



ORIGINAL ARTICLE

# Ovulation induction by metformin among obese versus non-obese women with polycystic ovary syndrome



Yazed Sulaiman Al-Ruthia<sup>a,\*</sup>, Hazem Al-Mandeel<sup>b</sup>, Hisham AlSanawi<sup>c</sup>,  
Wael Mansy<sup>d</sup>, Reem AlGasem<sup>e</sup>, Lama AlMutairi<sup>f</sup>

<sup>a</sup> Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2454, Riyadh 11451, Saudi Arabia

<sup>b</sup> Department of Obstetrics and Gynecology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

<sup>c</sup> Department of Orthopedic Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia

<sup>d</sup> Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

<sup>e</sup> Prince Mohammed bin Abdulaziz Hospital, Riyadh, Saudi Arabia

<sup>f</sup> King Abdulaziz University Hospital, Riyadh, Saudi Arabia

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## KEYWORDS

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**Abstract** *Objectives:* There is some evidence that the efficacy of metformin as an ovulation stimulation agent depends on the body mass index (BMI) of the treated anovulatory women with polycystic ovary syndrome (PCOS). The aim of this study was to examine the likelihood of successful ovulation among obese (BMI  $\geq 30$  kg/m<sup>2</sup>) versus non-obese (BMI  $< 30$  kg/m<sup>2</sup>) women with PCOS.

*Methods:* A total of 243 medical charts of women with PCOS who visited King Khaled University Hospital (KKUH) in Riyadh, Saudi Arabia, between 2006 and 2012 were reviewed. Patients' sociodemographic, laboratory, and medical data were collected. Descriptive statistics and multiple logistic regression analyses were performed to compare the patients' baseline data and successful ovulation among the obese and non-obese anovulatory women with PCOS, respectively.

*Results:* One hundred and nine women with PCOS who were prescribed metformin for  $\geq 3$  months were included in the study. Almost 60% of the women who were included in the study were obese. The likelihood of ovulation among obese women with PCOS was 77.9% (odds ratio = 0.221, 95% CI 0.052–0.947,  $P = 0.042$ ) less than that in their non-obese counterparts.

\* Corresponding author. Fax: +966 114677480.

E-mail address: yazeed@ksu.edu.sa (Y.S. Al-Ruthia).

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*Conclusion:* The findings of this study suggest that metformin is more effective as an ovulation stimulation agent when administered to non-obese women with PCOS. Lifestyle modifications such as diet and exercise should be emphasized upon as an integral part of any treatment plan for PCOS. © 2016 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive disorder affecting 6–10% women of childbearing age (Norman et al., 2007). Furthermore, it is believed to be one of the leading causes of infertility worldwide (Barthelmeß and Naz, 2014). PCOS is characterized by hyperandrogenism, polycystic ovaries, and ovulatory dysfunction (Carmina et al., 2010; Gambineri et al., 2002). Moreover, multiple features of metabolic syndrome such as obesity, insulin resistance, and hyperinsulinemia are usually present in a majority of women with PCOS (Gambineri et al., 2002). Although the pathogenesis of PCOS is not well understood, insulin resistance is considered one of its main underlying causes, especially among obese people (Barber et al., 2015; Kahn and Flier, 2000). Therefore, it is important to assess the abdominal adiposity or upper body fat distribution in women as they correlate with insulin resistance (Moran et al., 2012). Insulin resistance increases the level of serum insulin, which interacts synergistically with the luteinizing hormone (LH) within the ovarian theca cells, causing a significant increase in the cholesterol level, a reduction in glucose transport, an increased production and release of androgens, and ultimately infertility (Barber et al., 2015). In a systematic review and meta-analysis that included 35 studies to determine the prevalence of overweight, obesity, and central obesity in women with or without PCOS, the prevalence of overweight, obesity, and central obesity was significantly higher among women with PCOS than in their counterparts without PCOS (Lim et al., 2012). Furthermore, women with upper-body adiposity are at a higher risk of insulin-related metabolic and reproductive disorders such as hyperandrogenemia, anovulation, and dyslipidemia compared to those with lower-body adiposity (Moran et al., 2012; Lim et al., 2012).

