

Protocol for a randomized controlled trial of pre-pregnancy lifestyle intervention to reduce recurrence of gestational diabetes: Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional

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Abstract

Background

Gestational diabetes mellitus (GDM) is associated with several maternal complications in pregnancy, including preeclampsia, preterm labor, need for induction of labor, and cesarean delivery as well as increased long-term risks of type 2 diabetes, metabolic syndrome, and cardiovascular disease. Intrauterine exposure to GDM raises the risk for complications in offspring as well, including stillbirth, macrosomia, and birth trauma and long-term risk of metabolic disease. One of the strongest risk factors for GDM is the occurrence of GDM in a prior pregnancy. Preliminary data from epidemiologic and bariatric surgery studies suggest that reducing body weight before pregnancy can prevent development of GDM, but no adequately powered trial has tested the effects of a maternal lifestyle intervention before pregnancy to reduce body weight and prevent GDM recurrence.

Methods

The principal aim of Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional is to determine whether a lifestyle intervention to reduce body weight before pregnancy can reduce GDM recurrence. This two-site trial targets recruitment of 252 women with overweight and obesity who have previous histories of GDM and who plan to have another pregnancy in the next 1–3 years. Women are randomized within site to a comprehensive pre-pregnancy lifestyle intervention to promote weight loss with ongoing treatment until conception or an educational control group. Participants are assessed preconceptionally (at study entry, after 4 months, and at brief quarterly visits until conception), during pregnancy (at 26 weeks' gestation) and at 6 weeks postpartum. The primary outcome is GDM recurrence and secondary outcomes include fasting glucose, biomarkers of cardiometabolic disease, prenatal and perinatal complications, and changes over time in weight, diet, physical activity and psychosocial measures.

Discussion

Gestational Diabetes Prevention /Prevención de la Diabetes Gestacional is the first randomized controlled trial to evaluate the effects of a lifestyle intervention delivered before pregnancy to prevent GDM recurrence. If found effective, the proposed lifestyle intervention could lay the groundwork for shifting current treatment practices towards the interconception period and provide evidence-based preconception counseling to optimize reproductive outcomes and prevent GDM and associated health risks.

Trial registration

ClinicalTrials.gov Identifier: NCT02763150

Background And Rationale {6a}

Gestational diabetes mellitus (GDM) is a common complication of pregnancy that affects an estimated 7.6% of pregnant persons in the US.¹ Women with GDM have increased risks for preeclampsia, preterm labor, need for induction of labor, and cesarean delivery as well as increased long-term risks of type 2 diabetes, metabolic syndrome, renal disease, and cardiovascular disease (CVD). An estimated 15-25% of women with prior GDM will develop type 2 diabetes within 1-2 years after pregnancy,²⁻⁵ and 35%-70% will develop type 2 diabetes 10-15 years after pregnancy.⁶⁻⁹ Intrauterine exposure to maternal GDM conveys high risk of several short and long-term health problems in the offspring and may perpetuate a cycle of obesity.¹⁰⁻¹² Exposure to GDM has been associated with birth trauma, respiratory distress syndrome, neonatal hypoglycemia, and death.^{13,14} GDM increases the risk of excess fetal growth in utero,¹⁵ higher infant fat mass,¹⁶ neonatal macrosomia, and greater childhood prevalence of obesity (> 90th percentile) through adolescence.¹⁷

One of the strongest risk factors for GDM is the occurrence of GDM in a prior pregnancy. Between 40 and 73% of women with prior GDM will experience GDM recurrence.¹⁸⁻²⁷ Women with prior GDM have a 3- to 10-fold increased risk of having GDM in a subsequent pregnancy.^{28,29} Women with additional pregnancies complicated by GDM experience three-fold increases in the risks of prenatal and perinatal complications and long-term risks of type 2 diabetes, metabolic syndrome, renal disease, and CVD.³⁰⁻³²

Promising, preliminary research from epidemiologic and retrospective bariatric surgery studies suggest that reductions in body weight before pregnancy may hold the key to prevention of GDM recurrence.³³⁻³⁹ Emergent research suggests that it is feasible to recruit women before pregnancy and promote significant weight loss prior to conception.^{40,41} A lifestyle intervention before pregnancy in women with prior GDM may capitalize on a “teachable moment” when women appear more motivated to engage in behavior changes to prevent the recurrence of GDM in a subsequent pregnancy.⁴²⁻⁴⁵ However, an adequately powered randomized clinical trial to test the effects of maternal lifestyle intervention before pregnancy to reduce body weight and prevent GDM recurrence has never been conducted.

Risk factors for gestational diabetes

While prior GDM is perhaps the strongest risk factor for recurrence of GDM, maternal obesity is also strongly associated with developing GDM during pregnancy.^{35,46} Overweight and obesity affects an estimated 66% of adult women,⁴⁷ and an estimated 5-12% of women with obesity develop GDM during pregnancy compared with 1-3% of women with normal weight.⁴⁸ In epidemiologic studies, the risk of GDM has been four- to eight-times higher in women with overweight/obesity than normal weight.⁴⁸ A meta-analysis concluded that for every 1 kg increase in prepregnancy BMI, the prevalence of GDM was increased by 0.92%.⁴⁹ A BMI greater than 35 increases risk of GDM by about 6 fold.²⁹ Independent of GDM, maternal obesity is also associated with several other adverse pregnancy outcomes, including preeclampsia, stillbirth, fetal macrosomia, cesarean delivery, and post-surgical wound infection.^{50,51} Obesity is one of the few modifiable risk factors for GDM.

Other risk factors for GDM have been reported in observational^{52, 53} and clinical trial⁵⁴ studies and include maternal age > 35²⁹ (5 to 6 fold increased risk),⁵⁴ having a first-degree relative with diabetes (2- to 3-fold increased risk),^{28, 29, 54-56} fasting blood glucose of 100 – 125 mg/dl (7 fold increased risk),^{28, 55, 56} HbA1c 5.8-6.4 (5 to 8 fold increased risk)^{29, 54} and previous infant with macrosomia (3 to 4 fold increased risk).^{53, 54}

Race/ethnicity is another consistent predictor of GDM. People who report Hispanic ethnicity or Native American, Asian, and African-American race have consistently been found to have increased risk of GDM and recurrent GDM compared with non-Hispanic white women.^{19, 57-59} The reasons for higher prevalence of GDM in non-white women remain unclear. Possible reasons include acculturation among migrant populations and greater exposures to stress, the obesogenic environment, high energy dense foods, and obesity.⁵⁹

Prenatal and postpartum interventions to reduce gestational diabetes and related risk factors

Several trials have tested interventions during pregnancy to reduce the incidence of GDM.^{54, 60-65} A variety of prenatal interventions have been tried, including approaches that target lifestyle,^{54, 64} exercise,^{61, 65} dietary supplementation,⁶⁰ and/or metformin.⁶⁶ Although these trials find positive effects on reducing weight gain during pregnancy, they have shown no significant effects on reducing GDM incidence. A network meta-analysis of 23 studies thus concluded that interventions to prevent the development of GDM were not effective when applied during pregnancy. GDM prevention interventions that begin during pregnancy may be limited by several factors: 1) low intervention intensity during pregnancy out of concerns over effects on the growing fetus; 2) biological changes in pregnancy creating added barriers to adherence (e.g., craving, nausea, edema, weight gain); and, 3) a very short intervention window (≤ 2 months) prior to GDM diagnosis.

