



Liraglutide as a Novel Strategy for Improving Metabolic and Hormonal Profiles in Obese Women with Polycystic Ovary Syndrome

Sara Medhat Georgy¹ · Nada Farag Elnaidany¹ · Nora A Abdelmoneum² · Sara Abdallah Mohamed Salem³ · Heba F. Salem⁴ · Rania M. Sarhan^{5,6}

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Abstract

Purpose This study aimed to investigate the effect of liraglutide and metformin as monotherapies on the hormonal, metabolic and clinical parameters of Poly Cystic Ovary Syndrome (PCOS). Participants were assigned to receive either Liraglutide (gradually titrated up to 3.0 mg/day as tolerated), Metformin (1000 mg/day), or standard lifestyle modification as a control group for 6 months.

Methods A randomized, parallel, clinical trial was conducted on 150 patients (50 per group) who completed the study, out of 183 initially randomized patients diagnosed with PCOS.

Results Out of 183 randomized patients, 150 completed the 24-week protocol (n = 50 per group). Most baseline characteristics were comparable across groups. Following 24 weeks of treatment, baseline-adjusted linear regression demonstrated that liraglutide induced significantly greater weight reduction compared to control (adjusted mean difference: -10.13 kg, FDR-adjusted p < 0.001). Furthermore, liraglutide yielded substantial improvements in insulin resistance, as evidenced by a significantly lower HOMA-IR compared to control (adjusted mean difference: -0.58, FDR-adjusted p < 0.001). Menstrual cycle regularity markedly improved in the liraglutide group (76.0%) compared to metformin (50.0%) and control (32.0%) (p < 0.001). Clinical pregnancy rates were 29.0% Control, 65.7% Liraglutide, 52.9% Metformin; overall between-group difference remained significant after FDR correction ($\chi^2=9.026$, FDR-adjusted p=0.044). Nausea, heartburn, and constipation were more frequent with liraglutide than metformin.

Conclusion Liraglutide is significantly more effective than metformin in improving body weight, glycemic control, and menstrual frequency in women with PCOS and metabolic dysfunction. These findings support liraglutide as a primary therapeutic approach, particularly in obesity-associated PCOS. It was registered at ClinicalTrials.gov under the identifier NCT05965908, registered on July 20, 2023.

Key Message

- PCOS is a common endocrine disorder often associated with obesity and insulin resistance.
- Liraglutide improves metabolic and hormonal profiles by promoting weight loss and enhancing insulin sensitivity.
- It represents a promising therapeutic option for managing obese women with PCOS, though further studies are needed.

Keywords Liraglutide · Metformin · Polycystic Ovary Syndrome (PCOS) · Obesity · Insulin Resistance · HOMA-IR · Hyperandrogenism · Testosterone · Menstrual Regularity · Ovulation

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrinopathy among women [1], with a frequency that varies from 8 to 13% [2], and its presentation is complex

and changes throughout the course of a person's life [3]. It is characterized by ovulatory failure, ovarian alterations, and elevated androgen levels resulting from augmented ovarian steroidogenesis attributed to mainly altered expression of critical enzymes (Cytochrome P450 enzymes: CYP17,

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CYP21, CYP19, CYP11A) in the steroid hormone biosynthesis pathway [4]. It is frequently linked to cardiovascular disease [5], obesity, hypertension, dyslipidemia, glucose irregularities, and pancreatic dysfunction, all of which significantly affect women's health [6]. Obesity is characterized as a chronic, complex, and relapsing condition marked by excessive adipose tissue and is a common occurrence among women with PCOS, with a prevalence rate ranging from 50% to 80%. Obesity intensifies the reproductive and metabolic complications linked to this condition [7]. First-line therapeutic strategies for PCOS typically emphasize lifestyle modifications, including dietary adjustments and increased physical activity. While these interventions remain foundational, the addition of pharmacological agents has been shown to further enhance clinical outcomes, particularly in addressing hyperandrogenic features, menstrual irregularities, and infertility [8]. Among pharmacological options, liraglutide has demonstrated superior effects on glycemic control and central adiposity when compared to lifestyle interventions alone [9].

Metformin, a widely used insulin sensitizer, primarily functions by improving peripheral insulin sensitivity and reducing hepatic gluconeogenesis. In contrast, liraglutide (LIRA), a glucagon-like peptide-1 receptor agonist (GLP-1RA), promotes satiety via central nervous system pathways [10], and has been associated with significant reductions in body weight and visceral adiposity in individuals with obesity and type 2 diabetes mellitus (T2DM). Additionally, liraglutide contributes positively to glucose metabolism [9].

Given these properties, it is hypothesized that GLP-1 receptor agonist therapy may improve ovarian function in overweight women with PCOS, potentially mediated by weight loss and improved metabolic profiles. Accordingly, this randomized clinical trial was conducted to examine the

effects of liraglutide on reproductive and metabolic parameters within this patient population as indexed in Fig. 1.

Patients and Method

Study Design

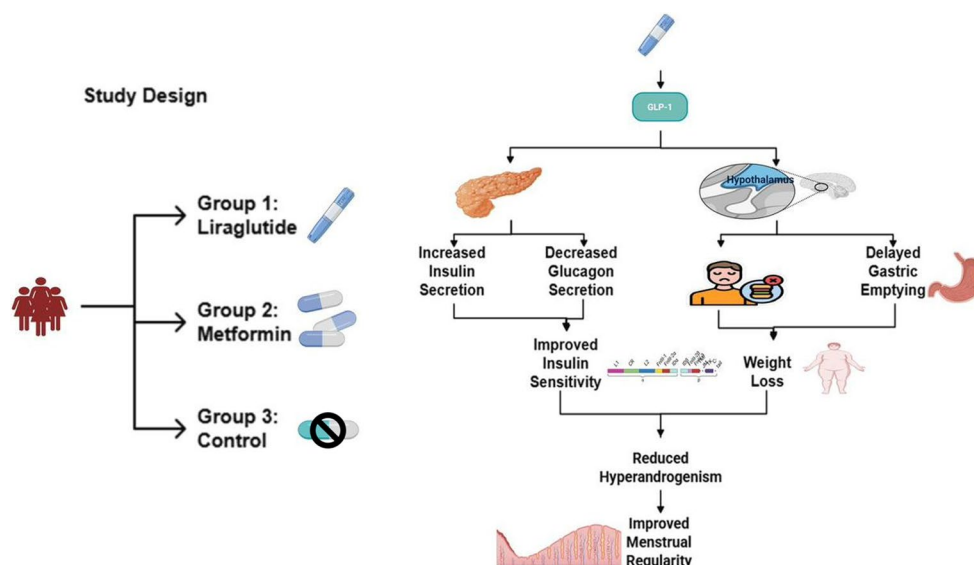
This prospective randomized clinical trial was conducted at Gynecology and obstetrics department in Beni Suef University Hospital, Beni suef, Egypt. The study employed a randomized controlled design to ensure rigorous methods and minimize bias. Eligible participants were randomly assigned to one of the three treatment groups (Control, Liraglutide, or Metformin).

This was a 6-month, randomized, active-controlled, parallel-group clinical trial. A total of 229 participants were assessed for eligibility. Of these, 46 were excluded: 20 did not meet the inclusion criteria and 26 declined to participate. The remaining 183 participants were randomized. 150 patients completed the 6-month follow-up. Detailed participant flow and dropout reasons were illustrated in the CONSORT flow diagram. Hormonal assessments included testosterone levels and insulin resistance (HOMA-IR). Clinical outcomes measured were included menstrual regularity, hirsutism and acne.

Study Population

The trial enrolled 150 women aged 18–45 years with Polycystic ovary syndrome based on the Rotterdam criteria. A computer-generated list randomly assigned patients to three groups using sequential numbers. Group A ($n=50$) treated with Liraglutide, Group B ($n=50$) treated with Metformin

Fig. 1 Graphical abstract



and Group C ($n=50$) was control group, for 6 months follow up. Participants had to show signs of metabolic syndrome and have a body mass index (BMI) of ≥ 25 kg/m².

Participants randomized to the Liraglutide group ($n=50$) received the drug via daily subcutaneous injection following the standard obesity management protocol. Treatment was initiated at a dose of 0.6 mg/day for the first week. To ensure optimal tolerability, the dose was titrated upward weekly by increments of 0.6 mg (i.e., 1.2 mg/day in week 2, 1.8 mg/day in week 3, 2.4 mg/day in week 4) until reaching the target therapeutic dose of 3.0 mg/day by the fifth week. This dose was maintained for the remainder of the 6-month study duration.

In cases of transient, moderate gastrointestinal adverse effects (such as persistent nausea or vomiting), a temporary dose reduction to the previously tolerated lower step (e.g., from 3.0 mg to 2.4 mg) was permitted for up to one week before re-attempting escalation. Participants who could not tolerate a minimum maintenance dose of 1.2 mg/day after dose reduction attempts were discontinued from the study. The mean tolerated dose of Liraglutide among the final analyzed cohort was 2.4 ± 0.6 mg/day.

Eligible participants were overweight or obese (body mass index [BMI] ≥ 25 kg/m², calculated as weight in kilograms divided by height in meters squared) adults (age ≥ 18 years) with a stable body weight (< 5 -kg change in the last 3 months).

Exclusion criteria included: (1) congenital adrenal hyperplasia, (2) poorly controlled thyroid disease (3) Taking antidiabetic drugs which can affect insulin resistance, (4) chronic kidney disease (5) liver dysfunction (AST or ALT (6) Documented use of oral hormonal contraceptives and hormone-releasing implants (7) intolerance or allergy to liraglutide or metformin.

Clinical Outcomes and Operational Definitions

Demographic and clinical data were collected from the patients at baseline including age, hirsutism, acne, free and total testosterone, Follicle Stimulating Hormone and Luteinizing Hormone level, body weight, BMI, waist circumference, lipid profile, glycated hemoglobin and fasting blood glucose. Laboratory tests such as total testosterone, FSH and LH level, lipid profile, glycated hemoglobin and fasting blood glucose, body weight, BMI and waist circumference were assessed during schedule visits of study participants. In addition, many adverse events including nausea and vomiting, heartburn diarrhea and constipation, hypotension and syncope were recorded among the patients in all groups. The designated primary outcome was the absolute change in the Homeostatic Model Assessment for Insulin

Resistance (HOMA-IR) from baseline to the end of the 6-month treatment period. This key metabolic metric served as the basis for the study's sample size and statistical power calculations, whereas all other measured clinical parameters were evaluated as exploratory secondary outcomes. These included:

1-Anthropometric Profiles: Changes in Body Weight (kg), Body Mass Index (BMI, kg/m²), and Waist Circumference (cm).

2-Hormonal and Glycemic Profiles: Changes in serum total testosterone (ng/dL), fasting plasma glucose (FPG), fasting serum insulin, and lipid panel parameters.

3-Reproductive Outcomes: menstrual cycle regularity, and clinical pregnancy rates to ensure clarity and precision in interpreting our clinical outcomes, it is essential to establish baseline familiarity with the specific operational definitions utilized throughout this study. To robustly evaluate the therapeutic effects, we characterized our reproductive endpoints as follows:

Menstrual Cycle Patterns We characterized menstrual regularity based on the standardized FIGO classification systems. A participant was classified as having regular menses if her cycle length consistently remained within a 24-to-38-day window, with a cycle-to-cycle variation of no more than 7 to 9 days throughout the 6-month study. On the other hand, we defined menstrual irregularity as either oligomenorrhea (cycles lasting longer than 35 days or totaling fewer than 9 cycles per year) or polymenorrhea (cycles occurring at intervals of less than 21 days) [11, 12].

