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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Effect of metformin and exenatide on pregnancy rate and pregnancy outcomes in overweight or obese infertility PCOS women: long-term follow-up of an RCT

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Abstract

Purpose The majority of Polycystic ovary syndrome (PCOS) are overweight or obese with increased infertility and high risk of pregnancy complications. We aim to compare efficacy of metformin and exenatide on spontaneous pregnancy rate, overall pregnancy rate after assisted reproductive technology treatment (ART) and pregnancy outcomes in overweight or obese infertility PCOS.

Methods In this long-term follow-up study, 160 overweight or obese infertility Chinese PCOS were randomized to exenatide or metformin treatment for 12 weeks. Afterward, all were treated with metformin alone until pregnancy confirmed and followed until delivery. If patients failed spontaneous pregnancy during the second 12 weeks, ART could be offered until end of 64 weeks. The primary outcome was spontaneous pregnancy rate.

Results At week 24, 29.2% of women in exenatide group conceived spontaneously while 14.7% in metformin group ($p=0.03$). At week 64, total pregnancy rates were 79.2% in exenatide group and 76% in metformin group without significant difference ($p=0.65$). Between two groups, there was no significant difference of pregnancy outcomes ($p>0.05$). A stepwise logistic regression showed that spontaneous pregnancy was positively associated with body weight reduction and HOMA-IR improvement in either group.

Conclusion In overweight or obese infertility Chinese PCOS, 12 weeks pregestational exenatide treatment resulted in more spontaneous pregnancy likely due to greater weight reduction and improvement of insulin resistance compared with metformin treatment without obvious benefit on overall pregnancy rate after ART or pregnancy outcomes of successful conceived women.

Trial registration This clinical trial was registered at Chinese Clinical Trials Registry (ChiCTR-IIR-16008084) on 13/3/2016.

Keywords Polycystic ovary syndrome · Obese or overweight · Exenatide · Metformin · Pregnancy rate · Pregnancy outcome

Abbreviations

AG	Abdominal girth
AMH	Anti-Mullerian hormone
ART	Assisted reproductive technology treatment
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
DM	Diabetes mellitus
EXE	Exenatide treatment
FPG	Fasting plasma glucose
Fins	Fasting insulin
HDL-c	High density lipopretein cholesterol
HPO	Hypothalamic-pituitary-ovarian
HOMA-β	Homeostasis model assessment of b-cell function
HOMA-IR	Homoeostasis model assessment of insulin resistance
2hPPG	2 Hours postprandial plasma glucose
2hIns	2 Hours postglucose load insulin
GLP-1RA	Glucagon-like peptide-1 receptor agonist
GDM	Gestational diabetes
GI	Gastrointestinal

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IVF-ET	In-vitro fertilization and embryo transfer
IADPSG	International Association of Diabetes and Pregnancy Study Groups
ITT	Intention-to-treat
LDL-c	Low density lipoprotein cholesterol
MET	Metformin treatment
OGTT	Oral glucose tolerant test
OCP	Oral contraceptive pill
PP	Per-protocol
PCOS	Polycystic ovary syndrome
T2DM	Type 2 diabetes mellitus
TG	Total triglyceride
TC	Total cholesterol
SAS	Statistics Analysis System
SD	Standard deviation
WHR	Waist-hip rate

What does this study add to the clinical work

Pregestational exenatide improved not only metabolism markers, but also spontaneous pregnancy rate resulted from greater weight reduction and amelioration of insulin resistance in comparison with metformin treatment without obvious benefit on overall pregnancy rate after ART or pregnancy outcomes of successful conceived women.

Introduction

Polycystic ovary syndrome (PCOS) is a complicated clinical syndrome characterized by not only chronic anovulation, hyperandrogenemia, insulin resistance, obesity, metabolic disorders, atherogenic dyslipidemia and hypertension, but also increased infertility, prevalence of pregnancy complications, including miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, and maternal or fetal long-term risk of type 2 diabetes mellitus (DM) [1]. According to Rotterdam criteria, the prevalence of PCOS in reproductive age were reported between 2.4 and 5.6% in China and up to 20% worldwide [2–4]. Moreover, PCOS is a most common cause of anovulatory infertility associated with an incremental risk of maternal pregnancy complications in reproductive-age women [5].

Metformin, as the most extensively employed insulin sensitizer acting by several mechanisms, such as inhibiting gluconeogenesis and lipogenesis, reducing hepatic glucose output, restoring peripheral insulin sensitivity, and augmenting insulin-mediated glucose uptake in skeletal muscle, had been used initially to target at insulin resistance which is an important clinical phenotype of PCOS, affecting a large majority of women with PCOS [6]. From 1994, series of study indicated beneficial effects of metformin on body weight, insulin resistance, ovulation and fertility [7–9]. In consequence, international evidence-based recommendations have proposed that in addition to lifestyle intervention, metformin could be applied for first-line treatment of weight, hormonal, and metabolic outcomes in adult women with PCOS [10].

