Adv Ther (2025) 42:3762–3773
https://doi.org/10.1007/s12325-025-03251-2

ORIGINAL RESEARCH

# Sustained Metabolic Improvements with Low-Dose Metformin Combined with Oral Contraceptives in Female Adolescents with PCOS: A Single-Center Retrospective Cohort Study

Salvatore Giovanni Vitale · Stefano Di Michele · Alice Tassi · Claudia Succu · Stefano Angioni · Anna Maria Fulghesu

Received: March 17, 2025 / Accepted: May 15, 2025 / Published online: June 6, 2025


## ABSTRACT

***Introduction*:** This study aimed to evaluate metformin treatment's immediate and long-term efficacy in adolescent patients with polycystic ovary syndrome (PCOS) and hyperinsulinemia and the subsequent metabolic evolution post-treatment discontinuation.

***Methods*:** This single-center, retrospective cohort study included 168 adolescent girls (12–17 years) diagnosed with PCOS between December 2018 and August 2024. All participants underwent an oral glucose tolerance test to evaluate insulin sensitivity and were stratified into two groups: patients with normal insulinemia ($n=21$) and patients with hyperinsulinemia ($n=147$). Patients with hyperinsulinemia were offered low-dose metformin (500 mg twice daily); 80 accepted and formed the treatment arm, while 53 declined and served as controls. Simultaneously, every subject received a continuous regimen of combined oral contraceptives (COCs) (30 µg ethinyl estradiol/3 mg drospirenone). Clinical, biochemical, and ultrasound assessments were conducted at baseline, at regular intervals during therapy, at the end of treatment, and at least 24 months after metformin discontinuation to evaluate immediate and long-term outcomes.

***Results*:** Metformin therapy yielded favorable body mass index, insulin sensitivity, and androgenic profile outcomes. Remarkably, these benefits persisted beyond the cessation of treatment. Metformin responders showed a ≥ 20% decrease in the insulin area under the curve values post-treatment. Our investigation revealed a substantial reduction in insulin resistance indices, evident both after therapy ($p<0.001$) and during post-therapy follow-up ($p=0.001$) compared to baseline values. Furthermore, patients showed improvements in clinical hyperandrogenism and reductions in ovarian volume.

***Conclusions*:** Our study highlights the effectiveness of low-dose metformin therapy in improving insulin resistance and metabolic parameters among adolescent patients with PCOS. Sustained benefits were observed even after treatment cessation. These findings underscore the potential for early intervention with metformin during adolescence to confer long-lasting advantages in managing metabolic abnormalities associated with PCOS.

S. G. Vitale · S. Di Michele (✉) · C. Succu · S. Angioni · A. M. Fulghesu
Division of Gynecology and Obstetrics, Department of Surgical Sciences, University of Cagliari, Via Università 40, 09124 Cagliari, Italy
e-mail: dr.dimichelestefano@gmail.com

A. Tassi
Obstetrics and Gynecology Unit, Morgagni-Pierantoni Hospital, Forlì, Italy

**Keywords:** Adolescents; Hyperandrogenism; Insulin; Insulin resistance; Metformin; Ovary; PCOS

**Key Summary Points**

*Why carry out this study?*

Addressing insulin resistance in polycystic ovary syndrome (PCOS), the study explores a low-dose metformin regimen as a potential strategy to mitigate these adverse effects in a real-world clinical setting.

The investigation tested the hypothesis that a low-dose metformin protocol, when combined with standardized oral contraceptives, would improve insulin sensitivity and reduce hyperinsulinemia in patients with PCOS.

*What was learned from the study?*

Metformin responders exhibited a significant (≥ 20%) reduction in insulin area under the curve (AUC) alongside improvements in the homeostasis model assessment index (HOMA) and ovarian morphology, indicating enhanced metabolic control.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder in reproductive-age women, characterized by a combination of symptoms and diagnostic features. According to the Rotterdam criteria, PCOS is diagnosed by two of the following: anovulatory dysfunction, clinical/biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM) [1]. For adolescents, the criteria differ and include menstrual irregularity, clinical hyperandrogenism, and/or hyperandrogenemia, without needing a pelvic ultrasound. Adolescents showing PCOS features are considered "at risk for PCOS" [2]. While PCOM is often observed during adolescence as part of the normal ovarian maturation phase, it is known that when there is an increased stromal-to-ovarian area ratio with PCOM, it is significantly associated with hyperandrogenism and may act as an early indicator of the development of PCOS [3, 4]. Given the limitations and potential inaccuracies of current diagnostic methods, many adolescents find the prospect of undergoing an ovarian ultrasound particularly daunting [5]. This fear is well founded, considering that the adverse effects of PCOS on quality of life are intimately connected with elevated risks of infertility, hyperandrogenic consequences (including obesity, insulin resistance, hirsutism, and acne) [6], contributing to cardiovascular disease, adverse pregnancy outcomes requiring specific supplementation [7], type two diabetes, and depressive disorders [8–12]. Obesity-related dyslipidemia combined with altered insulin release in adolescents with PCOS illustrates the tight interconnection between metabolic and hormonal disruptions [13].