Infertility and Pregnancy Tracking In this study, infertility was operationally defined as the inability of a couple to conceive after 12 months or more of regular, unprotected intercourse while actively intending to do so. We confirmed clinical pregnancy first through a positive serum β -hCG test (> 25 mIU/mL) following a missed period, which was then clinically verified by the visualization of at least one gestational sac with an active fetal heartbeat on transvaginal ultrasound during the 6th to 8th week of gestation [13]. During the 6-month follow-up period, all patients received weekly follow-up by the clinical nutrition specialist, incorporating periodic evaluation of treatment response and clinical outcomes.

Sample Size Calculation

An a priori sample size calculation was performed using G*Power software (version 3.1.9.7) for an F-test (ANOVA: Fixed effects, omnibus, one-way). Based on an expected medium-to-large effect size (Cohen's $f=0.28$) for the

primary outcome, an alpha level of 0.05, and a statistical power of 85%, the minimum required sample size was 135 participants (45 per group). To account for an anticipated 10% dropout and discontinuation rate over the 6-month period, the target enrollment was expanded to 183 randomized participants to ensure a final evaluable sample of 150 participants (50 per group) [14].

Ethics Statement

Prior to enrollment, all participants were requested to complete an informed consent form. The Research Ethical Committee of Beni-Suef University, Faculty of Medicine, validated this study (FMBSUREC/07072024/ Fekry). Approval No In accordance with of the Helsinki Declaration. It was registered at ClinicalTrials.gov under the identifier NCT05965908, registered on July 20, 2023.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics v27.0. Continuous variables were assessed for normality using Kolmogorov Smirnov and Shapiro Wilk tests and expressed as mean $\pm$ SD, whereas categorical variables were presented as frequencies and percentages.

Between group differences for continuous variables were evaluated at baseline and post-treatment using one-way ANOVA. Longitudinal within group changes (before vs. after treatment) were assessed using repeated-measures time-effect ANOVA computed within each treatment cohort. To account for baseline imbalances, baseline-adjusted linear regression models were constructed for post-treatment continuous outcomes, regressing each post-treatment parameter on treatment group and its baseline value to yield adjusted mean differences. To control for type I error inflation across the continuous outcomes, P values were adjusted using the Benjamini–Hochberg False Discovery Rate (FDR) procedure. Treatment effect sizes were quantified using eta-squared (η^2) for between-group variance and paired Cohen's d_z for within-group changes, with 95% confidence intervals (CIs).

Categorical and fertility outcomes were analyzed using Pearson's chi-squared test, or the Fisher–Freeman–Halton exact test for sparse event frequencies (miscarriage). Association strengths were quantified using Cramer's V with 95% CIs. Within-group categorical transitions were evaluated using McNemar analysis, with clinical impact expressed as Risk Difference (RD) and 95% CIs. To evaluate treatment effects on binary outcomes while controlling for baseline status, baseline-adjusted binary logistic regression models were applied. Between-group categorical P-values were adjusted via the Benjamini–Hochberg FDR procedure.

Results

Patient's Demographics

A total of 229 women were assessed for eligibility. Of these, 46 were excluded: 20 did not meet the inclusion criteria and 26 declined to participate. The remaining 183 participants were randomized to three groups. After attrition and treatment discontinuation, 150 participants completed the 6 months follow-up with 50 participants analyzed in each study arm (Fig. 2).

Patients' Clinical Features and Baseline Characters

At baseline, most measured parameters were comparable across the control, Liraglutide, and Metformin groups (Tables 1 and 2). Age, weight, body mass index (BMI), parity, waist circumference, menstrual cycle irregularity, infertility duration, FSH, LH, fasting blood glucose, and HOMA-IR did not differ significantly ($P > 0.05$). However HbA1c showed a nominal raw between-group difference (ANOVA $P = 0.023$). Likewise, baseline evaluation of clinical hyperandrogenism markers (acne and hirsutism prevalence), circulating androgen profiles (free and total testosterone), and lipid panels revealed no significant between-group variations ($P > 0.05$; Table 2), confirming well-balanced group allocation prior to intervention.

Within-Group Comparisons of Outcomes of Anthropometric, Hormonal and Glycemic Parameters and Lipid Profile in Each Studied Group

Anthropometric Parameters

Table 3 indicated the baseline and post-treatment anthropometric parameters across the three study arms. At baseline, no statistically significant between-group differences were observed for weight ($F=0.505$, FDR-adjusted $P=0.756$), BMI ($F=2.473$, FDR-adjusted $P=0.328$), or waist circumference ($F=2.796$, FDR-adjusted $P=0.328$). Following the intervention, between-group differences in body weight (94.92 ± 15.32 kg for Control, 87.73 ± 15.21 kg for liraglutide, and 94.10 ± 14.53 kg for Metformin) were not statistically significant after multiple-testing correction ($F=3.430$, FDR-adjusted $P=0.105$, $\eta^2 = 0.045$, 95%CI : 0.005 to 0.137). Post-treatment BMI values were similarly comparable among groups ($F=0.259$, FDR-adjusted $P=0.772$). Conversely, post-treatment waist circumference demonstrated a statistically significant variation between groups ($F=7.034$, FDR-adjusted $P=0.005$, $\eta^2 = 0.087$, 95%CI: 0.019 to 0.213), with the liraglutide arm reaching the lowest mean value (97.46 ± 10.63 cm) compared with the

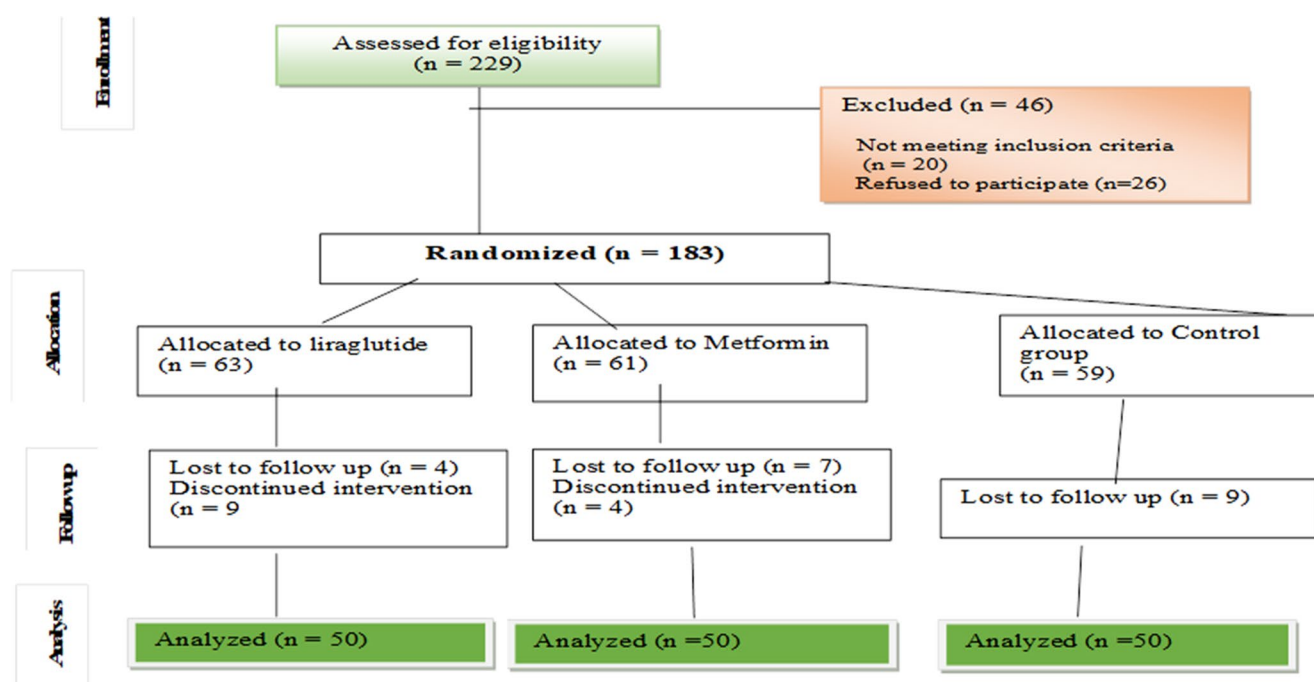


Fig. 2 A CONSORT Diagram showing the flow of the participants through each stage of the randomized clinical trial to test the role of liraglutide in PCOS patients

Control (103.50 ± 8.96) and Metformin (103.02 ± 6.86 cm) arms. Longitudinal within-group analyses revealed that all three groups experienced statistically significant reductions over time in body weight, BMI, and waist circumference ($P < 0.05$ across all groups). The largest standardized within-group reductions for body weight ($F = 442.416$, Cohen's $d_z = -2.975$, 95%CI to -4.044 to -2.367) and waist circumference ($F = 286.433$, Cohen's $d_z = -2.393$, 95% CI -2.908 to -2.090) were observed in the Liraglutide arm. Meanwhile, the most pronounced standardized within-group change for BMI was reported in the Metformin arm ($F = 84.911$, Cohen's $d_z = -1.303$, 95% CI: -1.733 to -1.030).

Hormonal Parameters

Baseline hormonal levels, including FSH, LH, total testosterone, free testosterone, and DHEA, were statistically comparable across all three study arms ($P > 0.05$) as shown in Table 4. Following the treatment period, a statistically significant between-group difference emerged solely for free testosterone levels ($F = 8.734$, FDR-adjusted $P = 0.001$), accounting for a meaningful proportion of variance explained by group allocation ($\eta^2 = 0.106$, 95% CI: 0.033 to 0.227); post-treatment free testosterone was lowest in the Liraglutide group (0.96 ± 0.33 pg/mL) and Metformin group (1.07 ± 0.39 pg/mL) compared with the Control group (1.39 ± 0.77 pg/mL). No significant between-group differences were found post-treatment for FSH ($P = 0.670$), LH ($P = 0.152$), total testosterone ($P = 0.635$), or DHEA ($F =$

1.086 , FDR-adjusted $P = 0.464$). Within-group evaluations indicated that FSH remained statistically unchanged in all arms ($P > 0.05$). DHEA decreased in all three groups, but none of the within-group changes were statistically significant: Control ($F = 1.497$, $P = 0.227$, Cohen's $d_z = -0.173$), Liraglutide ($F = 1.889$, $P = 0.176$, Cohen's $d_z = -0.194$), and Metformin ($F = 0.296$, $P = 0.589$, Cohen's $d_z = -0.077$). However, both the Liraglutide and Metformin groups displayed statistically significant longitudinal decreases in LH levels ($F = 28.419$, $P < 0.001$, Cohen's $d_z = -0.754$ and $F = 28.675$, $P < 0.001$, Cohen's $d_z = -0.757$, respectively), whereas the Control group showed no change ($P = 0.874$). Furthermore, total testosterone levels significantly decreased within all three groups over time, with the strongest effect observed in the Liraglutide cohort ($F = 23.714$, $P < 0.001$, Cohen's $d_z = -0.689$) followed by Metformin ($P = 0.017$) and Control ($P = 0.035$). Free testosterone levels also declined significantly within the Liraglutide ($F = 5.741$, $P = 0.020$, Cohen's $d_z = -0.339$) and Metformin arms ($F = 8.427$, $P = 0.006$, Cohen's $d_z = -0.411$), while remaining stable in the Control arm ($P = 0.736$).