Postpartum diet and exercise interventions in women with prior GDM have also been tested and shown more promise in reducing risk factors for subsequent diabetes and CVD,⁶⁷⁻⁷⁸ although low engagement,⁷⁹ modest effects on weight,⁸⁰ and poor adherence remain problematic.⁸¹ The Diabetes Prevention Program included women with previous GDM,⁷⁴ and, consistent with the full sample results, lifestyle intervention for weight loss or metformin significantly reduced the incidence of diabetes by 50% compared with the placebo group.^{74,82} While postpartum interventions in women with prior GDM reduce risk of diabetes, the effects of postpartum interventions on recurrence of GDM in a subsequent pregnancy and effects on future maternal and child health outcomes have not been investigated. Intervening in the immediate postpartum period to help women lose weight may be too distal from subsequent pregnancy to exert a protective effect on GDM recurrence, but clinical trial data are lacking.

Preconception weight loss to reduce gestational diabetes and associated health risks

Observational research suggests that women who experience even modest weight losses (> 10 pounds)^{33, 34, 83} or less weight gain⁸⁴⁻⁸⁶ prior to pregnancy significantly reduce their risk of GDM development

compared to women who maintain weight or gain >10 pounds. Kim et al.⁴⁸ estimated that up to half of GDM cases could be prevented by reducing pre-pregnancy obesity. Retrospective data from bariatric surgery populations also suggest that weight loss in women with obesity prior to pregnancy may reduce the risk of GDM and its recurrence^{37,87,88} and prevent transmission of obesity to children.³⁶ Other observational research has shown that maternal consumption of healthy food and avoidance of unhealthy foods⁸⁹ and engagement in regular physical activity before pregnancy were independently associated with reduced risk of subsequent GDM.⁸⁹ Honein et al⁹⁰ estimated that if 10% of women with pre-pregnancy obesity achieved a healthy weight (BMI < 25) before pregnancy, nearly 300 congenital heart defects and 700 fetal deaths per year could be prevented each year.

However, few clinical trials have examined the effects of weight loss during the preconception period on subsequent outcomes.^{41,91} The PREPARE randomized trial⁴¹ tested a phone-based weight loss intervention in 326, non-Hispanic (94%) women with a BMI \geq 27 and found that, relative to the control group, women in the lifestyle intervention lost more weight prior to conception (3.7 vs 0.6 kg, respectively). After 24 months, 169 (52%) became pregnant and were included in analysis. Results indicated that those in the preconception intervention group surprisingly gained more weight during their subsequent pregnancy than those in the control group (13.2 vs 10.3 kg gain, respectively; $p=0.03$); there were no significant differences in GDM or other pregnancy outcomes, with the exception of spontaneous pregnancy losses, which were less common in the intervention arm. Participants in the intervention arm had a 10% lower absolute rate of GDM than in the control arm (25% vs 35%, respectively), but the study had insufficient power to evaluate whether or not a difference of this size was due to chance.

A trial in Finland⁹¹ randomized women with obesity and/or prior GDM to a nurse-led preconception lifestyle intervention or a control group. Among the 65% who became pregnant during the trial, there were no significant differences by randomized group in the cumulative incidence of GDM, which was 60% ($n=39/65$) in the intervention group and 54% ($n=34/63$) in the control group ($p=0.49$). However, 45% of the participants included in the final analyses received only 1 preconception visit or no intervention at all; and, thus, preconception weight change was not analyzed.⁹¹ Other studies have demonstrated feasibility,⁴⁰ examined effects in women with fertility issues⁹² and other trials are in progress.⁹³ Clinical trial data are needed to test whether preconception weight loss can prevent GDM recurrence.^{35,46}

Lifestyle interventions based on social-cognitive-theory

Lifestyle interventions based on social-cognitive-theory (SCT) and “teachable moment” models provide a rich foundation for effective intervention to prevent GDM recurrence. SCT-based interventions have been effective in promoting weight control in a variety of patient populations and treatment modalities, including the DPP program.^{94,95} SCT emphasizes the dynamic interplay of the individual and the environment in adopting behavior changes and posits that a sense of self-efficacy must be developed through use of self-regulation skills (i.e., goal-setting, self-monitoring, problem solving, incentives) that foster weight control and healthy eating and physical activity behaviors. SCT-based interventions

delivered prior to pregnancy may capitalize on a “teachable moment” for promoting long-term behavior change. “Teachable moments” are naturally occurring life transitions or health events thought to augment motivation for adopting risk-reducing health behaviors.^{96,97} Women who are planning pregnancy may be more motivated to change their eating and exercise behaviors and lose weight for the health of their pregnancy.

Moreover, focusing on women with a history of GDM may maximize motivation. To date, the trials testing weight loss interventions before pregnancy have focused on a general population of women with obesity. An alternative approach is to focus on women who are at particularly high risk of GDM because they had GDM in a prior pregnancy. Women with prior GDM report high motivation to change behaviors to prevent GDM recurrence and protect the health of their future child.⁴²⁻⁴⁵ A SCT-based lifestyle intervention may capitalize on this motivation and promote significant pre-pregnancy weight loss and maintenance. Optimizing maternal weight and the intrauterine environment before pregnancy holds promise for preventing GDM recurrence and improving short and long-term maternal/child health. However, no study to date has been designed to test the efficacy of a comprehensive pre-pregnancy lifestyle weight loss intervention to prevent GDM recurrence in a racially/ethnically diverse group of women.

Potential mechanisms

Lifestyle treatment targeting weight, physical activity, and dietary intake before pregnancy may reduce GDM through effects on insulin and inflammatory factors. While pathogenesis linking prepregnancy obesity and GDM remains under investigation, obesity during pregnancy appears to augment a systemic inflammatory response that leads to greater insulin resistance and glucose dysregulation.⁹⁸ Both obesity and GDM are associated with increased circulating levels of leptin⁹⁹ and the inflammatory markers TNF-alpha¹⁰⁰ and C-reactive protein⁹⁸ and decreased levels of adiponectin.¹⁰¹ Over time, the chronic and acute insulin resistance and inflammation independently associated with obesity and pregnancy, respectively, may lead to a progressive loss of insulin secretion that increases the risk of developing diabetes and other diseases later in life.¹⁰² Clinical trial data are needed to identify the mechanisms most impacted by pre-pregnancy weight loss and linked with prevention of GDM and improved insulin resistance.