Additionally, intrauterine life and maternal environmental exposure are thought to influence fetal development and increase PCOS risk, though this is debated [14, 15]. Overweight pregnant women are more likely to have PCOS and often need dietary supplements and complementary strategies [16]. Understanding the link between insulin resistance and reproductive health underscores the need for therapeutic interventions. At the same time, many young women are increasingly concerned about their future fertility. Conditions such as endometriosis, now diagnosed earlier and known to compromise fertility and cause systemic complications, intensify these worries [17, 18]. Prompt and accurate identification of PCOS and any co-existing gynecological disorders is therefore essential to begin a targeted treatment without delay. The most recent 2023 International Evidence-based Guideline for the Assessment and Management of PCOS recommends a multimodal approach in adolescents, combining lifestyle modification, hormonal contraceptives, and, when indicated, insulin-sensitizing agents such as metformin [19]. In routine clinical practice, first-line therapy typically includes dietary and exercise counseling alongside combined oral contraceptives (COCs) to regulate menstrual cycles and reduce signs of hyperandrogenism. However, COCs alone frequently fail to improve insulin resistance, even when given in

early adolescent PCOS [20]. Insulin can directly increase androstenedione secretion in thecal cells, and in concert with luteinizing hormone (LH), upregulates its expression to enhance androgen synthesis, thus reinforcing the reciprocal amplification mechanism between insulin resistance and hyperandrogenism [21]. Adding metformin significantly improves insulin sensitivity, lowers hyperinsulinemia, and helps break the vicious insulin-resistance–hyperandrogenism cycle that drives PCOS pathogenesis [20, 22].

This study aimed to evaluate the immediate and long-term efficacy of metformin in adolescents with PCOS and hyperinsulinemia and the evolution of their metabolic status post-treatment.

## METHODS

### Study Design

This single-center retrospective cohort study enrolled patients from a clinical database collected at the Outpatient Pediatric and Adolescent Gynecology Clinic of the University Hospital "*Duilio Casula*," Monserrato, University of Cagliari, Italy, between December 2018 and August 2024.

### Ethical Approval

The study adhered to the Declaration of Helsinki. Regarding informed consent, in our university gynecology outpatient clinic, it is standard practice to have patients sign a general consent form stating that their data may be used for retrospective studies and potentially published in the future. Specifically, for adolescent and therefore underage patients, such as those included in this retrospective study, parental consent is obtained for both participation in the study and potential publication of the data in our database. Informed consent was obtained from parents for each subject. Institutional review board approval was secured from the Sardinia Regional Territorial Ethics Committee (prot. no. 41, 27-5-2024 All. 2.10).

### Participants and Diagnostic Criteria

We included patients newly diagnosed with PCOS at our clinic with no prior PCOS diagnosis. The diagnosis of PCOS was adapted for age based on the 2019 update by Witchel and Carmina's recommendation [2, 23, 24]. Our study included 168 white patients with PCOS aged 12 to 17 years.

### Clinical and Lifestyle Assessment

Each participant underwent a focused physical examination, a structured medical interview, fasting blood collection, and pelvic ultrasonography. We documented gynecological age (years since menarche) and calculated body mass index (BMI). Degree of hirsutism was scored with the modified Ferriman-Gallwey score [25], while acne severity was graded according to the Cremoncini classification [26]. All adolescents received personalized counselling on diet and exercise. Practical guidance covered food groups, portion sizes, and macronutrient balance as outlined in the Italian LARN recommendations. Consistent with the 2023 International PCOS guideline, we advised a weekly minimum of 150 min of moderate aerobic activity (or 75 min of vigorous activity) plus two sessions of resistance training to limit weight gain and sedentary behavior [19].

### Laboratory Testing and Ultrasound

Blood samples were drawn after an overnight fast (10–12 h) during the early follicular phase (cycle days 3–7). Amenorrhoeic patients first received medroxyprogesterone acetate, 10 mg daily for 5 days, to induce withdrawal of bleeding. Serum concentrations of follicle-stimulating hormone (FSH), LH, 17-β estradiol (E2), total testosterone (TT), delta-4-androstenedione (A), 17-hydroxyprogesterone (17-OH-P), and sex hormone-binding globulin (SHBG) were measured by chemiluminescent immunoassay. The following morning at 09:00, a 75-g oral-glucose-tolerance test (OGTT) was performed. Venous blood was taken at 0, 60,

90, 120, and 180 min for glucose and insulin. Areas under the curve (AUC) were computed by the trapezoidal method and expressed as mIU/ml/180 min for insulin. Glycemic responses were classified with National Diabetes Data Group criteria [27]; an insulin AUC < 16,900 mIU/ml/180 min was considered normal [28]. Insulin resistance was estimated using the homeostatic model assessment index (HOMA) [29]. On the same day, a single experienced sonographer assessed ovarian morphology and volume using a 7.5-MHz transabdominal probe with a full bladder or, when appropriate, a transvaginal probe. Ovarian volume was calculated with the prolate-ellipsoid equation, averaged across both ovaries, and adjusted for gynecological age to account for developmental differences. No dominant follicles or cysts were observed in any participant.

### Group Allocation and Interventions

Based on the results of the OGTT, patients with PCOS exhibited normal insulinemia or hyperinsulinemia. After the OGTT, those with normal insulinemia were excluded, and the remaining patients were categorized into two groups: the study group, which included patients who underwent metformin therapy, and the control group, which encompassed those who refused to participate in this treatment throughout the study. Patients were allocated to the metformin or control groups based on standardized clinical criteria and informed patient choice, reflecting real-world clinical practice. Robust statistical adjustments were applied to control for potential confounding factors associated with this allocation method. Specifically, the study group (metformin + COCs) received metformin at a dosage determined according to Fulghesu et al. [30], who demonstrated that "low-dose" metformin (1000 mg/day) has comparable efficacy to higher doses (1500–1700 mg/day). Therefore, patients initially received half of the intended dose (250 mg twice daily), which was increased over 1 week to reach the target dose (500 mg twice daily), minimizing gastrointestinal side effects. Both the study and control groups received the same COCs, containing drospirenone 3 mg and ethinyl estradiol 20 µg (3 mg DRSP/20 µg EE-24/4).

