Lifestyle Intervention for Overweight/Obese Pregnant Women with Polycystic Ovarian Syndrome: Lessons and Challenges

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Keywords

Polycystic ovarian syndrome · Obesity · Overweight · Lifestyle intervention · Pregnancy

Abstract

Introduction and Objective: Polycystic ovary syndrome (PCOS) is the most common reproductive disorder in women of reproductive age, and overweight and obesity are highly prevalent in women with PCOS. This study aims to explore whether lifestyle intervention can improve gestational weight gain (GWG), glucolipid metabolism, and perinatal outcomes in overweight/obese pregnant women with PCOS. **Methods:** This study is a randomized controlled trial that included overweight and obese pregnant women with PCOS who met the inclusion criteria of 8–12 gestational weeks. They were randomly allocated to the intervention group and the control group. Women in the intervention group were given individualized counseling on diet and exercise from a trained dietitian and followed up regularly by a trained dietitian. Women in the control group received guidance on diet and exercise in the form of group education. **Results:** A total of 296 pregnant women were enrolled in the study, including 164 in the intervention group and 132

in the control group. GWG was 11.93 ± 5.67 kg in the intervention group and 11.86 ± 5.35 kg in the control group and did not differ between the 2 groups. According to the per-protocol analyses, women with good compliance had a lower weight gain (10.11 ± 5.56 vs. 12.70 ± 5.31 , $p = 0.0042$). The incidence of gestational diabetes mellitus and other perinatal outcomes did not differ between the 2 groups. For the lipid profile, we did not find significant improvement in the intervention group. **Conclusions:** Our study showed that lifestyle intervention of diet and exercise did not affect GWG, glucolipid metabolism, and perinatal outcomes of overweight/obese pregnant women with PCOS. However, women with good compliance can benefit from the lifestyle intervention for GWG. We believe that future studies should focus on trial design and increasing compliance to improve the quality of the study.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common reproductive disorder in women of reproductive age. It is characterized by hyperandrogenism, chronic anovu-

lation, and polycystic ovaries [1]. It has been demonstrated that PCOS is associated with an increased risk of adverse maternal and neonatal complications including gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), preeclampsia, preterm birth, and elevated perinatal mortality [2]. Overweight and obesity are highly prevalent in women with PCOS, and obesity seems to worsen the endocrinologic disturbances of the disorder. Moreover, up to 64% of overweight/obese women experience excess gestational weight gain (GWG) [3]. This not only elevates the risks for GDM, fetal macrosomia, and cesarean delivery but also increases the risk for type 2 diabetes in later years for both mothers and their offspring [4–6]. However, the exact effect of overweight and obesity on pregnant women with PCOS remains unclear [7]. The relationship between overweight and PCOS is further complicated by a potential bidirectional relationship [8].

Lifestyle interventions (diet, exercise, or combined) are recommended as first-line management in the international evidence-based guideline on PCOS [9]. Lifestyle interventions have been found to improve both metabolic and reproductive manifestations of the syndrome. Weight management (prevention of weight gain, achieving modest weight loss, and maintenance of reduced weight) is thus recommended as first-line treatment for PCOS [10]. However, for overweight and obese women, the effectiveness of dietary and/or exercise interventions on weight gain had limited efficacy [11]. In addition, intensive interventions may not be feasible for many women, especially for pregnant women, and may be difficult to implement in healthcare delivery settings.

This study was designed to investigate whether lifestyle intervention including diet and exercise during pregnancy can reduce weight gain and improve the glucolipid metabolism of overweight/obese women with PCOS. Furthermore, we also examined if lifestyle intervention can ameliorate the maternal complications and neonatal outcomes related to excess weight gain in these pregnant women.

Methods

Design

This study was carried out at the Division of Endocrinology and Metabolism, Department of Obstetrics, Beijing Obstetrics and Gynecology Hospital, Capital Medical University. This was a randomized controlled trial encompassing 296 cases of overweight/obese pregnant women with PCOS. The inclusion criteria were pregnant women between 18 and 45 years of age with PCOS, singleton birth, and BMI ≥ 25 kg/m². Overweight was defined as BMI 25.0–29.9 kg/m² and obesity as BMI ≥ 30.0 kg/m². PCOS was diag-

nosed before conception according to the modified Rotterdam criteria. Women with polyembryony, type 2 diabetes, hypertension, or thyroid diseases, or who could not obey the exercise and diet intervention for their personal reasons were excluded. The participants began participating in the study at 8–12 gestational weeks (according to the last menstrual period or B-mode ultrasound). All of the eligible women were referred to specifically trained obstetricians to obtain informed consent. They were randomized by trial statisticians using a computer to generate the group lists. The trial was approved by the Beijing Obstetrics and Gynecology Hospital, Capital Medical University Ethics Committee, and was registered at ClinicalTrials.gov (NCT04216485).