Objectives {7}

Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional is a two-site randomized clinical trial testing the efficacy of a pre-pregnancy lifestyle intervention to reduce GDM recurrence in women with overweight and obesity. The trial is following CONSORT guidelines.¹⁰³ The primary hypothesis is that the recurrence of GDM will be reduced among participants assigned to pre-pregnancy lifestyle intervention vs. educational control group. Test for GDM will be conducted at 24 to 28 weeks gestation. Secondary hypotheses are that the pre-pregnancy lifestyle intervention (vs. educational control group) will result in improved maternal fasting glucose and biomarkers of insulin resistance (insulin, leptin, TNF-alpha, and C-reactive protein, adiponectin) and CVD risk (lipids and blood pressure) assessed before pregnancy, after

16 weeks of intervention, and at 26 weeks' gestation. The pre-pregnancy lifestyle intervention (vs. educational control group) is expected to reduce adverse perinatal health outcomes for mothers (gestational hypertension, preeclampsia, preterm delivery, excessive gestational weight gain, induction of labor, cesarean delivery) and neonates (admission to the neonatal nursery, hyperbilirubinemia, birth trauma, weight for length z scores \geq 95% at birth and 6 weeks). Also, the pre-pregnancy lifestyle intervention (vs. educational control group) is hypothesized to result in greater pre-pregnancy weight loss and improvements in diet (calories, % fat, fast food) and physical activity (minutes of moderate activity). In exploratory mediator analyses, treatment-related changes in pre-pregnancy weight, eating, and activity are expected to be related to improvements in maternal physiology and reduced odds of GDM recurrence.

Trial design {8}

This study is a two-site, randomized clinical trial comparing a pre-pregnancy lifestyle modification intervention vs. educational control. A total of 252 women with overweight or obesity and a history of GDM will be randomized to either a pre-pregnancy lifestyle weight loss intervention vs. control condition. Assessments occur before pregnancy (at study entry, after 16 weeks, and brief visits every 16 weeks until conception), during pregnancy (at 26 weeks gestation), and at delivery and 6 weeks postpartum.

Methods

Participants

Study setting {9}. The study includes two clinical sites. One site is at California Polytechnic State University, San Luis Obispo, California (S. Phelan, PI), and the other site is at Brown University & the Miriam Hospital in Providence, Rhode Island (R. Wing, PI).

Source population. GDM recurrence rates are higher in Hispanic and African-American populations,⁵⁷ thus, our targeted recruitment plan includes 35% Hispanic, 9% African American, 6% Asian, and 50% non-Hispanic white at each site. The geographical regions and recruitment clinic populations selected for this study have a high prevalence of obesity (\geq 35%) and client diversity (35-45% Hispanic; 9% African American).

Recruitment {15}. To reach the target sample size of 252, both sites recruit participants through direct and indirect methods and via administrative databases. As described in **Table 1** direct recruitment methods include clinic staff and research assistants at the recruitment clinics providing information about the study at the time of prenatal or postnatal visits for patients with GDM or prior GDM. Indirect methods include presentations in healthcare settings that interact with mothers (e.g., Ob/Gyn, pediatrician, WIC offices). Administrative databases are also used to identify and offer the program to women with history of GDM who might not regularly engage with the targeted healthcare settings after having a baby.

Eligibility criteria {10}. **Table 2** describes the eligibility and exclusion criteria for this trial. Participants must have physician documentation of GDM during any prior pregnancy. Given the diversity of clinically

acceptable methods used to diagnose GDM,¹⁰⁴⁻¹⁰⁷ several diagnostic methods for prior GDM are eligible. Acceptable documentation to confirm prior GDM are as follows: 1) a 3-hour 100 gram oral glucose tolerance test (OGTT) performed at ≥ 20 weeks' gestation in which 1 or more values exceeded the Carpenter and Coustan criteria¹⁰⁸ (i.e., fasting ≥ 95 mg/dL; 1 hour ≥ 180 mg/dL; 2 hour ≥ 155 mg/dL or 3 hour ≥ 140 mg/dL); 2) a 75 gram OGTT performed at ≥ 20 weeks' gestation and 1 or more values exceeded International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria¹⁰⁹ (i.e., fasting ≥ 92 , 1 hour ≥ 180 ; 2 our ≥ 153); 3) a 1-hour 50 gram test performed at any time during pregnancy with a value ≥ 185 mg/dL (if ≥ 130 mg/dL but < 185 mg/dL and clinic did not do a follow-up 100 g OGTT, participant would be ineligible); 4) a fasting glucose value prior to 20 weeks' gestation was ≥ 92 mg/dL and < 125 mg/dL and treatment with medication or insulin; or, 5) an HbA1c conducted anytime during pregnancy with a value $> 5.6\%$ and the treatment with medication or insulin.

Women must also report chances of having a baby in the next 1-3years; this is determined based on a response to the question, "On a scale of 0-10, what are the chances you see yourself ever having any more children?" Participants reporting ≥ 1 on this scale and who report plans for pregnancy within the study's timeframe (1-3 years depending on study enrollment year) are considered eligible. Other eligibility criteria include BMI ≥ 25 kg/m²; age ≥ 18 years; and English or Spanish speaking. Breastfeeding women are eligible to enroll, as moderate weight loss does not appear to adversely affect lactation.¹¹⁰⁻¹¹⁴ At study enrollment, participants are encouraged to use medically proven forms of contraception until completion of the initial 16-weeks of intervention, but this is not an eligibility requirement.

Women with Type 2 or Type 1 diabetes are excluded; lack of diabetes is confirmed prior to randomization with an HbA1c test ($> 6.5\%$). Women with a family history of diabetes or with impaired glucose tolerance ("prediabetes"; HbA1c of 5.7-6.4%) may be at increased risk of GDM¹¹⁵ but are included because weight loss could potentially still modify risk of GDM. Other exclusions include: Age < 18 years; current pregnancy; tubal ligation; semi-permanent form of birth control with no plans for removal (e.g., hormonal progesterone intrauterine device or hormonal contraceptive implant); relocating in the next 2 years, medications that affect weight/diabetes (e.g., oral corticosteroid and metformin), serious current physical disease (e.g., heart disease, cancer, renal disease) for which physician supervision of diet and exercise prescription is needed, orthopedic problems that limit the ability to exercise,¹¹⁶ problems with drug abuse and/or symptoms of an eating disorders,¹¹⁷ history or plans of bariatric surgery, and hospitalization for depression or psychological problems in the past year. Also, women who do not show to orientation visit and fail to reschedule are excluded.

Enrollment process and consenting. Figure 1 shows the process of study enrollment - from recruitment to randomization. Women who appear interested in the program are screened by phone. If still eligible after phone screening, patients are asked to attend an orientation and consenting visit followed by their baseline assessment visit.

Who will take informed consent? {26a} Trained study staff collect informed consent.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

The process of informed consent includes discussion of an option to allow collection and storing of additional biospecimens for future research that may include analyses on genetic material.

Intervention descriptions {11a}

Explanation for the choice of comparators {6b} Two groups are compared in this study. Group 1 is a standard care plus education control group and was selected because the intervention provides a level of care that is consistent with the typically minimal amount of lifestyle counseling received by women before pregnancy and also is not expected to promote clinically significant weight loss. Group 2 is standard care plus education plus weight loss intervention and was selected in order to isolate the effects of pre-conception weight loss on GDM recurrence and other health outcomes.

