiring stronger plans for pregnancy[32] have reported a much higher conception rate (63%), but also had higher rates of participants becoming pregnant after the first study visit and thus receiving minimal to no intervention (45% vs 27% in current study).

Systematic reviews and meta-analyses have affirmed the lack of large, prospective randomized controlled trials testing prepregnancy interventions.[35,36] The trials with the largest sample sizes to date include RADIEL,[32] Price et al,[30] and PREPARE.[31] RADIEL[32] found no significant differences between the preconception intervention and the control group in incidences of subsequent GDM (60% vs 54%, respectively; P=.49); magnitude of preconception weight loss was not reported. Price et al[30] compared a very-low-energy diet (VLED) intervention with the control and found greater preconception weight loss (11.2 vs 2.1 kg, respectively) but no significant effect on midpregnancy fasting glucose or incidences of GDM, which were 40% vs 25%, respectively. The PREPARE trial[31] reported greater preconception weight loss in the lifestyle intervention than in the control group (3.7 vs 0.6 kg, respectively), but intervention participants gained more weight during pregnancy (13.2 vs 10.3 kg, respectively). In a post hoc analysis,[37] GDM occurrence was lower in the intervention than in the control group among the 70% of women who had GDM assessed during their first trimester (13.6% vs 29.8%), but did not differ in the full sample of women (18% in both arms).[37]

The authors of the PREPARE study raise the possibility that later weight regain in the intervention arm may have negated the positive effect of intervention on GDM rates. Our study provides some evidence supporting this possibility. Collapsing across the intervention and control arm, we found a marginal association between weight gain after the initial 16 weeks of intervention and increased risk of developing GDM. A nonsignificant but greater proportion of intervention than control participants gained above National Academy of Sciences recommendations during pregnancy (53% vs 37%; P=.27) and significantly fewer gained within guidelines (20.0% vs 53%; P=.04). These findings raise potential concerns about efforts to increase prepregnancy weight loss leading to greater regain and subsequently increased risk of GDM.

The current trial and others[32,38] have found no evidence that preconception weight loss adversely affected perinatal complications for pregnant persons and infants. The trial of VLED[30] found that the preconception intervention reduced a composite score of adverse pregnancy outcomes. In PREPARE,[31] there were no significant differences in pregnancy outcomes, with the exception of spontaneous pregnancy losses, which were less common in the intervention arm. Small trials, such as ours, and ongoing preconception trials may be underpowered to detect effects on perinatal outcomes. Further multicentered trials and the use of individual patient data meta-analysis may be necessary to achieve the numbers required to detect differences in rare but severe morbidities related to GDM, obesity, and pregnancy.

This trial was designed to evaluate the effects of a lifestyle intervention before pregnancy to prevent GDM recurrence. Participants represented a diverse sample, which included 55.6% Hispanic ethnicity and 43% with ≤high-school education but few Black people. The study also had some limitations. GDM is measured in a variety of different ways in clinical practice, and the lack of standardization in timing and type of test used to diagnose both previous and current GDM could have introduced bias, although diagnostic methods did not differ by randomized group. The COVID-19 pandemic resulted in many OGTT measures being done clinically instead of by research staff. Moreover, lack of in-person blood draws prevented us from measuring inflammatory factors. The analysis collapsing across

TABLE 2
Intervention and educational control group effects on perinatal complications for mothers and neonates

