A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women

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BACKGROUND: Obesity and being overweight are becoming epidemic, and indeed, the proportion of such women of reproductive age has increased in recent times. Being overweight or obese prior to pregnancy is a risk factor for gestational diabetes mellitus, and increases the risk of adverse pregnancy outcome for both mothers and their offspring. Furthermore, the combination of gestational diabetes mellitus with obesity/overweight status may increase the risk of adverse pregnancy outcome attributable to either factor alone. Regular exercise has the potential to reduce the risk of developing gestational diabetes mellitus and can be used during pregnancy; however, its efficacy remain controversial. At present, most exercise training interventions are implemented on Caucasian women and in the second trimester, and there is a paucity of studies focusing on overweight/obese pregnant women.

OBJECTIVE: We sought to test the efficacy of regular exercise in early pregnancy to prevent gestational diabetes mellitus in Chinese overweight/obese pregnant women.

STUDY DESIGN: This was a prospective randomized clinical trial in which nonsmoking women age >18 years with a singleton pregnancy who met the criteria for overweight/obese status (body mass index $24 \leq 28$ kg/m^2) and had an uncomplicated pregnancy at $<12^{+6}$ weeks of gestation were randomly allocated to either exercise or a control group. Patients did not have contraindications to physical activity. Patients allocated to the exercise group were assigned to exercise 3 times per week (at least 30 min/session with a rating of perceived exertion between 12-14) via a cycling program begun within 3 days of randomization until 37 weeks of gestation. Those in the control group continued their usual daily activities. Both groups received standard prenatal care, albeit without special dietary recommendations. The primary outcome was incidence of gestational diabetes mellitus.

RESULTS: From December 2014 through July 2016, 300 singleton women at 10 weeks' gestational age and with a mean prepregnancy body mass index of 26.78 ± 2.75 kg/m^2 were recruited. They were randomized into an exercise group (n = 150) or a control group (n = 150). In all, 39 (26.0%) and 38 (25.3%) participants were obese in each group, respectively. Women randomized to the exercise group had a significantly lower incidence of gestational diabetes mellitus (22.0% vs 40.6%; $P <$ .001). These women also had significantly less gestational weight gain by 25 gestational weeks (4.08 ± 3.02 vs 5.92 ± 2.58 kg; $P <$ .001) and at the end of pregnancy (8.38 ± 3.65 vs 10.47 ± 3.33 kg; $P <$ .001), and reduced insulin resistance levels (2.92 ± 1.27 vs 3.38 ± 2.00; $P =$ .033) at 25 gestational weeks. Other secondary outcomes, including gestational weight gain between 25-36 gestational weeks (4.55 ± 2.06 vs 4.59 ± 2.31 kg; $P =$ .9), insulin resistance levels at 36 gestational weeks (3.56 ± 1.89 vs 4.07 ± 2.33; $P =$ .1), hypertensive disorders of pregnancy (17.0% vs 19.3%; odds ratio, 0.854; 95% confidence interval, 0.434—2.683; $P =$ .6), cesarean delivery (except for scar uterus) (29.5% vs 32.5%; odds ratio, 0.869; 95% confidence interval, 0.494—1.529; $P =$ .6), mean gestational age at birth (39.02 ± 1.29 vs 38.89 ± 1.37 weeks' gestation; $P =$ .5); preterm birth (2.7% vs 4.4%, odds ratio, 0.600; 95% confidence interval, 0.140—2.573; $P =$ .5), macrosomia (defined as birthweight >4000 g) (6.3% vs 9.6%; odds ratio, 0.624; 95% confidence interval, 0.233—1.673; $P =$ .3), and large-for-gestational-age infants (14.3% vs 22.8%; odds ratio, 0.564; 95% confidence interval, 0.284—1.121; $P =$ .1) were also lower in the exercise group compared to the control group, but without significant difference. However, infants born to women following the exercise intervention had a significantly lower birthweight compared with those born to women allocated to the control group (3345.27 ± 397.07 vs 3457.46 ± 446.00 g; $P =$ .049).

CONCLUSION: Cycling exercise initiated early in pregnancy and performed at least 30 minutes, 3 times per week, is associated with a significant reduction in the frequency of gestational diabetes mellitus in overweight/obese pregnant women. And this effect is very relevant to that exercise at the beginning of pregnancy decreases the gestational weight gain before the mid-second trimester. Furthermore, there was no evidence that the exercise prescribed in this study increased the risk of preterm birth or reduced the mean gestational age at birth.

Key words: adverse pregnancy outcome, exercise, gestational diabetes mellitus, obesity, overweight, pregnant women

Introduction

The global epidemics of overweight and obesity are leading health burdens worldwide; moreover, the proportion of overweight and obese women of reproductive age is increasing.[1,2] Overweight and obesity are widely accepted to affect the entire pregnancy process and to constitute major risk factors for perinatal complications, such as gestational diabetes mellitus (GDM), hypertensive syndrome, fetal growth disorders, cesarean delivery, postoperative complications, wound infections, and deep vein thrombosis.[3-7] Among them, GDM is a particular concern because of its own effects on other adverse pregnancy outcomes, such as preeclampsia, macrosomia, or cesarean delivery.[8] Our previous study showed that overweight and obese pregnant women have a >2-fold increased risk of developing GDM compared with nonobese women.[4]

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2017.01.037

Related editorials, pages 335 and 338.

Furthermore, the combination of GDM and overweight or obesity aggravates the adverse pregnancy outcomes caused by either factor alone.[9] Importantly, these poor outcomes also potentially impact the long-term health of both the mothers and their offspring.[10-12] Thus, focusing on women who are overweight or obese before pregnancy and seeking ways to decrease their risk of GDM and other adverse pregnancy outcomes are of great importance.