Group 1: Standard Care + Education Women in this condition receive usual medical care before and during pregnancy and throughout the trial. Also, these women meet with a study interventionist for 20-minute individual sessions at study entry and again after 16 weeks. The first meeting at study entry encourages women to spend the next 16 weeks improving overall health before pregnancy and reviews nutrition (e.g., consuming multivitamins, folic acid) and physical activity recommendations. The second face-to-face meeting occurs after 16 weeks and focuses on managing stress and also includes a “*Pregnancy Primer*.” Since all women in the study have expressed a desire to have another pregnancy within 1-3 years, this module provides participants with standard information on methods to track ovulation. Participants also receive information on recommended amount of weight gain¹¹⁸ during pregnancy. Throughout the study, women receive quarterly study newsletters with study updates and general information about preconception health and wellness.

Group 2: Standard Care + Education + Weight Loss Intervention

Overview: This group receives all aspects of Group 1 plus a standard lifestyle modification program implemented to induce $\geq 10\%$ weight loss over 16 weeks and promote weight loss maintenance over subsequent months (12-36 months depending on enrollment year) until conception. This comprehensive, individually focused, SCT-based weight control program includes education, behavioral self-regulatory strategies, ongoing contact, feedback, and social support. The intervention is based on the DPP and Look Ahead lifestyle interventions,^{119, 120} which have been proven effective in promoting significant weight loss and maintenance in multiethnic, English and Spanish speaking individuals across the country.^{119, 120} The intervention provides guidance and resources for English and Spanish-speaking individuals from a variety of different cultures and backgrounds.

Format and contact: The intervention focuses on ongoing, individual contact with a study interventionist to promote weight loss prior to conception. Visits may be conducted in person, on the phone, or through video conferencing. For the first 16 weeks, participants meet weekly for ~30 minutes. Thereafter, participants meet bi-weekly (or more frequently in the context of weight regain) to maintain weight loss until conception. After conception, intervention contacts are discontinued.

Weight Loss Goals: Participants are given a scale and told to aim for a weight loss of 1-2 lbs per week for the first 16 weeks. Patients desiring to lose more weight during the program are encouraged to do so, provided they maintain reasonable eating and activity patterns and do not reduce below normal weight. After 16 weeks, participants may work on weight loss maintenance or continue to lose weight at a moderate rate (1-2 pounds/week) until confirmed conception.

Dietary Goals: Participants are instructed to follow a standard calorie restriction diet used in lifestyle modification programs. Calorie goals are based on study entry weight with 300 calorie/d adjustments for breastfeeding status, if applicable. Participants with an entry weight < 91 kg are prescribed a 1200 kcal/day, self-selected diet, and those with entry weight > 91 kg are prescribed a 1500 kcal/day. A standard, low fat diet is prescribed (35% fat, 20% protein, 45% CHO), since prior research has suggested that recurrence of GDM was greater in women who consumed more fat between pregnancies.¹²¹ After the 16 week program, dietary goals may be adjusted to help women maintain their weight loss or weight maintenance goal until conception.

Exercise Goals: Participants are instructed to increase their physical activity to at least 150 minutes per week during the initial 16-week program (e.g., 30 minutes per day, 5 days per week). Thereafter, they are advised of higher goals (60 min/day) to promote long-term weight loss maintenance. Brisk walking, “child-friendly,” and inexpensive activities are suggested, taking into consideration potentially unsafe neighborhoods. Participants are provided with a pedometer and encouraged to gradually increase the number of steps they walk per day (with an increase of ~250 steps/day each week) until reaching an ultimate goal of about 10,000 steps per day.¹²²

Behavioral Goals. The major features of behavior modification include self-monitoring, behavior chains, stimulus control, goal-setting, self-reinforcement, problem-solving, social assertion, cognitive strategies.¹²³ Participants complete weekly behavioral assignments, which are reviewed by the interventionist. Participants are given self-monitoring records or encouraged to use apps, if preferred, to facilitate self-monitoring.

Criteria for discontinuing or modifying allocated interventions before conception {11b} Site physicians who are trained in obstetrics/gynecology guide decisions as to whether or not to continue intervention or assessments in women with medical difficulties. If needed, the study physicians contact a participant’s provider to discuss treatment/assessment continuation for participants. The study physicians do not provide medical care during the course of the study but refer and help participants obtain appropriate medical or psychiatric care, if needed. Rate of weight loss and caloric restriction are monitored and if any extreme and overly rapid weight losses occur, healthier practices are encouraged and adherence to these recommendations is monitored. A subset of women may be breastfeeding upon enrollment. Moderate weight loss does not appear to adversely impact breastfeeding,^{124, 125} but study staff are monitoring such occurrences and provide referrals, as needed. To reduce the risk of muscle soreness, muscle strain, or joint sprain, loss of balance, or trauma by falling, the physical activity (walking) is moderate, progressive, and volitional and goals may be modified, as needed for an individual participant.

Strategies to improve adherence to interventions {11c}. The behavioral weight loss program includes a variety of strategies to improve adherence. These include strategies related to appropriate goal setting, cognitive restructuring, relapse prevention, and problem solving. In addition, the study interventionist provides support for all positive behavioral changes. Weekly supervision meetings with the intervention team are designed to promote treatment fidelity. Participant cases are reviewed and strategies discussed with the intervention team to promote participant adherence to attending treatment sessions, completing food and exercise records, engaging in daily self-weighing, and following calorie and activity goals. Intervention fidelity measures (coded audiotaped sessions) are further reviewed and discussed to guide and promote adherence.

Relevant concomitant care permitted or prohibited during the trial {11d} During the trial, participants are not restricted from receiving concomitant care and/or interventions.

Provisions for post-trial care {30} There are no provisions for post-trial care.

Outcomes {12}

Participant timeline {13} Table 3 shows when participants complete the measures in Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional. Bilingual (English/Spanish speaking) assessors are masked to randomization and conduct all major assessments occurring at baseline, after 16 weeks, at 26 weeks' gestation, and at 6 weeks postpartum. These assessments occur at the study's research centers or affiliate locations most proximal to participants. If necessary, assessments are conducted at participants' homes. After 16 weeks, quarterly brief assessments occur until conception. The brief assessments may be conducted in person or over the phone/video conferencing.