It is important to consider the link between insulin resistance and obesity in the diagnosis of PCOS since obesity management plays a vital role in the treatment of this syndrome (Lim et al., 2012). Hence, lifestyle modification (e.g., diet and exercise) is considered the first-line therapy as it reduces the abnormal high plasma androgen level, improves hirsutism symptoms, reduces weight and waist circumference, and lowers the level of insulin resistance among PCOS women (Lim et al., 2012). Apart from the lifestyle modifications, practicing gynecologists usually start their PCOS patients with oral pharmacological agents such as metformin and clomiphene, which lower the level of insulin resistance and induce ovulation (Badawy and Elnashar, 2011). Metformin has been widely used in the management of PCOS and has been showed to be safe and effective (Johnson, 2014). In addition to its efficacy in inducing ovulation among PCOS women, metformin has shown a positive effect when accompanied with an exercise program on body weight, as measured by the waist to hip ratio (WHR) Fux Ota et al. (2010). Furthermore, metformin has been shown to reduce fasting plasma glucose and

free testosterone levels, resulting in a significant improvement in the clinical manifestations of hyperandrogenism (Kazerooni and Dehghan-Kooshkghazi, 2003; Farimani Sanoee et al., 2011). The mechanism by which metformin exerts its ovulation stimulatory effect is believed to be through its insulin-sensitizing effect (Katsiki and Hatzitolios, 2010; Franks, 2011). The elevated plasma level of insulin results in a decrease in the synthesis of sex hormone binding globulin (SHBG) and insulin-like growth factor binding protein-1 (IGFBP-1), and an increase in the plasma level of insulin growth factor 1 (IGF-1) (Tock et al., 2014). Both insulin and IGF-1 have a negative effect on the ovaries, resulting in an increase in androgen hormone synthesis as well as the production of immature small ovarian follicles (Tock et al., 2014). Insulin sensitizers such as pioglitazone and metformin enhance the utilization of glucose by improving the peripheral insulin sensitivity, inhibiting the hepatic production of glucose, and increasing skeletal muscles uptake of glucose (Pasquali and Gambineri, 2006).

Interestingly, the efficacy of metformin in improving the metabolic parameters such as the plasma insulin level and in ovulation induction is variable based on the patients' BMI (Badawy and Elnashar, 2011; Johnson, 2014, 2011; Genazzani et al., 2007). In a randomized, double-blind, placebo-controlled, cross-over study that was conducted in Denmark, metformin lowered the testosterone level and increased the insulin sensitivity in only obese women (e.g., BMI  $\geq 30$  kg/m<sup>2</sup>) with PCOS (Trolle et al., 2007). On the other hand, metformin has been shown to be more effective in inducing ovulation among non-obese women in comparison with their obese counterparts in a post hoc analysis of a randomized, multicenter, double-blind, clinical trial that was conducted in the United States (Legro et al., 2007). Moreover, in a study that was conducted in Russia to examine the efficacy of metformin in ovulation induction among anovulatory lean and obese women with PCOS, the lean women had significantly higher rates of menstrual restoration and ovulation in comparison with their obese counterparts (Popova et al., 2011). Whether ovulation induction by metformin is more successful among obese or non-obese women with PCOS in Saudi Arabia, a country where > 30% of women are obese (Memish et al., 2014), remains to be seen. The objective of this study was to compare the rate of ovulation among anovulatory obese and non-obese women with PCOS, who were treated with metformin.

## 2. Methods

### 2.1. Study design

This was a retrospective cohort chart review study conducted in the department of obstetrics and gynecology at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. The

study was approved by the institutional review board of the College of Medicine at King Saud University.

## 2.2. Study population

Women aged between 18 and 40 years with an established diagnosis of PCOS according to Rotterdam diagnostic criteria (Rotterdam and ASRM-Sponsored, 2004), who filled their metformin prescriptions at KKHU pharmacy, and who were followed for  $\geq 3$  months after their first metformin prescription were included in the study. The minimum sample size needed for this study was calculated using GPower® 3.1 software based on a medium effect size (0.3), power of 80 (beta = 0.2), and  $\alpha = 0.05$ , and was found to be 81 patients (Faul et al., 2009).

## 2.3. Data collection

Paper and electronic medical files for patients who visited the gynecology clinics at KKHU from 2006 to 2012 were reviewed by two research assistants. Furthermore, the outpatient pharmacy records for patients who met the inclusion criteria were also reviewed. Patients' age, anthropometric (e.g., height, weight), laboratory, other medical conditions, and medication data were collected. The data collection took place between September 2015 and February 2016.