As an important part of lifestyle interventions, exercise has received increasing attention from investigators worldwide. In nonpregnant subjects, the value of regular exercise for reducing the risk of type 2 diabetes and cardiovascular disease is well established.[13,14] However, whether exercise is effective in reducing the risk of GDM and other adverse pregnancy outcomes is not clear because the few randomized controlled trials (RCTs) that investigated these topics showed conflicting results.[15-21] Moreover, most of the current correlative researches were carried out on Caucasian women and few focus on overweight and obese pregnant women. In particular, most exercise training interventions are implemented in the second trimester. However, a recent meta-analysis including 29 RCTs with 11,487 pregnant women addressed that exercise could only play a role in preventing GDM in women with intervention <15 gestational weeks, whereas, among women with intervention afterward, it did not work.[22] In addition, a quasiexperimental study of Chinese pregnant women pointed out that lifestyle intervention including exercise, diet, and weight-gain counseling from 8-12 gestational weeks could lower the risk of GDM.[23]

Therefore, the objective of this study was to determine whether a program of regular exercise begun in early pregnancy could reduce the frequency of GDM in Chinese overweight/obese women.

Materials and Methods

Study design and participants

We conducted a RCT at Peking University First Hospital from December 2014 through July 2016. A flow chart of the protocol is shown in the Figure. Overweight and obesity were determined based on body mass index (BMI) recommendations of the Group of China Obesity Task Force of the Chinese Ministry of Health[24] accounting for interracial differences: overweight BMI $\geq$24-<28 kg/m^2 and obese BMI $\geq$28 kg/m^2. Singleton, nonsmoking pregnant women with a prepregnancy BMI (p-BMI) of $\geq$24 kg/m^2 at $<12^{+6}$ weeks' gestation were eligible for the study. The exclusion criteria were the following: (1) age <18 years; (2) women unwilling to provide informed consent; (3) women with cervical insufficiency (historical painless cervical dilation leading to recurrent second-trimester births in the absence of other causes; dilated cervix on manual or speculum examination; transvaginal ultrasound cervical length <25 mm at <24 weeks of gestation in singleton gestations with $\geq$1 prior spontaneous preterm births at 14-36 weeks)[25]; (4) women on any medication for preexisting hypertension, diabetes, cardiac disease, renal disease, systemic lupus erythematosus, thyroid disease, or psychosis; and (5) women who were currently being treated with metformin or corticosteroids.

This study was reviewed and approved by the Institutional Review Board of Peking University First Hospital (reference number: 2014[726]) and registered at www.clinicaltrials.gov (NCT02304718). All participants provided written informed consent, and the ethics committee approved the consent procedure.

Randomization and masking

Eligible women were randomly allocated (ratio 1:1) into either an exercise intervention group or a control group following an allocation concealment process using an automatic computer-generated random number table. The 3 parts of the randomization process, that is, sequence generation, allocation concealment, and implementation, were conducted by 3 different individuals. Due to the nature of the intervention, all participants and research staff were aware of the allocations.