Additionally, both groups received structured guidance on lifestyle modifications, including dietary changes and regular physical activity. None of these patients were already on hormonal treatment at the baseline evaluation, and all the patients among the two groups continued COC therapy for the entire 24-month follow-up period, deliberately inducing regular withdrawal bleeding and precluding assessment of spontaneous oligomenorrhea or amenorrhea during the study period. Patients kept detailed physical activity logs, medication regimens, and dietary intake using electronic forms. Investigators monitored these logs in real time, correcting errors and maintaining direct patient communication.

### Follow-up and Outcome Measures

Follow-ups were conducted every 3–6 months in the first year and after 12 months using OGTT and clinical evaluations. After 24 months of treatment, patients repeated clinical and laboratory examinations and continued assessment at least 24 months after discontinuing metformin therapy. Baseline data are expressed as b-AUC, b-HOMA, and b-BMI. End-of-therapy data are described as e-AUC, e-HOMA, and e-BMI. Post-therapy data are reported as ae-AUC, ae-HOMA, and ae-BMI. Post-treatment assessments were performed 24–30 months after metformin discontinuation. Dietary intake and physical activity logs were maintained and reviewed at each visit, including the post-treatment assessments, to confirm no systematic differences in lifestyle between groups.

### Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics version 26. Measurement data were expressed as mean ± SD, and the paired samples *t*-test was used. Count data were expressed as *n* (%), with the beta coefficient of linear regression and 95% CI reported. In all analyses, a *p*-value < 0.05 was considered significant. Moreover, group differences at follow-up

were evaluated with an analysis of covariance (ANCOVA). The insulin area under the curve at follow-up (ae-AUC) was the dependent variable; treatment allocation (metformin + COCs vs COCs) was entered as a fixed factor, while baseline AUC (b-AUC) and baseline body mass index (BMI) served as covariates. The "Group × b-AUC" interaction term was added to test the homogeneity-of-regression-slopes assumption; because this term was not significant ($p > 0.10$), the final model excluded the interaction. We report Type III $F$-statistics, partial $\eta^2$, and adjusted (estimated) marginal means with 95% confidence intervals. A sensitivity analysis compared change scores (Δ = ae-AUC − b-AUC) between groups using an independent samples $t$-test. Two-tailed $p < 0.05$ was considered statistically significant.

## RESULTS

Our population comprises 168 patients with PCOS aged 12–17 years at the time of recruitment. The patients' gynecological age at recruitment was 3.4 ± 1.4 years. Patients were divided, after OGTT, into normoinsulinemic ($n = 21$) and hyperinsulinemic ($n = 147$). Among patients with PCOS and hyperinsulinemia, nine dropped out of the study, and five withdrew from the study because of persistent gastrointestinal side effects (nausea and diarrhea). No severe side effects related to the therapy have been reported. We separately evaluated patients with PCOS and hyperinsulinemia undergoing metformin therapy ($n = 80$) and patients with PCOS and hyperinsulinemia who did not receive metformin treatment ($n = 53$). Figure 1 shows the study enrollment flow chart. The baseline clinical, anthropometric, and hormonal characteristics are similar in patients undergoing therapy and the control group (Table 1). Data from 80 patients with hyperinsulinemia treated with metformin were analyzed. This population had a mean age of 15.7 ± 2.0 years, and the average BMI was 28.7 ± 7.2 kg/m$^2$. At the first evaluation, the mean value of the area under the insulin curve (b-AUC) was 22,653 ± 5307 µUI/ml. The initial mean value of the HOMA index was 3.2 ± 1.7. The mean duration of metformin