The control group was given guidance on diet, exercise, and weight gain during pregnancy in the form of group education according to the recommendations of the Maternal Dietary Guidelines and Dietary Pagodas developed by the Chinese Maternal and Child Nutrition Society and followed by routine prenatal checkup with the obstetrician. The intervention group, based on the control group, was given individualized diet and exercise guidance by a trained dietitian (registered dietitian with an obstetrician background). They were required to see the dietitian every 2–4 weeks from the first intervention until the end of pregnancy. The specific schedule included formulating a diet prescription according to pre-pregnancy BMI and physical activities. For those who are overweight with light physical activity, 25–30 kcal/kg of ideal body weight was recommended. For obese women with light physical activity, 20–25 kcal/kg of ideal body weight was recommended. The intake of the 3 energy-yielding nutrients was distributed as carbohydrate 50–55%, protein 15–20%, and fat 25–30%. The recommended energy for the 1st trimester is not <1,500 kcal/day, and the 2nd trimester is not <1,600 kcal/day. Subjects were recommended a hypocaloric, low-glycemic, low-saturatedfat diet and provided a sample meal plan and recipes. They were also taught how to record their dietary log. Exercise intervention followed the FITT principle. It included moderate-intensity physical activity with brisk walking, swimming, dancing, pregnancy yoga, or other aerobic exercises for at least 30 min a day for at least 5 days each week. Heart rate was monitored during or after each exercise session by taking their pulse. It is regarded as reaching the standard if the heart rate reached 50–70% of maximum heart rate (220–age). The dietitian also sets subjects' weight gain targets according to their BMI. The total weight gain of overweight pregnant women is 7–11.5 kg, and the average weekly weight gain is recommended to be 0.3 kg. Obese pregnant women's total weight gain during pregnancy is 5–9 kg, and the average weekly weight gain is recommended to be 0.2 kg. All the instructions were given by individual sessions of face-to-face instruction and video teaching for 1-h duration. At follow-up, they were asked to bring back their dietary and exercise log and reported their body weight and increase in body weight every week. Women in the intervention group should record their diet and exercise at least 3 days a week and bring their notes back to the dietitian to obtain an evaluation. Women who could not visit the dietitian face to face performed their follow-up through WeChat. Furthermore, anyone who was diagnosed with GDM was treated with standardized management protocols for GDM.

Outcome Measures and Data Collection

The primary outcomes were GWG, glucose and lipid parameters, maternal complications, and neonatal outcomes. Subjects were followed every month until delivery.

Fig. 1. Flow diagram of participants. This figure describes the flow of participants in the intervention and control groups from screening through enrollment and completion of the study.

The subjects' weight was routinely monitored at the hospital during each antenatal visit and they were asked to self-monitor at home. We asked the subjects to record their weight in the morning wearing underwear before breakfast and after urinating. Considering that not all of the pregnant women can go to the hospital for weight measurement every week, we recommended them to use their scales to record weight to reduce the deviation. Excessive GWG was defined according to the 2009 Institute of Medicine guideline by prepregnancy BMI. Glucose and lipid parameters were collected in the 1st, 2nd, and 3rd trimesters of pregnancy. We compared the cholesterol (CHOL, mmol/L), triglyceride (TG, mmol/L), high-density lipoprotein (HDL, mmol/L), low-density lipoprotein (LDL, mmol/L), and fasting plasma glucose (FPG, mmol/L). We also compared fasting insulin (FINS, $\mu\text{IU/mL}$) and homeostasis model assessment-insulin resistance (HOMA-IR). These parameters were compared between the 2 groups cross-sectionally and dynamically.