Of note, researches have demonstrated the efficacy of metformin on insulin resistance resulting in improved reproductive function [11, 12], so that glucagon-like peptide-1 receptor agonist (GLP-1RA) which is also approved to play a constructive role in meliorating insulin sensitivity and reducing weight, might be a capable treatment for PCOS [13, 14]. Exenatide, the first drug of GLP-1RA, mimics a gut-derived incretin hormone to modulate glucose homeostasis by restraining hepatic gluconeogenesis and augmenting glucose uptake in the peripheral muscle tissues to alleviate hepatic and extrahepatic insulin resistance [15]. To date, there is seldom research reported about the therapeutic efficacy of GLP-1 RA therapy on pregnancy rate or pregnancy outcomes in PCOS and head-to-head comparative trial between GLP-1 RA and metformin. Therefore, the present study was a long-term follow-up of a former published study by Liu et al. 2017 [16], to further assess the overall effects of 12-week pregestational exenatide treatment on spontaneous pregnancy and total pregnancy after assisted reproductive technology treatment (ART), pregnancy outcomes and of overweight or obese infertility PCOS women compared with metformin treatment.

Materials and methods

Study population

Chinese PCOS patients were screened at our outpatient clinical in The Third Affiliated Hospital of Guangzhou Medical University. The inclusion criteria were as follows: PCOS diagnosed according to the revised Rotterdam criteria [17], body mass index (BMI) ≥ 24 kg/m^2, age 20–40, fertility demand, inability to get pregnant more than 2 years without contraception, no male infertility. The exclusion criteria were as follows: type 1 or type 2 diabetes mellitus, history of carcinoma or autoimmune disease, significant cardiovascular, pulmonary, kidney, or liver disease, other endocrinology diseases affecting reproductive function like: hyperprolactinemia, congenital adrenal hyperplasia (CAH), use of medications known or suspected to affect reproductive or metabolic functions or statins within 90 days before study entry, and no coexisting reproductive organ pathology. To rule out other causes of infertility, all women received

routine examination, including laboratory assays and ultrasound for uterus, fallopian tubes, and ovaries, as well as hysteroscopy and hysterosalpingography. Their partners also underwent a sperm test to rule out abnormality too. Additionally, the patient who did not accepted ART or took ART in other centers was ruled out in this prolonged follow-up study.

All patients provided written informed consent before entering the study, which was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of The Third Affiliated Hospital of Guangzhou Medical University. The clinical trial was registered at Chinese Clinical Trials Registry (ChiCTR-IIR-16008084).

Study design

This is a long-term follow-up of a RCT which conducted in a single center. Totally, 160 patients were eligible and randomly assigned in a 1: 1 ratio to metformin (MET) treatment arm or exenatide (EXE) treatment arm. A randomization list was generated using Statistics Analysis System (SAS) (SAS Institute Inc., Cary, NC, USA).

For the first stage of the protocol, exenatide (Amylin Pharmaceuticals, Inc., San Diego, CA, USA) was initiated with a dose of 5 μg twice daily and increased to 10 μg twice daily after 4 weeks. The patients who could not tolerate adverse events were instructed to reduce the dose to 5 μg twice daily. Metformin (Bristol-Myers Squibb Co., New York, NY, USA) was initiated with a dose of 500 mg twice daily and titrated by 500 mg every 3 days up to 1000 mg twice daily. Both medical treatments lasted 12 weeks in intervention groups. Lifestyle intervention was actively promoted in all the groups according to international guideline [18]. Meanwhile, cyproterone and ethinyl estradiol (Bayer Technology and Engineering Co., Ltd. Leverkusen, Germany), a low-dose hormonal contraceptive pill was given to all the groups for modulating menstruation. Patients were followed up every 4 weeks and instructed to use barrier contraception with urine pregnancy test at week 12. Intervention safety, compliance and tolerability were assessed at each visit.