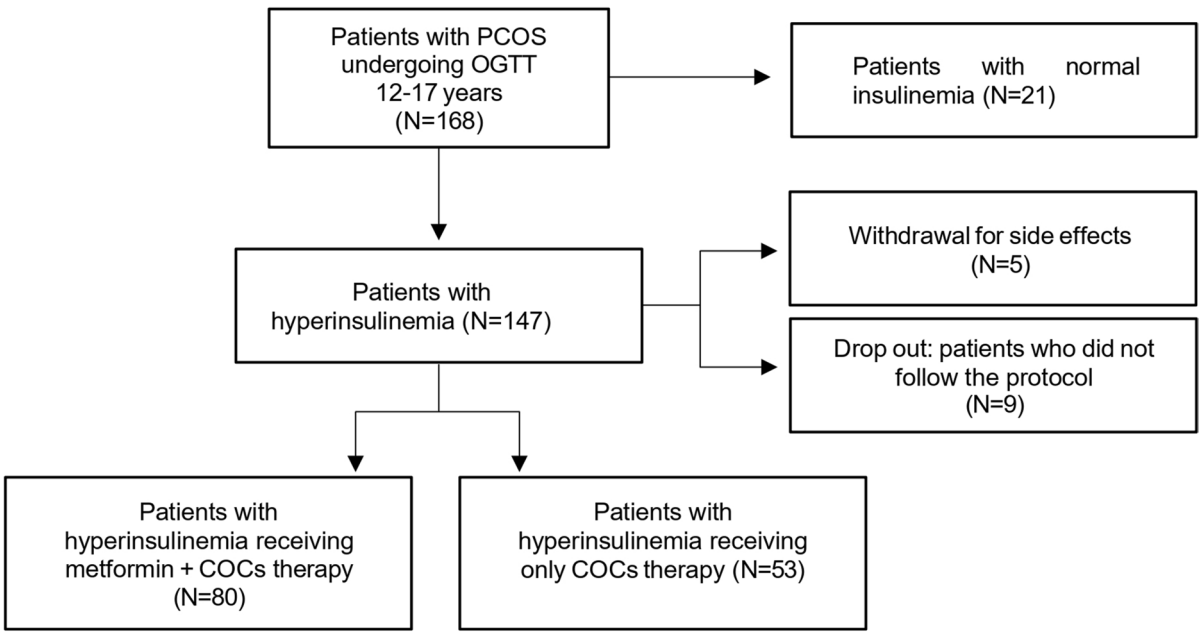


**Fig. 1** Study enrollment flow chart. *PCOS* polycystic ovary syndrome, *OGTT* oral glucose tolerance test, *COCs* combined oral contraceptives

**Table 1** Anthropometric, clinical, metabolic, hormonal, and ultrasound characteristics concerning metformin therapy and the control group

| | Metformin + COCs | | | | COCs | | |
|---|---|---|---|---|---|---|---|
| | Baseline ($n=80$) | End of metformin treatment ($n=80$) | After the end of the treatment ($n=80$) | $p$ | Baseline | After 2–3 years | $p$ |
| BMI (kg/m$^2$) | 28.7 ± 7.2 | 27.9 ± 5.9 | 26.5 ± 3.7 | 0.02a | 25.1 ± 6.4 | 24.1 ± 6.4 | NS |
| WHR | 0.9 ± 0.1 | 0.7 ± 0.1 | 0.6 ± 0.03 | NS | 0.9 ± 0.1 | 0.7 ± 0.0 | NS |
| Fasting glucose (mmol/l) | 84.6 ± 5.8 | 77.2 ± 5.4 | 82.9 ± 6.8 | 0.001[b] 0.001[a] | 79.6 ± 10.4 | 80.9 ± 8.8 | NS |
| Fasting insulin (μUI/ml) | 18.3 ± 9.7 | 15.2 ± 5.9 | 16.1 ± 6.0 | 0.003[a] 0.05[b] | 14.8 ± 9.7 | 16.1 ± 6.2 | NS |
| HOMA index | 3.2 ± 1.7 | 2.7 ± 1.5 | 2.5 ± 1.4 | 0.035[b] | 2.7 ± 1.7 | 2.8 ± 1.6 | NS |
| Ovarian volume (cm3) | 9.7 ± 5.7 | 5.8 ± 2.9 | 5.4 ± 2.7 | < 0.01[b] | 9.6 ± 2.3 | 9.3 ± 1.9 | NS |
| Androstenedione (ng/ml) | 2.3 ± 0.9 | 2.1 ± 0.8 | 2.0 ± 0.09 | NS | 2.6 ± 0.9 | 2.3 ± 1.1 | NS |
| Testosterone (ng/ml) | 0.7 ± 0.4 | 0.5 ± 0.3 | 0.4 ± 0.2 | 0.02[b] | 0.7 ± 0.4 | 0.6 ± 0.4 | NS |
| SHBG (nmol/l) | 66 ± 38.2 | 74.9 ± 39.0 | 76.8 ± 33.2 | 0.03[a] 0.05[b] | 66.9 ± 35.6 | 76.1 ± 40 | NS |
| 17-OHP (ng/ml) | 1.2 ± 0.7 | 1.1 ± 0.6 | 1.2 ± 0.7 | NS | 1.4 ± 0.8 | 1.2 ± 0.8 | NS |

The significant differences are indicated as follows: [a]baseline vs end of treatment; [b]baseline vs after end of treatment

*COCs* combined oral contraceptives, *BMI* body mass index, *WHR* waist-hip ratio, *HOMA* homeostatic model assessment index, *SHBG* sex hormone binding globulin, *17-OHP* 17-hydroxyprogesterone, *NS* not significant

therapy was 25.3 ± 2.1 months (Table 1). We compared the baseline AUC values (b-AUC) of patients who received metformin therapy with the AUC values at the end of treatment (e-AUC) and after the end of therapy (ae-AUC). The analysis showed a significant decrease in AUC values by both comparing the b-AUC and e-AUC values ($p<0.001$) and comparing the b-AUC values with the ae-AUC ($p=0.001$), as shown in Fig. 2. Table 1 shows that BMI is reduced during metformin therapy, but this benefit becomes significant after treatment. Similarly, the waist-to-hip ratio (WHR) appeared to decrease, but not significantly. Moreover, we compared the baseline HOMA values (b-HOMA) of patients who received metformin therapy with the HOMA values at the end of treatment (e-HOMA) and after the end of therapy (ae-HOMA). The analysis showed a significant decrease in HOMA values when comparing b-HOMA and ae-HOMA values ($p=0.035$). However, no significant reduction was found when comparing the values of b-HOMA with those of e-HOMA. Regarding ovarian volume, our data showed a significant reduction between baseline values and those after the end of treatment (9.7 ± 5.7 vs. 5.4 ± 2.7; $p<0.01$) and a minimum decrease in the untreated population after 2–3 years (9.6 ± 2.3 vs. 9.3 ± 1.9; $p<0.25$). Finally, we assessed the percentage of patients considered responders to metformin.

