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Original Research

THE EFFECTS OF METFORMIN ON CLINICAL FEATURES, ENDOCRINE AND METABOLIC PROFILES OF INFERTILE WOMEN WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Background: *Polycystic ovary syndrome is the most common endocrine disorder in women of reproductive age. Insulin resistance appears to be a critical factor in PCOS pathogenesis. Metformin, an insulin-sensitizing agent, is thus the preferred treatment option for PCOS. However, no studies on the impact of Metformin on Vietnamese women have been performed. This study aimed to determine the effects of Metformin on the clinical features, endocrine and metabolic profiles in infertile Vietnamese women with PCOS.*

Methods: *A clinical trial was conducted at the Center for Reproductive Endocrinology and Infertility on infertile women aged 18-40 years old with a diagnosis of PCOS from June 2018 to December 2020. Clinical, endocrine and metabolic characteristics of these patients were assessed before and after 3 months of Metformin treatment. Natural pregnancy rates, side effects and tolerance of Metformin have also been reported.*

Results: *Among 87 women recruited in this study, the average age was 28.9 ± 3.4 years, 88.5% of women had oligomenorrhea; 18.4% were overweight/obese; and 19.5% of women with PCOS had hirsutism. The most prevalent phenotype of women with PCOS was phenotype D, which accounted for 74.9%. The mean AMH concentration was 7.27 ±3.42 ng/mL. The prevalences of metabolic syndrome and dyslipidemia among PCOS women with infertility were 14.9% and 54%, respectively. After 3 months of Metformin treatment, menstrual regularity was achieved in 30% of patients with oligomenorrhea. Metformin therapy significantly reduced weight and BMI while not impacting the other clinical features, endocrine and metabolic profiles. Side effects have been reported in 19,5% of patients, mainly digestive disorders. Despite this, 100% of women tolerated Metformin and continued treatment. 21.8% of them achieved pregnancy resulting in 14.9% live birth.*

Conclusions: *3-month treatment with Metformin for infertile women with PCOS may improve menstrual cycle regularity, weight, BMI, resulting in a clinical pregnancy rate of 21.8% and live birth rate of 14.9%.*

Keywords: *PCOS, Metformin, Endocrine, Metabolic, Menstrual cycle, Pregnancy*

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I. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most prevalent endocrine condition in women of reproductive age, with a prevalence between 4 and 21%, depending on diagnostic criteria and research population [1,2]. Frequently, women with PCOS exhibit hyperandrogenism, insulin resistance, persistent anovulation, and dysfunctional adipose tissue leading to central obesity [3]. PCOS is the major cause of menstrual abnormalities that result

in infertility. An estimated 90% of anovulatory occurrences are attributed to PCOS [4]. In addition, there is evidence that women with PCOS had a 2.5-fold higher incidence of metabolic syndrome than those without PCOS [5]. In addition, the risk of developing impaired glucose tolerance and type 2 diabetes was 2.5 and 4.1 times greater in women with PCOS compared to women in the control group with the same body mass index [6]. The primary cause of this condition is uncertain, however, most writers concur that insulin resistance plays a significant role in the pathophysiology of PCOS [7].