Glycemic Parameters

Table 5 indicated that there were no statistically significant differences among the three groups at baseline regarding glycemic markers, including HbA1c ($P = 0.328$), fasting glucose ($P = 0.363$), and the HOMA-IR index ($P = 0.363$). Post treatment between-group analysis revealed a statistically

Table 1 Basic characteristics of the studied groups

Basic characteristics	Control (n=50)		Liraglutide(n=50)		Metformin(n=50)		Test of sig.	P
	No.	%	No.	%	No.	%		
Age (years)								
Mean ± SD.	27.36 ± 4.43		29.60 ± 6.82		29.14 ± 5.00		F=2.305	0.103
Median (Min. – Max.)	27.50 (20.0 – 36.0)		29.50 (18.0 – 44.0)		28.0 (18.0 – 40.0)			
Parity								
No	17	34.0	24	48.0	21	42.0	c ² =10.466	FE p=0.183
Once	21	42.0	9	18.0	12	24.0		
Twice	11	22.0	13	26.0	11	22.0		
Three times	1	2.0	3	6.0	5	10.0		
Four times	0	0.0	1	2.0	1	2.0		
FSH								
Mean ± SD.	6.44 ± 1.46		6.51 ± 1.76		6.38 ± 1.62		F=0.088	0.915
Median (Min. – Max.)	6.30 (4.10 – 8.60)		6.30 (3.60 – 10.80)		6.05 (3.40 – 10.40)			
LH								
Mean ± SD.	8.39 ± 2.39		9.45 ± 2.98		8.70 ± 2.69		H=4.215	0.122
Median (IQR)	8.0 (7.0 – 9.0)		9.0 (7.60 – 11.0)		8.0 (6.30 – 10.0)			
Menstrual Cycle								
Irregular	34	68.0	37	74.0	40	80.0	c ² =1.871	0.392
Regular	16	32.0	13	26.0	10	20.0		
Infertility								
No	19	38.0	15	30.0	16	32.0	c ² =0.780	0.677
Yes	31	62.0	35	70.0	34	68.0		
-Duration of infertility	(n=31)		(n=35)		(n=34)			
Mean ± SD.	2.34 ± 1.66		2.83 ± 2.10		2.65 ± 2.25		H=1.573	0.456
Median (IQR)	2.0 (1.0 – 3.0)		2.0 (2.0 – 3.0)		2.0 (1.0 – 3.0)			
Weight (kg)								
Mean ± SD.	97.05 ± 15.99		100.31 ± 16.98		98.84 ± 15.79		F=0.505	0.605
Median (Min. – Max.)	91.75 (71.0 – 135.0)		101.0 (71.0 – 135.0)		97.0 (71.0 – 135.0)			
BMI (kg/m ²)								
Mean ± SD.	36.69 ± 5.59		38.92 ± 5.13		37.12 ± 5.24		F=2.473	0.088
Median (Min. – Max.)	34.7 (27.70 – 48.10)		37.8 (31.0 – 53.10)		36.5 (26.10 – 48.80)			
Waist circumference (cm)								
Mean ± SD.	105.78 ± 8.04		109.54 ± 9.89		108.46 ± 6.21		F=2.796	0.064
Median (Min. – Max.)	107.0 (92.0 – 118.0)		109.8(93.0 – 140.0)		109.0 (90.0 – 120.0)			
HOMA IR								
Mean ± SD.	2.41 ± 0.66		2.40 ± 0.59		2.22 ± 0.58		F=1.539	0.218
Median (Min. – Max.)	2.30 (1.0 – 4.60)		2.40 (1.0 – 3.60)		2.25 (1.0 – 3.50)			
FBG mg								
Mean ± SD.	81.48 ± 10.35		83.12 ± 9.15		79.72 ± 9.06		F=1.590	0.207
Median (Min. – Max.)	80.0 (64.0 – 104.0)		82.0 (65.0 – 104.0)		80.0 (63.0 – 109.0)			
HbA1c (%)								
Mean ± SD.	5.39 ± 0.64		5.13 ± 0.52		5.10 ± 0.57		F=3.865	0.023
Median (Min. – Max.)	5.70 (4.0 – 6.20)		5.15 (4.0 – 6.10)		5.20 (4.0 – 6.0)			

IQR Inter quartile range,

SD Standard deviation,

 χ^2 Chi square test,

FET Fisher Exact test,

F F for One way ANOVA test,

H H for Kruskal Wallis test,

p p value for comparison between the three studied groups

* Statistically significant at $p \leq 0.05$

significant difference exclusively for the HOMA-IR index ($F=17.971$, FDR-adjusted $P<0.001$), demonstrating a strong between-group effect size ($\eta^2=0.196$, 95% CI: 0.100 to 0.332); the lowest post-treatment HOMA-IR values were achieved in the Liraglutide group (1.74 ± 0.53), followed by the Metformin group (2.05 ± 0.40), relative to the Control

(2.32 ± 0.52). Post treatment HbA1c ($P=0.152$) and fasting glucose ($P=0.110$) did not significantly differ among the groups. Intragroup temporal analysis demonstrated that both the Control and Liraglutide groups experienced significant within-group reductions in HbA1c ($F=15.832$, $P<0.001$ and $F=17.924$, $P<0.001$, respectively), while the

Table 2 Baseline clinical, hormonal, and lipid parameters of the studied groups

Basic characteristics	Control (n=50)		Liraglutide(n=50)		Metformin(n=50)		Test of sig.	P
	No.	%	No.	%	No.	%		
Hirsutism								
No	23	46.0	20	40.0	28	56.0	$\chi^2=2.621$	0.270
Yes	27	54.0	30	60.0	22	44.0		
Acne								
No	28	56.0	23	46.0	31	62.0	$\chi^2=2.636$	0.268
Yes	22	44.0	27	54.0	19	38.0		
Total testosterone (Ng/dl)								
Mean $\pm$ SD.	37.33 $\pm$ 24.37		40.59 $\pm$ 24.21		34.77 $\pm$ 24.18		H=2.951	0.229
Median (IQR)	25.0 (21.0 – 55.0)		29.5(20.30 – 65.0)		22.55 (18.2– 45)			
Free testosterone(Pg/ml)								
Mean $\pm$ SD.	1.37 $\pm$ 0.75		1.08 $\pm$ 0.47		1.25 $\pm$ 0.66		H=2.049	0.359
Median (IQR)	1.03 (0.80 – 1.70)		0.90 (0.80 – 1.20)		0.90 (0.80 – 1.60)			
DHEA (mcg/dl)								
Mean $\pm$ SD.	224.18 $\pm$ 46.79		226.10 $\pm$ 41.72		230.50 $\pm$ 40.38		F=0.283	0.754
Median (Min. – Max.)	227.5(122 – 356)		221 (152– 325)		225 (150 – 332)			
Cholesterol (mg/dL)								
Mean $\pm$ SD.	194.22 $\pm$ 33.30		203.02 $\pm$ 23.08		192.78 $\pm$ 27.96		F=1.902	0.153
Median (Min. – Max.)	200(145.0 – 258.0)		205(145.0 – 251.0)		190(145.0 – 258.0)			
TG (mg/dl)								
Mean $\pm$ SD.	124.98 $\pm$ 23.37		126.92 $\pm$ 21.55		130.80 $\pm$ 25.31		F=0.798	0.452
Median (Min. – Max.)	123.5(75 – 175)		123 (75 – 175)		123.5(86 – 196)			
LDL (mg/dL)								
Mean $\pm$ SD.	76.28 $\pm$ 10.83		73.46 $\pm$ 12.30		71.32 $\pm$ 14.54		F=1.934	0.148
Median (Min. – Max.)	77.0 (50.0 – 96.0)		75.0 (46.0 – 96.0)		73.50 (45.0 – 96.0)			
HDL (mg/dL)								
Mean $\pm$ SD.	57.40 $\pm$ 6.80		56.64 $\pm$ 6.72		56.94 $\pm$ 6.43		F=0.166	0.848
Median (Min. – Max.)	58.50 (44.0 – 79.0)		56.0 (44.0 – 79.0)		55.50 (44.0 – 79.0)			

IQR Inter quartile range,

SD Standard deviation,

 χ^2 Chi square test,

FET Fisher Exact test,

F F for One way ANOVA test,

H H for Kruskal Wallis test,

p p value for comparison between the three studied groups

* Statistically significant at $p \leq 0.05$

Metformin group did not ($P=0.637$). Fasting glucose levels declined significantly over time only within the Liraglutide group ($F=13.260$, $P<0.001$, Cohen's $d_z = -0.515$), remaining statistically unchanged in the Control ($P=0.977$) and Metformin arms ($P=0.334$). For the HOMA-IR index, the Liraglutide group demonstrated a profound within group reduction ($F=67.282$, $P<0.001$, Cohen's $d_z = -1.160$), and the Metformin group also achieved a significant longitudinal reduction ($F=10.657$, $P=0.002$, Cohen's $d_z = -0.462$); no significant within-group change was observed in the Control group ($P=0.219$).

Lipid Profile

Baseline concentrations of total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol displayed no statistically significant differences across the treatment groups ($P>0.05$) as shown in Table 6. Post-treatment between-group analysis showed a statistically significant difference among the groups only for total cholesterol ($F=9.942$, FDR-adjusted

$P<0.001$), showing a solid group effect size ($\eta^2=0.119$, 95% CI: 0.046 to 0.235); post treatment total cholesterol was lowest in the Liraglutide cohort (179.54 ± 15.62 mg/dL) and Metformin cohort (185.98 ± 17.47 mg/dL) compared to the Control group (195.52 ± 20.64 mg/dL). Post treatment triglycerides ($P=0.221$), LDL cholesterol ($P=0.152$), and HDL cholesterol ($P=0.624$) did not vary significantly among groups. Within-group analysis over time revealed that total cholesterol decreased significantly within the Liraglutide arm ($F=91.447$, $P<0.001$, Cohen's $d_z = -1.352$) and the Metformin arm ($F=5.142$, $P=0.028$, Cohen's $d_z = -0.321$), while remaining unchanged in the Control arm ($P=0.704$). Longitudinal within-group changes for triglycerides, LDL cholesterol, and HDL cholesterol failed to reach statistical significance across all three evaluated cohorts ($P>0.05$).

Clinical Outcomes

In Table 7, baseline between-group differences were not statistically significant for menstrual cycle irregularity

Table 3 Comparison of anthropometric parameters before and after treatment in each group

Variable	Control (<i>n</i> = 50)	Liraglutide (<i>n</i> = 50)	Metformin (<i>n</i> = 50)	ANOVA test	FDR-adjusted <i>P</i>	Between-group effect size eta-squared (95% CI)
	Mean ± SD	Mean ± SD	Mean ± SD	F statistic	Benjamini–Hochberg	
Weight (kg) – Before	97.05 ± 15.99	100.31 ± 16.98	98.84 ± 15.79	F = 0.505	0.756	0.007 (0.000 to 0.074)
Weight (kg) – After	94.92 ± 15.32	87.73 ± 15.21	94.10 ± 14.53	F = 3.430	0.105	0.045 (0.005 to 0.137)
ANOVA F Statistic + Cohen dz (within group)	23.143 dz = -0.680 (-1.080 to -0.390)	442.416 dz = -2.975 (-4.044 to -2.367)	87.258 dz = -1.321 (-1.737 to -1.049)			
ANOVA P value (within group)	< 0.001*	< 0.001*	< 0.001*			
BMI (kg/m ²) – Before	36.69 ± 5.59	38.92 ± 5.13	37.12 ± 5.24	F = 2.473	0.328	0.033 (0.003 to 0.122)
BMI (kg/m ²) – After	36.12 ± 5.44	35.20 ± 9.33	35.37 ± 4.85	F = 0.259	0.772	0.004 (0.001 to 0.086)
ANOVA F Statistic + Cohen dz (within group)	4.811 dz = -0.310 (-0.961 to -0.020)	9.109 dz = -0.427 (-3.817 to -0.077)	84.911 dz = -1.303 (-1.733 to -1.030)			
ANOVA P value (within group)	0.033*	0.004*	< 0.001*			
Waist circumference (cm) – Before	105.78 ± 8.04	109.54 ± 9.89	108.46 ± 6.21	F = 2.796	0.328	0.037 (0.005 to 0.118)
Waist circumference (cm) – After	103.50 ± 8.96	97.46 ± 10.63	103.02 ± 6.86	F = 7.034	0.005*	0.087 (0.019 to 0.213)
ANOVA F Statistic + Cohen dz (within group)	31.994 dz = -0.800 (-1.412 to -0.440)	286.433 dz = -2.393 (-2.908 to -2.090)	123.240 dz = -1.570 (-2.034 to -1.285)			
ANOVA P value (within group)	< 0.001*	< 0.001*	< 0.001*			

Values are mean ± SD. Between-group analysis: Before and after rows use one-way ANOVA among Control, Liraglutide, and Metformin; and FDR-adjusted *P* uses the Benjamini–Hochberg procedure across the comparable outcomes at each time point. Within-group analysis: the *F* statistic and *P* value were shown on separate rows for each group and represent the repeated-measures time effect with two measurements.