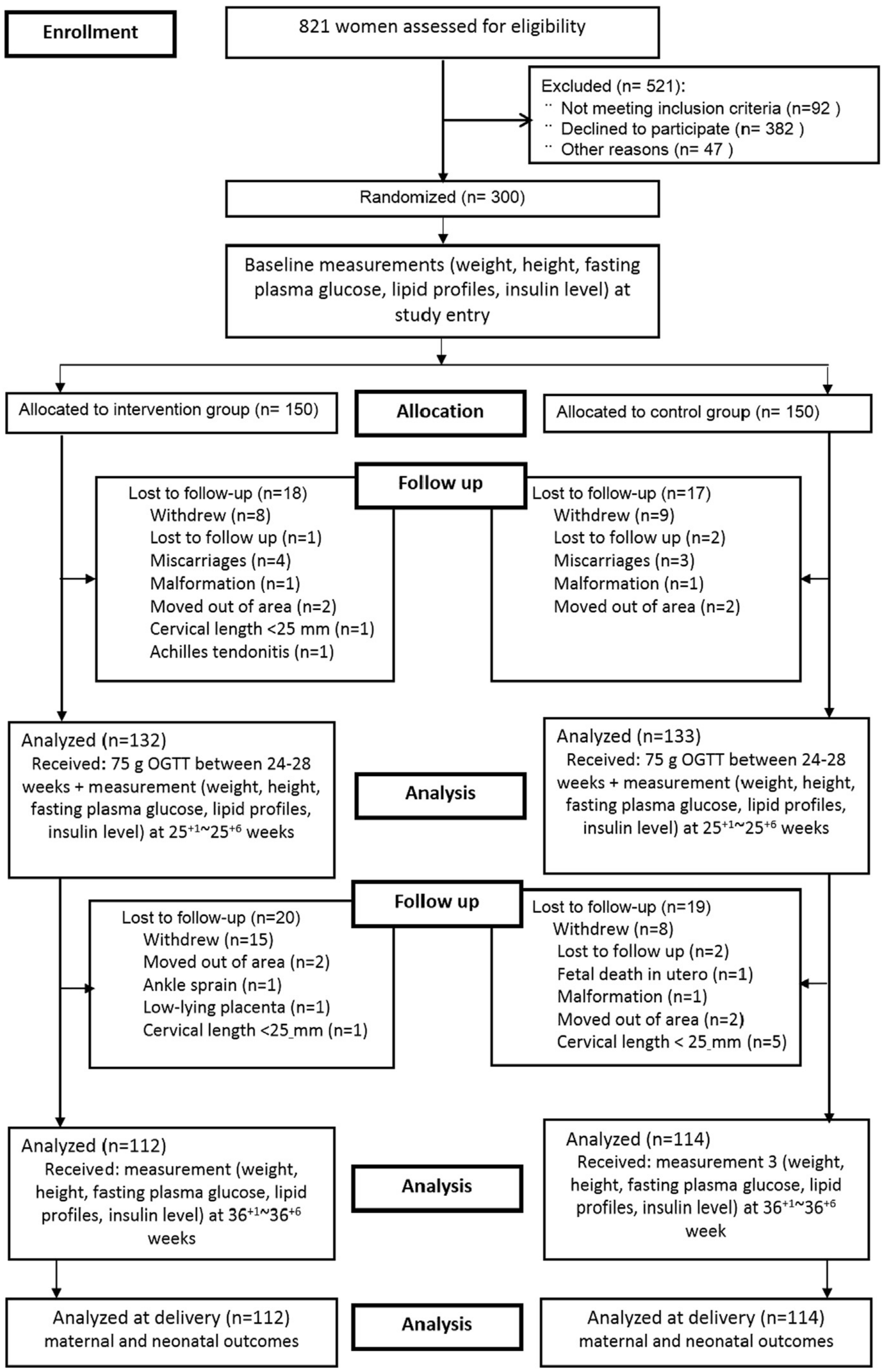
Research procedures

Eligible pregnant women were approached by research staff at a prenatal care class specifically for women in early pregnancy at the Department of Obstetrics and Gynecology, Peking University First Hospital, and provided the project details. Those who were willing to participate were asked to complete a questionnaire to assess demographic information, medical and family history, and current pregnancy information. Qualified participants were then asked to sign informed consent and randomly allocated into a group. Provided permission was granted, and demographic information was collected from women who declined participation.

Participants allocated to the control group continued with their usual daily activities and were not discouraged from participating in exercise sessions on their own. In contrast, the participants randomized to the exercise group engaged in a supervised cycling program involving at least 3 sessions per week. The intervention was initiated within 3 days of randomization and continued to the end of the third trimester (weeks 36-37). All women received standard prenatal care throughout the intervention period, and they had equal numbers of usual visits with their obstetricians during pregnancy. All women received general advice about the positive effects of physical activity during pregnancy, and no special dietary recommendation were given.

The exercise protocol was based on a previous study[26] showing the benefits of regular stationary cycling exercise for blood glucose control in women with GDM. All the exercise sessions occurred at Peking University First Hospital under supervision. Sessions were conducted on alternate days with the supervisor maintaining detailed records regarding the participants' physiological indexes and compliance. At the start of the intervention, each exercise session consisted of stationary cycling for 30 minutes, beginning with a 5-minute warm-up at low intensity, which was 55-65% of the age-predicted heart rate maximum (HRmax) and a rating of perceived exertion (RPE) according to Borg[27] scale between 9-11. RPE is the perceived score of difficulty when

FIGURE
Trial profile



Consolidated standards of reporting trials (CONSORT) 2010 flow diagram of study participants.

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exercising, and is frequently used to subjectively monitor the exercise intensity based on individual perception.[26,28] The Borg[27] scale is the most frequently used method to evaluate individual RPE. This scale ranges from 6-20, where exercise is perceived to be "no exertion at all" to "very very hard," respectively.[27] Subsequently, 5 minutes of continuous moderate-intensity cycling (65-75% of the age-predicted HRmax; RPE 12-14) ensued. Next, the participants completed a period of interval cycling consisting of 30 seconds of rapid pedaling (sprints, higher intensity efforts) at 75-85% of the age-predicted HRmax and RPE 15-16 every 2 minutes for 3-5 intervals. This sprinting was followed by 5 minutes of continuous cycling at low-to-moderate intensity (60-70% of the age-predicted HRmax; RPE 10-12) before beginning another period of interval cycling. During this interval phase, continuous moderate-intensity cycling at 65-75% of the age-predicted HRmax (RPE 12-14) was interspersed with 1-minute periods of pedaling against increased resistance (hill climb) at 75-85% of the age-predicted HRmax (RPE 13-15); these periods alternated every 2 minutes for 3 repeats. Each session ended with a 5-minute cool down of easy cycling. At the start of the intervention, the women exercised at the lower end of the calculated heart rate ranges, with progressive increases as the program continued. Additionally, the exercise duration was progressively increased to 45-60 minutes by adding 5 minutes to the intervals or the continuous moderate-intensity cycling phases according to individual ability. The inclusion of periods of interval cycling was based on a previous study showing benefits for energy expenditure and exercise enjoyment in pregnant women.[29]

All pregnant women who receive standard prenatal care at Peking University First Hospital have 4 routine ultrasound examinations throughout pregnancy at $11\text{-}13^{+6}$, $20\text{-}23^{+6}$, $30\text{-}30^{+6}$, and $36\text{-}36^{+6}$ gestational weeks. Cervical length was measured at each examination. Due to the possibility of an increased risk of preterm birth caused by cycling-induced shortening of cervical length, to ensure and evaluate the safety of exercise during pregnancy, we recorded and reviewed cervical length at each examination and excluded those women with a cervical length <25 mm at any time during the intervention because uterine cervix length is an accurate predictor of the risk of preterm birth.[30] For consistency, we also excluded those participants in the control group with a cervical length <25 mm.

Furthermore, at study entry, we measured each participant's height to the nearest 0.5 cm without shoes and weight accurate to 0.1 kg with light clothing. BMI was calculated as maternal weight divided by height (kg/m^2). Additionally, blood was drawn from the antecubital vein after the participant had fasted for at least 8 hours but not >14 hours and was collected in sterile vacutainer tubes preloaded with heparin. There was at least 24 hours between the last exercise bout and the time of blood draw. Blood was centrifuged at 1800*g* at 4°C for 10 minutes within 4 hours of collection; subsequently, the plasma was separated and glucose was measured immediately. The remaining plasma was stored at −80°C for later analysis of insulin and lipid parameters (triglyceride, total cholesterol, and low- and high-density lipoprotein cholesterol). Insulin was measured using radioimmunoassay commercial kits (Beifang Institute of Biochemical Technology, Beijing, China). The insulin resistance index was calculated according to the homeostasis model of assessment: fasting plasma insulin (μU/mL) × fasting glucose (mmol/L)/22.5.[31] Fasting lipid profiles were measured using an automatic analyzer (7600; Hitachi High-Technologies Corp, Tokyo, Japan) in the Department of Clinical Laboratory, Peking University First Hospital. Maternal body weight measurement and biochemical tests were repeated at 25 and 36 gestational weeks.