Metformin is an insulin sensitizer that increases the sensitivity of peripheral tissues to insulin, hence reducing circulating insulin levels, making it a potential treatment for reducing insulin resistance in women with PCOS [8]. Preliminary findings from uncontrolled research indicated that Metformin improves hyperinsulinemia, hyperandrogenism, ovarian steroid production, the menstrual cycle, and the clinical pregnancy rate [9, 10]. Recent prospective randomized studies and meta-analyses have reaffirmed Metformin's positive effects on metabolic diseases, hyperinsulinemia, hyperandrogenism, blood pressure, and clinical pregnancy rates [11 -13]. Data from controlled studies demonstrating the benefits of Metformin on menstrual cycle improvement were encouraging. Still, these benefits were inconsistent across studies due to differences in the duration of treatment (ranging from 3 months to 1 year). Previous studies were limited to obese and/or weight-gained patients rather than the full range of patients diagnosed using the Rotterdam criteria [12,14]. Even though insulin resistance tended to emerge in obese women with PCOS [15], women with PCOS were at risk for impaired glucose tolerance and type 2 diabetes even at a normal weight [16]. These risks rise with obesity [15]. In Vietnam, a study conducted by Le Minh Tam et al. (2018) on 441 women with PCOS in Central Vietnam found a frequency of insulin resistance of 27.0%, despite the characteristics of women with PCOS in Vietnam being a lean body, minimal hyperandrogenism, and a mild PCOS phenotype [17]. Therefore, it is necessary to evaluate the effect of Metformin on menstrual characteristics and metabolic and reproductive endocrine characteristics in women with non-selective PCOS, focusing on non-obese phenotypes. This study was conducted aimed to examine the impact of Metformin on the clinical, endocrine, and metabolic parameters of infertile women with PCOS, this study was conducted.

II. MATERIALS AND METHODS

2.1. Subjects

All women between the ages of 18 and 40 with PCOS were examined and treated at the Center for Reproductive Endocrinology and Infertility, Hue University Hospital of Medicine and Pharmacy (HueCREI). During June 2018 and December 2020 were recruited into this study.

PCOS was diagnosed when at least two of the following three criteria were present according to the Rotterdam criteria: 1. Amenorrhea and oligomenorrhea. 2. The clinical or subclinical presence of hyperandrogenism. 3. Evidence of polycystic ovaries (with 12 tiny follicles 2-9 mm in at least one ovary and/or ovary volume 10 cm3 on ultrasound. PCOS was diagnosed after other hyperandrogenic diseases had been ruled out [20].

Exclusion criteria: Use of oral contraceptives within the past three months; History of ovarian surgery, presence of ovarian tumors, ovarian endometriosis, or ovarian failure; Blockage of both fallopian tubes; Severe abnormality of husband's sperm

2.2. Study design: clinical trial

2.3. Methodologies

Evaluation of clinical characteristics including height, weight, BMI, waist circumference, hirsutism, acne, aclopia, and acanthosis nigricans.

On day 2-3 of menstrual cycle, the patient underwent a serum blood test that measured AMH, FSH, E2, LH, Testosterone, Prolactin, blood lipid bilan, fasting blood glucose, blood glucose levels, blood glucose 2 h after glucose tolerance test, and Hba1c. After analyzing and documenting the patient's clinical and laboratory parameters, they were treated with Metformin (Glucophage 850 mg x 2 tablets per day) within three months. After 3 months of treatment, the patient would be re-evaluated in all clinical features, endocrine levels and metabolism. In addition, the patient was interviewed about severe reactions and tolerance to Metformin. After 3 months of therapy, the rate of natural pregnancy was also evaluated.

2.4. Assessment of variables

Amenorrhea or oligomenorrhea was classified as menstrual cycles of more than 35 days or fewer than eight per year [20].

The level of hirsutism was determined using the mFG scale. Patients were diagnosed with hirsutism when their mFG score was less than 5 (the cutoff for the Asian population) [21].

Patients were classified as obese if their BMI was

greater than or equal to 25 kg/m2 and as overweight if their BMI was greater than or equal to 23 kg/m2 according to the World Health Organization obesity classification for Asia.

Hyperandrogenism were defined as total Testosterone > 0.88 ng/mL [21]

Based on the 2005 NCEP ATP III clinical practice guidelines for Asian populations, metabolic syndrome was defined as meeting at least three of the five following criteria: (1) waist circumference 80cm; (2) serum triglycerides 1.7 mmol/l; (3) lipoprotein levels (HDL-C) 1.3 mmol/l; (4) blood pressure 130/85 mmHg or usage of antihypertensive medications; and (5) fasting blood glucose 5.6mmol/L [22].