Evaluated maternal complications included GDM and PIH. The diagnosis of GDM was based on the 2013 American Diabetes Association criteria. Specifically, a 75-g oral glucose tolerance test was performed at gestational week 24–28. The participants were diagnosed with GDM if any one of the following criteria of plasma glucose was met: fasting ≥ 5.1 mmol/L, 1 h ≥ 10.0 mmol/L, or 2 h ≥ 8.5 mmol/L. PIH was defined as new onset of hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) in a previously normotensive woman. Perinatal outcomes included premature rupture of fetal membrane, fetal distress, preterm delivery, infant birth weight, and congenital anomaly. Low-birth weight infant and macrosomia were defined as neonatal birth weight $< 2,500$ and $> 4,000$ g, respectively. Delivery before a gestational age of 37 completed weeks was considered preterm delivery.

Baseline information of demographic data, gestation, ethnicity, and medical history was collected through medical records. Blinding of participants and obstetrician was not possible, but those who collected/entered the data remained blind to allocation. Prepregnancy weight was self-reported. Fasting blood samples were collected during the first prenatal visit at 8–12 gestational weeks. Weight gain was collected at every follow-up visit by self-reporting. FPG was determined by the hexokinase method using an ARCHITECT GLUCOSE (3L82-21) Kit following the standard protocol with an automatic biochemical analyzer (ARCHITECT ci16200 analyzer; Abbott Laboratories, Illinois, USA). Fasting lipid parameters including CHOL, TG, HDL, and LDL were measured by enzymatic method using ARCHITECT CHOLESTEROL (7D62-21), TRIGLYCERIDE (7D74-21), ULTRA HDL (3K33-21), DIRECT LDL (1E33-20), and QUANTA LP (a) (7K00-01) (ARCHITECT ci16200 analyzer; Abbott Laboratories, Illinois, USA). Additionally, the FINS level was assayed using a Human/Canine/Porcine Insulin Quantikine ELISA Kit (DINS00) following a standard protocol (R&D Systems, Minneapolis, MN, USA). Insulin resistance was assessed using the following HOMA-IR score ($\text{HOMA-IR} = \text{FINS} \times \text{FPG} / 22.5$).

All of these diagnoses and information were collected from the electronic data systems of the hospital. Some antenatal data were not recorded electronically, so they were collected by hand-abstract from notes.

Sample Size Justification

The estimation of the sample content in the study was based on the premise of observing the primary outcome of GWG. According to 2 previous researches, GWG of pregnant women who were

Table 1. Baseline characteristics of participants for ITT and per-protocol

	ITT analyses			Per-protocol analyses		
	intervention, N = 164	control, N = 132	p value	pp-compliant, N = 55	pp-non-compliant, N = 109	p value
Maternal age, years, mean±SD	31.79±3.38	32.31±3.79	0.7398	31.78±3.51	32.31±3.79	0.9554
Gravidity, mean±SD	1.68±0.83	1.71±0.85	0.7180	1.49±0.63	1.81±0.90	0.0193*
Parity, mean±SD	1.19±0.42	1.18±0.39	0.8798	1.16±0.42	1.23±0.45	0.3367
Height, cm, mean±SD	162.66±0.16	162.87±5.50	0.7335	162.18±4.19	162.73±5.04	0.4905
PP-weight, kg, mean±SD	72.81±9.69	73.50±10.90	0.5628	74.64±1.00	71.34±9.07	0.0360*
PPBMI, kg/m ² , mean±SD	27.50±0.24	27.63±0.28	0.6724	28.33±3.24	26.89±2.75	0.0036*
Overweight, n (%)	104 (63.4)	88 (66.7)	0.6245	33 (60)	71 (65.1)	0.6069
Obese, n (%)	60 (36.6)	44 (33.3)		22 (40)	38 (34.9)	
FPG, mmol/L, mean±SD	4.66±0.47	4.75±0.50	0.2325	4.78±0.55	4.77±0.63	0.9023
CHOL, mmol/L, mean±SD	4.52±0.70	4.51±0.65	0.8478	4.60±0.71	4.51±0.69	0.4451
TG, mmol/L, mean±SD	1.69±0.73	1.63±0.72	0.4370	1.89±0.90	1.62±0.61	0.0284*
HDL, mmol/L, mean±SD	1.30±0.30	1.30±0.26	0.9618	1.28±0.26	1.32±0.28	0.4472
LDL, mmol/L, mean±SD	2.56±0.64	2.56±0.67	1	2.56±0.51	2.52±0.58	0.6353
FINS, µIU/mL	97.90±41.62	97.05±63.48	0.9425	97.90±41.62	97.05±63.48	0.9425
HOMA-IR	14.68±12.14	13.42±15.65	0.4125	14.68±12.14	13.42±15.65	0.4125
IVF-ET, n (%)	39 (23.8)	24 (18.2)	0.2565	14 (25.5)	25 (22.9)	0.7032
Family history of DM, n (%)	30 (18.3)	32 (24.2)	0.2506	11 (20)	19 (17.4)	0.6751
Family history of hypertension, n (%)	34 (20.7)	37 (28.0)	0.1710	14 (25.5)	20 (18.3)	0.3120