**P* < 0.05; significant *P* values are bold. Effect sizes: eta-squared quantifies the proportion of total variance explained by group; paired Cohen *dz* quantifies standardized within-group change. Bootstrap percentile 95% CIs use 1,200 resamples

(FDR-adjusted *P* = 0.448), hirsutism (*P* = 0.432), or acne (*P* = 0.432). Following intervention, menstrual cycle outcomes differed significantly between groups ($\chi^2 = 19.629$, FDR-adjusted *P* < 0.001, Cramer's *V* = 0.362), driven by higher proportions of regular cycles in the Liraglutide group (76.0%) and Metformin group (50.0%) than in the Control group (32.0%). Post-treatment between-group differences were not significant for hirsutism (*P* = 0.448) or acne (*P* = 0.432). Pregnancy and miscarriage were evaluated after treatment. Positive post-treatment pregnancy occurred in 9 of 31 Control participants (29.0%), 23 of 35 Liraglutide participants (65.7%), and 18 of 34 Metformin participants (52.9%). The unadjusted Pearson chi-square test was significant ($\chi^2 = 9.026$, *P* = 0.011), and the difference remained significant after FDR correction (*P* = 0.044; Cramer's *V* = 0.300, 95% CI: 0.142 to 0.488). Post-treatment miscarriage was uncommon among participants with recorded miscarriage status (Control 0/8, Liraglutide 1/14, Metformin 0/12) and did not differ between groups (Fisher-Freeman-Halton exact *P* = 1.000; Cramer's *V* = 0.206, 95% CI: 0.000 to

0.368). Within-group longitudinal analyses remained limited to menstrual cycle, hirsutism, and acne: menstrual irregularity decreased significantly in the Liraglutide and Metformin groups, hirsutism decreased significantly only in the Liraglutide group, and acne did not change significantly in any group.

Baseline Adjusted Regression Analysis

Anthropometric Outcomes

Baseline-adjusted linear regression analyses revealed significant improvements in post-treatment anthropometric indices across the intervention arms relative to the control group. For body weight, both active treatment groups demonstrated statistically significant reductions compared to control (*n* = 50). The regression-adjusted mean difference for the liraglutide arm versus control was -10.13 kg (SE = 0.67, 95% CI -11.44 to -8.81, FDR-adjusted *p* < 0.001), whereas the metformin arm yielded an adjusted mean difference

Table 4 Comparison of hormonal parameters before and after treatment in each group

Variable	Control (n=50)	Liraglutide (n=50)	Metformin (n=50)	ANOVA test	FDR-adjusted P	Between-group effect size eta-squared (95% CI)
	Mean ± SD	Mean ± SD	Mean ± SD	F statistic	Benjamini–Hochberg	
FSH – Before	6.44 ± 1.46	6.51 ± 1.76	6.38 ± 1.62	F=0.088	0.915	0.001 (0.000 to 0.052)
FSH – After	6.31 ± 1.02	6.53 ± 1.45	6.34 ± 1.23	F=0.472	0.670	0.006 (0.001 to 0.070)
ANOVA F Statistic + Cohen dz (within group)	0.680dz=-0.117 (-0.407 to 0.166)	0.013dz=0.016 (-0.283 to 0.304)	0.062dz=-0.035 (-0.298 to 0.240)			
ANOVA P value (within group)	0.414	0.911	0.805			
LH – Before	8.39 ± 2.39	9.45 ± 2.98	8.70 ± 2.69	F=2.034	0.328	0.027 (0.003 to 0.111)
LH – After	8.44 ± 2.47	7.91 ± 1.91	7.47 ± 2.19	F=2.437	0.152	0.032 (0.003 to 0.113)
ANOVA F Statistic + Cohen dz (within group)	0.025dz=0.023 (-0.262 to 0.311)	28.419dz=-0.754 (-1.069 to -0.482)	28.675dz=-0.757 (-0.991 to -0.555)			
ANOVA P value (within group)	0.874	<0.001*	<0.001*			
Total testosterone (ng/dL) – Before	37.33 ± 24.37	40.59 ± 24.21	34.77 ± 24.18	F=0.725	0.663	0.010 (0.001 to 0.085)
Total testosterone (ng/dL) – After	31.14 ± 17.71	27.51 ± 14.17	29.54 ± 17.72	F=0.599	0.635	0.008 (0.001 to 0.068)
ANOVA F Statistic + Cohen dz (within group)	4.678dz=-0.306 (-0.508 to -0.052)	23.714dz=-0.689 (-0.878 to -0.525)	6.121dz=-0.350 (-0.555 to -0.134)			
ANOVA P value (within group)	0.035*	<0.001*	0.017*			
Free testosterone (pg/mL) – Before	1.37 ± 0.75	1.08 ± 0.47	1.25 ± 0.66	F=2.488	0.328	0.033 (0.006 to 0.111)
Free testosterone (pg/mL) – After	1.39 ± 0.77	0.96 ± 0.33	1.07 ± 0.39	F=8.734	0.001*	0.106 (0.033 to 0.227)
ANOVA F Statistic + Cohen dz (within group)	0.115dz=0.048 (-0.244 to 0.280)	5.741dz=-0.339 (-0.573 to -0.103)	8.427dz=-0.411 (-0.636 to -0.177)			
ANOVA P value (within group)	0.736	0.020*	0.006*			
DHEA (mcg/dL) – Before	224.18 ± 46.79	226.10 ± 41.72	230.50 ± 40.38	F=0.283	0.870	0.004 (0.000 to 0.055)
DHEA (mcg/dL) – After	223.16 ± 44.78	217.68 ± 41.92	230.02 ± 38.94	F=1.086	0.464	0.015 (0.001 to 0.082)
ANOVA F Statistic + Cohen dz (within group)	1.497 / dz=-0.173 (-0.436 to 0.107)	1.889dz=-0.194 (-0.500 to 0.098)	0.296 / dz=-0.077 (-0.294 to 0.242)			
ANOVA P value (within group)	0.227	0.176	0.589			

Values are mean ± SD. Between-group analysis: Before and After rows use one-way ANOVA among Control, Liraglutide, and Metformin; and FDR-adjusted P uses the Benjamini–Hochberg procedure across the comparable outcomes at each time point. Within-group analysis: the F statistic and P value are shown on separate rows for each group and represent the repeated-measures time effect with two measurements. * $P < 0.05$; significant P values are bold. Effect sizes: eta-squared quantifies the proportion of total variance explained by group; paired Cohen dz quantifies standardized within-group change. Bootstrap percentile 95% CIs use 1,200 resamples

of -2.44 (SE=0.66, 95% CI -3.75 to -1.13, FDR-adjusted $p < 0.001$).

Similarly, waist circumference was markedly reduced in both intervention groups. Liraglutide therapy resulted in an adjusted mean difference of -9.74 cm (SE=0.80, 95% CI -11.31 to -8.17, FDR-adjusted $p < 0.001$) relative to control, and metformin therapy resulted in an adjusted mean difference of -3.12 cm (SE=0.79, 95% CI -4.68 to -1.56, FDR-adjusted $p < 0.001$). Regarding body mass index (BMI), the liraglutide group achieved a statistically significant reduction compared to control, with an adjusted mean difference of -2.82 kg/m² (SE=1.05, 95% CI -4.88 to -0.75, FDR-adjusted $p = 0.008$). Conversely, the reduction in BMI within the metformin group did not achieve statistical significance relative to the control arm (adjusted mean

difference = -1.12 kg/m², SE=1.03, 95% CI -3.15 to 0.92, FDR-adjusted $p = 0.281$) (Table 8).

Hormonal Parameters

The baseline-adjusted linear regression models for hormonal endpoints indicated varying therapeutic responses between the two active treatment regimens. Post-treatment free testosterone was significantly lower in both intervention arms: the adjusted mean difference was -0.26 pg/mL for Liraglutide versus Control (SE = 0.07, 95% CI: -0.40 to -0.11, FDR-adjusted $P = 0.002$) and -0.25 pg/mL for Metformin versus Control (SE = 0.07, 95% CI: -0.40 to -0.11, FDR-adjusted $P = 0.002$). Post-treatment LH was also significantly lower in both active arms, with adjusted mean differences of -1.14

Table 5 Comparison of glycemic parameters before and after treatment in each group

Variable	Control (n=50)	Liraglutide (n=50)	Metformin (n=50)	ANOVA test	FDR-adjusted P	Between-group effect size eta-squared (95% CI)
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	F statistic	Benjamini–Hochberg	
HbA1c (%) – Before	5.39 $\pm$ 0.64	5.13 $\pm$ 0.52	5.10 $\pm$ 0.57	F=3.865	0.328	0.050 (0.007 to 0.156)
HbA1c (%) – After	5.02 $\pm$ 0.54	4.87 $\pm$ 0.37	5.06 $\pm$ 0.43	F=2.439	0.152	0.032 (0.005 to 0.118)
ANOVA F Statistic + Cohen dz (within group)	15.832dz=-0.563 (-0.968 to -0.256)	17.924dz=-0.599 (-1.004 to -0.291)	0.226dz=-0.067 (-0.378 to 0.200)			
ANOVA P value (within group)	<0.001*	<0.001*	0.637			
Fasting glucose (mg/dL) – Before	81.48 $\pm$ 10.35	83.12 $\pm$ 9.15	79.72 $\pm$ 9.06	F=1.590	0.363	0.021 (0.002 to 0.095)
Fasting glucose (mg/dL) – After	81.54 $\pm$ 11.06	78.06 $\pm$ 5.35	78.30 $\pm$ 5.17	F=3.189	0.110	0.042 (0.003 to 0.129)
ANOVA F Statistic + Cohen dz (within group)	0.001dz=0.004 (-0.273 to 0.308)	13.260dz=-0.515 (-0.817 to -0.285)	0.953dz=-0.138 (-0.385 to 0.119)			
ANOVA P value (within group)	0.977	<0.001*	0.334			
HOMA-IR index – Before	2.41 $\pm$ 0.66	2.40 $\pm$ 0.59	2.22 $\pm$ 0.58	F=1.539	0.363	0.021 (0.002 to 0.097)
HOMA-IR index – After	2.32 $\pm$ 0.52	1.74 $\pm$ 0.53	2.05 $\pm$ 0.40	F=17.971	<0.001*	0.196 (0.100 to 0.332)
ANOVA F Statistic + Cohen dz (within group)	1.550dz=-0.176 (-0.467 to 0.123)	67.282dz=-1.160 (-1.540 to -0.894)	10.657dz=-0.462 (-0.771 to -0.179)			
ANOVA P value (within group)	0.219	<0.001*	0.002*			

Values are mean $\pm$ SD. Between-group analysis: Before and After rows use one-way ANOVA among Control, Liraglutide, and Metformin; and FDR-adjusted P uses the Benjamini–Hochberg procedure across the comparable outcomes at each time point. Within-group analysis: the F statistic and P value are shown on separate rows for each group and represent the repeated-measures time effect with two measurements. * $P < 0.05$; significant P values are bold. Effect sizes: eta-squared quantifies the proportion of total variance explained by group; paired Cohen dz quantifies standardized within-group change. Bootstrap percentile 95% CIs use 1,200 resamples

IU/L for Liraglutide (SE = 0.31, 95% CI: -1.76 to -0.53, FDR-adjusted $P = 0.002$) and -1.15 IU/L for Metformin (SE = 0.31, 95% CI: -1.76 to -0.54, FDR-adjusted $P = 0.001$). Total testosterone did not remain statistically significant after FDR adjustment in either the Liraglutide arm (adjusted mean difference = -5.11 ng/dL, SE = 2.50, 95% CI: -10.06 to -0.16, FDR-adjusted $P = 0.072$) or the Metformin arm (adjusted mean difference = -0.44 ng/dL, SE = 2.50, 95% CI: -5.39 to 4.51, FDR-adjusted $P = 0.860$). DHEA likewise remained statistically non-significant after FDR adjustment: the adjusted mean difference was -7.01 mcg/dL for Liraglutide versus Control (SE = 4.81, 95% CI: -16.53 to 2.50, FDR-adjusted $P = 0.184$) and 1.81 mcg/dL for Metformin versus Control (SE = 4.82, 95% CI: -7.72 to 11.34, FDR-adjusted $P = 0.860$). FSH remained statistically unaltered, with adjusted mean differences of 0.18 IU/L for Liraglutide (FDR-adjusted $P = 0.289$) and 0.07 IU/L for Metformin (FDR-adjusted $P = 0.860$), as shown in Table 9.