According to the NIH 2012 classification of four PCOS phenotypes, women with PCOS were categorized into four groups. Phenotype A had ovulatory dysfunction, hyperandrogenism, and polycystic ovaries; phenotype B had ovulatory dysfunction and hyperandrogenism but normal ovarianimaging; phenotype Chadhyperandrogenism and polycystic ovaries but a normal ovulatory cycle; and phenotype D had ovulatory dysfunction and polycystic ovarian imaging but no clinical or subclinical hyperandrogenism.

2.5. Data analysis

The SPSS 20.0 medical statistical program was used for data entry and processing (SPSS Inc, Chicago III). Categorical data were expressed as the number and percentages, whereas normally distributed continuous variables were expressed as the mean ± standard deviation. Before and after therapy, differences in metabolic endocrine parameters were assessed using the paired t-test if the distribution was normal and the Wilcoxon test if the distribution was not normal. Using mc Nemar's test, the difference in rates before and after treatment was determined. With $p < 0.05$, the algorithms are statistically significant.

2.6. Research integrity

The study was approved by the Ethics Committee of Hue University of Medicine and Pharmacy. Before patients participated in the trial, they were given a thorough explanation and confirmation in writing.

III. RESULTS

Our study involved 87 patients who met the requirements for participation. Table 1 displayed the change in clinical features following three months of Metformin treatment. Consequently, 88.5% of women had irregular menstruation, 18.4% of women were overweight or obese, and 19.5% of women with PCOS had hirsutism. The mean mFG score ranged between 1.86 and 2.80. 74.9 percent of women with PCOS exhibit the phenotype D. 17 women who achieved pregnancy spontaneously within three months of beginning Metformin medication were excluded from the analysis. Compared to prior therapy, the rate of regular menstruation increased by 30%, while weight and BMI reduced considerably. The remaining characteristics either remained unchanged or their change was not statistically significant. In the non-obese group of women with PCOS, subgroup analysis revealed that Metformin treatment considerably enhanced the rate of monthly regularity (31.6%). Still, other characteristics remained stable or changed insignificantly meaningful. After therapy with Metformin, the menstrual cycle did not improve in the group of overweight and obese women with ACS, although weight, BMI, waist circumference, and hip circumference dropped dramatically. After treatment, clinical hyperandrogenism symptoms remained unchanged in all groups.

Table 1: Changes in clinical characteristics after 3 months of Metformin treatment in the group of patients with PCOS and the overweight/obese and non-overweight/obese subgroups

Subgroups	Before Metformin treatment (n=87)	After 3 months of Metformin treatment					
		All PCOS patients (n=70)		Non overweight/ obese PCOS (n=53)		Overweight/obese PCOS (n=17)	
Parameters		Deviant	P	Deviant	P	Deviant	P
Cycle							
Irregular	77 (88,5%)	-30%	**0,000**	-31,6%	**0,000**	-17,6%	0,250
SysP (mmHg)	106,8±7,6 (90 -120)	-0,43±4,72	0,450	-0,38±5,23	0,604	-0,59±2,42	0,317

Subgroups	Before Metformin treatment (n=87)	After 3 months of Metformin treatment					
		All PCOS patients (n=70)		Non overweight/ obese PCOS (n=53)		Overweight/obese PCOS (n=17)	
DiaP (mmHg)	67,7±6,6 (60-80)	-0,43±5,23	0,495	-0,38±5,54	0,622	-0,59±4,29	0,564
Weight (kg)	52,7±7,0 (39-75)	-0,54±1,71	**0,01**	-0,13±1,61	0,552	-1,82±1,38	**0,001**
BMI	21,4±2,6 (16,4 – 28,8)	-0,22	**0,01**	-0,06±0,66	0,543	-0,74±0,57	**0,001**
BMI ≥ 23 kg/ m^2	23 (26,4%)	-2,85%	0,727				
Waist circumferrene (cm)	76,8±8,3 (60 – 100)	-0,50±2,20	0,062	-0,17±2,31	0,596	-1,53±1,42	**0,003**
Hip circumferrence (cm)	91,8±6,1 (68 – 110)	-0,44±2,20	0,097	-0,25±2,33	0,447	-1,06±1,68	**0,021**
mFG	1,86±2,83 (0-15)	0	-	0	-	0	-
Hirsutism	17 (19,5%)	0	-	0	-	0	-
Acne	14 (16,1%)	0	-	0	-	0	-
Alopecia	9 (11,3%)	0	-	0	-	0	-
Acanthosis nigricans	3 (3,4%)	0	-	0	-	0	-
Phenotypes	A: 13 (14,9%) B: 1 (1,1%) C: 8 (9,2%) D: 65 (74,7%)						