Primary Outcome. The study's primary outcome is GDM diagnosis in next pregnancy. The 2-step approach of diagnosing GDM is done at 24-28 weeks' gestation and involves participants receiving as part of standard care a 50 g oral glucose solution followed by a 1-hour venous glucose determination. Participants meeting or exceeding the 1-hour screening criteria (a cutoff for an abnormal 1-hour screen of ≥ 130 mg/dL) are then referred to the study for completion of the 100-g, 3-hour diagnostic oral glucose tolerance test (OGTT). Positive diagnosis of GDM is based on the Carpenter and Coustan criteria¹⁰⁸ based on 2 abnormal values on the 3-hour OGTT that includes a fasting value >95 mg/dL; 1 hour > 180 mg/dL, 2 hour > 155 mg/dL, 3 hours >140 mg/dL. Results of the study's 100-g OGTT are immediately shared with participants' medical providers who interpret and inform patients of GDM screening results. If the study measured, 100-g, 3-hour diagnostic OGTT is not obtained, provider assessments done in standard care that are based on acceptable diagnostic methods (Table 4) are used to diagnose GDM. Final determination of GDM diagnosis is done by independent evaluation of records from the study's Ob/Gyn physician researchers who are masked to randomized group.

HbA1c tests. Diabetes is an exclusion criterion (based on HbA1c at screening $>6.5\%$). However, after screening, annual HbA1c tests are performed until conception and test results shared with participants'

providers. This is expected to minimize early clinical screenings for pre-existing DM; however, any participant receiving early (< 24 weeks gestation) clinical diagnosis of GDM is included in analysis.

Maternal insulin resistance/ physiologic parameters Maternal fasting glucose, insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), leptin, TNF-alpha, C-reactive protein, adiponectin, and lipids are measured by trained staff at each research site, following established protocols. Blood draws are scheduled 12-24 hours after the most recent bout of exercise and after an overnight fast. HOMA-IR is used to estimate insulin resistance. Systolic and diastolic blood pressure are measured using a standard mercury manometer and appropriate size cuffs with participants in the sitting position with both feet on the ground. After resting 5 minutes, the average of two measurements are recorded, with a 1-2 minute interval between measures.

Maternal anthropometrics Weight is measured to the nearest 0.1 kg using calibrated standard digital scales. Two measures are completed with participants measured in light clothing (without shoes). Scale calibration is checked weekly with known weights. Standing height is measured twice in patients without shoes in millimeters with a wall-mounted Harpenden stadiometers. Given emerging evidence of a relationship between abdominal fat and GDM,¹²⁶ waist circumference is measured over bare skin or underwear using a tape measure, and following standardized protocols.

Lifestyle behaviors are measured to examine treatment effects and relationships with maternal physiology and GDM recurrence. Physical Activity is measured for 7 days using the Actigraph accelerometer (MTI, Inc) which provides minutes and time spent in light, moderate, and vigorous activity over a period of days or weeks.¹²⁷⁻¹²⁹ TV and sedentary behavior are assessed by pre-established questionnaires.^{130, 131} Dietary intake is measured using 24-hour recalls on 2 random days over a week¹³²⁻¹³⁶ and completed in an interview format using the NCI Automated Self-Administered 24 hour recall (ASA24 <http://riskfactor.cancer.gov/tools/instruments/asa24.html>). The primary variables of interest are: calories, protein, carbohydrates, and fat; consumption of sugar-sweetened beverages, and fast food. Fast food consumption is also assessed based on validated self-report questions.¹³⁷ Weight Control Practices are assessed using the validated Weight Control Strategies scale.¹³⁸ A supplemental brief assessment¹³⁹ is administered to assess frequency of self-weighing, self-monitoring, and meal patterns. Given the association between perceptions of risk and adoption of lifestyle changes, perceived risk of GDM recurrence is measured at baseline and after 4 months using the Risk Perception Survey modified for GDM.¹⁴⁰ The Center for Epidemiologic Studies Depression (CES-D) screener¹⁴¹ is used to examine levels of depressive symptoms; the 14-item Perceived Stress Scale is used to measure levels of stress, which is a predictor of GDM¹⁴², and the Eating Inventory¹⁴³ assesses three dimensions of dietary restraint, including cognitive restraint, disinhibition, and hunger. The General Sleep Disturbance Scale (GSDS) is used for a subjective measure of sleep disturbance has been related to risk of GDM.¹⁴⁴

Maternal/infant consequences of GDM. Chart abstractions are conducted by trained research staff to determine whether the intervention results in fewer adverse maternal and neonatal health outcomes.

Consistent with prior research, rates of inadequate and excessive GWG are computed based on the National Academy of Medicine guidelines,¹¹⁸ using measured pre-pregnancy and last clinic visit weights. Other maternal adverse outcomes clinically defined based on chart abstractions include gestational hypertension, preeclampsia, cesarean delivery, labor induction, and delivery < 37, 0 weeks' gestation. Adverse outcomes among infants include birth weight greater than 4000 g, large size for gestational age (defined as birth weight above the 90th percentile), and small size for gestational age (birth weight below the 10th percentile).¹⁴⁵ A composite measure of serious perinatal complications is defined as one or more 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 the neonatal intensive care unit (NICU), and respiratory distress syndrome.^{146, 147} An additional composite morbidity outcome is computed based on prior research in women with obesity that includes at least one of the following: Cesarean delivery, hypertensive disorders of pregnancy (HDP), birth weight \geq 4000 g, birth weight < 2500 g, or NICU admission.¹⁴⁸ In women diagnosed with GDM, prescribed treatments are examined to explore whether the intervention impacted intensity of treatment/severity of GDM.

Infant measures. At 6 weeks, infant length, weight, and skinfold thickness measurements are performed by trained staff using standardized procedures. BMI z-scores are calculated using the WHO Child Growth Standards for age and sex.¹⁴⁹ A z score of > 1 will be used to define at risk for obesity.

Demographics & medical/reproductive history At baseline, participants complete a demographic questionnaire assessing age, race, ethnicity, and weight history (e.g., inter-pregnancy weight changes). Given prior relationships with GDM recurrence,¹⁵⁰ extensive pregnancy history information (maternal and neonatal) are collected.^{151, 152} At follow-ups, changes in smoking, prescription medications, unsafe dieting practices,¹¹⁷ job status, and participation in other weight loss programs, and changes in medical history are assessed. Pregnancy urine tests are used to assess pregnancy status at quarterly visits until conception. Pregnancy confirmation is documented through clinical ultrasound results.

Process measures. Recruitment, eligibility, refusal rates/reasons, and retention rates/reasons are tracked, as well as the number of women who conceive during the trial and the average duration until conception. Intervention acceptability is measured based on participants' ratings of various aspects of the program, the interventionist, content, and overall impression. To measure intervention fidelity, all intervention sessions are audiotaped and a randomly selected subset (10%) are coded for content by a trained study staff (not involved in any assessment data collection). Adherence to the intervention is measured via attendance at treatment sessions, number of self-monitoring records returned, and the activity, eating, and behavioral measures. To assess the safety of the intervention, levels of hunger, depressive symptoms, injuries due to physical activity, changes in medical status, and unintended reduction in milk supply (in breastfeeding women) are assessed.