ITT, intention to treat; PP-weight, prepregnancy weight; PPBMI, prepregnancy body mass index; FPG, fasting plasma glucose; CHOL, cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FINS, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance; IVF-ET, in vitro fertilization and embryo transfer; DM, diabetes mellitus; SD, standard deviation. * Values are statistically significant at $p < 0.05$.

overweight/obese decreased by 3.2 and 6.7 kg after lifestyle intervention [12, 13]. Referring to our intensity of intervention, we anticipated that the weight gain of pregnant women with good compliance can be decreased by 3.1 kg. We selected the sample size to provide a statistical power of 90%, with a 0.05 alpha level (2-tailed), and the required sample content is 188 cases. To allow for an expected 15% loss to follow-up, we aimed at including a minimum of 220 participants to meet the primary outcome of the observation. Thus, we have 110 participants in each group.

Statistical Analyses

The SPSS18 statistical software package was used for data analysis. First, the data were tested for normality. For the measurement data that conformed to the normal distribution, the statistical description was described by the mean and standard deviation. The comparison between the 2 groups was performed by *t* test. For metabolic biomarkers, log transformations for normality were done when appropriate. For the data that did not conform to the normal distribution, the statistical description was described by the median and percentile spacing, and the nonparametric test was used for comparison between the 2 groups. For binary outcomes, we reported the number (percentage) in each group. The comparison between the 2 groups was performed using the χ^2 test/Fisher's exact test. All tests were performed using a 2-side examination with a statistical significance of $p < 0.05$. Analyses were by intention to treat (ITT) and per-protocol. We considered women with face-to-face follow-up as good compliance and performed per-protocol analyses.

Results

Subjects and Follow-Up

Between October 2016 and January 2019, a total of 384 patients were randomized after being assessed for eligibility for enrollment, with 192 assigned to the control group and 192 assigned to the intervention group. Of the women who were allocated to the intervention group, 28 were not included in the analyses: 19 had subsequent miscarriage/termination, 4 had been transferred to another hospital for specific diseases, and 5 asked to quit for their personal reasons. Of the women allocated to the control group, 60 were not included: 32 had subsequent miscarriage/termination, 18 had been transferred to another hospital for specific diseases, and 10 asked to quit for their personal reasons. ITT analyses, therefore, included 296 women with 164 allocated to the intervention group and 132 allocated to the control group. Figure 1 shows the flow of study participants. Baseline characteristics were similar between the 2 groups (Table 1).

According to our design, women in the intervention group should have had at least 7 attendance times. Thus,

Fig. 2. Gestational weight gain. **a, b** Intention-to-treat (ITT) analysis. **c, d** Per-protocol analysis. **a** There was no significant difference in 0–24 gestational week weight gain and 0–36 gestational week weight gain between the intervention group and the control group. **b** There was no significant difference in gestational weight gain of overweight and obese women between the intervention group and the control group. **c** The 0–24 gestational week weight gain ($p = 0.0096$) and 0–36 gestational week weight gain ($p = 0.0042$) of women in the pp-compliant group were lower than that of women in the pp-non-compliant group. **d** Overweight pregnant women also showed no difference in GWG between the 2 groups, while obese pregnant women in the pp-compliant group had lower GWG than the pp-non-compliant group ($p = 0.0494$). GWG, gestational weight gain.

we did the per-protocol analyses in the intervention group. We only counted the face-to-face follow-up. Fifty-five women whose attendance time was >4 before gestational week 24 and whose total attendance time was >6 were regarded as the per-protocol compliant group (pp-compliant group), while 109 women whose attendance time did not meet the former criteria were regarded as the per-protocol non-compliant group (pp-non-compliant group). The mean attendance times in the pp-compliant group and the pp-non-compliant group were 8.7 and 2.9, respectively ($p < 0.0001$). The ratio of obese women in the pp-compliant group was slightly higher but had no significant difference. The prepregnancy weight and BMI in the pp-compliant group were larger than those in the pp-non-compliant group. Gravidity in the pp-non-compliant

group and the level of TG in the pp-compliant group were higher. Other baseline characteristics were similar between the 2 groups (Table 1).