Complications	Control	Intervention	OR (CI)	Mean difference (95% CI)	*P* value
Maternal					
Gestational hypertension	2/24 (8.3%)	5/32 (15.6%)	2.1 (0.3–14.0)		.42
Preeclampsia	0/24 (0%)	3/32 (9.4%)	0 (0–0)		.99
Preterm delivery at <37 wk	0/23 (0%)	4/33 (12.1%)	0 (0–0)		.99
GWG per wk (kg)	0.25 (0.16–0.33)	0.32 (0.26–0.40)		0.08 (−0.04 to 0.19)	.19
GWG (kg)	9.7 (6.3–13.1)	12.7 (10.1–15.4)		3.0 (−1.4 to 7.4)	.17
GWG above NAS	7/19 (36.8%)	16/30 (53.3%)	2.1 (0.6–8.0)		.27
GWG below NAS	2/19 (10.5%)	8/30 (26.7%)	1.2 (0.5–24.0)		.21
GWG within NAS	10/19 (52.6%)	6/30 (20.0%)	0.21 (0.1–0.9)		.04
Induction of labor	7/24 (29.2%)	12/33 (36.4%)	1.3 (0.4–4.6)		.69
Cesarean delivery	9/24 (37.5%)	17/33 (51.5%)	2.1 (0.6–7.1)		.24
Postpartum weight retention (kg)	−0.1 (−2.3 to 2.1)	0.2 (−1.5 to 2.0)		0.3 (−2.5 to 3.2)	.82
Fetal/neonatal					
NICU/intermediate nursery stay	1/17 (5.8%)	4/21 (19.0%)	7.5 (0.3–196.8)		.23
Birth trauma	2/23 (8.7%)	1/30 (3.3%)	0.6 (0.03–8.7)		.67
Macrosomia (birthweight ≥4000 g)	2/22 (9.1%)	6/30 (20.0%)	3.1 (0.44–21.5)		.25
LGA ≥90th birthweight percentile	1/19 (6.3%)	4/16 (25.0%)	0.04 (0.0–26.2)		.32
SGA <10th birthweight percentile	4/16 (25.0%)	3/16 (9.4%)	1.1 (0.7–1.8)		.99
WHO BMI z score					
Birth (n=32)	0.19 (−0.34 to 0.69)	−0.1 (−0.60 to 0.43)		−0.28 (−1.1 to 0.5)	.47
6 wk (n=35)	0.08 (−0.54 to 0.70)	0.40 (−0.2 to 1.0)		−0.33 (−0.58 to 1.2)	.47
WHO weight for length z score					
Birth (n=32)	−0.21 (−0.9 to 0.5)	−0.3 (−1.1 to 0.4)		−0.12 (−1.2 to 1.0)	.83
6 wk (n=35)	0.25 (−0.3 to 0.8)	0.20 (−0.4 to 0.8)		−0.04 (−0.9 to 0.8)	.93
Composite outcomes					
Serious perinatal complications (n=56)[a]	0.19 (−0.02 to 0.40)	0.20 (0.03–0.37)		0.01 (−0.29 to 2.7)	.94
Morbidity outcomes (n=56)[b]	2.2 (1.9–2.5)	2.3 (2.1–2.6)		0.13 (−0.3 to 0.6)	.56

Data presented as number (percentage; unadjusted) or mean parameter estimates (CI). Logistic regression or GDM models adjusted for site, parity, baseline age, education, income, smoking, ethnicity, baseline BMI, years since previous GDM. Rates of inadequate and excessive GWG were computed on the basis of the National Academy of Sciences guidelines.[10] For infants, LGA was defined as birthweight >90th percentile, and SGA as birthweight <10th percentile.[29]

BMI, body mass index; *CI*, confidence interval; *GDM*, gestational diabetes mellitus; *GWG*, gestational weight gain; *LGA*, large for gestational age; *NAS*, National Academy of Sciences; *NICU*, neonatal intensive care unit; *OR*, odds ratio; *SGA*, small for gestational age; *WHO*, World Health Organization.

[a] Total number of the following: death (stillbirth or neonatal death), hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia, shoulder dystocia/birth trauma (brachial plexus palsy or clavicular, humeral, or skull fracture), admission to NICU, and respiratory distress syndrome; [b] Total number of the following: cesarean delivery, hypertensive disorders of pregnancy, birthweight ≥4000 g, birthweight <2500 g, or NICU admission.

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groups was post hoc and did not take advantage of the randomized design; in these analyses, unmeasured variables could account for differences in weight loss or GDM.