Sample size {14} Power calculations assume a 60% GDM recurrence rate in women with overweight or obesity.^{19, 57, 58} With a target sample size of 252 participants and assumed $\geq 70\%$ pregnancy rate,^{153, 154} ≥ 176 pregnant participants (≥ 88 in each group) would provide adequate statistical power ($\geq 81.98\%$) to detect intervention effects on the proportions developing recurrent GDM,^{83, 155} taking into account estimations of site-specific clustering effects and effect modifiers (i.e., weight status, ethnicity, parity) of GDM recurrence.^{24, 57} Under this scenario, the minimum detectable effect size (odds ratio) would be 0.43 and proportions with GDM in educational control and intervention groups respectively would be 60% ($n = 53/88$) and 38% ($n = 33/88$). For secondary aims, 88 pregnancies in each group would yield $> 80\%$ power to detect effects equal to or smaller than those reported in prior work testing effects of lifestyle interventions on reductions in glucose, triglycerides, CRP,¹⁵⁶ insulin, leptin¹⁵⁷ adiponectin,¹⁵⁸ and blood pressure,¹⁵⁹ taking into account estimations of site-specific clustering effects and effect modifiers (i.e., weight status, ethnicity, parity) of insulin resistance,¹⁶⁰ and CVD risk factors.^{161, 162} For secondary aims examining effects of the intervention on prenatal and perinatal complications, the study would have $> 80\%$ power to detect moderate effect sizes.¹⁶³ For the fourth aim examining effects of the intervention on pre-pregnancy weight losses and improvements in eating (calories, macronutrient balance, fast food) and activity, 88 participants in each group would yield $> 90\%$ power to detect effects reported in prior work testing effects of lifestyle interventions on reductions in weight¹⁵⁹ and behavioral variables.^{164, 165} For exploratory mediator analyses, $> 80\%$ power is achieved to detect $> 21\%$ increase in the mediated odds of GDM per kg difference in prepregnancy weight loss (equivalent to a mediated slope in a logistic model of > 0.189).

Assignment of interventions: allocation

Sequence generation {16a} Eligible participants are randomized in a 1:1 ratio into the intervention or control group based on a computer-generated (R 4.0.4 for Windows) random sequence. Randomization is stratified by site, pre-diabetes status (HbA1c < 5.7 vs ≥ 5.7) and prior method of GDM diagnosis (one-step, 2 hour test vs other methods) to ensure a balance of the two interventions within each stratum.

Concealment mechanism {16b} Allocation sequence is implemented via sequentially numbered, opaque, sealed envelopes that are concealed until the interventions are assigned to a participant.

Implementation {16c} The study statistician generates the allocation sequence. Study interventionists enroll participants and, based on opening the envelope, assigns participants to interventions.

Assignment of interventions: Masking

Who will be masked {17a} Research Assistants are masked to randomization, and participants do not know assigned group until after baseline measures are completed.

Procedure for unmasking if needed {17b} Unmasking is not needed.

Data collection and management

Plans for assessment and collection of outcomes {18a} All staff involved in data collection must demonstrate competence in administering all measures. The Research Assistants collecting data are masked to the participants' intervention assignment. The Research Assistants review all assessment data for accuracy and completion. Participants are immediately re-contacted to provide missing data or to clarify responses. Loss to follow up and missing and incomplete data are monitored closely to solve potential issues of missing data before there is a substantial impact on the results.

Plans to promote participant retention and complete follow-up {18b} To minimize loss-to-follow up, at each data collection visit participants are scheduled by phone, sent written reminders, and called the day before. Missed visits are rescheduled and followed up. Costs for transportation and childcare are provided or, alternatively, home visits are arranged for participants with repeatedly missed assessments. Honoraria are provided to promote retention: \$25 for visits at study entry, 16 weeks, and 6 weeks postpartum visit, \$15 per quarterly visit until conception, and \$50 for the primary outcome assessment at 26 weeks' gestation. As a retention tool, women in both groups also receive quarterly newsletters with basic information about preconception health and wellness.

Data management {19} Research Electronic Data Capture (REDCap) is used for storing study outcome measurement data. A customized internal study tracking system is used to track enrollment and scheduling of visits. Both systems require a login identification and password in order to gain access to the data. Range checks are built into the data collection procedures to alert staff to data that should be clarified. Error checking and preliminary analyses of all data are done to ensure accuracy. Electronic data files are backed up; a copy is stored offsite at both locations to protect against loss or damage. The destruction of any paper files will be at least 7 years from the termination of the study and will be authorized by the PI.

Confidentiality {27}. Participant identification numbers are used to track questionnaires and data collection documents. A password-protected file is maintained that associates the participant name with the participant's study identification number. Access to electronic data is password protected and restricted to the study team. Paper data are stored in a locked file cabinet. Paper data may be removed for the purpose of coding, data entry, or auditing only. When taking participant files to intervention visits and assessments, files are transported in a locked box. Upon reaching the destination, these boxes are brought into the building or residence with the interventionists. Also, interventionists' files identify participants by first name and last initial only. Participant home addresses are not included in the files. The study's research coordinators in CA and RI work closely with the statistician and data manager to ensure the secure exchange and storage of all project databases and questionnaires. Data exchanged between study sites are de-identified, encrypted and, password protected.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33} As noted above, participants are asked to give explicit consent for the

DNA and RNA collection and use, and future research of data and samples. For DNA and RNA, the collected samples sit in the collection tube at room temperature for 2 hours then are placed in a -20°C freezer for the first 24 hours before moving to -80°C freezer.

Statistical methods

Statistical methods for primary and secondary outcomes {20a} and methods for additional analyses (e.g. subgroup analyses) {20b} A multiple logistic regression analysis will be used to examine the effect of treatment group on the proportion of women who develop GDM. The model will include site and covariates to adjust for pre-randomization variables that may relate to the outcome, including parity, age, education, income, smoking, race/ethnicity, BMI, and time since last pregnancy. The effects of the prepregnancy weight-loss intervention on weight, eating, activity, and physiologic outcomes will be examined using a linear mixed model with fixed effects for treatment condition (the between-groups factor), time (baseline, 16 weeks, 26 weeks gestation), site and baseline covariates. Linear regression and logistic regression analyses will be performed to address the possible effects of the intervention on cases of excessive GWG, gestational hypertension, cesarean delivery, and large for gestational age at birth and 6 weeks, with site and baseline covariates entered in the models. A multiple linear regression analysis will also be used to examine the effect of treatment group on composite scores of adverse maternal/neonatal outcomes, and logistic regressions will be used to examine separate effects on offspring obesity and odds of exceeding National Academy of Science guidelines, including the same covariates described above. Generalized logistic models will be used to examine relationships among pre-pregnancy changes in weight, eating, activity, and physiology and GDM recurrence; we will follow approaches outlined by Kraemer et al¹⁶⁶ to explore potential mediators of treatment outcome.