To assess the participants' physical activity levels during pregnancy, the International Physical Activity Questionnaire[32] was used at study entry and at 25 and 36 weeks' gestation. The questionnaire included questions about the number of days per week and the time spent sitting, walking, and doing moderate and vigorous activities, and then a score, which is expressed as metabolic equivalents of task min/wk, can be calculated using the formula 8.0 × vigorous activity + 4.0 × moderate activity + 3.3 × light activity (walking) for the different activity categories.[33]

At 24-28 weeks' gestation, all participants underwent a 75-g oral glucose tolerance test (OGTT) after an overnight fast to diagnose GDM. Similarly, at least 24 hours elapsed between the last exercise session and the OGTT. According to the new criteria amended in August 2014 in China, GDM was diagnosed when any 1 value was ≥5.1 mmol/L at 0 hours, ≥10.0 mmol/L at 1 hour, or ≥8.5 mmol/L at 2 hours. Values of 7.0 mmol/L at 0 hours or 11.1 mmol/L at 2 hours were diagnosed as diabetes mellitus, regardless of pregnancy stage.[34]

Outcomes

The primary outcome was the incidence of GDM (this has been reported as a letter in *Diabetes Care*,[35] but this article includes a number of other important outcomes). The secondary outcomes included physical activity levels; gestational weight gain; biochemical outcomes, including insulin resistance and lipid profiles; maternal outcomes, such as gestational hypertension (defined as blood pressure elevation [systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg] >20 weeks' gestation in the absence of proteinuria),[36] preeclampsia (defined as new-onset hypertension [systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg] and new-onset proteinuria [300 mg of protein in 24 hours or a urine protein/creatinine ratio of 0.3 mg/dL] >20 weeks' gestation or, in the absence of proteinuria, new-onset hypertension with new-onset thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual disturbances),[36] and mode of delivery (vaginal, operative vaginal, or cesarean); and neonatal outcomes, including gestational age at delivery, preterm birth (<37 and <34 weeks), Apgar score, birthweight, macrosomia (birthweight >4000 g), large-for-gestational-age (LGA) infants (birthweight >90th percentile for gestational age), and small-for-gestational-age (SGA) infants (birthweight <10th percentile for gestational age), both LGA and SGA were defined in accordance with international standards for sex-specific newborn size for each gestational age based on data from the Newborn Cross-Sectional Study subpopulation.[37]

Statistical analysis

We calculated that a sample size of 121 participants in each group was sufficient to detect a 50% reduction in the incidence of GDM with an α of 0.05 and a statistical power (1-β) of 0.8 based on our previous study.[4] Assuming a dropout rate of 10-15%, the target sample size was 150 in each group.

Data were analyzed using statistical software (SPSS, 17.0, IBM Corp, Armonk, NY). Continuous variables are presented as mean ± SD, and categorical variables are presented as numbers and percentages. Differences in the means between groups were evaluated using independent sample *t* tests and analysis of variance. Pearson χ^2 test was used for categorical variables. Analysis was by intention to treat. The level of statistical significance was set at .05.

Results

From December 2014 through July 2016, 821 pregnant women with a BMI ≥24 kg/m^2 were screened for eligibility. Among those individuals, 300 singleton women at 10 weeks' gestational age and with a mean p-BMI of 26.78 ± 2.75 kg/m^2 were recruited. They were randomized to either the exercise group (n = 150) or the control group (n = 150). In all, 39 (26.0%) and 38 (25.3%) participants were obese in each group, respectively. The baseline characteristics of these individuals are summarized in Table 1, and the 2 groups were well matched at baseline, with no significant differences in age, p-BMI, gestational age, family history of diabetes, personal history of GDM, or fasting plasma glucose at study entry. Compared with women who declined to participate but agreed to the use of their routine data, the participants had a fasting plasma glucose that was 0.08 mmol/L higher and were more likely to have a family history of diabetes mellitus ($P < .05$).

As shown in the Figure, a total of 38 and 36 participants did not complete the follow-up in the exercise group and the

TABLE 1
Baseline characteristics of participants

Characteristics	Exercise group n = 150	Control group n = 150	*P*
Age, y	32.14 ± 4.57	32.50 ± 4.91	.5
Weight, kg	70.83 ± 8.49	70.44 ± 8.55	.7
Height, cm	162.64 ± 5.07	161.97 ± 4.87	.2
p-BMI, kg/m^2	26.75 ± 2.74	26.82 ± 2.76	.8
Obese, BMI ≥28 kg/m^2	39 (26.0)	38 (25.3)	.9
Maternal birthweight, g	3302.38 ± 432.38	3244.46 ± 561.66	.3
≥College/university, %	119 (79.3)	110 (73.3)	.7
Gestational age, wk	10 ± 2	10 ± 2	.8
Primiparous	120 (80.0)	121 (80.7)	.9
Family history of diabetes, %	49 (32.7)	47 (31.3)	.8
Personal history of GDM, multiparous only, %	4 (13.33)	3 (10.34)	.7
Fasting plasma glucose at study entry, mmol/L	5.04 ± 0.37	5.04 ± 0.41	1.0

Continuous variables presented as mean ± SD; categorical variables presented as n (%).

BMI, prepregnancy body mass index; *GDM*, gestational diabetes mellitus; *p-BMI*, prepregnancy body mass index.

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control group, respectively, and the main reason was their unwillingness to participate further. The frequency of potential adverse events associated with exercise, such as miscarriage and fetal death in utero, did not differ between the exercise and control groups. Furthermore, the number of participants excluded due to a cervical length <25 mm was comparable between the groups. The 7 women with a cervical length <25 mm in our study were followed up for adverse events; however, none of them experienced a miscarriage or fetal loss during their pregnancy. Notably, 3 of these women in the control group had a preterm birth (1 case at <34 weeks' gestation; 2 cases between 34^{+1} and 36^{+6} weeks' gestation).