In the second stage, patients of EXE group were switched to metformin with starting dose of 500 mg twice daily and titrating up to 1000 mg twice daily by 500 mg every 3 days, while patients of MET group were continued with metformin 1000 mg twice daily as long as continued lifestyle intervention in both groups. All the patients were instructed to have regular copulation two to three times weekly and urine pregnancy test done every 4 weeks during second 12 weeks. Ovulation assessment and ART was offered to the patients, who failed successful pregnancy at week 24, in gynecology and obstetrics department of The Third Affiliated Hospital of Guangzhou Medical University. The provided ART followed the protocol initiated with ovulation induction for 3 circles. Without successful pregnancy, the rest of patients were supplied with in-vitro fertilization and embryo transfer (IVF-ET) once. The second stage lasted until patient was pregnant by any mode of conception with a singleton viable fetus (determined by ultrasound) between gestational week 6 and week 9 plus 6 days within 52 weeks. The medication and follow-up were ceased when patients failed pregnancy by the end of week 64. Patients were followed up at 4-week intervals until identified pregnancy or week 64. Intervention safety, compliance and tolerability were assessed at each visit.

The confirmed pregnant patients within 52 weeks of the second stage were spontaneously proceeded into the third stage of the protocol. Patients of both groups were instructed to discontinue metformin after pregnancy occurred. All the patients were instructed to follow routine perinatal care in gynecology and obstetrics department of local hospital. Moreover, telephone follow-up visits were scheduled every 4 weeks until delivery. Delivery data for both mother and newborn were obtained from medical charts or telephone interviews at 8 weeks postpartum.

Measurements

All patients underwent demographic and anthropometric assessment at baseline and week 12. Biochemical parameters including fasting plasma glucose (FPG), 2 h postprandial plasma glucose (2hPPG), fasting insulin (Fins) and 2 h postglucose load insulin (2hIns) via a 75 g oral glucose tolerant test (OGTT) and lipids were recorded at baseline and week 12. The homoeostasis model assessment of insulin resistance (HOMA-IR) was utilized to evaluate insulin resistance, respectively [HOMA-IR = Fins *FPG/22.5] [19].

Pregnancy was dated by any mode of conception with a singleton viable fetus (determined by transvaginal ultrasound) between gestational week 6 and week 9 plus 6 days. Biochemical pregnancy, defined as a positive β-HCG test in either serum or urine without the development of a gestational sac [20]; twin pregnancy, defined as twin pregnancies per clinical intrauterine pregnancies and confirmed by the ultrasound observation; miscarriage, defined as a pregnancy loss before week 28 of gestation and preterm delivery, defined as a delivery between week 28 and week 36 plus 6 days of gestation were recorded among pregnant women. Gestational diabetes (GDM) (according to the International Association of Diabetes and Pregnancy Study Groups [IADPSG] criteria [21] via a 75 g OGTT performed between week 24 and 28 of gestation), gestational hypertension (hypertension developed during pregnancy without pre-exist hypertension) and gestational

weight gain were recorded. Neonatal birthweight and fetal macrosomia (neonatal birthweight ≥ 4000 g) were dated too.

Outcomes

The primary outcome was analyzed for difference of spontaneous pregnancy rate. Secondary outcomes were total pregnancy rate and pregnancy outcomes including incidence of miscarriage, preterm delivery, GDM, gestational hypertension and fetal macrosomia, gestational weight gain and neonatal birthweight. Tertiary outcomes were metabolic parameters after first stage treatment.

Statistical analysis

Overall, 80 patients per group were required for enrollment to provide 80% power at the 5% significance level to detect a at least 15% difference in spontaneous pregnancy rate [16] among two arms with estimated dropout rate was 20%. The intention-to-treat (ITT) analysis included all randomized participants, and per-protocol (PP) analysis included those took the allocated treatment. The results are presented as means ± standard deviation (SD) or percentages as appropriate. Normal data distribution was checked with the Shapiro–Wilk test. For the normally distributed data, paired samples *t*-test was utilized for comparison of before/after parameters and independent samples *t*-test was utilized for comparison between the two arms or Mann–Whitney *U*-test for skewed data. Categorical variables were expressed as proportion (percentage) and analyzed by Chi-square test or Fisher's exact tests as appropriate. In either MET or EXE group, a stepwise logistic regression was performed to assess pregestational treatment effects on spontaneous pregnancy with explanatory variables body weight change and HOMA-IR change. *P* value of 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics, version 19 (IBM Corp, Armonk, NY).

Results

Population characteristics

The overall population was different slightly to former published study [16], since a few of patients rejected ART or underwent ART in other centers. 190 Chinese PCOS patients were evaluated while 160 patients meeting inclusion criteria were eligible and randomly assigned to receive either metformin ($n = 80$) or exenatide ($n = 80$) for ITT analysis. After randomization, 147 patients who completed the first stage treatment were proceed to second stage treatment and included in PP analysis (Fig. 1). In MET group, 2 patients discontinued intervention for moderate gastrointestinal discomfort, and 3 patients were lost to follow-up in the first 12 weeks. In EXE group, 5 patients failed to complete the study (3 for moderate gastrointestinal discomfort and 2 for subcutaneous induration with rash at the injection site), and 3 patients were lost to follow-up in the first stage of treatment (Fig. 1). However, discontinuation rate was still similar in both groups (5 of 80 women [6.3%] vs. 8 of 80 women [10.0%], $\chi^2 = 0.754$, $p = 0.385$). Baseline characteristics of two arms in either ITT (Table 1) or PP analysis (Table 2) were similar in any of the anthropometric, metabolic parameters.