Table 2: Changes in metabolic endocrine characteristics after 3 months of Metformin treatment in the group of patients with PCOS and the overweight/obese and non-overweight/obese subgroups

Parameters	Before Metformin treatment (n=87)	After 3 months of Metformin treatment					
		All PCOS patients (n=70)		Non overweight/obese PCOS (n=53)		Overweight/obese PCOS (n=17)	
		Deviant	P	Deviant	P	Deviant	P
Basal FSH (IU/L)	5,97±1,67 (0,87 – 12,02)	-0,22±1,36	0,183	-0,20±1,43	0,304	-0,26±1,12	0,463
Basal LH (IU/L)	9,17±5,45 (1,4 – 27,67)	-0,52±4,16	0,296	-0,71±4,00	0,199	+0,08±4,69	0,943
Basal Estradiol (pg/ml)	41,6±23,2 (5,0 – 145,0)	-2,99±22,63	0,272	-3,16±21.71	0,294	-2,38±26,02	0,356
Testosterone (nmol/L)	0,29±0,23 (0,02 – 1,93)	-0,04±0,21	0,086	-0,05±0,24	0,106	-0,15±0,09	0,535
Prolactin (IU/L)	388,7±203,5 (75,9 -1050,0)	+15,37±178,24	0,473	+10,75±129,83	0,549	+29,79±286,24	0,831

Parameters	Before Metformin treatment (n=87)	After 3 months of Metformin treatment					
		All PCOS patients (n=70)		Non overweight/obese PCOS (n=53)		Overweight/obese PCOS (n=17)	
		Deviant	P	Deviant	P	Deviant	P
AMH (ng/mL)	7,27±3,42 (2,84 – 21,05)						
Cholesterol (mmol/L)	4,65±1,05 (2,94 – 9,71)	-0,174±0,73	0,049	-0,08±0,48	0,224	-0,465±1,19	0,156
Triglycerides (mmol/L)	1,44±1,32 (0,39 – 11,2)	-0,13±0,79	0,895	+0,03±0,77	0,747	-0,16±0,86	0,831
LDL-Cholesterol (mmol/L)	3,08±0,89 (1,07 – 5,38)	-0,01±0,68	0,922	-0,06±0,73	0,553	+0,15±0,45	0,170
HDL-Cholesterol (mmol/L)	1,36±0,41 (0,64 – 3,50)	-0,36±0,46	0,517	-0,05±0,53	0,466	_ 0,02±0,14	0,740
G0 (mmol/L)	5,26±0,43 (4,58 – 6,75)	-0,01±0,35	0,821	+0,04±0,33	0,412	-0,16±0,37	0,109
G2 (mmol/L)	6,62±1,49 (3,89 – 11,04)	-0,10±	1,32	-0,07±1,41	0,712	-0,20±1,02	0,381
HbA1c (%)	5,18±0,37 (4,30 – 6,99)	+0,01±0,36	0,797	+0,03±0,37	0,602	-0,04±0,29	0,812
HCCH (NIH)	13 (14,9%)	-2,86%	0,687	-1,75%	1,00	-5,88 %	1,00
Dyslipidimia Elevated Cho: Elevated LDL-Cho: Decreased HDL-Cho:	Any: 47 (54,0%) 19 (21,8%) 32 (36,8%) 15 (17,2%)						

Table 2 demonstrates the metabolic endocrine changes. The mean concentration of AMH was 7.27 3.42 ng/mL, while the mean concentration of LH was 9.17 5.45 mIU/mL. 14,9% of women with PCOS had metabolic syndrome; 54% of women with PCOS had dyslipidemia, with elevated LDL-cholesterol (36%) being the most prevalent. Only cholesterol reduced significantly after three months of Metformin treatment; other endocrine and metabolic indicators remained unchanged. Analyses of subgroups of overweight and obese women with PCOS revealed no significant amelioration in any of the endocrine and metabolic markers evaluated.