The effect of exercise on the frequency of GDM

Overall, the total number (mean ± SD) of exercise sessions attended was 73 ± 10 (range 60-130) over a period of 27 ± 2 weeks; 90% of the participants in the exercise group were >80% compliant with the supervised cycling program, and the lowest attendance rate was 73%. The mean duration of each session was 35 ± 6 minutes at an RPE of 13 ± 1, equivalent to a perception of working out "somewhat hard."

In total, 132 participants (88.0%) in the exercise group and 133 (88.7%) in the control group underwent the 75-g OGTT, and their results were used for analysis of the primary outcome. The incidence of GDM was 22.0% (29/132) in the exercise group and 40.6% (54/133) in the control group (odds ratio [OR], 0.412; 95% confidence interval [CI], 0.240−0.705; $P < .001$). This represents a clinically important 45.8% reduction in the incidence of GDM. Furthermore, the exercise group had lower blood glucose levels at 0, 1, and 2 hours on the postintervention 75-g OGTT compared to the control group ($P = .001$, $P = .009$, and $P = .009$, respectively).

Physical activity

Physical activity levels preintervention and at 25 and 36 gestational weeks based on the International Physical Activity Questionnaire are shown in Table 2. The main form of physical activity in the control group was walking. The exercise group had higher total physical activity levels than the control group at 25 weeks' gestation (1741 ± 798 vs 1327 ± 1300 metabolic equivalents of task min/wk; $P = .010$) and at 36 weeks' gestation (1642 ± 862 vs 1388 ± 1044 metabolic equivalents of task min/wk; $P = .123$) and this was attributed to greater levels of moderate-intensity exercise at 25 weeks' gestation (484 ± 220 vs 64 ± 360 metabolic equivalents of task min/wk; $P < .001$) and at 36 weeks' gestation (436 ± 177 vs 81 ± 239 metabolic equivalents of task min/wk; $P < .001$). The levels of vigorous physical activity and walking were similar between and within groups at 25 and 36 gestational weeks.

Secondary outcomes

Following the intervention, the women randomized to the exercise group had significantly less gestational weight gain compared with those in the control group by 25 gestational weeks (4.08 ± 3.02 vs 5.92 ± 2.58 kg; $P < .001$) and at the end of pregnancy (8.38 ± 3.65 vs 10.47 ± 3.33 kg; $P < .001$). However, the 2 groups exhibited no significant difference in gestational weight gain between 25-36 weeks' gestation (4.55 ± 2.06 vs 4.59 ± 2.31 kg; $P = .896$). Furthermore, following the intervention, insulin resistance was significantly lower in the exercise group than in the control group

TABLE 2
Physical activity levels in overweight and obese pregnant women randomized to exercise intervention or control groups

	Exercise group	Control group	*P*
Vigorous exercise, metabolic equivalents of task min/wk			
At study entry	0, n = 150	0, n = 150	
At 25 wk gestation	34 ± 1630, n = 132	0, n = 133	.04
At 36 wk gestation	8 ± 48, n = 112	0, n = 114	.1
Moderate exercise, metabolic equivalents of task min/wk			
At study entry	33 ± 146, n = 150	11 ± 71, n = 150	.1
At 25 wk gestation	484 ± 220, n = 132	64 ± 360, n = 133	<.001
At 36 wk gestation	436 ± 177, n = 112	81 ± 239, n = 114	<.001
Walking, metabolic equivalents of task min/wk			
At study entry	1141 ± 1107, n = 150	1113 ± 1167, n = 150	.8
At 25 wk gestation	1224 ± 722, n = 132	1263 ± 1116, n = 133	.9
At 36 wk gestation	1198 ± 839, n = 112	1307 ± 996, n = 114	.5
Total, metabolic equivalents of task min/wk			
At study entry	1195 ± 1154, n = 150	1124 ± 1183, n = 150	.6
At 25 wk gestation	1741 ± 798, n = 132	1327 ± 1300, n = 133	.01
At 36 wk gestation	1642 ± 862, n = 112	1388 ± 1044, n = 114	.1

Data presented as mean ± SD unless otherwise specified.

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at 25 weeks' gestation (2.92 ± 1.27 vs 3.38 ± 2.00; *P* = .033). No differences were noted between the groups in the preintervention or postintervention levels of plasma triglycerides, total cholesterol, and low- and high-density lipoprotein cholesterol. The frequency of hypertensive disorders of pregnancy, including both gestational hypertension and preeclampsia (17.0% vs 19.3%; OR, 0.854; CI, 0.434–2.683; *P* = .649), and cesarean delivery (except for scar uterus) (29.5% vs 32.5%; OR, 0.869; 95% CI, 0.494–1.529; *P* = .627) did not differ significantly between the exercise and control groups. Similarly, no significant differences were observed between the 2 groups with regard to the gestational age at birth (39.02 ± 1.29 vs 38.89 ± 1.37 weeks' gestation; *P* = .486), the percentage of preterm births (2.7% vs 4.4%; OR, 0.600; 95% CI, 0.140–2.573; *P* = .487), or the Apgar score at 1 or 5 minutes. However, infants born to women following the exercise intervention had a significantly lower birthweight compared with those born to women allocated to the control group (3345.27 ± 397.07 vs 3457.46 ± 446.00; *P* = .049, *P* = .049). But, in the exercise group vs control group, there were no significant differences in the frequency of macrosomia (6.3% vs 9.6%; OR, 0.624; 95% CI, 0.233–1.673; *P* = .345) and LGA (14.3% vs 22.8%; OR, 0.564; 95% CI, 0.284–1.121; *P* = .100). Notably, 3 cases of SGA were observed in the exercise group with none in the control group (Table 3).

Comment

We conducted a prospective RCT to evaluate the efficacy of regular exercise begun in early pregnancy to prevent GDM in overweight and obese pregnant women. The main results of our study suggest the following. First, overweight/obese women allocated to the exercise group have a significantly lower frequency of gestational diabetes than those allocated to the control group. Second, the exercise group had significantly less gestational weight gain before mid-second trimester and at the end of pregnancy, and lower insulin resistance levels at 25 gestational weeks than the control group. Third, other pregnancy outcomes, including hypertensive disorders of pregnancy, cesarean delivery, mean gestational age at birth, macrosomia, and LGA infants, were also lower in the exercise group compared to the control group, but without significant difference. However, infants born to women following the exercise intervention had a significantly lower birthweight compared with those born to women allocated to the control group. Fourth, no increased exercise-related safety issues, such as miscarriage, fetal loss, short cervical length, or preterm birth, was observed in women allocated to the exercise group.