Glycemic and Lipid Profiles

Assessment of metabolic outcomes showed distinct variations among the cohorts. For glycemic variables, liraglutide therapy resulted in a statistically significant reduction in post treatment fasting glucose compared to control

(adjusted mean difference = -3.59 mg/dL, (SE=1.54, 95% CI: -6.64 to -0.54, FDR-adjusted $p = 0.040$). The metformin arm exhibited an adjusted mean difference of -3.12 mg/dL against control, which did not achieve significance after multiple testing corrections (SE=1.54, 95% CI: -6.17 to -0.07, FDR-adjusted, $p = 0.097$). Insulin resistance, quantified via the HOMA-IR index, was significantly improved in the liraglutide group relative to control (adjusted mean difference = -0.58 (SE=0.08, 95% CI: -0.73 to -0.42, FDR-adjusted $p < 0.001$). The reduction in HOMA-IR in the metformin group did not attain statistical significance (adjusted mean difference = -0.17, 95% CI: -0.33 to -0.02, FDR-adjusted $p = 0.072$). Post treatment glycated hemoglobin (HbA1c) percentages were statistically comparable to control in both the liraglutide (adjusted mean difference = -0.07, FDR-adjusted $p = 0.419$) and metformin arms (adjusted mean difference = 0.12, FDR-adjusted $p = 0.225$). Regarding the lipid profile, total cholesterol levels were significantly lowered by both active interventions. Liraglutide treatment achieved an adjusted mean difference of -19.74 mg/dL (SE=2.70, 95% CI: -25.07 to -14.40, FDR-adjusted $p < 0.001$), whereas metformin treatment yielded an adjusted mean difference of -8.93 mg/dL (SE=2.68, 95% CI: -14.22 to -3.63, FDR-adjusted $p = 0.003$). However, no statistically significant changes relative to control were observed in either group

Table 6 Comparison of lipid profile before and after treatment in each group

Variable	Control (n=50)	Liraglutide (n=50)	Metformin (n=50)	ANOVA test	FDR-adjusted P	Between-group effect size eta-squared (95% CI)
	Mean ± SD	Mean ± SD	Mean ± SD	F statistic	Benjamini–Hochberg	
Total cholesterol (mg/dL) – Before	194.22 ± 33.30	203.02 ± 23.08	192.78 ± 27.96	F=1.902	0.328	0.025 (0.004 to 0.098)
Total cholesterol (mg/dL) – After	195.52 ± 20.64	179.54 ± 15.62	185.98 ± 17.47	F=9.942	<0.001*	0.119 (0.046 to 0.235)
ANOVA F Statistic + Cohen dz (within group)	0.146dz=0.054 (-0.206 to 0.359)	91.447dz=-1.352 (-1.702 to -1.062)	5.142dz=-0.321 (-0.613 to -0.055)			
ANOVA P value (within group)	0.704	<0.001*	0.028*			
Triglycerides (mg/dL) – Before	124.98 ± 23.37	126.92 ± 21.55	130.80 ± 25.31	F=0.798	0.663	0.011 (0.001 to 0.079)
Triglycerides (mg/dL) – After	122.80 ± 23.40	123.74 ± 23.18	131.14 ± 23.02	F=1.938	0.221	0.026 (0.002 to 0.115)
ANOVA F Statistic + Cohen dz (within group)	0.201dz=-0.063 (-0.381 to 0.205)	0.583dz=-0.108 (-0.365 to 0.176)	0.006dz=0.011 (-0.281 to 0.278)			
ANOVA P value (within group)	0.656	0.449	0.939			
LDL cholesterol (mg/dL) – Before	76.28 ± 10.83	73.46 ± 12.30	71.32 ± 14.54	F=1.934	0.328	0.026 (0.003 to 0.108)
LDL cholesterol (mg/dL) – After	76.94 ± 15.09	71.92 ± 12.54	71.24 ± 13.54	F=2.559	0.152	0.034 (0.003 to 0.115)
ANOVA F Statistic + Cohen dz (within group)	0.076dz=0.039 (-0.237 to 0.315)	0.564dz=-0.106 (-0.413 to 0.169)	0.001dz=-0.004 (-0.280 to 0.310)			
ANOVA P value (within group)	0.784	0.456	0.976			
HDL cholesterol (mg/dL) – Before	57.40 ± 6.80	56.64 ± 6.72	56.94 ± 6.43	F=0.166	0.908	0.002 (0.000 to 0.056)
HDL cholesterol (mg/dL) – After	56.40 ± 5.61	55.30 ± 6.10	56.52 ± 5.33	F=0.698	0.624	0.009 (0.001 to 0.076)
ANOVA F Statistic + Cohen dz (within group)	0.678dz=-0.116 (-0.405 to 0.171)	1.041dz=-0.144 (-0.433 to 0.120)	0.159dz=-0.056 (-0.333 to 0.222)			
ANOVA P value (within group)	0.414	0.313	0.691			

Values are mean ± SD. Between-group analysis: Before and After rows use one-way ANOVA among Control, Liraglutide, and Metformin; and FDR-adjusted P uses the Benjamini–Hochberg procedure across the comparable outcomes at each time point. Within-group analysis: the F statistic and P value are shown on separate rows for each group and represent the repeated-measures time effect with two measurements. * $P < 0.05$; significant P values are bold. Effect sizes: eta-squared quantifies the proportion of total variance explained by group; paired Cohen dz quantifies standardized within-group change. Bootstrap percentile 95% CIs use 1,200 resamples

for low density lipoprotein (LDL) cholesterol (liraglutide: -4.45 mg/dL, FDR-adjusted $p = 0.143$; metformin: -4.70 mg/dL, FDR-adjusted $p = 0.153$), high-density lipoprotein (HDL) cholesterol (liraglutide: -1.06 mg/dL, FDR-adjusted $p = 0.410$; metformin: 0.15 mg/dL, FDR-adjusted $p = 0.899$), or serum triglycerides (liraglutide: 0.80 mg/dL, FDR-adjusted $p = 0.864$; metformin: 7.92 mg/dL, FDR-adjusted $p = 0.153$) (Table 10).

Categorical Clinical Outcomes

Baseline-adjusted logistic regression models were applied to evaluate categorical clinical variables, including hirsutism, acne, and menstrual regularity. Clinical improvements in menstrual cycle status were highly significant across both pharmacological arms. The odds of achieving a regular menstrual cycle post-treatment were substantially higher in the liraglutide arm compared to control, yielding an adjusted odds ratio (aOR) of 19.32 (Standard Error of log OR = 0.63, 95% CI: 5.63 to 66.36, FDR-adjusted $p < 0.001$). The metformin arm also demonstrated a significantly higher probability of regular menstrual cycles relative to control,

with an (aOR) of 5.71 (Standard Error of log OR = 0.61, 95% CI: 1.74 to 18.69, FDR-adjusted $p = 0.012$).

Conversely, resolution rates for cutaneous manifestations did not reveal statistically significant inter-group differences. The odds of presenting with persistent hirsutism post-treatment were lower but not statistically significant for both the liraglutide arm (aOR) = 0.26, 95% CI: 0.05 to 1.40, FDR-adjusted $p = 0.175$ and the metformin arm (aOR) = 0.36, 95% CI: 0.06 to 2.18, FDR-adjusted $p = 0.267$ compared to the control group. Similarly, the presence of post-treatment acne remained statistically unaltered relative to control in both the liraglutide group (aOR) = 0.60, 95% CI: 0.05 to 7.03, FDR-adjusted $p = 0.681$ and the metformin group (aOR) = 0.25, 95% CI: 0.02 to 2.68, FDR-adjusted $p = 0.267$) (Table 11).

Side Effects of the Studied Groups

The overall safety profile and adverse event distributions are detailed in Table 12; Fig. 3. Overall, Liraglutide therapy was associated with a higher incidence of gastrointestinal adverse events compared to Metformin. Specifically,

Table 7 Comparison of clinical outcomes before and after treatment in each group

Clinical outcome / category	Control	Liraglutide	Metformin	Between-group test	FDR-adjusted P	Effect size (95% CI)
	No. (%)	No. (%)	No. (%)	Chi-square or exact	Benjamini-Hochberg	Cramer V / risk difference
Menstrual cycle - Before: Irregular	34 (68.0%)	37 (74.0%)	40 (80.0%)	chi-square=1.871	0.448	0.112 (0.024 to 0.284)
Menstrual cycle - Before: Regular	16 (32.0%)	13 (26.0%)	10 (20.0%)			
Menstrual cycle - After: Irregular	34 (68.0%)	12 (24.0%)	25 (50.0%)	chi-square=19.629	<0.001*	0.362 (0.229 to 0.507)
Menstrual cycle - After: Regular	16 (32.0%)	38 (76.0%)	25 (50.0%)			
Menstrual cycle P value + risk difference (within group)	1.000RD=0.000 (-0.120 to 0.120)	<0.001*RD=0.500 (0.360 to 0.640)	<0.001*RD=0.300 (0.180 to 0.420)			
Hirsutism - Before: No	23 (46.0%)	20 (40.0%)	28 (56.0%)	chi-square=2.621	0.432	0.132 (0.033 to 0.307)
Hirsutism - Before: Yes	27 (54.0%)	30 (60.0%)	22 (44.0%)			
Hirsutism - After: No	25 (50.0%)	27 (54.0%)	32 (64.0%)	chi-square=2.110	0.448	0.119 (0.033 to 0.292)
Hirsutism - After: Yes	25 (50.0%)	23 (46.0%)	18 (36.0%)			
Hirsutism P value + risk difference (within group)	0.500RD=-0.040 (-0.100 to 0.000)	0.016*RD=-0.140 (-0.240 to -0.060)	0.125RD=-0.080 (-0.160 to -0.020)			
Acne - Before: No	28 (56.0%)	23 (46.0%)	31 (62.0%)	chi-square=2.636	0.432	0.133 (0.034 to 0.308)
Acne - Before: Yes	22 (44.0%)	27 (54.0%)	19 (38.0%)			
Acne - After: No	29 (58.0%)	25 (50.0%)	34 (68.0%)	chi-square=3.354	0.432	0.150 (0.050 to 0.321)
Acne - After: Yes	21 (42.0%)	25 (50.0%)	16 (32.0%)			
Acne P value + risk difference (within group)	1.000RD=-0.020 (-0.060 to 0.000)	0.480RD=-0.040 (-0.100 to 0.000)	0.248RD=-0.060 (-0.140 to 0.000)			
Pregnancy - After: Negative	22 (71.0%)	12 (34.3%)	16 (47.1%)	chi-square=9.026	0.044*	0.300 (0.142 to 0.488)
Pregnancy - After: Positive	9 (29.0%)	23 (65.7%)	18 (52.9%)			
Miscarriage - After: Negative	8 (100.0%)	13 (92.9%)	12 (100.0%)	Fisher-Freeman-Halton exact	1.000	0.208 (0.000 to 0.372)
Miscarriage - After: Positive	0 (0.0%)	1 (7.1%)	0 (0.0%)			