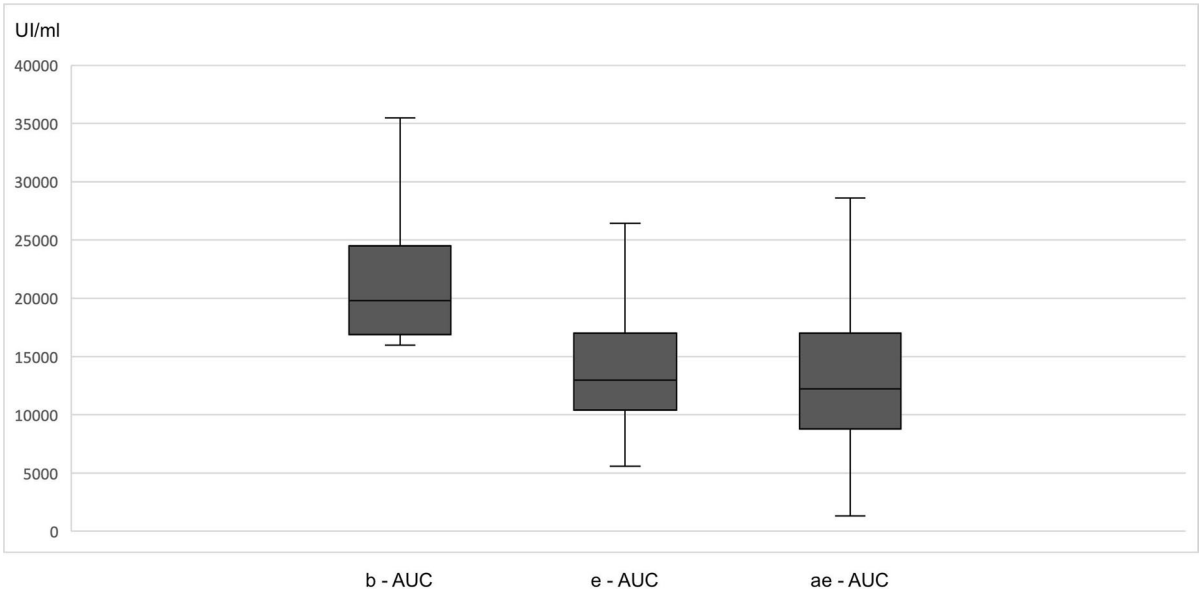


**Fig. 2** Area under the curve (AUC) values at baseline (b-AUC), at the end of therapy (e-AUC), and after the end of treatment (ae-AUC)

Eventually, approximately 70% of the patients responded to therapy, while about 23% were non-responders. Metformin responders had a ≥ 20% decrease in insulin AUC values during and after therapy, while non-responders had a decline of < 10%. Furthermore, about 75% of the patients reacted to insulin levels after the end of metformin therapy, with a decrease in AUC > 20%. At the same time, 13% of this population showed a reduction of < 10%. Furthermore, we analyzed data from patients not treated with metformin ($n = 53$). This population had a mean age of 15.6 ± 1.6 years at the time of recruitment, and the mean BMI was 25.1 ± 6.4 kg/m$^2$. At the first evaluation, the mean value of the area under the insulin curve (b-AUC) was 18,712 ± 2004 µUI/ml. The initial mean value of the HOMA index was 2.7 ± 1.7. We compared the baseline AUC values of the control patients with the AUC values after 2–3 years without metformin therapy. Without insulin sensitizer therapy, we found no substantial changes over time. There was almost a decrease in the area under the insulin curve in control patients, but this variation was not significant. Clinical hyperandrogenism, assessed by the FG score, showed a notable improvement in both groups. At baseline, the combined mean score across study and control patients was 14.3 ± 3.2. After treatment (or follow-up in the control group), the mean FG score decreased to 9.9 ± 2.8, corresponding to an overall average reduction of approximately 30%. No significant difference in FG score reduction was observed between the two groups. Additionally, as depicted in Table 1, patients receiving metformin in combination with the COCs showed a significant decrease in testosterone levels ($p < 0.02$). Moreover, the free androgen index (FAI) decreased significantly from 3.7 ± 1.2 at baseline to 1.8 ± 0.7 after therapy. In contrast, the COC-only group showed a non-significant reduction from 3.5 ± 1.1 to 3.2 ± 1.0. This difference was not relevant in those taking the COCs alone. After adjusting for baseline AUC and BMI, ANCOVA confirmed the efficacy of metformin [$F(1, 129) = 95.1$, $p < 0.001$, partial $\eta^2 = 0.42$]. The adjusted mean ae-AUC was 15,047 mIU/ml/180 min (95% CI 14,445–15,649) in the metformin group versus 20,092 mIU/ml/180 min (95% CI 19,334–20,851) in controls. The Group × b-AUC interaction was not significant ($p = 0.78$).

## DISCUSSION

Metformin is among the most prescribed drugs for women with PCOS despite its mostly off-label use in this population [31]. The indications for its use have yet to be established, but the metabolic health effects of metformin on PCOS are multiple. However, its efficacy in preventing insulin resistance and diabetes appears well determined [32, 33]. According to the literature, patients with insulin resistance benefited from metformin therapy [34, 35].

Our study confirmed the generally positive effects of metformin on the clinical, hormonal, and metabolic characteristics of patients with PCOS. Furthermore, once metformin treatment has been finished, AUC values are reduced even at a distance. This reduction is not evident in the untreated population.