The role of exercise in preventing and treating diseases has been widely studied. In particular, various studies have confirmed that exercise is effective in delaying the progression of glucose

TABLE 3
Maternal and neonatal outcomes

	Exercise group	Control group	OR (95% CI)	*P*
GDM, %	29 (22.0), n = 132	54 (40.6), n = 133	0.412 (0.240–0.705)	<.001
75-g OGTT glucose level, mmol/L				
0 h	4.76 ± 0.41[b]	4.96 ± 0.51[c]	/	.001
1 h	7.99 ± 1.67[b]	8.57 ± 1.86[c]	/	.009
2 h	6.57 ± 1.18[b]	7.03 ± 1.62[c]	/	.009
Gestational weight gain, kg				
Study entry to 25^{+6} wk gestation	4.08 ± 3.02[b]	5.92 ± 2.58[c]	/	<.001
26^{+1} to 36^{+6} wk gestation	4.55 ± 2.06[d]	4.59 ± 2.31[e]	/	.9
Total	8.38 ± 3.65[d]	10.47 ± 3.33[e]	/	<.001
HOMA-IR				
At study entry	2.70 ± 1.33[a]	2.69 ± 1.25[a]	/	.9
At 25 wk gestation	2.92 ± 1.27[b]	3.38 ± 2.00[c]	/	.033
At 36 wk gestation	3.56 ± 1.89[d]	4.07 ± 2.33[e]	/	.1
Plasma triglycerides, mmol/L				
At study entry	1.33 ± 0.78[a]	1.34 ± 0.63[a]	/	.9
At 25 wk gestation	2.53 ± 1.14[b]	2.67 ± 0.85[c]	/	.3
At 36 wk gestation	3.39 ± 1.19[d]	3.50 ± 1.11[e]	/	.5
Plasma total cholesterol, mmol/L				
At study entry	4.27 ± 0.74[a]	4.30 ± 0.68[a]	/	.7
At 25 wk gestation	5.54 ± 1.03[b]	5.67 ± 0.90[c]	/	.3
At 36 wk gestation	5.82 ± 1.09[d]	5.81 ± 1.11[e]	/	.9
Plasma HDL-C, mmol/L				
At study entry	1.46 ± 0.32[a]	1.46 ± 0.31[a]	/	.9
At 25 wk gestation	1.79 ± 0.34[b]	1.77 ± 0.32[c]	/	.9
At 36 wk gestation	1.72 ± 0.32[d]	1.65 ± 0.30[e]	/	.1
Plasma LDL-C, mmol/L				
At study entry	2.32 ± 0.56[a]	2.30 ± 0.60[a]	/	.9
At 25 wk gestation	2.78 ± 0.78[b]	2.91 ± 0.72[c]	/	.2
At 36 wk gestation	2.94 ± 0.82[d]	2.93 ± 0.84[e]	/	.9
Hypertensive disorders of pregnancy	19/112 (17.0)	22/114 (19.3)	0.854 (0.434–1.683)	.6
PE	8/112 (7.1)	7/114 (6.1)	1.176 (0.412–3.359)	.8
Gestational hypertension	11/112 (9.8)	15/114 (13.2)	0.719 (0.315–1.642)	.4
Labor and delivery				
Unassisted vaginal delivery	59/112 (52.7)	50/114 (43.9)	1.425 (0.844–2.406)	.2
Operative vaginal delivery	7/112 (6.3)	15/114 (13.2)	0.440 (0.172–1.124)	.1
Cesarean delivery (except for scar uterus)	33/112 (29.5)	37/114 (32.5)	0.869 (0.494–1.529)	.6
Gestational age at birth	39.02 ± 1.29[d]	38.89 ± 1.37[e]	/	.5

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TABLE 3
Maternal and neonatal outcomes *(continued)*

	Exercise group	Control group	OR (95% CI)	*P*
Preterm birth				
<34 wk gestation	0	1/114 (0.9)	/	
34^{+1} to 36^{+6} wk gestation	3/112 (2.7)	4/114 (3.5)	0.757 (0.166–3.461)	.7
Total	3/112 (2.7)	5/114 (4.4)	0.600 (0.140–2.573)	.5
Apgar score				
At 1 min	9.95 ± 0.30[d]	9.80 ± 1.03[e]	/	.1
At 5 min	10[d]	9.93 ± 0.51[e]	/	.1
Birthweight, g	3345.27 ± 397.07, n = 112	3457.46 ± 446.00[e]	/	.049
Macrosomia	7/112 (6.3)	11/114 (9.6)	0.624 (0.233–1.673)	.3
LGA	16/112 (14.3)	26/114 (22.8)	0.564 (0.284–1.121)	.1
SGA	3/112 (2.7)	0	/	

Data are presented as n (%) or mean ± SD unless otherwise specified.

Acrosomia is defined as birthweight >4000 g; LGA and SGA are defined as birthweight >90th or <10th percentile for gestational age, respectively; furthermore, both LGA and SGA were defined in accordance with international standards for sex-specific newborn size for each gestational age based on data from Newborn Cross-Sectional Study subpopulation.[37]

CI, confidence interval; *GDM*, gestational diabetes mellitus; *HDL-C*, high-density lipoprotein cholesterol; *HOMA-IR*, homeostasis model assessment of insulin resistance index [fasting plasma insulin (μU/mL) × fasting glucose (mmol/L)/22.5][31]; *LDL-C*, low-density lipoprotein cholesterol; *LGA*, large for gestational age; *OGTT*, oral glucose tolerance test; *OR*, odds ratio; *PE*, preeclampsia; *SGA*, small for gestational age.