Table 7 presents Before and After category counts for menstrual cycle (regular/irregular), hirsutism (yes/no), and acne (yes/no). Pregnancy (positive/negative) and miscarriage (positive/negative). Between-group comparisons use Pearson chi-square tests except miscarriage, for which the Fisher-Freeman-Halton exact test is used. Within-group P values use McNemar analysis only for outcomes with paired Before and After measurements. FDR-adjusted P values use the Benjamini-Hochberg correction. *P<0.05; significant P values are bold. Cramer's V quantifies between-group association; risk difference (RD) quantifies within-group change only for outcomes with paired Before and After measurements. Cramer's V CIs use 5,000 bootstrap samples; paired RD CIs use 2,000 bootstrap samples

Table 8 Baseline-adjusted linear regression for anthropometric outcomes

Parameter	Adjusted mean difference (treatment - control)	SE	95% CI	FDR <i>P</i> -value	Dependent variable	Baseline covariate(s) used
Weight (kg)	Liraglutide versus Control: -10.13	0.67	-11.44 to -8.81	<0.001***	Post-treatment Weight	Baseline Weight
	Metformin versus Control: -2.44	0.66	-3.75 to -1.13	<0.001***		
BMI (kg/m ²)	Liraglutide versus Control: -2.82	1.05	-4.88 to -0.75	0.008**	Post-treatment BMI	Baseline BMI
	Metformin versus Control: -1.12	1.03	-3.15 to 0.92	0.281		
Waist circumference (cm)	Liraglutide versus Control: -9.74	0.80	-11.31 to -8.17	<0.001***	Post-treatment Waist circumference	Baseline Waist circumference
	Metformin versus Control: -3.12	0.79	-4.68 to -1.56	<0.001***		

For each parameter, the first comparison row is Liraglutide versus Control and the second is Metformin versus Control. The post-treatment anthropometric value was regressed on treatment group and its corresponding baseline value. Adjusted mean differences are reported with standard errors, 95% confidence intervals, and Benjamini-Hochberg false discovery rate-adjusted *p* values across the three anthropometric outcomes separately for each treatment-versus-Control comparison family. *adjusted *p*<0.05; **adjusted *p*<0.01; ***adjusted *p*<0.001. There were 50 participants in each treatment arm

Table 9 Baseline-Adjusted Linear Regression for hormonal parameters

Parameter	Treatment vs. Control	Adjusted Mean Difference (Treatment - Control)	SE	95% CI	FDR <i>P</i> -value	Dependent Variable	Baseline Covariate(s) Used
Total Testosterone (ng/dL)	Liraglutide vs. Control	-5.11	2.5	-10.06 to -0.16	0.072	Post-treatment Total Testosterone	Baseline Total Testosterone
	Metformin vs. Control	-0.44	2.5	-5.39 to 4.51	0.860		
Free testosterone (pg/mL)	Liraglutide vs. Control	-0.26	0.07	-0.40 to -0.11	0.002**	Post-treatment Free testosterone	Baseline Free testosterone
	Metformin vs. Control	-0.25	0.07	-0.40 to -0.11	0.002**		
DHEA (mcg/dL)	Liraglutide vs. Control	-7.01	4.81	-16.53 to 2.50	0.184	Post-treatment DHEA	Baseline DHEA
	Metformin vs. Control	1.81	4.82	-7.72 to 11.34	0.860		
FSH (IU/L)	Liraglutide vs. Control	0.18	0.17	-0.16 to 0.53	0.289	Post-treatment FSH	Baseline FSH
	Metformin vs. Control	0.07	0.17	-0.27 to 0.41	0.860		
LH (IU/L)	Liraglutide vs. Control	-1.14	0.31	-1.76 to -0.53	0.002**	Post-treatment LH	Baseline LH
	Metformin vs. Control	-1.15	0.31	-1.76 to -0.54	0.001**		

For every parameter, the first comparison row is Liraglutide versus Control and the second is Metformin versus Control. Linear regression model: post-treatment outcome = treatment group + corresponding baseline value. Differences are regression-adjusted at the pooled baseline mean. Benjamini-Hochberg false discovery rate adjustment was applied across the outcomes separately for each treatment-versus-control comparison family. *adjusted *p*<0.05; **adjusted *p*<0.01; ***adjusted *p*<0.001. There were 50 participants in each treatment arm

nausea was significantly more frequent in the Liraglutide group (62.0% vs. 24.0% χ^2 , = 14.729, *P*<0.001), as were heartburn (22.0% vs. 6.0%, *P*=0.021) and constipation (20.0% vs. 4.0%, *P*=0.014). Rates of diarrhea, vomiting, and non-gastrointestinal side effects (such as dizziness and headache) were comparable between arms (*P*>0.05). Injection-site reactions (10.0%) and transient alopecia (4.0%) were exclusively reported in Liraglutide-treated patients. Discontinuation due to tolerability issues remained low across all cohorts (4.0% vs. 2.0%), with zero serious adverse events reported.

Predictors of Therapeutic Response

The potential predictors of clinical response was evaluated which defined operationally as achieving a $\geq 20\%$ reduction in HOMA-IR from baseline to 6 months (*n*=43/150, 28.7% (using univariate and multivariable binary logistic regression analyses as shown in Table 13.

In the univariate analysis, treatment with Liraglutide was strongly linked to higher odds of response compared to Control OR=6.291, 95% CI: 2.521 to 15.696, FDR- *P*<0.001). Similarly, patients with higher baseline HOMA-IR values

Table 10 Baseline-Adjusted Linear Regression for glycemic and lipid parameters

Parameter	Treatment vs. Control	Adjusted Mean Difference (Treatment - Control)	SE	95% CI	FDR P-value	Dependent Variable	Baseline Covariate(s) Used
HbA1c (%)	Liraglutide vs. Control	-0.07	0.09	-0.24 to 0.10	0.419	Post-treatment HbA1c	Baseline HbA1c
	Metformin vs. Control	0.12	0.09	-0.05 to 0.29	0.225		
Fasting glucose (mg/dL)	Liraglutide vs. Control	-3.59	1.54	-6.64 to -0.54	0.040*	Post-treatment Fasting glucose	Baseline Fasting glucose
	Metformin vs. Control	-3.12	1.54	-6.17 to -0.07	0.097		
HOMA-IR (index)	Liraglutide vs. Control	-0.58	0.08	-0.73 to -0.42	<0.001***	Post-treatment HOMA-IR	Baseline HOMA-IR
	Metformin vs. Control	-0.17	0.08	-0.33 to -0.02	0.072		
Cholesterol (mg/dL)	Liraglutide vs. Control	-19.74	2.7	-25.07 to -14.40	<0.001***	Post-treatment Cholesterol	Baseline Cholesterol
	Metformin vs. Control	-8.93	2.68	-14.22 to -3.63	0.003**		
Triglycerides (mg/dL)	Liraglutide vs. Control	0.8	4.65	-8.38 to 9.98	0.864	Post-treatment Triglycerides	Baseline Triglycerides
	Metformin vs. Control	7.92	4.67	-1.31 to 17.14	0.153		
LDL (mg/dL)	Liraglutide vs. Control	-4.45	2.73	-9.84 to 0.93	0.143	Post-treatment LDL	Baseline LDL
	Metformin vs. Control	-4.7	2.75	-10.13 to 0.73	0.153		
HDL (mg/dL)	Liraglutide vs. Control	-1.06	1.14	-3.31 to 1.20	0.41	Post-treatment LDL	Baseline LDL
	Metformin vs. Control	0.15	1.14	-2.11 to 2.40	0.899		

For every parameter, the first comparison row is Liraglutide versus Control and the second is Metformin versus Control. Linear regression model: post-treatment outcome = treatment group + corresponding baseline value. Differences are regression-adjusted at the pooled baseline mean. Benjamini-Hochberg false discovery rate adjustment was applied across the outcomes separately for each treatment-versus-control comparison family. *adjusted $p < 0.05$; **adjusted $p < 0.01$; ***adjusted $p < 0.001$. There were 50 participants in each treatment arm

Table 11 Categorical outcomes: baseline – adjusted logistic regression

Parameter	Adjusted odds ratio (treatment versus control)	Standard error of log odds ratio	95% CI	FDR P-value	Dependent variable	Baseline covariate(s) used
Hirsutism	Liraglutide versus Control: 0.26	0.85	0.05 to 1.40	0.175	Presence of hirsutism	Hirsutism Before
	Metformin versus Control: 0.36	0.92	0.06 to 2.18	0.267		
Acne	Liraglutide versus Control: 0.60	1.26	0.05 to 7.03	0.681	Presence of acne	Acne Before
	Metformin versus Control: 0.25	1.20	0.02 to 2.68	0.267		
Menstrual regularity	Liraglutide versus Control: 19.32	0.63	5.63 to 66.36	<0.001***	Regular menstrual cycle	Menstrual Cycle Before
	Metformin versus Control: 5.71	0.61	1.74 to 18.69	0.012*		

Odds ratios above indicate greater odds of the modeled event. Modeled events were presence of hirsutism, presence of acne, and regular menstrual cycle. Every logistic regression model adjusted for the corresponding baseline outcome status. False discovery rate adjustment was applied across the three categorical outcomes separately for each treatment-versus-control comparison family

were significantly more likely to achieve responder status (OR=4.694, 95% CI: 2.264–9.734, FDR- $P < 0.001$). Conversely, Metformin treatment (OR=0.506, FDR- $P = 0.425$), age (OR = 0.973, FDR- $P = 0.518$), and baseline BMI (OR=0.995, FDR- $P = 0.888$) showed no significant association with treatment response.

After adjusting for age, baseline BMI, and baseline HOMA-IR in the multivariable model, Liraglutide remained an independent predictor of success, increasing the odds of response by more than 11-fold relative to Control (OR = 11.310, 95 % CI: 3.695–34.614, FDR- $P < 0.001$). Higher baseline HOMA-IR also continued to serve

as an independent predictor of response (OR= 5.716, 95 % CI: 2.430–13.446, FDR- $P < 0.001$). In contrast, Metformin (OR = 0.743, FDR- $P = 0.648$), age (OR = 0.956, FDR- $P = 0.447$), and baseline BMI (OR = 0.971, FDR- $P = 0.633$) remained non-significant in the adjusted model.