Outcomes

Weight gain during pregnancy: There was no significant difference in 0–24 gestational week weight gain and 0–36 gestational week weight gain during pregnancy between the intervention group and the control group (Fig. 2a). The GWG of women in the intervention group and the control group were 11.93 ± 5.67 and 11.86 ± 5.35 kg, respectively (Table 2). Overweight and obese pregnant women also showed no difference in weight gain between the 2 groups separately (Fig. 2b). In the per-protocol analyses, the 0–36 gestational week weight gain of

Table 2. Maternal complications and newborn outcomes for ITT and per-protocol

	ITT analyses			Per-protocol analyses		
	intervention, N = 164	control, N = 132	p value	pp-compliant, N = 55	pp-non-compliant, N = 109	p value
GWG, kg, mean±SD	11.93±5.67	11.86±5.35	0.8026	10.11±5.56	12.70±5.31	0.0042*
0–24W GWG, kg, mean±SD	5.64±3.85	5.67±4.08	0.9441	3.20±3.44	6.12±3.76	0.0096*
Overweight GWG, kg, mean±SD	10.14±5.89	9.91±5.47	0.8369	11.31±5.05	13.14±4.81	0.0979
Obesity GWG, kg, mean±SD	12.95±5.29	12.83±5.04	0.8676	8.30±4.25	11.40±6.29	0.0494*
GDM, n (%)	50 (30.5)	36 (27.3)	0.6070	20 (36.4)	30 (27.5)	0.2826
PIH, n (%)	36 (22.0)	31 (23.5)	0.7821	10 (18.2)	26 (23.9)	0.5492
PROM, n (%)	50 (30.5)	44 (33.33)	0.6012	22 (40)	28 (25.7)	0.0730
Fetal distress, n (%)	41 (25)	27 (20.5)	0.4051	17 (30.9)	24 (22.0)	0.2529
Delivery week, mean (SD)	38.7 (1.9)	38.8 (1.6)	0.3441	38.3 (2.2)	38.7 (1.8)	0.2193
Premature delivery, n (%)	16 (9.8)	6 (4.5)	0.1180	7 (12.7)	9 (8.3)	0.4078
Birth weight	3,418±574	3,465±502	0.3441	3,309±677	3,455±547	0.2463
C-section, n (%)	68 (41.5)	62 (47.0)	0.3489	16 (29.1)	52 (47.7)	0.0289*
Macrosomia, n (%)	21 (12.8)	14 (10.6)	0.5919	4 (7.3)	17 (7.3)	1
LBWI, n (%)	8 (4.9)	2 (1.5)	0.1937	4 (7.3)	4 (3.7)	0.4436
Gender, male/female	90/74	67/65	0.4455	30/25	60/49	1

ITT, intention to treat; GWG, gestational weight gain; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; PROM, premature rupture of fetal membrane; C-section, cesarean section; LBWI, low-birth weight infant; SD, standard deviation. * Values are statistically significant at $p < 0.05$.