National practice recommendations and viewpoints have called for aggressive preconception weight loss intervention.[4–9,11,13] However, presently, there remains insufficient evidence to support that preconception weight loss in women with obesity leads to reduced GDM or a greater chance of a healthy pregnancy.[39] The current trial and others have demonstrated that we can achieve significant weight loss through an intensive lifestyle intervention in women with previous GDM. Future, larger, multicenter trials are needed to determine whether improved weight loss prevents GDM and other perinatal morbidities. ■

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This study was registered on ClinicalTrials.gov:
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Deidentified individual participant data collected during the trial and data dictionaries will be shared at 2 years after article publication with no end date. These data will be available to researchers who provide a methodologically sound proposal for the purposes of achieving specific aims outlined in that proposal. Proposals should be directed to Suzanne Phelan via email sphelan@calpoly.edu and will be reviewed by the study team. Requests to access data to undertake hypothesis-driven research will not be unreasonably withheld. To gain access, data requesters will need to sign a data access agreement and to confirm that data will only be used for the agreed purpose for which access was granted. Note that the protocol for this trial has been published.

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SUPPLEMENTAL TABLE 1

Educational control and intervention group changes in glucose, blood pressure, and behavioral variables

Variable	Educational control Mean (95% CI)[b]		Intervention Mean (95% CI)[b]		Between-group differences Mean (95% CI)[b]; *P* value	Model *P* values[a]		
						Grp	Time	Grp×time
Glucose, mg/dL		n		n		.34	.001	.14
Study entry	86.3 (81.2–91.3)	23	84.9 (80.7–88.9)	36				
Change from study entry to 16 wk	−5.2 (−11.6 to 1.1)	18	−2.5 (−2.9 to 8.0)	27	3.0 (−2.0 to 7.7); *P*=.446			
Change from entry to 26 wk of gestation	−13.8 (20.6 to −7.0)	15	−4.9 (−11.1 to 1.4)	19	9.1 (−1.0 to 19.2); *P*=.08			
Diastolic blood pressure, mm Hg		n		n		.81	.001	.04
Study entry	69.4 (65.7–73.2)	23	72.3 (69.3–75.4)	35				
Change from study entry to 16 wk	2.6 (0.9–6.1)	20	−4.4 (−8.4 to −0.5)	28	−7.1 (−13.0 to −1.3); *P*=.02			
Change from entry to 26 wk of gestation	−4.1 (−7.9 to −0.5)	19	−7.9 (−12.3 to −3.6)	22	−3.1 (−9.9 to 3.8); *P*=.37			
Systolic blood pressure, mm Hg		n		n		.35	.19	.22
Study entry	109.6 (105.4–114.7)	23	110.0 (105.8–114.1)	36				
Change from study entry to 16 wk	1.8 (−3.4 to 7.0)	20	−5.1 (−10.1 to −0.1)	27	−6.1 (−13.2 to 1.1); *P*=.09			
Change from entry to 26 wk of gestation	−1.9 (−7.2 to 3.4)	19	−0.8 (−6.0 to 4.5)	19	−2.4 (−10.3 to 5.5); *P*=.54			
Total calories, kcal/d		n		N		.50	.09	.91
Study entry	1724 (1515–1933)	22	1624 (1458–1772)	35				
Change from study entry to 16 wk	−139.5 (−389 to 111)	22	−43.5 (−327 to 240)	26	93.7 (−262 to 450); *P*=.60			
Change from entry to 26 wk of gestation	104.1 (−164 to 372)	18	145.1 (−168 to 459)	20	55.3 (−342 to 452); *P*=.78			
% Calories Carbohydrates		N		N		.76	.15	.56
Study entry	41.7 (37.9–45.5)	22	43.4 (40.4–46.4)	35				
Change from study entry to 16 wk	3.5 (−0.1 to 7.1)	22	1.7 (−3.4 to 6.7)	26	−3.7 (−10.7 to 3.3); *P*=.30			
Change from entry to 26 wk of gestation	1.5 (−2.5 to 5.6)	18	1.2 (−4.8 to 7.2)	20	−3.1 (−10.3 to 4.0); *P*=.38			
% Calories fat		n		n		.57	.11	.88
Study entry	37.8 (31.1–44.4)	22	37.8 (32.5–43.0)	35				
Change from study entry to 16 wk	−3.5 (−10.7 to 3.6)	22	−0.7 (−9.8 to 8.3)	26	2.7 (−8.3 to 13.7); *P*=.63			
Change from entry to 26 wk of gestation	3.5 (−4.2 to 11.2)	18	5.8 (−4.3 to 15.8)	20	3.2 (−7.4 to 13.9); *P*=.55			
% Calories protein		N		n		.08	.11	.07
Study entry	19.8 (18.2–21.5)	22	18.9 (17.6–20.3)	35				
Change from study entry to 16 wk	−2.7 (−5.3 to −0.1)	22	0.5 (−1.5 to 2.4)	26	3.2 (0.2–6.4); *P*=.04			