Our data indicate that the metabolic improvements achieved with metformin persist for at least 2 years after the drug has been discontinued. In contrast, earlier studies have reported that these benefits generally disappear within 12 months of stopping treatment [36]. A significant reduction in mean BMI after metformin therapy was found. This difference was not reported in patients who refused treatment. According to the study by Hostalek et al. [37], metformin therapy can significantly reduce BMI, and several studies have shown that metformin can cause positive changes in the microbiota in conjunction with diet and exercise [38–40]. All patients reported increased physical activity and attention to nutrition. During follow-ups, detailed activity logs and food diaries showed no significant differences in physical activity and diet. Despite overall lifestyle improvements in both groups, only those treated with metformin showed significant metabolic improvements, indicating metformin's essential role. Covariance analysis revealed that baseline BMI, fasting insulin, fasting glucose, and HOMA index did not significantly affect outcomes, confirming metformin's efficacy. These findings underscore the reliability of the study and the effectiveness of metformin therapy in adolescent patients with PCOS.

Regarding ultrasound, assessment of ovarian stroma and its correlation with circulating androgens has been validated as a valid diagnostic criterion in PCOS [41] and remains an important yet underutilized diagnostic tool in adolescents with PCOS. Although the most recent international guidelines discourage ultrasound diagnosis in adolescents because of high variability and overlap with normal ovarian physiology [19], emerging evidence suggests that specific sonographic parameters, such as stromal echogenicity, follicle number, size, and spatial distribution, may provide crucial insights into early PCOS diagnosis. Stromal echogenicity and altered follicular distribution might represent early manifestations of hyperandrogenism-driven follicular dysplasia, even before clinical hyperandrogenism or metabolic alterations [3, 4]. Consistent with the literature [42], we found that metformin therapy can reduce ovarian volume; our result shows that metformin use effectively reduces ovarian volume and androgens on top of the COCs treatment. Indeed, our study also highlights an improvement in the hormonal profile, with a reduction in testosterone levels and an increase in SHBG levels. Metformin plus COCs appears to improve androgenic control compared to using COCs alone. This observation aligns with previous studies showing that metformin reduces hyperandrogenism in insulin-resistant women with PCOS. Indeed, a study by Ohara et al. [43] reported that metformin administration could act on androgen receptors (epithelial and stromal), reducing their expression. These and other findings reported in the literature demonstrate that insulin resistance can contribute to hyperandrogenism and that metformin can reduce it [35, 44, 45]. In our population, the study and control groups took COCs during follow-up. Our data confirm what was found in a recent Cochrane review, where metformin therapy associated with COCs improves androgen control compared to COCs alone [46]. However, in our study, it is noteworthy that while both groups experienced improvements in clinical hyperandrogenism, only patients treated with metformin reported a significant improvement in biochemical hyperandrogenism. Moreover, approximately 70% of

treated patients responded to metformin therapy. A study by Fulghesu et al. showed that patients with a higher baseline BMI and weight had a better response to metformin [30]. Our findings further reinforce the concept that metabolic dysregulation plays a pivotal role in the pathogenesis and clinical expression of PCOS, particularly in adolescents. Metformin-induced improvement in insulin sensitivity and metabolic parameters significantly improves clinical hyperandrogenism, supporting the hypothesis of a central role for insulin resistance in the pathophysiology of hyperandrogenic PCOS. This aligns with the recent classification proposed by the Expert Group on Integrated PCOS (EGOI-PCOS), which emphasizes metabolic dysfunction as a key factor underlying hyperandrogenic phenotypes, highlighting the need for tailored therapy to correct underlying metabolic disturbances [47]. Indeed, the sustained metabolic improvements observed here underscore insulin resistance as a key upstream driver of hyperandrogenism and support early metabolic intervention in adolescents.

Furthermore, the sensitivity of patients with PCOS to metformin has been found to be related to genetic variations, such as OCT1, that may be associated with the metabolic response to metformin heterogeneity in women with PCOS [48]. Significant limitations of this study include its retrospective design and small population; large-scale randomized controlled trials are needed for confirmation. Although combined oral contraceptives are typically expected to lower circulating androgens and raise SHBG, our control cohort showed no statistically significant change in testosterone, androstenedione, SHBG, or ovarian volume. This paradoxical result is most plausibly explained by the limited sample size, the pronounced inter-individual hormonal variability characteristic of adolescence, and the use of fixed sampling windows, which may have obscured more gradual or modest shifts occurring outside the scheduled assay times.

Despite these limitations, low-dose metformin therapy showed short- and long-term improvements in insulin resistance, BMI, and androgen profile. Treating PCOS in adolescence could enhance women's long-term metabolic profile. Low-dose metformin effectively improves insulin profiles over time, similar to higher doses but with fewer side effects [30].

## CONCLUSION

In this single-center cohort, low-dose metformin added to combined oral contraceptives produced significant and durable improvements in insulin sensitivity, BMI, androgen profile, and ovarian volume in adolescents with PCOS and hyperinsulinemia. Benefits persisted for at least 2 years after drug discontinuation, suggesting that early metabolic intervention during adolescence may confer long-lasting protection against the cardiometabolic sequelae of PCOS. These findings support the consideration of initiating low-dose metformin as soon as possible, given that adolescence is a time when the metabolism can still be influenced, as part of a multimodal management strategy in this population, pending confirmation by randomized trials.

## ACKNOWLEDGEMENTS

We are deeply grateful to the adolescents and their families, whose willingness to participate and commitment to follow-up made this study possible.

***Author Contributions.*** Salvatore Giovanni Vitale: conceptualization, formal analysis, validation, supervision, and writing-original draft; Stefano Di Michele: writing-original draft, writing-review & editing, data curation, formal analysis, investigation, and validation; Alice Tassi: conceptualization, data curation, writing-original draft; Claudia Succu: data curation; Stefano Angioni: validation. Anna Maria Fulghesu: conceptualization, investigation, methodology, project administration, supervision, and validation.