The enrollment was conducted from January 2017 to December 2017. The follow-up for the whole study was completed in November 2019.

Metabolic parameters changes

After 12 weeks treatment, the body weight, BMI, AG (abdominal girth), WHR (waist-hip rate), 2hPPG, Fins, 2hIns and HOMA-IR showed improvements in both arms ($p < 0.05$), whereas the between-group difference was statistically significant in relation to body weight, BMI, AG, WHR, 2hPPG, Fins, 2hIns and HOMA-IR at week 12 from baseline ($p < 0.05$) (Table 2).

Pregnancy rate

At week 24, 32 patients were capable to conceive spontaneously. The remaining 115 patients attended ART eventually (Fig. 1). At week 64, although 19 was reported as biochemical pregnancy, overall, 114 patients conceived and proceeded to third stage follow-up for PP analysis (Spontaneous pregnancy rate: 11 of 75 women [14.7%] vs. 21 of 72 women [29.2%], $p = 0.03$; Total pregnancy rate: 57 of 75 women [76.0%] vs. 57 of 72 women [79.2%], $p = 0.65$; Table 3). With comparison to previous study [16], the spontaneous pregnancy rate differs to a certain degree because of lost follow-up.

In a stepwise logistic regression model, with 75 patients in MET group, spontaneous pregnancy was positively related with body weight reduction (OR 0.727, $p = 0.011$) and HOMA-IR improvement (OR 0.208, $p = 0.009$). Likewise, spontaneous pregnancy was also positively correlated with body weight reduction (OR 0.812, $p = 0.006$) and HOMA-IR improvement (OR 0.245, $p = 0.008$) through a stepwise logistic regression in EXE group with 72 patients.