Table 3. Lipid profiles and insulin parameters for ITT and per-protocol

	ITT analyses			Per-protocol analyses		
	intervention, N = 164	control, N = 132	p value	pp-compliant, N = 55	pp-non-compliant, N = 109	p value
T2 CHOL, mmol/L, mean±SD	5.75±1.04	5.57±0.90	0.2041	5.65±0.86	5.81±1.13	0.4587
T3 CHOL, mmol/L, mean±SD	6.04±1.11	5.96±1.08	0.5797	6.07±1.03	6.07±1.17	0.9815
Δ, mmol/L, mean±SD	0.38±0.49	0.39±0.63	0.8898	0.43±0.44	0.37±0.52	0.5687
T2 TG, mmol/L, mean±SD	2.81±0.87	2.91±1.00	0.4319	2.88±0.85	2.80±0.89	0.6282
T3 TG, mmol/L, mean±SD	3.56±1.19	3.71±1.92	0.4461	3.88±1.77	3.52±1.23	0.1655
Δ, mmol/L, mean±SD	0.68±0.78	0.80±1.41	0.4584	0.72±0.78	0.65±0.77	0.6821
T2 HDL, mmol/L, mean±SD	1.68±0.35	1.62±0.30	0.1702	1.58±0.27	1.72±0.37	0.0567
T3 HDL, mmol/L, mean±SD	1.63±0.31	1.61±0.31	0.5143	1.55±0.24	1.67±0.32	0.0254*
Δ, mmol/L, mean±SD	−0.03±0.18	−0.02±0.17	0.6733	0±0.13	−0.04±0.20	0.2213
T2 LDL, mmol/L, mean±SD	2.93±0.84	2.78±0.76	0.1908	2.87±0.72	2.98±0.92	0.5433
T3 LDL, mmol/L, mean±SD	3.08±1.12	3.01±0.93	0.6348	2.99±0.82	3.13±1.26	0.5131
Δ, mmol/L, mean±SD	0.25±0.90	0.17±0.43	0.4587	0.17±0.37	0.29±1.06	0.5449
T2 FINS, μIU/mL, mean±SD	104.61±41.06	106.77±59.40	0.8426	101.33±29.46	108.67±43.02	0.4879
T2 HOMA-IR, mean±SD	3.96±4.53	4.30±6.60	0.6324	3.21±5.28	3.63±4.96	0.1952

Δ, Lipid change from the 2nd to 3rd trimester. ITT, intention to treat; T2, 2nd trimester; T3, 3rd trimester; CHOL, cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FINS, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance. * Values are statistically significant at $p < 0.05$.

women in the pp-compliant group was lower than that of women in the pp-non-compliant group (10.11 ± 5.56 vs. 12.70 ± 5.31 kg, $p = 0.0042$), and 0–24 gestational week weight gain also showed a significant difference (3.20 ± 3.44 vs. 6.12 ± 3.76 kg, $p = 0.0096$) (Fig. 2c). Overweight pregnant women also showed no difference in GWG between the 2 groups, while obese pregnant women in the pp-compliant group had lower GWG than the pp-non-compliant group (8.30 ± 4.25 vs. 11.40 ± 6.29 kg, $p = 0.0494$) (Fig. 2d).

Maternal complications and neonatal outcomes: The primary complications, GDM and PIH, did not significantly differ between the 2 groups in both ITT and per-protocol analyses (Table 2). The incidence of GDM in the intervention group and the control group was 30.5 and 27.3% ($p > 0.05$), while in the pp-compliant group and the pp-non-compliant group, it was 36.4 and 27.5% ($p > 0.05$). The incidence of PIH in the intervention group and the control group was 22.0 and 23.5%, while in the pp-compliant group and the pp-non-compliant group, it was 18.2 and 23.9%. When the incidence of premature rupture of fetal membrane, fetal distress, and preterm delivery was compared, there were still no differences. We also compared the delivery week, fetal gender, and birth weight (including the ratio of macrosomia and low-birth weight infant), which had no significant difference both in ITT and per-protocol analyses. However, the ratio of cesarean section was much lower in the pp-compliant group than in the pp-non-compliant group ($p < 0.05$).

Metabolic parameters: In ITT analyses (Table 3), there were no significant differences in lipid levels in the 2nd and 3rd trimesters between the 2 groups. In per-protocol analyses (Table 3), we found that HDL in the 3rd trimester was higher in the pp-non-compliant group ($p < 0.05$). While TG in the 1st trimester was already higher in the pp-compliant group ($p < 0.05$) (Table 1), we found that in the 2nd and 3rd trimesters, there was no significant difference in TG between the pp-compliant group and the pp-non-compliant group. Other lipid profiles did not show any difference. There were no significant differences in FINS and HOMA-IR in both ITT and per-protocol analyses.

We analyzed the change of lipid parameters during pregnancy within groups. In ITT analyses, CHOL and TG levels were increased in both groups from the 2nd to 3rd trimester ($p < 0.05$), while HDL and LDL levels did not change significantly. In per-protocol analysis, only TG levels increased from the 2nd to 3rd trimester in both groups ($p < 0.05$). CHOL, HDL, and LDL did not show significant changes from the 2nd to 3rd trimester. We also

compared the change of lipid profiles from the 2nd to 3rd trimester between the 2 groups (Table 3). The results showed no difference in both ITT and per-protocol analyses.