Interim analyses {21b} The trial has no interim analyses or stopping rules.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c} Under intention-to-treat principles, all participants with confirmed pregnancy will be included in the primary analysis. If study measured OGTT results are not available, provider assessments will be used (based on chart abstraction). Missing data related to outcomes will be evaluated to assess whether the missing mechanism may be ignorable or non-ignorable.¹⁶⁷⁻¹⁶⁹ If the missing data mechanism is judged to be ignorable, where appropriate, analyses involving mixed models may be used such that all existing values are analyzed, and no observations are deleted due to missing values. Alternatively, multiple imputation may be carried out to create several complete data sets. For each complete data set, overall tests of interest for the outcome will be conducted and the results of each combined to create a single test result. For completeness, a pattern-missing analysis will be conducted to investigate non-ignorable missingness. If the missing data mechanism is likely to be non-ignorable, multiple imputations can be conducted using a version of the approximate Bayesian bootstrap based on distance-based selection criteria.¹⁷⁰ Sensitivity analyses under various assumptions regarding the missing data will be conducted to confirm the robustness of the results.

Plans to give access to the full protocol, participant level-data {31c}. Upon publication of study's pre-specified outcomes, a de-identified version of the database will be made available upon reasonable request to the PI.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The trial does not include a coordinating center or steering committee.

Composition of the data monitoring committee, its role and reporting structure {21a} The trial includes two external safety officers with expertise in clinical trial weight control research and maternal/fetal health. Twice per year, safety officers review reports of recruitment, retention, fidelity, and safety information on all participants, including number of pregnancies before the 4-month intervention is over, number of injuries due to physical activity, number of miscarriages, and other serious adverse events. Weekly internal investigator meetings also occur to review recruitment, attendance, retention, and safety data on an ongoing basis.

Adverse event reporting and harms {22} Adverse events (AE) include any event that causes or increases risk of harm to the participant or others. Serious adverse events (SAE) include any event that results in death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. A fatality, including fetal, are reported within 24 hrs. AEs reported at core assessment visits or informally at any time are evaluated by the research team and the investigators to determine if they are unanticipated problems involving risk to subjects and others or not. The participant's situation is also assessed with regard to study and/or intervention continuation. Any SAEs are recorded by the research coordinator, reported to the PI and investigative team, the Safety Officers, and the IRB.

Frequency and plans for auditing trial conduct {23} The trial includes close monitoring by the PI/Co-Is, IRBs, and two external safety officers. Annual progress reports are provided to the sponsor and IRBs. Sponsor or other external site visitor audits are not planned.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}. Any changes to eligibility criteria, outcomes, or analyses are reviewed by the IRB and updated in Clinicaltrials.gov.

Dissemination plans {31a}. Results of the trial will be presented at professional conferences and local community events and shared via clinicaltrials.gov and formal publications and furthermore to the general public through social media outlets. A summary of primary outcome findings will be created in English and Spanish and shared with study participants.

Discussion

GDM is recognized as major adverse perinatal outcome and has been linked with a range of maternal and child complications and poor outcomes, including long-term development of type 2 diabetes. Recurrent GDM affects about 66 - 80% of women with obesity^{19, 57, 58} and increases a number of maternal and child health risks significantly.¹⁸⁻²⁷ Additionally, identification and treatment of GDM exacts a high cost to the health care system.¹⁷¹⁻¹⁷³ Preventing GDM and its recurrence has been identified as a national health priority.^{174, 175}

To date, efforts to prevent GDM have focused primarily on interventions occurring during pregnancy, and these have met with limited success.^{54, 60-65} Promising, preliminary research from epidemiologic and retrospective bariatric surgery studies suggest that reductions in body weight before pregnancy may hold the key to prevention of GDM and its recurrence.³³⁻³⁹ Emergent research suggests that it is feasible to recruit women before pregnancy and promote significant weight loss prior to conception.^{40, 41} A lifestyle intervention before pregnancy in women with prior GDM may capitalize on a “teachable moment” when women appear more motivated to engage in behavior changes to prevent the recurrence of GDM in a subsequent pregnancy.⁴²⁻⁴⁵ However, a fully powered trial to test the effects of maternal lifestyle intervention before pregnancy to reduce body weight and prevent GDM recurrence has never been conducted.

Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional is the first trial designed to determine whether preconception weight loss can prevent GDM recurrence in a diverse population of Hispanic and non-Hispanic women who are disproportionately impacted by GDM.^{57, 176, 177} The SCT-based intervention is uniquely designed to capitalize on the potential “teachable moment” for women with prior GDM who report high motivation to change behaviors to prevent GDM recurrence and protect the health of their future baby.⁴²⁻⁴⁵ The study’s battery of measures before pregnancy will provide the first comprehensive picture of how maternal weight, diet, activity, and physiology *before pregnancy* impact GDM, insulin resistance, and cardiometabolic health. The study is providing a new scientific framework for future pre-pregnancy trials by informing optimal methods for reaching women before pregnancy and the best timing, content, and duration of effective GDM prevention interventions. The American College of Obstetricians and Gynecologists (ACOG), the National Academy of Medicine, and other governmental bodies and researchers^{174, 175, 178-184} have identified the interconception interval as one of the best potential times for weight control intervention to minimize the risk of a GDM and its recurrence. If successful, results of this study will yield a novel, empirically-based intervention that can be used during the interconception period to prevent GDM.

Trial status

Protocol version 1.0; February 15, 2021. Recruitment was initiated on August, 2016 and approximate date for completion is December, 2021.

Abbreviations

NAS: National Academy of Science

BMI: Body mass index

OGTT: Oral Glucose Tolerance Test

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Declarations

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Authors' contributions {31b} SP, RW conceived and designed the research and helped draft the manuscript; DC, KC, AC, TH, AS, RW, EJ, SP, KMC, LS, CH, AM participated in the design and coordination of the study and data acquisition methods and helped draft the manuscript; EJ, SP, RW, CH, AM participated in design and development of the intervention; AS developed the statistical analyses and power calculations; CH, AM, TH participated in the design of the visits. All authors read and approved the final manuscript.

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Availability of data and materials {29} The Principal Investigator and co-investigators will have access to the final trial dataset.

Ethics approval and consent to participate {24} This study was approved by the Cal Poly Institutional Review Board (IRB) (2017-019) and the Miriam Hospital IRB (2039-11).

Consent for publication {32} All participants in the study provide informed, written consent using an IRB-approved consent forms.

Competing interests {28} SP has a grant from WW, unrelated to this work. RW is on the Scientific Advisory Board for Noom. No other competing interests are reported.

