Effect of Metformin in adolescents with polycystic ovary syndrome

Original Article

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a frequent endocrine disorder affecting females in reproductive age and adolescent girls, frequently presenting with hyperandrogenism, menstrual irregularities, and metabolic dysfunction.

Aim: To evaluate the effect of metformin on ovulatory function, hormonal profiles, and hyperandrogenic features in adolescent girls with PCOS.

Methods: A prospective randomized controlled study was performed on 120 adolescent girls aged 15–18 years with PCOS attending Mansoura University Hospital. Participants have been randomly assigned to receive either 850 milligrams metformin tow times per day (Group A) or placebo (Group B) for 6 months. Clinical assessments included menstrual pattern, hirsutism (via Ferriman–Gallwey score), and acne. Hormonal and metabolic evaluations included LH, FSH, TSH, prolactin, testosterone, fasting insulin, glucose, HOMA-IR, and serum progesterone on cycle days 21.

Results: Metformin significantly reduced LH (47%) and testosterone (22.1%) levels compared to placebo ($p<0.001$, $p= 0.003$). Fasting insulin and HOMA-IR also diminished significantly in the metformin group ($p<0.001$). Serum progesterone levels and menstrual regularity improved, with oligomenorrhea declining from 52% to 18% ($p= 0.015$). However, changes in FSH, TSH, prolactin, and hirsutism scores were not statistically significant.

Conclusion: Metformin therapy significantly improves ovulatory and metabolic variables in adolescents with PCOS but has limited effects on hirsutism and other hormonal markers, suggesting the need for individualized treatment strategies and longer follow-up.

Key Words: Adolescents, metformin, ovulation polycystic ovary syndrome.

Received: 22 September 2025, **Accepted:** 27 September 2025.

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ISSN: 2090-7265, Vol. 15, 2025.

INTRODUCTION

PCOS is the most prevalent endocrinopathy between women, with an occurrence of six to ten percent according to National Institute of Health criteria and as high as fifteen percent when Rotterdam criteria are utilized. This is a chronic condition characterized by the onset of irregular menstruation and hyperandrogenic manifestations, typically beginning in adolescence, that can lead to issues involving infertility and metabolic complications over time[1].

PCOS is characterized by increased ovarian production of androgens and hyperinsulinemia; these manifestations are present in fifty to seventy percent of all females had PCOS and in about eighty percent of obese females had Polycystic ovary syndrome[2]. Hyperinsulinemia is more strongly associated with anovulation than any other feature of the syndrome. Hyperinsulinemia rises ovarian androgen secretion leading to abnormal ovarian follicular development and menstrual irregularities[3]. Females had Polycystic ovary syndromes are frequently overweight or obese (thirty-eight to sixty-six percent), though this doesn't form part of the diagnostic criteria for the disorder. Obesity on the other hand exacerbates symptoms and signs of insulin resistance and aggravates numerous of reproductive and metabolic features of PCOS such as menstrual irregularities and anovulation additionally diminishes the probability of natural conception and even conception after fertility management. Therefore, reduction of weight must be the 1st line treatement in obese females with anovulatory infertility related to Polycystic ovary syndrome[3].

De Leo *et al*., [4] assessed the influence of metformin therapy on ovulatory function, hirsutism, acne, hormonal patterns, and body weight in adult girls had PCOS, validated the positive influence of metformin on periods, and demonstrated that the medication may be given to young female to enhance ovulation and hyperandrogenic symptoms like hirsutism, acne, as well as weight gain.

DOI: 10.21608/EBWHJ.2025.424508.1508

This study aimed to evaluate influence of metformin management on ovulatory function, acne, hirsutism, hormone patterns in addition body weight in Adolescent girls had Polycystic ovary syndrome at Mansoura university hospitals in the period between 2022 to 2023.