Discussion

Our study showed that intensive lifestyle intervention including dieting and exercise did not affect GWG and glucose and lipid profile of overweight/obese women with PCOS. There were also no differences in perinatal outcomes between the intervention group and the control group. However, when per-protocol analyses according to compliance were done, a reduction in maternal weight gain and a trend of improvement in lipid profile were seen in women who followed the lifestyle intervention protocol. In addition, women with higher prepregnancy BMI were more compliant. This might suggest that women with high BMI pay more attention to their lifestyle during pregnancy and are more willing to comply with lifestyle changes.

In recent years, several large-scale prenatal lifestyle interventions for obese pregnant women were studied with the aim to reduce GWG and GDM occurrence [14–17]. The DALI (vitamin D and lifestyle intervention in the prevention of GDM) trial reported that a combined physical activity and healthy eating lifestyle intervention could lower GWG but did not affect fasting glucose, HOMA-IR, or birth outcomes [14]. The lifestyle intervention in the DALI study was based on behavioral and empowerment techniques using motivational interviewing methods and involved 5 face-to-face office visits and 4 telephone calls or electronic messaging in between. These diet and exercise interventions were similar to our protocol. In the UPBEAT [15] and LIMIT [17] trials, a combination of nutritional and physical activity interventions along with standard prenatal care was not able to reduce the risk of GDM development compared with the control group which only received standard prenatal care. There was also no significant difference in GWG and risk of GDM between the intervention and control groups in LIMIT and UPBEAT trials. The Finnish Gestational Diabetes Prevention Study (RADIEL) was designed slightly differently regarding the target population (overweight, many with a history of GDM, but with normal glucose tolerance study in early pregnancy), but also used healthy diet and physical activity intervention methods and reported a significant GDM reduction of 39% in the intervention group after correction for baseline parameters [16]. In their subsequent study

[18], the same intervention was used in a different population (overweight, many with a history of GDM, 37% with impaired glucose tolerance in early pregnancy) but resulted in no reduction of GDM, suggesting that those with preexisting impaired glucose metabolism may not benefit from intensive lifestyle intervention. Our study population was overweight/obese women with PCOS. We did not assess the glucose tolerance and insulin resistance before intervention. However, a meta-analysis [19] reported that, compared with controls, the risks of impaired glucose tolerance and insulin resistance were 2–4-fold higher in women with PCOS. Accordingly, we speculate that our subjects may have insulin resistance before or during the 1st trimester, which may explain the lack of effect of combined intervention on GDM in our study.

Our results showed that the intervention had no improvement on blood glucose. A RADIEL-based study found that lifestyle interventions during pregnancy can improve impaired glucose metabolism during the first postpartum year, but did not demonstrate an effect on fasting glucose or OGTT during pregnancy [20]. The DALI trial reported that overweight and obese women developed a higher fasting glucose and free fatty acids on a lower carbohydrate diet [21]. They hypothesize that dietary restriction, including carbohydrates, could increase free fatty acid level by the induction of lipolysis. Impaired lipid metabolism in pregnancy is associated with a higher risk of maternal and neonatal complications, such as GDM, preeclampsia, LGA, preterm delivery, and childhood obesity [22]. The UPBEAT trial reported that lifestyle intervention had beneficial effects on VLDL and TG. However, other RCTs of lifestyle intervention in obese/overweight pregnant women have reported little or no effect on lipid profiles [23–26]. Previous study showed that overweight/obese pregnant women with PCOS experience more significant insulin resistance and disordered lipid profiles in the 1st trimester [27]. In our study, the increase in CHOL and TGs is consistent with observations in other pregnant populations [28–30]. This may suggest that the intervention in our study may not be intense enough to overcome the high levels of plasma lipids in overweight/obese pregnant women with PCOS.