***Funding.*** No funding or sponsorship was received for this study or publication of this article.

***Data Availability.*** Due to the sensitive nature of the information obtained in this study,

survey respondents were assured that raw data would remain confidential and would not be shared.

### *Declarations*

***Conflict of Interest.*** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Salvatore Giovanni Vitale is an Editorial Board Member of Advances in Therapy and was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Stefano Di Michele, Alice Tassi, Claudia Succu, Stefano Angioni, and Anna Maria Fulghesu have nothing to disclose.

***Ethical Approval.*** The study adhered to the Declaration of Helsinki. Informed consent was obtained from parents for each subject. Institutional review board approval was secured from the Sardinia Regional Territorial Ethics Committee (prot. no. 41, 27-5-2024 All. 2.10). Regarding informed consent, in our university gynecology outpatient clinic, it is standard practice to have patients sign a general consent form, which states that their data may be used for retrospective studies and potentially published in the future. Specifically, for adolescent and therefore underage patients, such as those included in this retrospective study, parental consent is obtained for both participation in the study and the potential publication of the data within our database.



## REFERENCES

1. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19:41–7.

2. Witchel SF, Oberfield SE, Peña AS. Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. J Endocr Soc. 2019;3:1545–73.

3. Fulghesu AM, Di Michele S, Zangaris I, Cordella M, Pittui E, Scalise G, et al. Clinical and ultrasound features of normocyclic non-hyperandrogenic adolescents in early gynecological life. Gynecol Obstet Investig. 2024. https://doi.org/10.1159/000542393.

4. Di Michele S, Fulghesu AM, Pittui E, Cordella M, Sicilia G, Mandurino G, et al. Ultrasound assessment in polycystic ovary syndrome diagnosis: from origins to future perspectives—a comprehensive review. Biomedicines. 2025;13:453.

5. Kolhe JV, Chhipa AS, Butani S, Chavda V, Patel SS. PCOS and depression: common links and potential targets. Reprod Sci. 2022;29:3106–23.

6. Cussons AJ, Stuckey BGA, Watts GF. Cardiovascular disease in the polycystic ovary syndrome: new insights and perspectives. Atherosclerosis. 2006;185:227–39.

7. Vitale SG, Fiore M, La Rosa VL, Rapisarda AMC, Mazza G, Paratore M, et al. Liposomal ferric pyrophosphate and ascorbic acid supplementation in pregnant women with iron deficiency anaemia: haematochemical, obstetric, neonatal and psychological outcomes in a prospective observational study. Int J Food Sci Nutr. 2022;73:221–9.

8. Fulghesu AM, Piras C, Dessì A, Succu C, Atzori L, Pintus R, et al. Urinary metabolites reveal hyperinsulinemia and insulin resistance in polycystic ovarian syndrome (PCOS). Metabolites. 2021;11:437.

9. D'Alterio MN, Sigilli M, Succu AG, Ghisu V, Laganà AS, Sorrentino F, et al. Pregnancy outcomes in

women with polycystic ovarian syndrome. Minerva Obstet Gynecol. 2022;74:45–59.

10. Vitale SG, Fulghesu AM, Mikuš M, Watrowski R, D'Alterio MN, Lin L-T, et al. The translational role of miRNA in polycystic ovary syndrome: from bench to bedside-a systematic literature review. Biomedicines. 2022;10:1816.

11. Fulghesu AM, Manca R, Loi S, Fruzzetti F. Insulin resistance and hyperandrogenism have no substantive association with birth weight in adolescents with polycystic ovary syndrome. Fertil Steril. 2015;103:808–14.

12. Salman H, Shah M, Ali A, Aziz A, Vitale SG. Assessment of relationship of serum neurokinin-B level in the pathophysiology of pre-eclampsia: a case-control study. Adv Ther. 2018;35:1114–21.

13. Fulghesu A, Magnini R, Portoghese E, Angioni S, Minerba L, Melis GB. Obesity-related lipid profile and altered insulin incretion in adolescents with polycystic ovary syndrome. J Adolesc Health. 2010;46:474–81.

14. Sanchez-Garrido MA, Tena-Sempere M. Metabolic dysfunction in polycystic ovary syndrome: pathogenic role of androgen excess and potential therapeutic strategies. Mol Metab. 2020;35: 100937.

15. Abdalla MA, Deshmukh H, Atkin S, Sathyapalan T. A review of therapeutic options for managing the metabolic aspects of polycystic ovary syndrome. Ther Adv Endocrinol Metab. 2020;11:2042018820938305.

16. Vitale SG, Corrado F, Caruso S, Di Benedetto A, Giunta L, Cianci A, et al. Myo-inositol supplementation to prevent gestational diabetes in overweight non-obese women: bioelectrical impedance analysis, metabolic aspects, obstetric and neonatal outcomes - a randomized and open-label, placebo-controlled clinical trial. Int J Food Sci Nutr. 2021;72:670–9.

17. Di Michele S, Bramante S, Angioni S, Bernassola M, De Vita T, Iaccarino DA, et al. Superficial peritoneal endometriosis vaporization using a $CO_2$ laser: a long-term single-center experience. J Clin Med. 2024;13:1722.

18. Di Michele S, Bramante S, Rosati M. A systematic review of ureteral reimplantation techniques in endometriosis: laparoscopic versus robotic-assisted approach. J Clin Med. 2024;13:5677.

19. Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod. 2023;38:1655–79.

20. de Zegher F, Ibáñez L. Leader vs follower in the tango of polycystic ovary syndrome: Insulin resistance vs androgen excess. Acta Obstet Gynecol Scand. 2024;103:1680–1.