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Tables

Table 1. Recruitment methods for reaching preconception women with prior gestational diabetes mellitus
Direct to patient
In person recruitment by clinic or study staff during pregnancy or 6 week postpartum visits
Brochures and posters in clinics and waiting rooms
Social Media (Facebook, Instagram) Posts, videos, and advertisements
Traditional media (television, radio, flyers)
Online forums posts
Indirect through women’s health providers (e.g., Ob/Gyn, WIC)
Presentation and clinic meetings
1 page fact sheets
Study write up for newsletters directed at providers
Administrative databases
Hospital patient databases
Community health center patient database
Review of research center database
Research Match

Table 2 Inclusion and exclusion criteria for Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional

Inclusion Criteria	
	Prior diagnosis of GDM
	Planning to have a baby in the next 1-3 years
	BMI > 25 kg/m ²
	English- or Spanish speaking
	Breastfeeding or non-breastfeeding
	Literacy ≥5 th grade level
	Access to a cell phone
Exclusion criteria	
	Age < 18 years
	HbA1c test (> 6.5%)
	≥ 3 months postpartum
	Current pregnancy
	Tubal ligation
	Semi-permanent form of birth control with no plans for removal (e.g., hormonal progesterone intrauterine device or hormonal contraceptive implant)
	Relocating in the next 2 years
	Medications that affect weight or diabetes (e.g., oral corticosteroid and metformin)
	Use of weight loss medications
	Serious current physical disease (e.g., heart disease, cancer, renal disease, and diabetes) for which physician supervision of diet and exercise prescription is needed
	Orthopedic limitations to aerobic exercise
	History or plans of bariatric surgery
	Current problems with drug abuse and/or symptoms of an eating disorder, which occurred less than three years year ago.
-	Hospitalization for depression or psychological problems in the last year.
-	No show to a scheduled orientation and fail to reschedule

Table 3. Measures in Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional

	Assessment Time Point				
	Pre-pregnancy			Pregnancy	Postpartum
	Baseline	4 month	Every 4 months until pregnancy	26 weeks' gestation	6 weeks
Demographics & medical history	X	X	—	X	X
Weight, height, waist circumference	X	X	X	X	X
Pregnancy test	X	X	X	—	—
Maternal physiology					
HbA1c (screening then annually until conception)	X	—	—	—	—
GDM assessment	—	—	—	X	—
Glucose, insulin	X	X	—	X	—
Inflammatory factors	X	X	—	X	—
Lipids	X	X	—	X	—
Blood pressure	X	X	—	X	—
Lifestyle behaviors					
Physical Activity	X	X	—	X	—
Dietary Intake	X	X	—	X	—
Behavioral and Psychosocial	X	X	brief	X	—
Infant weight, length	—	—	—	—	X
Maternal/infant complications	—	—	—	—	X
Process measures	—	X	X	—	—

Table 4. Diagnostic Criteria for GDM in Gestational Diabetes Prevention/ Prevención de la Diabetes Gestacional	
1.	3-hour 100 gram OGTT performed at ≥ 20 weeks gestation in which 2 or more values exceed criteria as follows: fasting ≥ 95 mg/dL; 1 hour ≥ 180 mg/dL; 2 hour ≥ 155 mg/dL or 3 hour ≥ 140 mg/dL ¹⁰⁸
2.	75 gram OGTT performed at ≥ 20 weeks gestation and 1 or more values exceed (fasting ≥ 92 , 1 hour ≥ 180 ; 2 our ≥ 153) ¹⁰⁹
3.	1-hour 50 gram test performed at any time during pregnancy with a value ≥ 200 mg/dL
4.	Fasting glucose value prior to 20 weeks gestation ≥ 92 mg/dL and < 125 mg/dL and clinic treats patient for GDM with medication or insulin
5.	HbA1c conducted anytime during pregnancy with a value $\geq 5.7\%$ and the clinic treats patient for GDM with medication or insulin

Figures

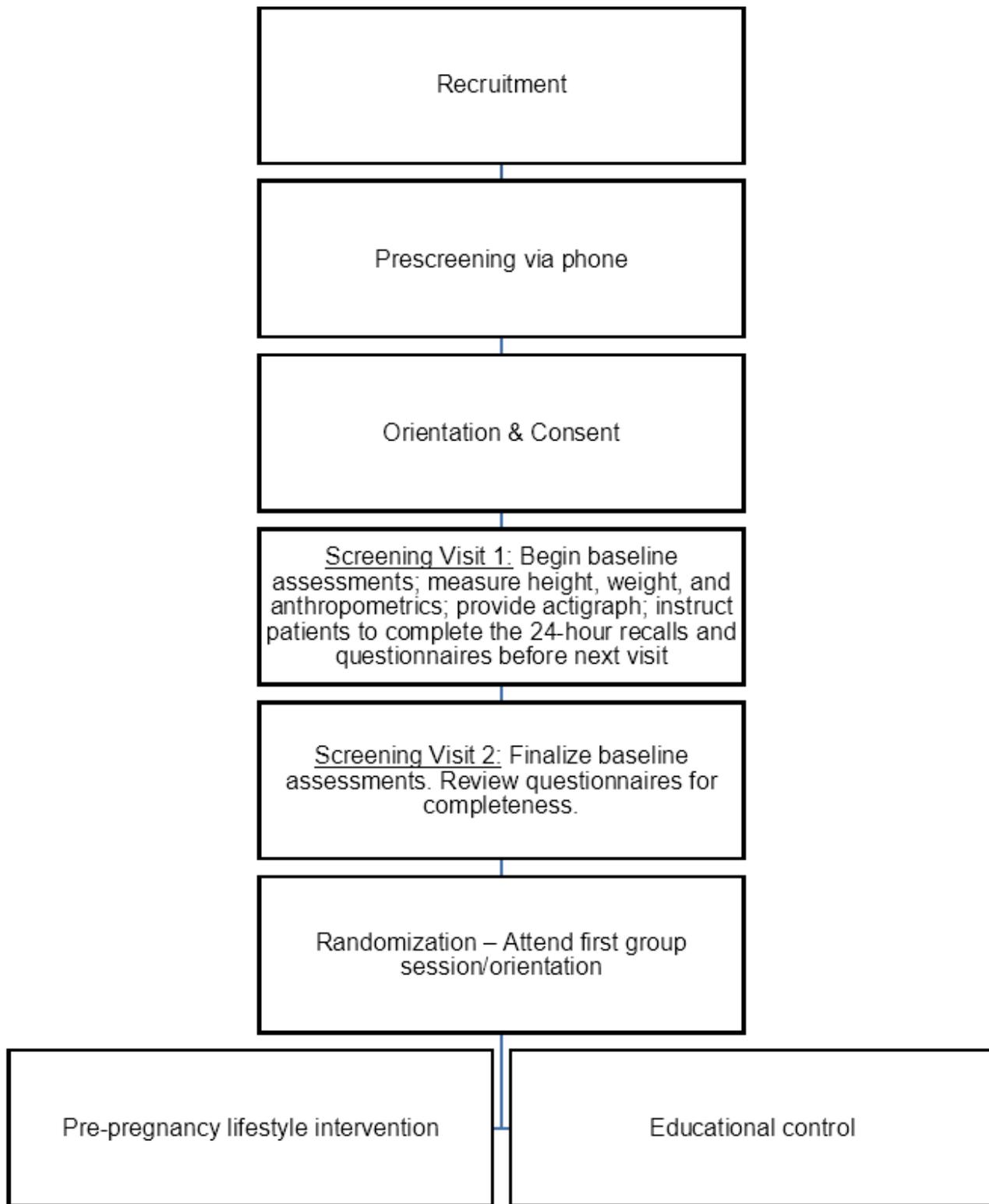


Figure 1

Overview of entry into Gestational Diabetes Prevention/Prevención de la Diabetes Gestacional