Table 3: Side effects, tolerance and natural pregnancy rate of Metformin

Parameters	N	%
Side effects	17	19,5
Gastrointestinal effects	13	14,9
Weakness	6	9,2
Tolerance	87	100
hCG positive	19	21,8
Clinical pregnancy	15	17,2
Live birth	13	14,9

According to Table 3, 19.5% of women who used Metformin experienced adverse effects, primarily digestive issues. Despite this, all women tolerated the drug and continued the treatment. 21.8% of them achieved pregnancy, resulting in 14.9% live births.

IV. DISCUSSION

4.1. The clinical and subclinical characteristics of infertile women with PCOS in Vietnam

Regarding clinical features, our study found that 88.5% of women had irregular menstrual cycles and 18.4% were overweight/obese, similar to the findings of Le Quynh Trang et al. [24], in which the respective percentages were 86.0% and 19.1%. Similarly, the prevalence of overweight and obesity was 19.2% in the study by Le Minh Tam et al [25] and 19.8% in the study by Cao Ngoc Thanh et al [18]. In our study, only 19.5% of women had hirsutism, and

the average mFG score was 1.86 ± 2.70. Cao Ngoc Thanh et al. [18] likewise found a low incidence of hirsutism and an average mFG score of 1.4 ± 2.2 points. Moreover, our study found that phenotype D was the dominant phenotype with 74.7%, the second most common was phenotype A but only 14.9%; phenotype C accounted for 9.2% and phenotype B accounted for only 1.1%. This model resembled the research conducted by Le Viet Nguyen Sa et al. [26] and Cao Ngoc Thanh et al. [18].

Concerning the endocrine parameters, our study revealed that infertile women with PCOS had a high LH concentration (9.17 5.45 IU/L), a high LH:FSH ratio (1.56 0.91), and a high AMH concentration (7.27 3.50 ng/mL), which was consistent with prior research [18,25,26]. Similar to the study conducted by Cao Ngoc Thanh et al. on 479 infertile women with PCOS in Central Vietnam (12.5%) [18], only 14.9% of women with PCOS in this study had metabolic problems. Metabolic parameters revealed that 54% of women with PCOS had dyslipidemia, with LDL-Cho disorder being the most prevalent at 36.6%; Total cholesterol disorder was also prevalent at 26.4%; this was identical to the study on lipid metabolism disorders by Le Quynh Trang et al with the rates of 5.7%, 34.9%, and 23.9%, respectively [24].

In conclusion, our study validated the characteristic phenotype of women with PCOS in Vietnam, which included slim body, less obesity, less hyperandrogenism expression, a low risk of metabolic syndrome, but dyslipidemia was extremely common in these women [18].