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(continued)

SUPPLEMENTAL TABLE 1

Educational control and intervention group changes in glucose, blood pressure, and behavioral variables *(continued)*

Variable	Educational control Mean (95% CI)[b]		Intervention Mean (95% CI)[b]		Between-group differences Mean (95% CI)[b]; *P* value	Model *P* values[a]		
						Grp	Time	Grp×time
Change from entry to 26 wk of gestation	−0.7 (−3.5 to 2.1)	18	2.4 (0.3–4.6)	20	3.1 (−0.1 to 6.5); *P*=.06			
Total MVPA (unbouted), min/d		n		n		.15	.0001	.16
Study entry	62.9 (57.9–67.9)	22	64.2 (60.1–68.3)	32				
Change from study entry to 16 wk	5.5 (−0.8 to 11.9)	20	15.1 (7.2–23.2)	25	−9.9 (−18.2 to 1.6); *P*=.02			
Change from entry to 26 wk of gestation	−9.6 (3.1–16.1)	17	−14.5 (5.59–23.0)	18	4.8 (0.5–9.0); *P*=.03			
Weight control practices Total score		n		n		.0001	.0001	.0001
Study entry	63.4 (56.7–69.9)	24	64.1 (59.0–69.3)	38				
Change from study entry to 16 wk	9.0 (−0.1 to 18.1)	23	32.9 (25.4–40.3)	29	24.9 (13.5–36.4); *P*=.0001			
Change from entry to 26 wk of gestation	5.7 (−3.7 to 15.0)	21	11.0 (3.7–18.3)	30	6.0 (−5.2 to 17.1); *P*=.29			
Time watching TV/video programming (total h/wk)		n		n		.54	.23	.88
Study entry	13.9 (10.7–17.0)	23	13.6 (11.1–16.0)	38				
Change from study entry to 16 wk	−1.7 (−5.8 to 2.5)	23	−3.1 (−6.9 to 0.8)	29	−1.3 (−6.5 to 3.9); *P*=.61			
Change from entry to 26 wk of gestation	−0.8 (−5.1 to 3.5)	21	−1.0 (−4.8 to 2.9)	28	−0.6 (−7.0 to 5.8); *P*=.85			
Dietary restraint		n		n		.004	.0001	.004
Study entry	11.2 (9.7–12.7)	24	11.1 (9.8–12.3)	38				
Change from study entry to 16 wk	0.7 (−1.1 to 2.5)	23	5.3 (3.4–7.2)	29	4.7 (2.0–7.4); *P*=.001			
Change from entry to 26 wk of gestation	1.2 (−0.7 to 3.1)	21	3.1 (1.2–5.0)	30	2.1 (−0.5 to 4.8); *P*=.11			
Disinhibition		n		n		.77	.0001	.62
Study entry	6.8 (6.1–7.6)	24	6.9 (6.2–7.5)	38				
Change from study entry to 16 wk	−0.5 (−1.6 to 0.6)	23	−1.0 (−1.8 to −0.3)	29	−0.5 (−1.9 to 0.8); *P*=.43			
Change from entry to 26 wk of gestation	−1.6 (−2.7 to −0.4)	21	−1.5 (−2.2 to −0.8}	30	0.1 (−1.2 to 1.5); *P*=.86			
Sleep		n		n		.76	.05	.13
Study entry	2.3 (2.0–2.6)	24	2.2 (2.0–2.4)	38				
Change from study entry to 16 wk	−0.3 (−0.5 to 0.4)	23	−0.2 (−0.6 to 0.1)	29	−0.2 (−0.6 to 0.2); *P*=.36			
Change from entry to 26 wk of gestation	0.1 (−0.4 to 0.5)	21	0.4 (0.1–0.8)	30	0.4 (−0.2 to 1.0); *P*=.20			
Perceived stress		N		n		.30	.70	.26
Study entry	28.1 (26.4–29.8)	24	28.0 (26.7–29.4)	38				