## 2.4. Statistical analysis

Descriptive statistics were conducted using Student's *t*-test, chi-square test, Fisher's exact test, and one-way ANOVA as appropriate. In addition, a multiple logistic regression analysis was conducted to compare the rate of ovulation between obese (BMI  $\geq 30$  kg/m<sup>2</sup>) and non-obese women with PCOS, who had been treated with metformin, controlling for potential

confounders such as age, metformin daily dosage, duration of infertility, baseline prolactin and testosterone levels, fasting serum insulin concentration (FSIC) and fasting plasma glucose (FPG) levels, other medical conditions (e.g., hypertension, diabetes, hypothyroidism), and concomitant utilization of other ovulation-stimulating agents (e.g., clomiphene). For descriptive purposes, the BMI was categorized into three categories (normal, overweight, and obese) based on the World Health Organization (WHO) definition About Adult BMI; however, the BMI was dichotomized into two groups (obese and non-obese) for the logistic regression analysis. Statistical significance was determined at  $\alpha$  value of 0.05. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

## 3. Results

Out of 243 women with PCOS who were treated at KKHU's gynecology clinics between 2006 and 2012, 109 women with PCOS met the inclusion criteria and were included in the study. Most of the included patients (59.63%) were obese (BMI  $\geq 30$  kg/m<sup>2</sup>), whereas 40.36% were non-obese (e.g., either overweight or with normal weight). The mean age of the included patients was 27 years with little variation between the BMI groups. The mean values of the lipid panel (e.g., total cholesterol, LDL, and HDL) were within normal range for the different BMI groups. The mean fasting serum insulin concentration (FSIC), fasting plasma glucose (FPG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone (DHEA), testosterone, estradiol, and prolactin levels were all within the normal range (Table 1). Most of the women who were included in the study had been infertile for  $\geq 2$  years and were oligomenorrhic. Furthermore, the majority did not have children at the time of treatment with no significant difference between the BMI groups ( $P \geq 0.05$ ).

**Table 1** Anthropometric, clinical, and biochemical baseline data.

Groups	BMI			Total (n = 109)
	Normal (BMI < 25) (N = 20)	Overweight (25 $\geq$ BMI < 30) (N = 24)	Obese (BMI $\geq$ 30) (N = 65)	
Age (yrs.)	25.70 $\pm$ 4.378	27.166 $\pm$ 4.678	28.446 $\pm$ 5.157	27.66 $\pm$ 4.99
BMI (kg/m <sup>2</sup> )	22.80 $\pm$ 1.735	27.125 $\pm$ 0.991	34.888 $\pm$ 4.348	30.96 $\pm$ 6.07
Total cholesterol (mmol/l)	4.343 $\pm$ 0.175	4.247 $\pm$ 0.897	4.444 $\pm$ 0.647	4.38 $\pm$ 0.66
LDL (mmol/l)	3.058 $\pm$ 0.204	3.092 $\pm$ 0.116	3.149 $\pm$ 0.334	3.12 $\pm$ 0.28
HDL (mmol/l)	1.119 $\pm$ 0.025	1.117 $\pm$ 0.110	1.118 $\pm$ 0.094	1.12 $\pm$ 0.09
Triglyceride (mmol/l)	1.016 $\pm$ 0.145	1.043 $\pm$ 0.157	1.063 $\pm$ 0.155	1.05 $\pm$ 0.15
FSIC (mIU/L)	19.212 $\pm$ 11.025	17.452 $\pm$ 7.258	17.328 $\pm$ 4.429	17.70 $\pm$ 6.69
FPG (mmol/l)	4.905 $\pm$ 0.543	5.094 $\pm$ 0.466	5.092 $\pm$ 0.563	5.06 $\pm$ 0.54
FSH (mIU/ml)	5.001 $\pm$ 1.198	5.753 $\pm$ 1.146	5.124 $\pm$ 1.597	5.24 $\pm$ 1.46
LH (mIU/ml)	9.497 $\pm$ 4.6398	8.307 $\pm$ 5.152	6.962 $\pm$ 4.138	7.72 $\pm$ 4.54
DHEA (mol/l)	5.303 $\pm$ 1.860	5.234 $\pm$ 1.878	5.015 $\pm$ 2.108	5.12 $\pm$ 2.00
Testosterone (nmol/l)	1.419 $\pm$ 0.375	1.406 $\pm$ 0.505	1.435 $\pm$ 0.552	1.43 $\pm$ 0.51
Estradiol (pg/ml)	161.281 $\pm$ 42.081	147.659 $\pm$ 43.853	163.886 $\pm$ 72.029	159.84 $\pm$ 61.96
Prolactin (ng/ml)	4.442 $\pm$ 3.591	4.18 $\pm$ 2.089	3.342 $\pm$ 2.172	3.727 $\pm$ 2.495

Note: data are expressed as mean  $\pm$  standard deviation. BMI: body mass index, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FSIC: fasting serum insulin concentration, FPG: fasting plasma glucose, FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEA: dehydroepiandrosterone.