[a] n = 150; [b] n = 132; [c] n = 133; [d] n = 112; [e] n = 114.

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intolerance in type 2 diabetes.[38] Considering the similar pathogenesis of GDM and type 2 diabetes, recent research focused on the relationship between exercise and the incidence of GDM. However, the results of the few well-designed RCTs are inconsistent. Particularly, a recent meta-analysis including 10 RCTs of physical activity and GDM from 1966 through 2014 showed that exercise interventions had a 28% (95% CI, 9–42%) reduction in the incidence of GDM (relative risk, 0.72; $P = .005$) compared to controls.[39] However, only 2 of the 10 included studies showed a protective effect of exercise on GDM independently. This finding may be due to small sample size, low adherence, and loss to follow-up in some of these individual studies.

Cordero et al[15] showed that moderate exercise implemented 3 times per week from 10-12 weeks of gestation was effective in preventing the development of GDM. In contrast, Nobles et al[40] reported that an exercise intervention started in the second trimester did not reduce the relative odds for GDM in women at high risk (those with at least 1 of the following: p-BMI ≥25 kg/m^2, family history of diabetes, GDM in previous pregnancy). Recently, a study using a supervised stationary cycling exercise program similar to that used in the current study reported no effect on GDM incidence. However, it is important to point out critical differences between the studies, including the commencement of exercise earlier in pregnancy, as well as a focus on overweight and obese women in the present trial, rather than women with GDM in a previous pregnancy with higher background levels of physical activity in the prior study.[28]

These results suggest that preventing the development of GDM in women with risk factors might be challenging. Alternatively, they highlight the importance of seeking effective ways to reduce the incidence of GDM in high-risk populations.

Among the established risk factors for GDM, prepregnancy overweight and obesity are the main health care challenges.[41] Our previous study showed that the incidence of GDM was 29.55% and 35.88% in women with p-BMI ≥24-<28 kg/m^2 and ≥28 kg/m^2, respectively.[4] Moreover, the prevalence of overweight and obesity in recent decades is increasing worldwide. As shown in one study, the global number of overweight and obese individuals was 2.1 billion in 2013, accounting for 38% of the total population.[41] Similar trends were observed in China, with the prevalence of overweight and obesity increasing from 10.7-14.4% and 5.0-10.1%, respectively, from 1993 through 2009.[42] And one of our studies based on 15 hospitals in Beijing with 14,168 pregnant women showed that the prevalence of overweight and obesity in pregnant women was as high as 19.1% in 2013.[43] Therefore, an urgent need exists to address health issues surrounding GDM, overweight/obesity, and diabetes.

Our study targeted overweight/obese pregnant women and demonstrated the robust ability of regular exercise to reduce GDM risk. These positive results may be attributed, at least in part, to the supervision of the program, which ensured the exercise intensity and the high level of adherence. Moreover, starting the intervention early in pregnancy may have played an important role in the effectiveness of our protocol.

For example, 2 recent well-designed RCTs, The United Kingdom Pregnancies Better Eating and Activity Trial (UPBEAT)[16] and the pilot study of Vitamin D and Lifestyle Intervention for GDM Prevention,[18] focused on the role of lifestyle intervention in preventing GDM in women with obesity. Unfortunately, neither study proved the efficacy of exercise in reducing the incidence of GDM. However, the exercise was not supervised, and both trials initiated the interventions in the second trimester, which may be too late to prevent the development of GDM considering that endocrine and metabolic changes begin in the first trimester[44] and placental function may be programmed by this time.[45] Thus, early intervention may be more effective. This hypothesis is supported by a meta-analysis suggesting that prepregnancy exercise may have a greater role in reducing the risk of developing GDM than exercise started in early pregnancy. Moreover, prepregnancy exercise continued into early pregnancy had the strongest beneficial effect.[46]

Numerous studies suggest that excessive gestational weight gain is another vital independent risk factor for GDM; the risk of GDM increases as the rate of gestational weight gain increases.[47,48] This may be due to the reason that excess gestational weight gain is associated primarily with maternal adipose tissue, but not with lean body mass accrual.[49] Furthermore, studies have indicated that the association between the rate of gestational weight gain and GDM has been primarily attributed to the increased weight gain in the first trimester.[48,50] Importantly, in our study, women in the exercise group had significantly less gestational weight gain than women in the control group by 25 weeks' gestation and at the end of pregnancy. However, no significant difference in gestational weight gain was observed between the 2 groups between 25-36 weeks' gestation, perhaps because all the women with GDM initiated lifestyle interventions after their GDM diagnosis, and the proportion of women with GDM in the control group was as high as 40%. Nevertheless, our study is one of several other studies showing that physical exercise at the beginning of pregnancy decreases mean gestational weight gain and is associated with decrease of GDM incidence.[23,51]

Additionally, our study clearly shows that exercise attenuates the increase in insulin resistance in the population of overweight-obese pregnant women at 25 weeks of gestation, possibly revealing the underlying mechanism by which exercise prevents GDM. And this result was supported by other studies. Davenport et al[52] reported that walking intervention could significantly lower glucose concentrations in the fasted state and 1 hour after meals in women with GDM, moreover, women with walking intervention required fewer units of insulin per day and less injection frequency. Similarly, the RCT conducted by Brankston et al[53] showed that compared to GDM women treated with diet alone, women treated with diet plus resistance exercise were prescribed less insulin and had a longer delay from diagnosis to the initiation of insulin therapy. However, the exact pathogenesis for exercise on improving insulin sensitivity and subsequently reducing the frequency of GDM remains unclear. Several mechanisms, such as stimulating insulin sensitivity by muscle contraction, enhancing antioxidant defense mechanisms, and altering adipokine profiles, such as adiponectin, leptin, resistin, might be implicated.[54]

Besides, our results favored a significant reduction in neonatal birthweight in overweight and obese women following an exercise intervention, and the frequency of hypertensive disorders of pregnancy, cesarean delivery, macrosomia, and LGA was also lower than those of the control group, even though were not significant. These findings probably were because the sample size in our study was calculated on the incidence of GDM, and may be too small to demonstrate a positive result on these perinatal outcomes.