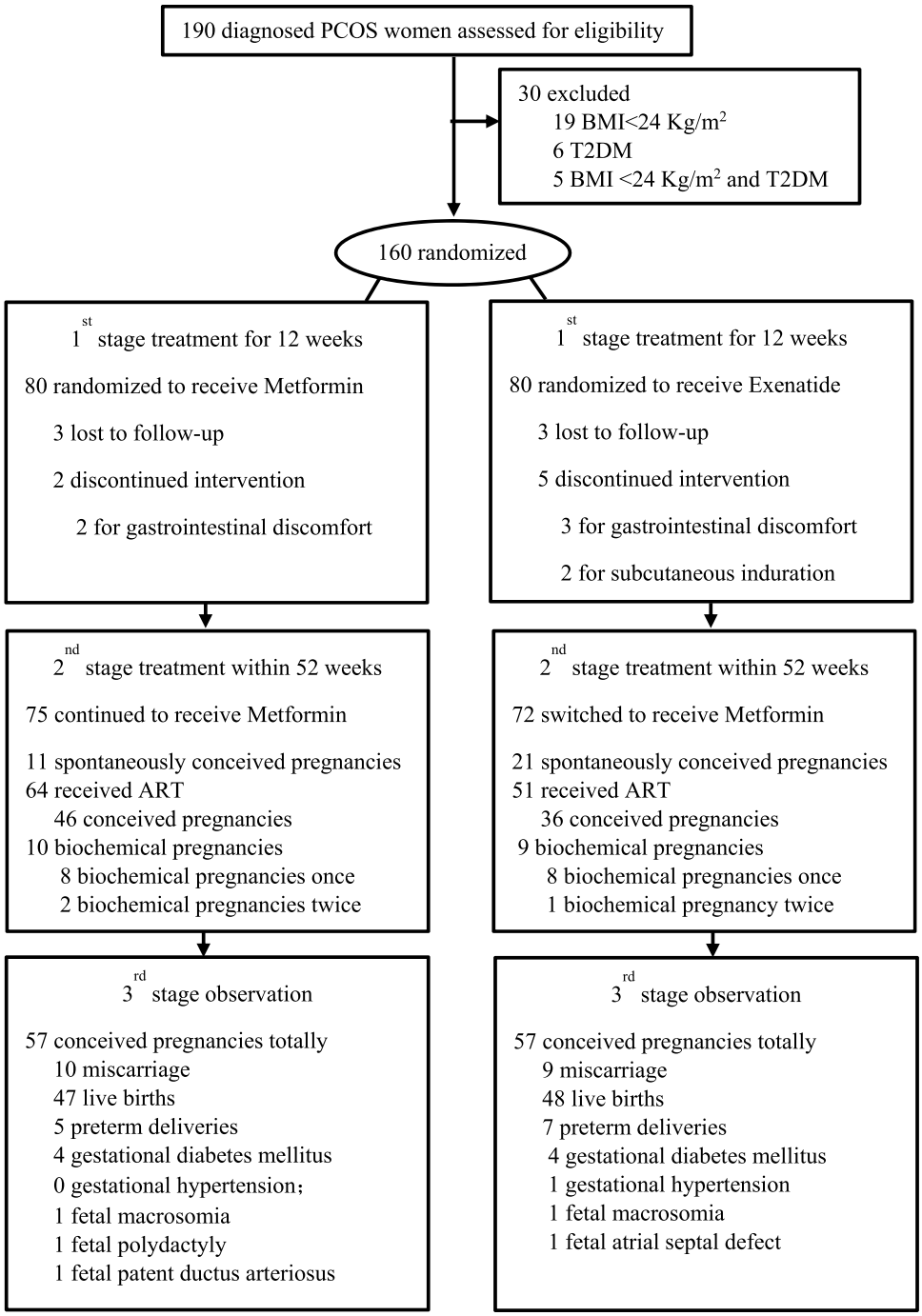

Fig. 1 Flow diagram of the randomized controlled trial

Pregnancy outcomes

For all of 114 pregnant women included in PP analysis, rate of miscarriage, live birth and preterm delivery and incidence of GDM and gestational hypertension were similar in two arms (Table 4). Meanwhile, there was no significant difference of maternal gestational weight gain or neonatal birth weight yet (gestational weight gain: 9.62 ± 1.90 kg vs. 9.81 ± 1.78 kg, $p = 0.72$; neonatal birth weight: 3.05 ± 0.33 kg vs. 3.02 ± 0.30 kg; $p = 0.90$).

Adverse events

The most frequent adverse events were mild or moderate gastrointestinal (GI) discomfort. GI discomfort appeared more frequently in EXE group compared with MET group. Adverse events associated with metformin treatment were

Table 1 Baseline characteristics of the intention-to-treat population ($n=160$)

Characteristics	MET ($n=80$)	EXE ($n=80$)	p values
Age (y)	27.83 ± 3.52	28.19 ± 3.96	0.679
Weight (kg)	72.37 ± 10.98	73.72 ± 11.43	0.716
BMI (kg/m^2)	29.15 ± 4.11	29.07 ± 3.92	0.891
AG (cm)	92.47 ± 8.61	93.79 ± 10.37	0.703
WHR	0.90 ± 0.05	0.91 ± 0.04	0.719
TG (mmol/L)	1.72 ± 0.76	1.66 ± 0.79	0.553
TC (mmol/L)	4.97 ± 1.22	4.86 ± 0.98	0.882
HDL-C (mmol/L)	1.32 ± 0.48	1.27 ± 0.77	0.638
LDL-C (mmol/L)	3.29 ± 1.76	3.24 ± 0.78	0.904
FBG (mmol/L)	5.02 ± 0.66	5.11 ± 0.73	0.787
2hPPG (mmol/L)	8.36 ± 2.45	8.56 ± 2.57	0.717
Fins (mU/L)	17.11 ± 8.16	18.27 ± 11.88	0.475
2hIns (mU/L)	150.08 ± 75.70	138.72 ± 78.54	0.311
HOMA-IR	3.85 ± 1.90	3.92 ± 2.14	0.668
HOMA-β	0.012 ± 0.007	0.011 ± 0.008	0.846

included nausea (7/80), diarrhea (4/80), bloating (4/80), vomiting (3/80), and stomachache (4/80), and constipation (4/80). Patients who were on exenatide treatment experienced nausea (13/80), bloating (4/80), vomiting (6/80), dizziness (2/80), and subcutaneous induration with rash at the injection site (2/80). No patients reported hypoglycemic events.

Discussion

This was the first prospective clinical trial designed with long-term follow-up to compare the efficacy of exenatide with metformin on pregnancy rate and pregnancy outcomes in obese or overweight infertility PCOS women. In contrast to metformin, 12 weeks pregestational exenatide treatment promoted spontaneous pregnancy and ameliorated metabolic biomarkers (normalization of weight, BMI, AG, WHR, 2hPPG, Fins, 2hIns and HOMA-IR), but did not improve total pregnancy rate after ART or pregnancy outcomes of women who successfully conceived.