**Table 2** Patient characteristics across the BMI groups.

Groups	BMI			p-value	Total (n = 109)
	Normal (BMI < 25) (N = 20)	Overweight (25 ≥ BMI < 30) (N = 24)	Obese (BMI ≥ 30) (N = 65)		
<i>Duration of infertility (yrs.)</i>					
≤1	0 (0%)	3 (12.5%)	3 (4.62%)	0.787	6 (5.5%)
2–3	4 (20%)	4 (16.67%)	10 (15.38%)		18 (16.51%)
4–5	4 (3.67%)	7 (6.42%)	20 (18.35%)		31 (28.44%)
6–7	6 (30%)	5 (20.83%)	14 (21.54%)		25 (22.94%)
8–10	3 (15%)	4 (16.67%)	8 (12.31%)		15 (13.76%)
> 10	3 (15%)	1 (4.17%)	10 (15.38%)		14 (12.84%)
<i>Oligomenorrhea</i>					
Yes	2 (10%)	10 (41.67%)	19 (29.23%)	0.052	31 (28.44%)
No	17 (85%)	12 (50%)	34 (52.31%)		63 (57.80%)
Unknown <sup>a</sup>	1 (5%)	2 (8.33%)	12 (18.46%)		15 (13.76%)
<i>Did they have children?</i>					
Yes	8 (40%)	7 (29.17%)	24 (36.92%)	0.723	39 (35.78%)
No	12 (60%)	17 (70.83%)	41 (63.08%)		70 (64.22%)
<i>Did they successfully ovulate while on treatment?</i>					
Yes	18 (90%)	23 (95.83%)	51 (78.46%)	0.106	92 (84.40%)
No	2 (10%)	1 (4.17%)	14 (21.54%)		17 (15.60%)

Note: Data are expressed as frequency and percentage.

BMI: body mass index.

<sup>a</sup> Data were missing.

**Table 3** Patient healthcare characteristics.

Comorbidity	BMI			p-value	Total (n = 109)
	Normal (BMI < 25) (N = 20)	Overweight (25 ≥ BMI < 30) (N = 24)	Obese (BMI ≥ 30) (N = 65)		
Hypertension (HTN)	0 (0%)	2 (8.33%)	1 (1.54%)	0.207	3 (2.75%)
Diabetes	1 (5%)	2 (8.33%)	0 (0%)	0.063	3 (2.75%)
Hypercholesterolemia	1 (5%)	0 (0%)	1 (1.54%)	0.382	2 (1.83%)
Hyperprolactinemia	3 (15%)	4 (16.67%)	3 (4.62%)	0.083	10 (9.17%)
Hypothyroidism	1 (5%)	0 (0%)	0 (0%)	0.184	1 (0.92%)
Mental health disorders (e.g., depression, anxiety)	0 (0%)	0 (0%)	1 (1.54%)	1.00	1 (0.92%)

Note: Data are expressed as frequency and percentage.

BMI: body mass index.

More than 84% of the women in the study successfully ovulated while on treatment, with overweight women having the highest rates of successful ovulation among the three BMI groups (95.83%) (Table 2). Very few patients (e.g., ≤3 women) had hypertension, diabetes, hypercholesterolemia, or mental illness (e.g., depression); however, 10 patients had hyperprolactinemia and were taking medications for that medical condition at the time of treatment with no significant difference in the percentages of patients who had hyperprolactinemia between the different BMI groups ( $P \geq 0.05$ ) (Table 3). The numbers of women who were co-treated with clomiphene together with metformin were 8 and 9 in the non-obese (e.g., BMI < 30 kg/m<sup>2</sup>) obese groups, respectively. Most of the women received at least 1000 mg of metformin daily for the treatment of PCOS with no significant difference between the BMI groups ( $P \geq 0.05$ ) (Table 4). The odds ratio (OR) of ovulation for PCOS women who received metformin and were obese (BMI ≥ 30) was 0.221 (95% CI 0.052–0.947,

$P = 0.042$ ) controlling for their age, baseline prolactin level, testosterone level, FSIC, FPG, comorbidities, duration of infertility, metformin daily dosage, and the use of clomiphene (Table 5).