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(continued)

SUPPLEMENTAL TABLE 1

Educational control and intervention group changes in glucose, blood pressure, and behavioral variables *(continued)*

Variable	Educational control Mean (95% CI)[b]		Intervention Mean (95% CI)[b]		Between-group differences Mean (95% CI)[b]; *P* value	Model *P* values[a]		
						Grp	Time	Grp×time
Change from study entry to 16 wk	−1.7 (−4.2 to −0.7)	23	0.6 (−1.3 to 2.5)	29	2.2 (−0.5 to 4.9); *P*=.11			
Change from entry to 26 wk of gestation	−0.1 (−2.6 to 2.4)	21	−0.02 (−1.9 to 1.9)	30	0.2 (−2.9 to 3.2); *P*=.93			
Depressive symptoms		n		n		.14	.82	.007
Study entry	17.6 (16.3−18.9)	24	17.5 (16.3−18.8)	38				
Change from study entry to 16 wk	1.6 (−0.8 to 4.0)	23	−2.1 (−3.8 to −0.4)	29	−3.6 (−6.3 to −1.0); *P*=.008			
Change from entry to 26 wk of gestation	0.1 (−2.5 to 2.4)	21	0.6 (−1.1 to 2.3)	30	0.8 (−2.0 to 3.7); *P*=.56			

Diet was measured using the ASA24 (Automated Self-Administered Dietary Assessment Tool). Physical activity measurement was based on objective assessment (actigraphy) for a 1-week period. Acceptable wear time was classified as ≥1-day wear time with ≥19.2 h/d. We processed the data using the R GGIR package, which uses a linear threshold-based method to estimate time spent (unbouted) in moderate to vigorous activity. The Weight Control Strategies Scale was used to assess the extent to which participants practiced behavioral weight control strategies. The Eating Inventory was used to assess restraint (ie, self-initiated, cognitive attempts to restrict food intake) and disinhibition (ie, loss of control over eating). The General Sleep Disturbance Scale was used for a subjective measure of sleep disturbance; scores >3 are considered of concern. Stress was measured using the 14-item Perceived Stress Scale. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale.

CI, confidence interval; *GDM*, gestational diabetes mellitus; *Grp*, group; *MVPA*, moderate-to-vigorous physical activity (≥3 metabolic equivalents of task).

[a] Linear mixed-effects models with covariates (ie, site, parity, baseline age, education, income, smoking, ethnicity, baseline body mass index (BMI), years since previous GDM, baseline value of outcome variable). The "Grp" column reflects whether or not there were any significant group differences in the outcome measure overall, regardless of time. The "Time" column indicates whether the outcome changed over time, regardless of group. The "Grp×time" column indicates group differences in the outcome over time;
[b] Least-squares mean (95% CI), which is the model-estimated response under each treatment condition evaluated for covariates (ie, site, parity, baseline age, education, income, smoking, ethnicity, baseline BMI, years since previous GDM, baseline value of outcome variable) at their mean levels.

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SUPPLEMENTAL TABLE 2

Safety alerts and adverse events by condition[a]

Safety alerts and adverse events	Education control N=94	Preconception intervention N=104
Early pregnancy loss or miscarriage	5[b]	7[c]
Late pregnancy loss (>20 wk)	0	1
Preterm labor	0	4
Injury from physical activity	1	6
Hospitalized for any reason	2	4
Hospitalization owing to pregnancy-related complication	1	0
Pregnancy during 16-wk phase	7	10
Unintended reduction in milk supply	0	0
Total	16	32

[a] Data presented as number of participants and events occurring throughout the trial; [b] Four participants experienced a total of 5 events; [c] Five participants experienced a total of 7 events.

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