As we known, metformin is utilized as first-line regimen in PCOS women with metabolic abnormalities in term of insulin resistance, an essential pathophysiology of PCOS [22]. Studies of metformin in both obese and lean PCOS women have documented significant improvement in fasting insulin and androgen levels, as well as a restoration of menstrual cyclicity [23, 24]. Then, more and more clinical trials of GLP-1 RA versus metformin have been performed and display significant advance of GLP-1 RA in weight reduction and insulin resistance improvement in PCOS women [25, 26]. Furthermore, impact of GLP-1 RA on reproductive system of PCOS women need intensive exploration in mechanism and clinical study since there is evidence that exenatide therapy improves histological degeneration and fibrosis of endometrium and ovary in diabetic rats [13, 27]. Thus, the present study was intentionally designed to compare the efficacy of 12 weeks pregestational exenatide with metformin on pregnancy rate and pregnancy outcomes in obese or overweight infertility PCOS women.

In line with previous studies, we have demonstrated positive and superior efficacies of exenatide on weight reduction over metformin for overweight or obese Chinese PCOS women [16, 28, 29]. As we known, obesity, a treatment target, accounting for 30–75% of PCOS, exacerbates phenotype, infertility, poor response to ovulation induction and adverse pregnancy outcomes of PCOS [30, 31]. Whereas GLP-1 RA appears to be an efficient therapy for body weight reduction on account of less food intake with inhibited appetite and increased sensation of satiety mainly via direct hypothalamic influence, delayed gastric emptying and bowel movement partly modulated by central action of autonomous system, and thermogenic browning of white adipose tissue through activation of adipose-resident invariant natural killer T (iNKT) cells [32]. In primary endpoint analysis of current study with result of stepwise logistic regression, short term exenatide treatment facilitated more spontaneous pregnancy, positively associated with substantial advantage in weight reduction compared to metformin treatment. Supportive results of effectiveness in reducing body weight, BMI, and waist circumference with combined therapy of metformin and exenatide have been elucidated in other study [33]. However, the underlining mechanism between weight reduction arising from exenatide usage and alteration of reproductive system need further exploration.

Beyond that, in accordance with other studies, 12 weeks exenatide of present study was more effective for overweight or obese Chinese PCOS women to meliorate insulin resistance in comparison with metformin. Further, a stepwise logistic regression also manifested that this greater influence on insulin resistance also contributed to higher spontaneous pregnancy rate, which was probably independent to weight reduction. Insulin resistance and consequent hyperinsulinemia, as primary feature affecting 65–70% of PCOS, causes augmentation of luteinizing hormone (LH) to stimulate excess androgen secretion in theca cell of ovary with negative effects on reproductive function [8, 34]. In rodent model of insulin resistance, there is not only insulin resistance in peripheral tissue, but also uterine insulin resistance associated with altered uterine morphology, cell phenotype and cell function of glandular epithelial cells via suppression of PI3K/Akt and MAPK/ERK signaling pathways [35]. Additionally, compared with metformin, exenatide or combined therapy of exenatide and metformin improves insulin

Table 2 Baseline characteristics and changes from baseline at week 12 after first stage treatment in the per-protocol population ($n=147$)

Characteristics	MET ($n=75$)	EXE ($n=72$)	p values (between groups)
Age (y)	28.22 ± 3.89	27.78 ± 3.81	0.502
Weight (kg)			
Baseline	72.36 ± 12.20	72.16 ± 13.67	0.871
Change from baseline	− 3.55 ± 2.13	− 5.21 ± 3.94	0.001
p values[a]	0.026	0.011	
BMI (kg/m^2)			
Baseline	28.77 ± 4.81	28.32 ± 4.76	0.920
Change from baseline	− 1.39 ± 0.89	− 2.16 ± 1.53	0.002
p values[a]	0.041	0.023	
AG (cm)			
Baseline	93.61 ± 11.67	92.13 ± 12.88	0.807
Change from baseline	− 3.87 ± 2.69	− 6.02 ± 3.51	< 0.001
p values[a]	0.045	0.016	
WHR			
Baseline	0.88 ± 0.07	0.89 ± 0.08	0.727
Change from baseline	− 0.03 ± 0.04	− 0.05 ± 0.05	0.008
p values[a]	0.039	0.015	
TG (mmol/L)			
Baseline	1.69 ± 0.84	1.72 ± 0.85	0.107
Change from baseline	− 0.08 ± 0.11	− 0.07 ± 0.12	0.189
p values[a]	0.182	0.165	
TC (mmol/L)			
Baseline	4.82 ± 0.81	4.90 ± 0.79	0.673
Change from baseline	0.22 ± 0.39	0.17 ± 0.38	0.520
p values[a]	0.153	0.179	
HDL-C (mmol/L)			
Baseline	1.27 ± 0.31	1.25 ± 0.38	0.564
Change from baseline	0.07 ± 0.12	0.04 ± 0.14	0.102
p values[a]	0.113	0.268	
LDL-C (mmol/L)			
Baseline	3.42 ± 1.11	3.45 ± 1.09	0.694
Change from baseline	0.09 ± 0.57	0.12 ± 0.53	0.198
p values[a]	0.117	0.131	
FPG (mmol/L)			
Baseline	4.90 ± 0.26	4.89 ± 0.31	0.656
Change from baseline	− 0.23 ± 0.15	− 0.21 ± 0.19	0.369
p values[a]	0.088	0.096	
2hPPG (mmol/L)			
Baseline	7.72 ± 1.39	7.83 ± 1.35	0.358
Change from baseline	− 0.97 ± 0.68	− 1.51 ± 0.65	< 0.001
p values[a]	< 0.001	< 0.001	
Fins (mU/L)			
Baseline	17.73 ± 7.08	18.65 ± 6.63	0.494
Change from baseline	− 4.02 ± 3.11	− 5.67 ± 3.17	< 0.001
p values[a]	< 0.001	< 0.001	
2hIns (mU/L)			
Baseline	143.98 ± 28.61	145.32 ± 25.17	0.428
Change from baseline	− 34.65 ± 12.82	− 53.98 ± 11.61	< 0.001
p values[a]	< 0.001	< 0.001	