### 3.1. Discussion

In this study, obese women (BMI ≥ 30 kg/m<sup>2</sup>) were 77.9% (OR = 0.221, 95% CI 0.052–0.947,  $P = 0.042$ ) less likely to ovulate than their non-obese counterparts (BMI < 30 kg/m<sup>2</sup>). Although some studies have suggested that metformin might be more effective in the treatment PCOS among obese women (Trolle et al., 2007), the results of this study confirm the findings of other studies which have reported that the efficacy of metformin as an ovulation stimulating agent is boosted when prescribed for non-obese women with PCOS (Legro et al., 2007; Popova et al., 2011). Therefore, such research findings

**Table 4** Dosage frequencies among metformin users.

Dosage	BMI			p-value	Total (n = 109)
	Normal BMI < 25 (n = 20)	Overweight BMI < 30 (n = 24)	Obese BMI > 30 (n = 65)		
500 mg once daily	4 (20%)	2 (8.33%)	4 (6.15%)	0.443	10 (9.17%)
750 mg once daily	0 (0%)	1 (4.17%)	2 (3.08%)		3 (2.75%)
500 mg twice daily	7 (35%)	10 (41.67%)	33 (50.77%)		50 (45.87%)
500 mg three times daily	7 (35%)	11 (45.83%)	23 (35.38%)		41 (37.61%)
850 mg twice daily	1 (5%)	0 (0%)	1 (1.54%)		2 (1.83%)
1000 mg once daily	1 (5%)	0 (0%)	0 (0%)		1 (0.92%)
850 mg three times daily	0 (0%)	0 (0%)	2 (3.08%)		2 (1.83%)

BMI: body mass index.

**Table 5** Odds ratios of successful ovulation among women with PCOS on Metformin.

Variable	Odds ratio	95% Confidence interval (CI)		p-value
Obesity (BMI $\geq$ 30 kg/m <sup>2</sup> )	0.221	0.052	0.947	0.042*
Age (yrs.)	1.096	0.958	1.255	0.1828
Metformin total daily dose (mg)	0.869	0.496	1.523	0.6236
Duration of infertility (yrs.)	0.777	0.494	1.223	0.2755
Prolactin (ng/ml)	1.001	0.998	1.005	0.485
Testosterone (nmol/l)	0.485	0.167	1.407	0.1831
Clomiphene co-treatment	0.486	0.100	2.368	0.3716
FSIC (mIU/L)	1.073	0.938	1.228	0.3031
FPG (mmol/l)	3.547	0.635	19.820	0.1492
Number of chronic health conditions (e.g., diabetes, hypertension)	0.655	0.192	2.234	0.4994

FSIC: fasting serum insulin concentration; FPG: fasting plasma glucose; BMI: body mass index.

\* p-value < 0.05; considered significant.

should emphasize the need to include a diet-and-exercise program along with any treatment plan for women with PCOS (Lim et al., 2012). Furthermore, the prevalence of obesity and overweight among this study sample is over 81%, which sheds light on the importance of campaigns to raise the public awareness of the obesity epidemic and its adverse consequences, especially in Saudi Arabia (Memish et al., 2014).

Although this study has controlled for a group of potential confounders, there are some limitations to its findings. First, this study was conducted in a single center, so the generalizability of its findings is limited. Secondly, this was a retrospective cohort study, which is more prone to misclassification bias or recall bias than a prospective study design (Kaji et al., 2014). Thirdly, the study sample was not homogenous with few patients having other medical conditions such as diabetes and hypothyroidism. Lastly, despite the fact that metformin was prescribed for  $\geq$  3 months, medication adherence cannot be ensured.

In summary, the findings of this study highlight the fact of variable efficacy of metformin as an ovulation stimulation agent among anovulatory women with PCOS based on their BMI. Pharmacotherapy should be adjunct to lifestyle modifications such as diet and exercise in the management of PCOS particularly among obese women. Future research should examine whether combining lifestyle modifications with metformin treatment would result in more favorable outcomes in comparison with metformin treatment alone, among anovulatory obese women with PCOS.

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