Decades ago, researchers began to focus on the relationship between exercise and maternal and neonatal outcomes. However, the results have been inconsistent due to the considerable variation in study design. The UPBEAT study showed no significant differences between groups in the frequency of LGA and other outcomes such as mode of delivery, preeclampsia, postpartum hemorrhage, and birthweight.[16] The Australian LIMIT RCT[19] also showed that lifestyle interventions addressing diet and exercise, which were similar to those used in the UPBEAT study, had no effect on reducing the proportion of LGA in overweight and obese pregnant women; however, the proportion of infants weighing >4 kg was lower in the women allocated to the intervention group. A recent meta-analysis[55] including 14 RCTs reported that an exercise program during pregnancy was effective at reducing neonatal birthweight, moreover, did not negatively affect gestational age at delivery. Barakat et al[56] showed that a 3 d/wk exercise program with sessions lasting 50-55 minutes from 9-11 gestational weeks until 38-39 weeks was effective in preventing the development of hypertension and reducing the incidence of macrosomia.

High birthweight is the top concerns of overweight and obese women, for it is well recognized to be associated with immediate birth consequences, such as shoulder dystocia and fetal asphyxia.[57] Furthermore, it may lead to a long-term increase in the risks of obesity and metabolic syndrome in childhood and adulthood,[58] Thus, according to the results of our study and those of other investigators, the modest reduction in neonatal birthweight caused by an exercise intervention during pregnancy may have positive health benefits not only during the perinatal phase but also in the long term.

Notably, even though not significant, 3 women in the exercise group gave birth to SGA infants in our study. The birthweights of their infants were 2470, 2605, and 2280 g at 40, 39, and 38 gestational weeks, respectively. The respective total gestational weight gain of these 3 mothers was 0.8 kg loss, 2.5 kg, and

3.6 kg, and all of them had high compliance with the cycling program (98%, 90%, and 85%, respectively). Therefore, we reasoned that these women additionally might have been strict with their diet, which together with exercise caused the development of SGA. Thus, when we provide exercise recommendations to pregnant women, we must comprehensively evaluate their diet and gestational weight gain and direct close attention to fetal development.

Generally, the amount of physical activity during pregnancy is low. Very few pregnant women meet the minimum American Congress of Obstetricians and Gynecologists recommendations regarding the amount of exercise during pregnancy.[59] Based on the International Physical Activity Questionnaire, the data in our study showed that only 10.7% and 9.1% of the subjects in the exercise group and the control group participated in moderate physical activity at study entry, and the predominant physical activity performed by pregnant Chinese women was walking. However, the exercise intervention was effective in providing an incremental increase in physical activity in the exercise group, whereas the level of physical activity in the control group remained stable.

We previously reported that excessive fatigue and concerns about the safety of exercise are the greatest barriers to exercise during pregnancy in Chinese women.[60] However, our study showed that moderate exercise will not cause the cervix to shorten; increase the risk of miscarriage, fetal loss, or preterm birth; or reduce the mean gestational age at delivery. In addition, a recent meta-analysis including 9 RCTs also showed that aerobic exercise (35-90 min/session, 3-4 times/wk) during pregnancy was not associated with increased risk of preterm birth.[61] Thus, considering the benefits and safety of exercise demonstrated in our study and other studies, increasing the physical activity level of pregnant women is important. However, specific recommendations on the type, form, frequency, intensity, duration, or starting time of exercise to prevent diseases during pregnancy are lacking. According to our study, regular moderate-intensity cycling at a frequency of at least 3 sessions per week with each session lasting at least 30 minutes begun in early pregnancy was safe and effective in preventing GDM in overweight and obese pregnant women.

Strengths and weaknesses

Our study is the first RCT performed in China to assess the effectiveness and safety of regular exercise in preventing GDM and improving adverse pregnancy outcomes in overweight and obese women. The major strength of our study is the supervised cycling exercise intervention we employed, which ensured the appropriate amount and intensity of exercise and high adherence to the intervention program. Furthermore, our intervention did not include a dietary component, which facilitated our ability to discern the effect of exercise itself on outcomes. Assuredly, this intervention was also a study weakness that restrained us from further analyzing and comparing the respective and combined roles of exercise and dietary interventions. However, women in the 2 groups all received standard care, which included information regarding how to maintain a healthy lifestyle during pregnancy. Notwithstanding, further studies with detailed descriptions of the different types of dietary interventions and physical activity are needed.

The impracticality of instituting this type of a supervised activity program for pregnant women on a mass scale may be another potential limitation of the present study. Furthermore, our study focused on a Chinese population and was conducted in a tertiary care hospital in Beijing, which may lower the external validity of our findings. Nonetheless, our study confirmed the safety and potential of thrice weekly cycling initiated early in pregnancy to improve the health of overweight and obese pregnant women. Large longitudinal prospective studies involving multiple centers or ethnicities remain warranted to fully address the ability of different types of interventions to diminish long-term and other complications associated with pregnancy and delivery.

In summary, we observed that cycling exercises initiated early in pregnancy and performed at least 30 minutes 3 times per week had a significant effect on lowering the risk of GDM in overweight and obese pregnant women and may affect their offspring size at birth. And the decrease of GDM is very relevant to the reduced gestational weight gain in pregnancy. Furthermore, such exercise does not increase the risk of preterm birth or reduce the mean gestational age at birth and should therefore be recommended. Thus, in the absence of contraindications, regular exercise should be recommended as an important part of antenatal care. ■

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Received Sept. 13, 2016; revised Jan. 20, 2017; accepted Jan. 25, 2017.

This study was supported by "The role of exercise on preventing the development of gestational diabetes mellitus in overweight and obese pregnant women" from the Capital Characteristic Clinical Application Research Fund (Z151100004015088) and "Diabetes management beyond pregnancy" from the World Diabetes Foundation (WDF 14-908). The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had the final responsibility for the decision to submit for publication.

The authors report no conflict of interest.

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