Table 2 (continued)

Characteristics	MET ($n=75$)	EXE ($n=72$)	p values (between groups)
HOMA-IR			
Baseline	3.96 ± 1.88	4.22 ± 1.79	0.465
Change from baseline	− 0.95 ± 0.54	− 1.56 ± 0.78	< 0.001
p values[a]	0.007	0.003	

[a]$p < 0.05$, statistically significant differences within group (value after therapy versus baseline)

Table 3 Pregnancy rate of the participants

Primary outcome	No. (no/total no. (%))		χ^2	p value
	MET ($n=75$)	EXE ($n=72$)		
Total pregnancy	57 (76.0)	57 (79.2)	0.21	0.65
Spontaneous pregnancy	11 (14.7)	21 (29.2)	4.54	0.03
Twin pregnancy	7 (9.3)	6 (8.3)	0.09	0.77

Table 4 Pregnancy outcomes of the participants who successfully conceived

Pregnancy outcomes	No. (No/total No. (%))		χ^2	p value
	MET ($n=57$)	EXE ($n=57$)		
Miscarriage	10 (17.5)	9 (15.8)	0.06	0.80
Live birth	47 (82.5)	48 (84.2)	0.06	0.80
Preterm delivery	5 (8.8)	7 (12.3)	0.37	0.54
GDM	4 (7.0)	4 (7.0)	0.00	1.00
Gestational hypertension	0 (0.0)	1 (1.8)	0.00	1.00
Fetal macrosomia	1 (1.8)	1 (1.8)	0.00	1.00

secretion, achieving higher rate of remission of prediabetes among PCOS patients [36]. GLP-1 RA possibly induces peripheral insulin sensitivity through a series of mechanisms, such as adding insulin secretion and β cell function, increasing GLUT-4 expression and glucose translocation, amplifying insulin signal transduction, modulating lipid metabolism, reducing oxidative stress, relieving inflammatory responses, and decreasing endoplasmic reticulum stress [37]. Hence, in PCOS women, GLP-1 RA might be capable to promote reproductive function via multiple molecular mechanism correlated with modification of insulin resistance in peripheral tissue or even in reproductive system.

Moreover, GLP-1RA has direct effects on hypothalamic-pituitary-ovarian (HPO) axis. The study implicated that HPO axis disruption resulting from insulin resistance participates in ovulatory dysfunction of PCOS [38]. Hyperinsulinemia not only increases the amplitude and frequency of GnRH-stimulated LH pulses, leading to stimulation of androgen secretion and in turn to ovulatory dysfunction and amenorrhea, but also brings about follicular arrest by enhanced anti-Mullerian hormone (AMH) production [39]. On the other hand, GLP-1 receptor is expressed at three levels, hypothalamus, pituitary and ovary of HPO axis in adult female rats and GLP-1 RA exerts a regulatory influence on this gonadal axis in both adult and prepubertal female rats [37].Mechanism study proves that GLP-1 RA positively affects GnRH expression through directly regulation of Kisspeptin expression in hypothalamic cell lines and in neuronal cells of fetal rat brain [40]. Accordingly, for infertility overweight or obese PCOS women, present study addressed improved spontaneous pregnancy rate by utilize of exenatide and other study presents incremental pregnancy rate following IVF-ET by adding liraglutide on metformin treatment [13]. Although these clinical evidences might not confirm direct impact of GLP-1 RA on HPO axis, they have given a hint for further basic and clinical studies about GLP-1 RA, a possible innovative therapy for metabolism related infertility and reproductive system disease.