PATIENTS AND METHODS

This was an observational prospective research performed on 120 cases attending there due to Menstrual irrigularitis and hyperandrogenic features at Obstetrics and Gynecology outpatient clinics at Mansoura university hospital clinics in the period between 2022 and 2023. Participants were distributed randomly in two groups with sixty participants in each one, Group A: Adolescents with pcos for Metformin Treatment and Group B: Placebo Group.

Inclusion criteria:

Patients Diagnosed to have PCOS regarding the revised 2004 Rotterdam criteria: Oligo- ovulation and or anovulation, hyperandrogenism (clinical or laboratory), aged between 15-18, BMI≥ 25 and <35 kilograms per square meter and no history of taking drug or dietary modification presently or for the preceding three months.

Exclusion criteria:

Untreated hypothyroidism, hepatic or renal impairment, hyperprolactinemia, malabsorption syndrome, age <15 years and>18 years old and cases refused to participate in study.

Sampling method:

Method of randomization: double blind randomized clinical research (both investigator and study groups won't be aware of random allocation). Simple random sampling has been performed, every participant in the investigation have the equal chance to be allocated to either group. Group A (Intervention group) and Group B (Control group). Examined groups have been matched for counfounding parameters (age, socioeconomic level).

Sample Size Justification:

The determined sample size of the research were 55 participants at five percent level of significance and ninety percent power of the study, using the following formula:

$N= (Z1-\alpha/2+Z1-\beta)^2 *\sigma1*\sigma2*2/\delta^2$.

$Z1-\alpha/2= 2.58$, $Z1-\beta=1.28$.

$\sigma1= 55$, $\sigma2= 78$.

Mean triglyceride among metformin group= 133.9.

Mean triglyceride among placebo group= 168 based on Bridger,. *et al.,*[5].

δ= Predicted variance to be noticed among examined groups (34).

α= Level of acceptability of a false positive result (level of significance= 0.05).

β= Level of acceptability of a false negative result (0.01), $1-\beta$= power (0.90).

The sample size was raised to 60 participants to compensate for incomplete information and to rise the research power.

Methods:

All patients have been subjected to the following:

A total of 120 cases attending Mansoura University Hospital clinics were enrolled and separated into 2 equal groups (60 each). Group A received 850 mg of metformin twice daily starting from days 6–8 of induced menstrual bleeding and continued for 6 months. Group B received placebo tablets on the same schedule. All participants underwent clinical evaluation including detailed history, abdominal and local examination for hyperandrogenic features (acne and hirsutism), and laboratory investigations (FSH, LH, TSH, serum prolactin, free testosterone, and HbA1c). Hirsutism has been evaluated utilizing a modified Ferriman–Gallwey score, with scores>8 considered indicative of hirsutism. This score was recorded before and after treatment. Ovulatory function was monitored through plasma progesterone levels determined on days twenty one of the menstrual cycle during the 6-month follow-up period.

Study outcomes:

Primary Outcome: Menstrual irrigularities and Ovulation: Serum 21 progesterone and Secondary Outcome: Hyperandrogenic Features (Acne and Hirsutism).

Statistical Analysis:

The gathered information was coded, processed and examined utilizing SPSS program (Version 26) for windows. The suitable statistical tests were applied when required. *P* values below 0.05 (5%) will be considered to be statically significant.

Ethical consideration:

Research protocol was submitted for approval by IRB. Approval of the mangers of the health care facilities in which the research was performed. Informed consent was gained from each participant sharing in the investigation. Confidentiality and personal privacy was respected in all levels of the investigation. Gathered information weren't being utilized for any other goal.

RESULTS

Mean age of metformin group is 16.32±0.999 years versus 16.56±1.05 years for control group without statistically significant variance among studied group (*p* equal 0.245). Mean body mass index is 28.70±3.30 and 28.99±4.06 kg/m2 for Metformin and Control groups respectively without statistically significant variance among examined group (*p*= 0.691) (Table 1).