4.2. Changes in clinical and laboratory parameters and pregnancy rate following three months of Metformin therapy

Metformin treatment for three months significantly improved menstrual cycle regularity (30% increase), weight loss, and body mass index. Metformin did not induce substantial changes in weight and BMI in non-obese women with PCOS, although it significantly improved menstrual cycle regularity. In contrast, the menstrual cycle improved but did not approach statistical significance in the group of overweight/obese women with PCOS, whereas weight, waist circumference, hip circumference, and BMI all dropped considerably after 3 months of Metformin therapy. Numerous studies have evaluated Metformin's effects on obese women with PCOS, and the results have been inconclusive. Regarding weight and BMI, most research found comparable findings to ours, namely that Metformin dramatically lowered weight and BMI in obese women with PCOS, but remained characteristics varied from research to study. In a research conducted by Pasquali et al. on a group of obese women with PCOS, a combination of a low-calorie diet and Metformin for six months dramatically improved menstrual cycle, hirsutism, weight reduction, BMI, and testosterone levels. Meanwhile, FSH, LH, dehydroepiandrosterone sulphate, and Progesterone concentrations did not change statistically significantly [27]. Guan et al. have conducted a meta-analysis and meta-analysis of controlled clinical trials to assess the efficacy of Metformin in obese women with PCOS. Metformin effectively lowered these patients' BMI, weight, and waist circumference, according to a meta-analysis comprising twelve randomized trials. Metformin has been demonstrated in all investigations to considerably enhance endocrine and metabolic indicators, including Testosterone, FSH, LH, and LDL-Cho. Metformin did not change the fasting insulin index, HOMA, SHBG, HDL-Chol, Total Cholesterol, TG, and Androstedione patterns [28]. Differences between studies may be accounted for by variations in race, participants, dosage regimens, and duration of Metformin administration.

In contrast, there are few research on the effects of Metformin on the group of non-obese PCOS-affected women. Our study revealed that Metformin had little effect on this group of women, except for a significant improvement in menstrual cycle regularity. Similar to our findings, Trolle et al. found in a double-blind, placebo-controlled clinical trial that metformin did not affect menstrual cycle despite reducing weight, systolic blood pressure, weight and raising HDL-cholesterol in obese PCOS women. The use of metformin in non-obese women with PCOS did not appear advantageous [29]. Long-term effects of Metformin in obese and non-obese women with PCOS were also examined; long-term Metformin enhanced menstrual cycle regularity and decreased BMI, Testosterone, and LH in women. Similarly, Swathi et al. observed that after 6 months of Metformin treatment, non-obese women experienced a statistically significant reduction in BMI and an increase in HDL levels. However, LDL and TG levels remained similar in obese and non-obesity groups. In the non-obese group, total cholesterol was high at baseline, whereas it was reduced in the obese group following therapy [31].

In our study, 19.5% of women who took Metformin experienced adverse effects, primarily

digestive issues. 14.9% of live births resulted from 14.8% of pregnancies. Metformin enhances ovulation rates in women with PCOS, according to numerous controlled clinical trials, cohort studies, and descriptive studies; however, few of these investigations have identified the ovulation rate as an endpoint clinical pregnancy [32]. Despite this, a meta-analysis by Tang et al. [10] revealed that metformin might improve clinical pregnancy rates relative to placebo (OR 2.31; 95% CI 1.52-3.41) Metformin may enhance the rate of live births, according to a new meta-analysis by Sharpe et al. (2019) comparing Metformin with placebo/no therapy; however, Metformin use was frequently associated with gastrointestinal side effects. With placebo, the live birth rate was 19%, whereas it ranged between 19-37% in the Metformin group. In comparison, only 10% of women in the placebo group experienced gastrointestinal problems, compared to 22-40% in the Metformin group [33].

This was one of the first studies in Vietnam to investigate the efficacy of Metformin on women with PCOS, and the first findings were impressive. Nevertheless, our study had certain drawbacks. First, this was not a randomized, controlled trial. Second, the sample size was small and the duration of the intervention was brief. This prevented us from reaching definitive conclusions. There is a need for prospective controlled clinical trial intervention studies to more accurately evaluate the effects of short-term metformin on women with PCOS in Vietnam.

V. CONCLUSION

In Vietnam, the frequent phenotypes of women with PCOS were a lean body with minimal hyperandrogenism, a low risk of metabolic syndrome, and a significant prevalence of dyslipidemia. Three-month treatment with Metformin improved menstrual cycle regularity in non-obese women with PCOS, with little change in other parameters. Short-term metformin treatment appeared to improve weight, BMI, waist circumference, and hip circumference in overweight/obese women with PCOS. Metformin's short-term use led to a clinical pregnancy rate of 21.8% and a live birth rate of 14.9%.

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