Otherwise, the study recorded pregnancy outcomes of successful conceived PCOS women after pregestational treatment. There were no significant differences between two arms. By contrast, both regimens along with lifestyle intervention were correlated with less pregnancy complications than results demonstrated in recent meta-analysis.34 In current study, only 7% of conceived PCOS women had GDM compared with average 20.26% of Chinese PCOS women who eventually developed GDM [41]. Similarly, gestational hypertension occurred in 0.9% of pregnant PCOS women in this study, while it has happened in around 13.94% of Chinese PCOS women.34 Furthermore, fetal macrosomia happened in 1.8% of neonates in our study, whereas about 9.84% of Chinese PCOS women delivered neonates with fetal macrosomia. It implied that pregestational treatment and lifestyle intervention during gestation together might reduce pregnancy complications for high-risk population like obese or overweight PCOS women. However, a randomized clinical trial is necessary to confirm this prevention effect of pregestational treatment and lifestyle intervention versus placebo in larger population.

Limitations of current study will be addressed too. It was conducted at a single center, although multicentric study is preferred. In addition, short term utilization of exenatide at first stage treatment in our study might lead to

insignificant results of total pregnancy rate and pregnancy outcomes. But prolonged exenatide treatment in the whole study was restricted as a result of limited safety date of GLP-1 RA in pregnancy [42]. Meanwhile, another randomized study implicated that pregnancy rate following IVF-ET in obese PCOS women is significant increased by preceding 12 weeks combined liraglutide and metformin therapy compared to solo metformin therapy [13]. The exact underling reasons of diverse results are unknown, might refer to different metabolic memory efficiency of varies GLP-1 RA or prolonged metformin therapy in the second stage treatment of our study. For the best interest of patients, especially concerned about strategies applied in real-world practice, we designed to continue metformin for all the patients after first 12 weeks during their trial of conception since metformin was considered as safe therapy in pregnant women [12, 43]. Nevertheless, this design might hinder long-term effect of exenatide on pregnancy rate or pregnant outcomes. Besides, some clinical evidences imply cyclical pretreatment of successive oral contraceptive pill (OCP) could benefit pregnancy outcome of PCOS patients, associated with reduction of hyperandrogenism and antral follicle excess [44, 45]. On behalf of the patients, both groups had been given combined OCP in the first stage of treatment. Although there is no solid data indicating adverse effects of OCP on glucose metabolism [46], it is necessary to profoundly explore any synergistic effect between OCP and GLP1-RA. Accordingly, we also need other study to demonstrate impact of GLP-RA on pregnancy rate and pregnancy outcomes.

Conclusion

The present study showed that 12 week pregestational exenatide treatment improved spontaneous pregnancy rate associated with significant weight reduction and improvement of insulin resistance in overweight or obese infertility Chinese PCOS, but did not alter overall pregnancy rate after following ART or pregnancy outcomes of successful conceived women, compared with metformin treatment. These novel results suggest that exenatide should be a better treatment for endocrine and metabolic dysfunction of overweight or obese Chinese PCOS women, and it should also be an alternative therapy rerecommended to them for fertility due to its superior benefit on spontaneous rate. Our observations do encourage further explorations, which are warranted to examine the long-term efficacy and safety of exenatide or this class of medication on reproductive outcomes in diverse overweight or obese populations for the purpose to elucidate the precise role of GLP-1 in female reproductive system.

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Author contributions SZ and TM contributed to the preliminary study design, data collection and statistical analysis. RL was involved in the integrity and interpretation of the data, and manuscript writing. And YZ is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for finial study design and quality control of clinical trial. All the authors approved the final version of the manuscript.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical approval All the procedures performed in this clinical trial were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. On January 8th, 2016, the study was approved by the Medical Ethics Committee of The Third Affiliated Hospital of Guangzhou Medical University (Approved ethic committee number: 002/2016). The study was registered at Chinese Clinical Trials Registry (ChiCTR-IIR-16008084) on 13/3/2016. The long-term follow-up procedures of this clinical trial was reapproved by the Medical Ethics Committee of The Third Affiliated Hospital of Guangzhou Medical University (Approved ethic committee number: 061/2018) on July 18th, 2018. The study was reregistered at Chinese Clinical Trials Registry (ChiCTR1900020516).

Informed consent Informed consent was obtained from all individual participants included in the study.

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