Following treatment, a statistically significant diminution in LH concentrations was observed in both the Metformin and Control groups, with a greater percent

change in the Metformin group (47% vs. 4.7%, $p<0.001$). No significant changes were noted in FSH, prolactin, or TSH levels in either group, with minimal percent changes and no statistically significant differences between them. However, testosterone levels showed a significant decrease in the Metformin group in comparison with the Control group (22.1% against 2.4%, $p= 0.003$) (Table 2).

There was a statistically significant difference between studied groups as regard fasting insulin after treatment ($p<0.001$) and HOMA-IR after treatment ($p= 0.001$) with higher mean values for control than metformin group (Table 3).

There was no statistically significant variance among examined groups according hirsutism degree before treatment ($p= 0.207$). However; after treatment, no statistically significant difference between studied groups as regard hirsutism degree ($p= 0.483$) (Table 4).

There was statistically significant variance among examined groups regarding progesterone level ($p= 0.001$). Higher mean progesterone level was detected among metformin compared to control group (Table 5).

There was no statistically significant variance among examined groups according to oligomenorrhea before treatment ($p= 0.688$). However; after treatment, a statistically significant variance has been observed among examined groups ($p= 0.003$). Oligomenorrhea improved from 52% before treatment to 18% after treatment for metformin group (Table 6).

A statistically insignificant difference among studied groups as regard menstrual irregularities before treatment ($p= 0.688$). However; after treatment, a statistically significant variance has been noticed among examined groups ($p= 0.011$). Menstrual irregularities improved from 48% before treatment to 14% after treatment for metformin group (Table 7).

Table 1: Comparison of demographic characters between studied groups:

	Metformin group	**Control group**	**test of significance**	***P* value**
	***N*= 50**	***N*= 50**		
Age/ years	16.32±0.999	16.56±1.05	*t*= 1.17	0.245
Body mass index (kg/m^2)	28.70±3.30	28.99±4.06	*t*= 0.399	0.691

Information is described as mean ±SD, *t*: Student t test.

Table 2: Comparison of hormonal assay before and after treatment within each of examined groups:

		Before	**After**	**test of significance**	***P* value**	**Mean Difference**	**% of change**	**#**
		***N*= 50**	***N*= 50**			95% CI		
LH	Metformin group	10.53±4.27	5.58±2.26	***t*= 17.42**	0.001*	4.95(4.37-5.52)	47.0%	<0.001*
	Control group	9.52±3.54	9.07±3.65	***t*= 2.28**	0.03*	0.446(0.052-0.839)	4.7%	
FSH	Metformin group	4.74±1.68	4.84±1.58	***t*= 1.74**	0.088	-0.101(-0.217, 0.015)	2.1%	0.988
	Control group	4.53±1.30	4.58±1.29	***t*= 1.744**	0.087	-0.06(-0.129, 0.009)	1.3%	
Prolactin	Metformin group	36.35±13.41	35.78±13.05	***t*= 1.0**	0.322	0.57(-0.57, 1.72)	1.5%	0.879
	Control group	34.64±14.27	34.49±14.11	***t*= 1.24**	0.220	0.144(-0.088, 0.376)	0.4%	
TSH	Metformin group	2.45±0.89	2.44±0.90	***t*= 0.296**	0.769	0.138(0.296-0.769)	5.6%	0.575
	Control group	2.69±0.79	2.60±0.82	***t*= 1.96**	0.06	0.09(-0.002, 0.182)	3.3%	
Testosterone	Metformin group	0.402±0.087	0.313±0.07	***t*= 32.61**	0.001*	(0.083-0.094)0.089	22.1%	*0.003
	Control group	0.446±0.132	0.458±0.129	***t*= 1.15**	0.254	-0.011(-0.032, 0.009)	2.4%	

comparison of percent of change data are described as mean ±SD; *statistically significant.