21. Zeng X, Xie Y, Liu Y, Long S, Mo Z. Polycystic ovarian syndrome: correlation between hyperandrogenism, insulin resistance and obesity. Clin Chim Acta. 2020;502:214–21.

22. Unfer V, Lepore E, Forte G, Hernández Marín I, Wdowiak A, Pkhaladze L. Hyperandrogenism in polycystic ovary syndrome and adrenal hyperplasia: finding differences to make a specific diagnosis. Arch Gynecol Obstet. 2025;311:25–32.

23. Peña AS, Codner E, Witchel S. Criteria for diagnosis of polycystic ovary syndrome during adolescence: literature review. Diagnostics (Basel). 2022;12:1931.

24. Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. Am J Obstet Gynecol. 2010;203(201):e1-5.

25. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab. 1961;21:1440–7.

26. Cremoncini C, Vignati E, Libroia A. Treatment of hirsutism and acne in women with two combinations of cyproterone acetate and ethinylestradiol. Acta Eur Fertil. 1976;7:299–314.

27. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1979;28:1039–57.

28. Fulghesu AM, Angioni S, Portoghese E, Milano F, Batetta B, Paoletti AM, et al. Failure of the homeostatic model assessment calculation score for detecting metabolic deterioration in young patients with polycystic ovary syndrome. Fertil Steril. 2006;86:398–404.

29. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.

30. Fulghesu AM, Romualdi D, Di Florio C, Sanna S, Tagliaferri V, Gambineri A, et al. Is there a dose-response relationship of metformin treatment in patients with polycystic ovary syndrome? Results from a multicentric study. Hum Reprod. 2012;27:3057–66.

31. Ali D, Shah M, Ali A, Malik MO, Rehman F, Badshah H, et al. Treatment with metformin and combination of metformin plus pioglitazone on serum levels of IL-6 and IL-8 in polycystic ovary

syndrome: a randomized clinical trial. Horm Metab Res. 2019;51:714–22.

32. McCartney CR, Marshall JC. Clinical practice. Polycystic ovary syndrome. N Engl J Med. 2016;375:54–64.

33. Sam S, Ehrmann DA. Metformin therapy for the reproductive and metabolic consequences of polycystic ovary syndrome. Diabetologia. 2017;60:1656–61.

34. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. J Clin Endocrinol Metab. 2000;85:139–46.

35. Ding H, Zhang J, Zhang F, Zhang S, Chen X, Liang W, et al. Resistance to the insulin and elevated level of androgen: a major cause of polycystic ovary syndrome. Front Endocrinol (Lausanne). 2021;12: 741764.

36. Palomba S, Falbo A, Russo T, Manguso F, Tolino A, Zullo F, et al. Insulin sensitivity after metformin suspension in normal-weight women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2007;92:3128–35.

37. Hostalek U, Campbell I. Metformin for diabetes prevention: update of the evidence base. Curr Med Res Opin. 2021;37:1705–17.

38. Deledda A, Annunziata G, Tenore GC, Palmas V, Manzin A, Velluzzi F. Diet-derived antioxidants and their role in inflammation, obesity and gut microbiota modulation. Antioxidants (Basel). 2021;10:708.

39. Jevtovic F. Combination of metformin and exercise in management of metabolic abnormalities observed in type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2021;14:4043–57.

40. Kimura T, Kaneto H. Metformin induces insulin secretion by preserving pancreatic aquaporin 7 expression in type 2 diabetes mellitus. J Diabetes Investig. 2022;13:227–9.

41. Fulghesu AM, Angioni S, Frau E, Belosi C, Apa R, Mioni R, et al. Ultrasound in polycystic ovary syndrome—the measuring of ovarian stroma and relationship with circulating androgens: results of a multicentric study. Hum Reprod. 2007;22:2501–8.

42. Farimani Sanoee M, Neghab N, Rabiee S, Amiri I. Metformin therapy decreases hyperandrogenism and ovarian volume in women with polycystic ovary syndrome. Iran J Med Sci. 2011;36:90–5.

43. Ohara M, Yoshida-Komiya H, Ono-Okutsu M, Yamaguchi-Ito A, Takahashi T, Fujimori K. Metformin reduces androgen receptor and upregulates homeobox A10 expression in uterine endometrium in women with polycystic ovary syndrome. Reprod Biol Endocrinol. 2021;19:77.

44. Sørensen AE, Udesen PB, Wissing ML, Englund ALM, Dalgaard LT. MicroRNAs related to androgen metabolism and polycystic ovary syndrome. Chem Biol Interact. 2016;259:8–16.

45. Bridger T, MacDonald S, Baltzer F, Rodd C. Randomized placebo-controlled trial of metformin for adolescents with polycystic ovary syndrome. Arch Pediatr Adolesc Med. 2006;160:241–6.

46. Fraison E, Kostova E, Moran LJ, Bilal S, Ee CC, Venetis C, et al. Metformin versus the combined oral contraceptive pill for hirsutism, acne, and menstrual pattern in polycystic ovary syndrome. Cochrane Database Syst Rev. 2020;8:CD005552.

47. Myers SH, Russo M, Dinicola S, Forte G, Unfer V. Questioning PCOS phenotypes for reclassification and tailored therapy. Trends Endocrinol Metab. 2023;34:694–703.

48. Gambineri A, Tomassoni F, Gasparini DI, Di Rocco A, Mantovani V, Pagotto U, et al. Organic cation transporter 1 polymorphisms predict the metabolic response to metformin in women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 2010;95:E204-208.