Discussion

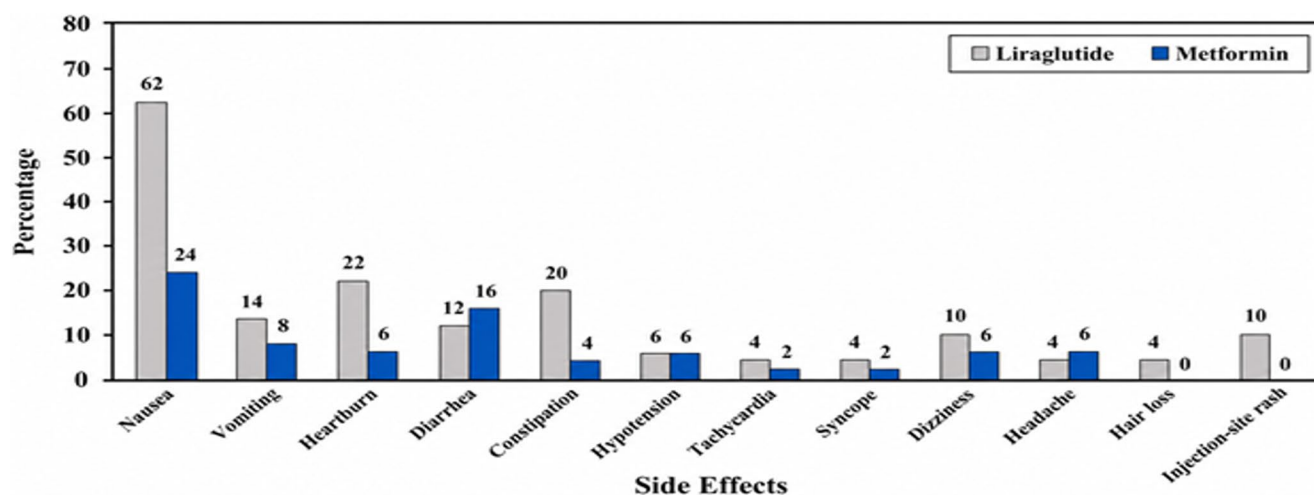
Polycystic ovarian syndrome (PCOS) is a hormonal and metabolic condition characterized by malfunction in several organs via diverse molecular mechanisms. It is the

Table 12 Side Effects

Side effects	Liraglutide (<i>n</i> =50)		Metformin (<i>n</i> =50)		χ^2	<i>p</i>
	No.	%	No.	%		
Nausea	31	62.0	12	24.0	14.729*	<0.001*
Vomiting	7	14.0	4	8.0	0.919	0.338
Heart burn	11	22.0	3	6.0	5.316*	0.021*
Diarrhea	6	12.0	8	16.0	0.332	0.564
Constipation	10	20.0	2	4.0	6.061*	0.014*
Hypotension	3	6.0	3	6.0	0.0	^{FE} <i>p</i> = 1.000
Tachycardia	2	4.0	1	2.0	0.344	^{FE} <i>p</i> = 1.000
Syncope	2	4.0	1	2.0	0.344	^{FE} <i>p</i> = 1.000
Dizziness	5	10.0	3	6.0	0.543	^{FE} <i>p</i> = 0.715
Headache	2	4.0	3	6.0	0.211	^{FE} <i>p</i> = 1.000
Hair loss	2	4.0	0	0.0	-	-
Rash injection	5	10.0	0	0.0	-	-

χ^2 :Chi square test FET:Fisher Exact test *p*:*p* value for comparison between the two studied groups

*:Statistically significant at *p*≤0.05

**Fig. 3** Comparison between the studied groups according to Side effects

most prevalent endocrine problem in women, responsible for over 90% of anovulatory infertility cases, and is associated with elevated risk of metabolic syndrome, metabolic-associated fatty liver disease (MAFLD) and cardiovascular disorders [15].

PCOS is directly linked to obesity and insulin resistance, affecting both overweight and obese phenotype as well as those with normal weight. Weight reduction has demonstrated efficacy in enhancing hirsutism, insulin resistance, and hyperinsulinemia, thereby improving monthly regularity and ovulation. Consequently, therapeutic options that integrate lifestyle modifications and pharmacological therapies have garnered interest [16].

Liraglutide is a glucagon-like peptide-1 receptor agonist (GLP1-RA) that promotes weight loss by ameliorating metabolic dysfunction in overweight women with polycystic ovary syndrome (PCOS) [17].

The impact of liraglutide in comparison to alternative dietary interventions or placebo is significant not only for weight reduction but also for ameliorating hyperandrogenism and menstrual regularity in women with PCOS [18]. Additional study had investigated the effects of combining liraglutide with metformin and demonstrated its superior efficacy over metformin alone in enhancing PCOS outcomes [19].

Both liraglutide 3 mg monotherapy and a combination of liraglutide 1.2 mg and metformin significantly lowered weight in a randomized study investigating obese women with PCOS; however, liraglutide 3 mg showed better effects on anthropometric parameters. However, combination therapy improve androgen profiles and has fewer side effects [20].

A pilot study revealed that the incorporation of liraglutide with metformin markedly enhanced in vitro fertilization

Table 13 Univariate and multivariable logistic regression analyses of factors associated with the study outcome

Variable	Univariate analysis OR (95% CI)	Raw <i>P</i> / FDR-adjusted <i>P</i>	Multivariable analysis Adjusted OR (95% CI)	Raw <i>P</i> / FDR-adjusted <i>P</i>
Liraglutide vs. Control	6.291 (2.521–15.696)	<0.001* / <0.001*	11.310(3.695–34.614)	<0.001* / <0.001*
Metformin vs. Control	0.506 (0.157–1.635)	0.255/0.425	0.743 (0.207–2.662)	0.648 / 0.648
Age (years)	0.973(0.913–1.038)	0.414 / 0.518	0.956(0.883–1.035)	0.268 / 0.447
Baseline BMI (kg/m ²)	0.995 (0.932–1.063)	0.888 / 0.888	0.971 (0.891–1.059)	0.506 / 0.633
Baseline HOMA-IR	4.694 (2.264–9.734)	<0.001* / <0.001*	5.716 (2.430–13.446)	<0.001* / <0.001*

OR odds ratio, CI confidence interval. Control is the reference group. The multivariable model includes treatment group, age, baseline BMI, and baseline HOMA-IR; all are measured before treatment and were selected as plausible determinants/confounders. Post-treatment weight loss was excluded because it may be a mediator. FDR-adjusted *P* values use the Benjamini-Hochberg procedure separately for the five univariate and five adjusted coefficients. Values are Raw *P* / FDR-adjusted *P*. **P*<0.05; significant *P* values are bold. The 20% threshold is an operational responder definition and is not presented as a validated HOMA-IR minimal clinically important difference

pregnancy rates per embryo transfer (85.7% vs. 28.6%) and cumulative pregnancy rates (69.2% vs. 35.7%) in compared with metformin alone [21].

Other studies have indicated that liraglutide monotherapy in obese PCOS women leads to substantial weight loss (approximately 5–7%) and enhancements in SHBG, ovarian volume, and menstrual regularity over a 26-week period [22]. Recent meta-analyses have demonstrated that combined liraglutide–metformin therapy is more effective than either agent alone in reducing BMI, insulin resistance, and hyperandrogenism in women with PCOS [23]. Therefore, this study aimed to compare the hormonal, metabolic and clinical effects of metformin and liraglutide as monotherapies in infertile women with PCOS.

Rather than merely echoing historical literature on GLP-1 therapy, the localized data from our trial warrant a deeper mechanistic interpretation. A primary finding of this study was the robust metabolic clearing capacity of GLP-1 receptor agonism, evidenced by the post-treatment between-group HOMA-IR index analysis ($F=17.971$, FDR-adjusted $P<0.001$), which accounted for nearly 20% of the total outcome variance ($\eta^2=0.196$, 95% CI: 0.100 to 0.332). Liraglutide induced a pronounced baseline-adjusted reduction in HOMA-IR compared to control (adjusted mean difference: -0.58, 95% CI: -0.73 to

-0.42, FDR $P<0.001$), whereas metformin demonstrated a more modest effect that reached borderline significance after FDR adjustment (adjusted mean difference: -0.17, 95% CI: -0.33 to -0.02, FDR $P=0.072$) [24].

To further dissect the direct drivers of metabolic restoration, our multivariable logistic regression for HOMA-IR responders (>20% reduction from baseline) identified liraglutide treatment as a strong independent predictor of metabolic improvement compared with the control group (adjusted OR = 11.310, 95% CI: 3.695 to 34.614, FDR $P<0.001$), after adjusting for age, baseline BMI, and baseline HOMA-IR. Conversely, metformin failed to establish an independent predictive advantage for achieving this high-threshold responder status (adjusted OR = 0.743, 95% CI: 0.207 to 2.662, FDR $P=0.648$). Furthermore, baseline HOMA-IR strongly predicted responder status (adjusted OR = 5.716, 95% CI: 2.430 to 13.446, FDR $P<0.001$), demonstrating that patients with more severe baseline metabolic disturbances derive the greatest proportional clearing benefit from Liraglutide intervention. The parallel, marked declines in both anthropometric measures (body weight and waist circumference) and the primary biochemical marker (HOMA-IR) strongly suggest a close physiological interplay. In PCOS, visceral adiposity perpetuates a chronic low-grade inflammatory state that impairs insulin signaling pathways in skeletal muscle and the liver [25]. By inducing clinically meaningful weight loss in the liraglutide group, the treatment likely alleviated the metabolic burden on these peripheral tissues. This observation aligns with the mechanisms discussed by Neeland et al. (2021) regarding GLP-1 receptor agonists and the reversal of adipose tissue dysfunction [26]. Consequently, this pathway restores insulin sensitivity more effectively than the weight-neutral or modestly weight-reducing mechanisms traditionally associated with Metformin, a finding that mirrors the clinical trends reported by Elkind-Hirsch et al. (2021) in overweight PCOS populations [17] and Cannarella et al. [27].

Hormonal Analysis

Detailed within-group analyses in our cohort demonstrated that both the liraglutide group ($F=28.419$, $dz=-0.754$, $P<0.001$) and the metformin group ($F=28.675$, $dz=-0.757$, $P<0.001$) successfully achieved significant reductions in elevated LH levels. This reduction in LH pulsatility may underlie the marked restoration of regular menstrual cyclicity observed clinically. Conversely, the complete stability of FSH across all study arms post treatment ($F=0.472$, FDR-adjusted $P=0.670$; within group $P>0.05$) verifies that these pharmacological agents specifically target the neuroendocrine defects of LH hypersecretion rather than altering basal follicular recruitment pathways.

Biochemically, Baseline-Adjusted Linear Regression Revealed that Both Liraglutide (-0.26 pg/mL, FDR $P=0.002$) and Metformin (-0.25 pg/mL, FDR $P=0.003$) significantly reduced circulating free testosterone relative to control. Total testosterone reductions did not remain statistically significant after FDR adjustment (Liraglutide: -5.11 ng/dL, FDR $P=0.072$; Metformin: -0.44 ng/dL, FDR $P=0.860$). DHEA showed no significant post-treatment between-group difference (FDR-adjusted $P=0.464$). Within groups, DHEA decreased in Control ($P=0.227$), Liraglutide ($P=0.176$), and Metformin ($P=0.589$), with none of these changes reaching statistical significance. In the baseline-adjusted model, both contrasts were non-significant after FDR correction (Liraglutide: adjusted mean difference = -7.01 mcg/dL, FDR $P=0.184$; Metformin: 1.81 mcg/dL, FDR $P=0.860$).

These findings align with observations by Frøssing et al. [28] and Nylander et al. [29] who found decreased free testosterone levels while total testosterone remained unaltered after liraglutide treatment. Corroborating these findings, Liraglutide was found to maintain total testosterone levels in a 12-week study [30], and other open-label studies with smaller populations or lower doses similarly reported unaffected total testosterone [17, 28–30]. Because ovarian stroma volume and androgen levels are closely connected, the trend toward decreasing stroma volume may suggest that liraglutide reduces ovarian androgen production [31]. Furthermore, lowered androgenic hypersecretion driven by weight loss and decreased free testosterone assists in breaking the vicious cycle of hyperinsulinism and hyperandrogenism in PCOS pathophysiology [32, 33].