RCTs of lifestyle intervention study are always challenging. Although lifestyle management is the simplest and most economical way and can avoid invasive manipulation and long-term drug intervention to improve the metabolic syndrome caused by PCOS and obesity, the low compliance is the common challenge in lifestyle intervention study. In an RCT focused on exercise intervention, only 16.3% of the women attended 50% of the training

sessions [31]. Thornton et al. [32] confirmed the importance of nutrition intervention adherence in preventing GDM, with adherent participants gaining only 2.3 versus 14.1 kg in controls. The study also showed a GDM prevalence of 2.2% in the adherent group versus 34.6% in the “nonadherent” group. Many attempts have been made to increase the adherence rate, such as DVDs [33], smart-phone apps [34], and telephone calls [35] as a supplement to face-to-face follow-up. In our study, we used WeChat app to set up a group to increase the communication between dietitians and our subjects. This app allowed the patients to upload their meals and exercise records through the WeChat online to complete the follow-up. But, the loss of follow-up in our trial was still 22.9%. A total of 77.1% of the women completed the follow-up. In our intervention group, 66.5% of subjects completed follow-up on the WeChat app, while only 33.5% of them completed the face-to-face follow-up. This may be a contributing factor to the lack of effect of intervention on our outcomes.

In addition, considering the routine prenatal care in our hospital, including recommendations on diet and physical activity for all women, we suspected that the intensity of the given lifestyle intervention in our trial was probably not high enough to provide additional benefit for participants in the intervention group. In some trials, physical activity intervention alone has been effective. Previous studies showed that supervised 3-times-weekly exercise sessions could reduce the incidence of GDM [36, 37], PIH, preeclampsia, and macrosomia [36]. Physical activity intensity in our trial might be lower than that in other trials with a positive effect on obstetric and perinatal outcomes.

Lessons and Reflections

Until now, it is unclear whether lifestyle intervention in overweight/obese women with PCOS without impaired glucose tolerance and insulin resistance will result in improved metabolic outcomes. Studies focusing on subgroups of women with PCOS may be considered, given that the insulin resistance or dysglycemia may have already existed in women with PCOS before pregnancy. The timing of lifestyle intervention is also a critical issue to be considered in future studies. It is still unclear whether lifestyle interventions implemented before pregnancy can be beneficial for this high-risk population. Previous studies evaluating GWG are based on changes in total body weight. There are no studies documenting the effect of lifestyle intervention on changes in body composition during pregnancy, such as fat percentage and fat-free mass index. Improving the compliance of the subjects

should be a key factor to consider for future studies. In order to improve the evaluation of compliance, some new techniques can also be used including analyzing meal size/component using photos uploaded by the subjects, tracking of physical activities, real-time record of heart rates, etc. Moreover, exercise under supervision may be more beneficial to prevent cognitive decline and improve exercise adherence.

Strength and Limitation

This is the first RCT focused on lifestyle intervention in overweight/obese women with PCOS during pregnancy. We used an instant messaging app (WeChat) as a new strategy to minimize dropouts and enhance the compliance of the subjects. A limitation is that the compliance in the intervention group was not as good as we expected. Another limitation of our study is that the intervention was not performed under supervision. We can only rely on the self-reports of the subjects to estimate their compliance to the intervention. Furthermore, there are no objective indicators to assess compliance. Lastly, our subjects were from a metropolitan area in Northern China and may not represent a diverse population.

Conclusion

In our study, lifestyle intervention including control diet and exercise for overweight/obese pregnant women with PCOS had no effect on GWG, glucolipid metabolism, and perinatal outcomes. However, women with good compliance could benefit from the lifestyle intervention in terms of GWG. In future studies, the effect of intervention characteristics including target population, intervention pattern, timing, duration, intensity, and other aspects of implementation should be considered. Com-

pliance is another important factor related to the effect of lifestyle intervention. New methods should be designed to improve subjects' compliance with the intervention protocol.

Statement of Ethics

The study complied with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. The trial protocol was approved by the Beijing Obstetrics and Gynecology Hospital, Capital Medical University Ethics Committee and was registered at ClinicalTrials.gov (NCT04216485). All study participants provided their written informed consent to participate in the study.

Conflict of Interest Statement

I certify that none of the authors have any actual or potential conflict of interest in this article.

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Author Contributions

Guanghui Li contributed to the study design and interpretation of the data. Cheng Liu contributed to the drafting and revision of the manuscript. Cheng Liu and Wei Zheng coordinated and executed the statistical analysis. Lirui Zhang and Xin Liang contributed to the collection of data. Li Zhang and Zhihong Tian contributed to the enrollment and follow-up in clinic. All authors reviewed and approved the final submitted version.

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