Table 3: Comparison of laboratory findings between studied groups before and after treatment:

		Metformin group	Control group	Test of significance	*P* value
		N= 50	*N= 50*		
Fasting glucose	Before	89.48±11.59	92.16±15.42	*t*= 0.982	0.328
	After	93.1±12.19	90.08±13.73	*t*= 1.16	0.248
Fasting insulin	Before	17.89±4.28	16.62±4.38	*t*= 1.46	0.147
	After	10.91±2.61	16.16±4.49	*t*= 7.14	0.001*
HOMA-IR	Before	4.08±1.04	3.67±1.05	*t*= 1.97	0.052
	After	2.49±0.64	3.61±1.12	*t*= 6.13	0.001*

Table 4: Comparison of Hirsutism grading among examined groups:

Hirsutism grading	Metformin group	Control group	Test of significance	*P* value
	N= 50(%)	*N= 50(%)*		
Before				
• Mild	24(48)	18(36.0)	χ^2= 1.98	*P*= 0.371
• Moderate	13(26)	19(38.0)		
• Severe	13(26)	13(26)		
After				
• No	3(6)	1(2.0)	χ^2= 2.46	*P*= 0.483
• Mild	22(44)	19(38.0)		
• Moderate	12(24)	18(36.0)		
• Severe	13(26.0)	12(24.0)		
Wilcoxon signed rank test #	*P*= 0.051	*p*= 0.051		

Table (5): Comparison of Hirsutism grading among examined groups:

	Metformin group	Control group	Test of significance	*P* value
	N= 50	*N= 50*		
Progesterone level (ng/ml)	15.21±3.67	8.80±2.25	*t*= 10.52	*P*= 0.001*

Table 6: comparison of Oligomenorrhea between studied groups:

Oligomenorrhea	Metformin group	Control group	Test of significance (X^2)	*P* value
	N= 50(%)	*N*=50(%)		
Before	26(52%)	28(56%)	0.161	0.688
After	9(18%)	23(46%)	9.007	**0.003***

Table 7: Comparison of menstrual irregularities between studied groups:

Menstrual irregularities	Metformin group	Control group	Test of significance (X^2)	*P* value
	N= 50(%)	*N*= 50(%)		
Before	24(48%)	22(44%)	0.161	0.688
After	7(14%)	18(36%)	6.453	0.011*

DISCUSSION

In our study, the mean age and BMI among the metformin and control groups were (16.32±0.999 vs. 16.56±1.05 years, p= 0.245; BMI: 28.70±3.30 vs. 28.99±4.06kg/m2, p= 0.691), with no statistically significant differences observed. While this does not confirm equivalence, it suggests that the two groups were reasonably comparable at baseline.

Both groups presented with similar main complaints, with no statistically significant variance among them (p above 0.05). In the metformin group, oligomenorrhea and menstrual irregularities were reported by 52% and 48% of participants, respectively, 10% had acne, and all had hirsutism. In the control group, oligomenorrhea and menstrual irregularities were reported by 56% and 44%, respectively, 8% had acne, and hirsutism was present in all participants.

Our outcomes illustrated a statistically significant diminution in LH concentrations in the metformin group after treatment, from 10.53±4.27 to 5.58±2.26 mIU/mL (p= 0.001), reflecting a 47% decrease, compared to only a 4.7% decrease in the control group (p= 0.03). These results are consistent with Genazzani *et al*.,[6], who illustrated normalization of LH pulsatility following metformin therapy in non-obese females had Polycystic ovary syndrome. Similarly, Liu *et al.,*[7] stated a diminution in LH concentration among PCOS cases with normal insulin sensitivity. Oride *et al.*, [8] also observed metformin-related modulation of LH levels in women with infertility, suggesting a broader mechanism that may also apply to PCOS.

In contrast, Kazerooni and Dehghan-Kooshkghazi[9] found no significant influence of metformin on LH levels in females had Polycystic ovary syndrome.

FSH levels remained relatively stable in both groups with no statistically significant changes before or after treatment (metformin: 2.1% change, control: 1.3% change, p= 0.988). These results agree with Kazerooni and Dehghan-Kooshkghazi[9], who found that metformin didn't significantly influence FSH levels in females had PCOS.