Obesity and Other Anthropometric Indices

A BMI in the overweight or obese range is seen in around 38–88% of women with PCOS [34]. International recommendations suggest metformin and liraglutide for women with a BMI >25 kg/m² because they improve metabolic outcomes in women with PCOS [35]. In our baseline-adjusted linear regression analysis, Liraglutide demonstrated clear superiority in improving anthropometric outcomes, achieving a greater adjusted mean weight loss of -10.13 kg 95% CI: -11.44 to -8.81 , FDR $P<0.001$ and a waist circumference drop of -9.74 cm 95% CI: -11.31 to -8.17 , FDR $P<0.001$ relative to control. Metformin induced significant but more conservative reductions in weight -2.44 kg, FDR $P=0.002$ and waist circumference -3.12 cm, FDR $P=0.002$. Crucially, after adjusting for baseline values and FDR, metformin failed to maintain a significant reduction in BMI (-1.12 kg/m², FDR $P=0.383$), whereas liraglutide maintained significant BMI attenuation (-2.82 kg/m², FDR $P=0.017$).

This pronounced attenuation of abdominal obesity captured in our between-group analysis of waist circumference post-treatment ($F=7.034$, FDR-adjusted $P=0.005$, $\eta^2=0.087$) provides a mechanical rationale for the downstream clearing of peripheral insulin resistance. In line with our study, Cannarella et al. showed that BMI decreased significantly across intervention protocols [27]. Moreover, Livadas et al. indicated that there was no notable decrease in body weight or BMI post-treatment; however, a substantial enhancement in body composition was observed [30]. Similarly, Frøssing et al. indicated that Liraglutide treatment led to significant changes in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) evaluated by MRI compared to placebo [28]. Mean weight decreases with liraglutide+metformin, liraglutide alone, and metformin alone were reported in a 12-week open-label study [36]. Conversely, Kahal et al. showed no significant change in waist circumference or prevalence of metabolic syndrome in their specific cohort [34] whereas Jensterle Sever et al. [35] and Elkind-Hirsch et al. [24] observed beneficial effects on body weight following treatment with GLP-1 receptor agonists.

Glycemic/Diabetic Parameters

Regarding glycemic parameters, Liraglutide was uniquely effective in optimizing baseline-adjusted fasting plasma glucose (-3.59 mg/dL, FDR $P=0.040$), whereas Metformin failed to establish a significant baseline-adjusted change compared to control (-3.12 mg/dL, FDR $P=0.097$). Neither agent significantly altered HbA1c levels compared to control (Liraglutide FDR $P=0.419$; Metformin FDR $P=0.225$), highlighting that GLP-1 receptor agonism may provide more effective glycemic regulation in individuals with severe obesity-related insulin resistance, even within the normoglycemic range.

In agreement with our results, Cannarella et al. demonstrated that only their specialized intervention cohorts exhibited a statistically significant reduction in the HOMA index [27]. Moreover, Frøssing et al. reported that liraglutide treatment resulted in significant reductions in fasting plasma glucose and plasma glucose AUC compared to placebo [28]. Consistent with our results, Nylander et al. observed reduced fasting glucose and HbA1c levels in a liraglutide cohort relative to placebo, though they were unable to substantiate this through a reduction in HOMA2-IR [32]. Kahal et al. also showed that at 6 months FPG, fasting insulin, and HOMA-IR displayed significant improvements [34]. The reliance on fasting parameters of beta-cell function (such as HOMA-beta) reflects basal rather than glucose-stimulated insulin production and is impacted by insulin clearance, which underscores the value of direct HOMA-IR and glycemic parameter evaluation in this cohort [36, 37].

Clinical and Biochemical Hyperandrogenism

Liraglutide facilitated this effect, which may help interrupt the vicious cycle of hyperinsulinemia and hyperandrogenism that underlies the pathophysiology of PCOS [33].

Menstrual irregularity is a hallmark of PCOS, and Metformin and liraglutide help induce ovulation in women with PCOS [21]. Baseline-adjusted multivariable logistic regression demonstrated that the odds of achieving regular menstrual cycles post-treatment were significantly higher in the Liraglutide group (adjusted OR=19.32, 95% CI: 5.63 to 66.36, FDR $P<0.001$) and Metformin group (adjusted OR=5.71, 95% CI: 1.74 to 18.69, FDR $P=0.012$) compared to control, aligning with findings by Livadas et al. [30], and Elkind-Hirsch et al. [38]

Dermatologically, within-group McNemar analysis showed that liraglutide achieved a statistically significant reduction in active hirsutism cases ($P=0.016$, Risk Difference = -0.140, 95% CI: -0.240 to -0.060), whereas metformin failed to achieve significance ($P=0.125$, Risk Difference = -0.080, 95% CI: -0.160 to -0.020). However, in baseline-adjusted logistic regression, differences between control and either liraglutide (adjusted OR=0.26, FDR $P=0.175$) or metformin (adjusted OR = 0.36, FDR $P=0.267$) did not reach between-group statistical significance. Acne prevalence also remained statistically unaltered across all cohorts ($F=3.354$, FDR-adjusted $P=0.432$).

As detailed in the specialized dermatological review by Bayona, hair follicle cycles require prolonged androgen-depleted environments to exhibit dramatic physical regression [39]. Therefore, while liraglutide effectively restores metabolic homeostasis within 6 months, translating these systemic improvements into optimal clinical outcomes may require longer treatment duration. This aligns with mixed literature regarding metformin and metabolic modulators on cutaneous markers [40, 41].

Lipid Profile

The isolated impact on lipids is supported by our post-treatment between-group ANOVA for total cholesterol ($F=9.942$, FDR-adjusted $P<0.001$, eta-squared=0.119), driven by a prominent within-group drop in the liraglutide arm ($F=91.447$, $dz=-1.352$, $P<0.001$) and confirmed by baseline-adjusted linear regression (-19.74 mg/dL vs. Control, FDR $P<0.001$). Metformin also attained a significant baseline-adjusted cholesterol reduction (-8.93 mg/dL, FDR $P=0.003$).

Crucially, the lack of statistical movement in triglycerides ($F=1.938$, FDR-adjusted $P=0.221$), LDL ($F=2.559$, FDR-adjusted $P=0.152$), and HDL ($F=0.698$, FDR-adjusted $P=0.624$) across all study groups implies that

short-term GLP-1 receptor agonist monotherapy primarily clears circulating total cholesterol via weight-mediated metabolic pathways, but does not substantially alter the overall lipoprotein subfraction profile over a 6-month treatment period. Consistent with our results, Livadas et al. reported that levels of cholesterol, HDL, LDL, and triglycerides were not significantly altered [30] whereas Frössing et al. similarly observed no change in lipid subfractions during their treatment period [28]. In contrast, Kahal et al. [34] and Elkind-Hirsch et al. [38] observed variations in triglyceride responses, likely reflecting differences in study duration and baseline metabolic risk.

Clinical Outcomes

Positive post-treatment pregnancy was observed in 29.0% of the Control group, 65.7% of the Liraglutide group, and 52.9% of the Metformin group. The unadjusted between-group comparison was significant ($\chi^2=9.026$, $P=0.011$) and remained significant after FDR correction ($P=0.044$; Cramer's $V=0.300$, 95% CI: 0.142 to 0.488). Post-treatment miscarriage was rare among participants with recorded miscarriage status (0/8 in Control, 1/14 in Liraglutide, and 0/11 in Metformin) and did not differ significantly between groups (Fisher-Freeman-Halton exact $P=1.000$).

Clinically, the higher post-treatment pregnancy proportion in the Liraglutide group remains highly relevant [18]. It is important to note that timing of metformin initiation may influence miscarriage outcomes; Cheshire et al. indicated that continuing metformin throughout the first trimester was associated with a lower risk of miscarriage and higher live birth rates [42]. Additionally, Morin-Papunen et al. reported that metformin combined with standard infertility treatment significantly improved pregnancy rates in women with PCOS [40]. Consistent with our results, Zhu et al. found that metformin treatment did not significantly alter miscarriage rates in women with PCOS [43] aligning with findings by Løvvik et al. regarding pregnancy outcomes [44] and Cao et al. [45], whose meta-analysis of randomized controlled trials similarly found no significant effect of metformin on miscarriage rates in women with PCOS. Therefore, liraglutide may be considered to have an exploratory and potentially pregnancy-preparatory role in women with PCOS, warranting further investigation in adequately powered prospective studies.

Side Effects

In this study, we found a higher incidence of gastrointestinal side effects with liraglutide than with Metformin. Nausea, heartburn, and constipation were significantly more frequent in the liraglutide group, whereas no significant

differences were observed for vomiting, diarrhea, hypotension, tachycardia, syncope, dizziness, or headache. Additionally, liraglutide-specific side effects included hair loss and injection-site rash.

Treatment with liraglutide frequently causes gastrointestinal adverse effects in a dose-dependent way [46, 47]. Patients with PCOS taking metabolic modulators should be informed of these adverse events [43, 48]. According to Frøssing et al. [28] and Nylander et al. [29], constipation and nausea were the most frequent events, occurring primarily during the start-up and dose-escalation period. Nausea was generally brief, mild-to-moderate in intensity, and resolved over time. Localized countermeasures are usually sufficient to manage these side effects without requiring core therapy discontinuation [49]. Metformin use has also been linked to distinct gastrointestinal discomfort and systemic risks in complex clinical presentations [45, 50–52] requiring appropriate patient counseling [44].

Limitations

While the current study provided important clinical and mechanistic insights into the comparative efficacy of liraglutide and metformin in infertile women with PCOS, several limitations should be acknowledged. First, the single-center design may limit the generalizability of our findings to other ethnic populations and PCOS phenotypes. Second, the sample size was relatively modest, and the 6-month follow-up period was insufficient to evaluate long-term reproductive outcomes, such as cumulative live birth rates. Finally, because of the distinct routes of administration of the study medications, this trial employed an open-label design without blinding, which may have introduced performance and adherence bias. Future large-scale, multicenter, double-blind trials with longer follow-up periods are warranted to validate and extend these findings.

Conclusion

This randomized controlled trial provided strong clinical evidence that liraglutide is an effective therapeutic strategy for the management of PCOS. Over a 24-week intervention, liraglutide achieved superior metabolic and anthropometric outcomes compared with metformin, demonstrating greater reductions in body weight, body mass index, waist circumference, and HOMA-IR, along with significant restoration of menstrual regularity. A higher proportion of clinical pregnancies was observed in the liraglutide group, alongside its distinct advantage in reducing central obesity and severe insulin resistance. Overall, These findings support

liraglutide as a highly effective preconception metabolic strategy in obesity-associated PCOS.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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Authors and Affiliations

Sara Medhat Georgy¹ · Nada Farag Elnaidany¹ · Nora A Abdelmoneum² · Sara Abdallah Mohamed Salem³ · Heba F. Salem⁴ · Rania M. Sarhan^{5,6}

✉ Rania M. Sarhan
raniamohammad87@yahoo.com; raniamssarhan343@gmail.com

Sara Medhat Georgy
smfekry@msa.edu.eg

Nada Farag Elnaidany
nfarag@msa.edu.eg

Nora A Abdelmoneum
drnoraabdelmoneum@gmail.com

Sara Abdallah Mohamed Salem
sara.abdalla@med.bsu.edu.eg

Heba F. Salem
heba_salem2004@yahoo.co.uk

¹ Clinical Pharmacy Department, Faculty of Pharmacy, MSA October University, October City 6th, Egypt

² Clinical Nutrition Specialist, Rheumatology Specialist, Head of Clinical Nutrition Unit Beni Suef Special Hospital, Beni Suef, Egypt

³ Department of Obstetrics and Gynecology, Faculty of Medicine, Beni-Suef University, Beni-Suef 62511, Egypt

⁴ Pharmaceutics and Industrial Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, P.O. Box 62514, Beni-Suef, Egypt

⁵ Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef 62521, Egypt

⁶ Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef National University, Beni-Suef 62521, Egypt