Serum prolactin and TSH levels showed no statistically significant changes within or between groups following treatment. In the metformin group, prolactin decreased slightly from 36.35±13.41 to 35.78±13.05 ng/mL (1.5% reduction), whereas the control group illustrated a 0.4% decrease (34.64±14.27 to 34.49±14.11 ng/mL), with non-significant variance among groups (p= 0.879). These results are consistent with those of Kazerooni and Dehghan-Kooshkghazi[9], who also stated no significant change in prolactin levels in PCOS cases after metformin therapy.

Regarding TSH, no statistically significant differences were observed in either group. The metformin group demonstrated a slight reduction from 2.45 ± 0.89 to 2.4 ±0.90 µIU/mL (5.6%), and the control group illustrated a reduction from 2.69±0.79 to 2.60±0.82 µIU/mL (3.3%). These findings align with investigations by Rotondi *et al.,*[10] and Dhanpal *et al.,*[11], which concluded that metformin does not significantly alter TSH levels in euthyroid PCOS patients.

Testosterone concentrations decreased significantly in the metformin group, from 0.402±0.087 to 0.313±0.07ng/mL, reflecting a 22.1% reduction (p= 0.003). In contrast, the control group illustrated a minimal and insignificant change of 2.4% (0.446±0.132 to 0.458±0.129ng/mL, p= 0.254). This significant reduction confirms metformin's anti-androgenic effect in adolescent girls with PCOS. These results are consistent with earlier studies. Kazerooni and Dehghan-Kooshkghazi[9] and McCartney and Marshall[12] demonstrated a reduction in serum testosterone following metformin therapy, with clinical improvement in hyperandrogenic symptoms.

In the present research, metformin therapy was associated with significant improvements in metabolic parameters. Fasting insulin levels decreased from 17.89±4.28 to 10.91 2.61µIU/mL in the metformin group, reflecting a 39% reduction (p<0.001), whereas the control group illustrated only a minor and statistically insignificant reduction of 2.8% (p= 0.230). Similarly, HOMA-IR significantly declined in the metformin group by 38.9% (4.08±1.04 to 2.49±0.64, p<0.001), in comparison with a non-significant change in the control group (2.7% reduction, p= 0.542). However, fasting glucose levels didn't change significantly in either group (metformin group: 4% increase, p= 0.138; control group: 2.2% decrease, p= 0.281).

These findings align with those stated by El-Sharkawy *et al*.,[13], who demonstrated significant reductions in fasting glucose, insulin, and HOMA-IR following metformin treatment in adolescents with PCOS.

Although hirsutism grades didn't differ significantly among groups after treatment (p= 0.483), there was a noticeable shift toward improvement in the metformin group. Specifically, 6% of participants had complete resolution of hirsutism, and the proportion with mild hirsutism remained high (44%) after treatment. The within-group analysis using the Wilcoxon signed-rank test showed a near-significant trend (p= 0.051), suggesting that metformin may have a modest effect on reducing hirsutism severity over time, even if the change was not statistically significant between groups.

These observations align with findings from El-Sharkawy *et al*.,[13], who reported a significant reduction in hirsutism scores among adolescent girls receiving metformin.

These outcomes are consistent with those of Akhtar et al.,[14], who stated significant improvement in menstrual cycle regularity and serum progesterone levels following metformin therapy in females had Polycystic ovary syndrome.

CONCLUSION

Metformin significantly improves ovulatory function, insulin sensitivity, and androgen levels in adolescent girls with PCOS. It led to reductions in LH, testosterone, fasting insulin, and HOMA-IR, alongside improved menstrual regularity and ovulation. However, its effects on hirsutism and levels of FSH, prolactin, and TSH were limited, indicating the need for individualized treatment and longer follow-up.

CONFLICT OF INTERESTS

There are no conflict of interests.

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