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Original article

The effect of metformin use on pregnancy rates among polycystic ovary syndrome patients undergoing *in vitro* fertilization: A retrospective-cohort study

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ABSTRACT

Background: Metformin is widely used with gonadotropins by women with polycystic ovary syndrome (PCOS) during *in vitro* fertilization (IVF) to increase their chances of pregnancy. The aim of this study was to evaluate the efficacy of metformin in improving the rates of clinical pregnancy among women with PCOS undergoing IVF.

Methods: This was a retrospective cohort study of women with PCOS, aged 18–40 years, undergoing IVF during 2006–2012 at a University Hospital in Riyadh, Saudi Arabia. Baseline patient data including menstrual frequency, biochemical parameters such as fasting serum insulin (FSI) concentration, comorbidities, and the rates of ovulation and pregnancy were collected. Pregnancy rates were compared between the metformin and non-metformin groups.

Results: A total of 210 women with PCOS met the inclusion criteria and were included in the study. Of the 210 women with PCOS, 109 of them received metformin in addition to gonadotropins. Patients who received metformin were 16% less likely to be pregnant in comparison with those who did not receive metformin (OR = 0.840; 95% CI = 0.710–0.993; $P = 0.0415$), when controlled for baseline prolactin level, testosterone level, lipid panel, FSI concentration, fasting plasma glucose (FPG) concentration, comorbidities, duration of infertility, daily metformin dosage, and the previous use of clomiphene and/or leuprolide.

Conclusions: Metformin co-treatment during IVF may negatively affect pregnancy rates. Further well-designed, randomized, double-blind placebo-control clinical trials are needed to confirm the findings of this study.

1. Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder and the most common cause of anovulatory infertility, affecting 6–10% of women of reproductive age (Balen and Michelmore, 2002; Homburg, 1996). In patients with PCOS, insulin resistance is considered as an important contributing factor to the pathophysiology of the disease (Christianson et al., 2015). There is considerable evidence suggesting that hyperinsulinemia leads to increased ovarian androgen biosynthesis *in vitro* and *in vivo* (Adashi et al., 1985; Barbieri et al., 1986), and reduced synthesis of sex hormone-binding globulin (SHBG) in the liver, resulting in the increased bioavailability of free androgens (Nestler et al., 1991).

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Therefore, the use of insulin-sensitizing drugs has been recommended for infertility treatment in these populations of women (Christianson et al., 2015).

There is considerable evidence suggesting that hyperinsulinemia leads to increased ovarian androgen biosynthesis *in vitro* and *in vivo* (Adashi et al., 1985; Barbieri et al., 1986), and reduced synthesis of sex hormone-binding globulin (SHBG) in the liver, resulting in the increased bioavailability of free androgens (Nestler et al., 1991). Metformin is an anti-hyperglycemic agent and has been widely used in infertile women with PCOS who is seeking (Sivalingam et al., 2014). The use of metformin reduces insulin levels, luteinizing hormone (LH) production, and circulating androgen levels in anovulatory women with PCOS (Barbieri, 2003). A previous study reported increased ovulation and clinical pregnancy rates when metformin was used for ovulation induction in patients with PCOS (Tang et al., 2010). Clinicians commonly administer or continue metformin therapy in patients undergoing *in vitro* fertilization (IVF) because of its potential fertility benefits (Tarlatzis et al., 2008).

Nevertheless, studies to date have shown inconclusive results on reproductive outcomes when using metformin in patients with PCOS undergoing IVF treatment. In a systematic review, Costello et al. reported the insignificant effect of metformin treatment on ovulation and pregnancy or live birth rates in women with PCOS undergoing gonadotropin ovulation induction or IVF (Costello et al., 2006). In another systematic review, Costello et al. found inconclusive results on the effects and role of metformin in the treatment of anovulatory infertility (Costello and Eden, 2003). Similarly, Palomba et al. reported that metformin did not positively affect the rates of pregnancy or live birth in patients with PCOS receiving gonadotropins for IVF (Palomba et al., 2013). In addition, Swanton et al. reported the insignificant effect of metformin cotreatment before and during IVF in women with ovaries of polycystic morphology but without any other features of PCOS such as hirsutism and menstrual dysfunction (Swanton et al., 2011). Furthermore, Palomba et al. reported that metformin had a negative effect on the ovarian response to gonadotropins administered during IVF programs in patients with PCOS, and it also reduced ovarian reserve (Palomba et al., 2011).

In contrast, in a recent systematic review, Palomba et al. reported increased live birth and pregnancy rates following metformin administration in patients with PCOS receiving gonadotropins for ovulation induction (Palomba et al., 2014). In addition, in a Cochrane review, Tang et al. reported that metformin treatment was associated with an improvement in clinical pregnancy rates but not live birth rates (Tang et al., 2012).

More recently, Christianson et al. reported a lack of evidence to support the use of metformin as an adjunct to standard IVF protocols (Christianson et al., 2015). Furthermore, in a Cochrane review, Tso et al. found inconclusive evidence that metformin treatment before or during assisted reproductive technology cycles improved live birth rates in patients with PCOS (Tso et al., 2014). Therefore, the effect of metformin on reproductive outcomes in women with PCOS appears to be limited. The present study aimed to evaluate the efficacy of metformin in improving the rates of successful pregnancy among women with PCOS undergoing IVF.

2. Materials and methods

This was a retrospective cohort chart review of women aged 18–40 years with PCOS undergoing IVF during 2006–2012 at a University Hospital in Riyadh, Saudi Arabia. The study was approved by the Institutional Review Board, College of Medicine, King Saud University, Riyadh, Saudi Arabia. The data was retrieved from the electronic medical records of the patients. Diagnosis of PCOS was established according to the following criteria: clinical and/or biochemical signs of hyperandrogenism, oligo/amenorrhea (fewer than six menses during the previous year), and typical polycystic ovaries on a transvaginal ultrasound scan (presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume > 10 mL) (Rotterdam EA-SPCWG, 2003). A patient should meet at least two of the above criteria to be diagnosed with PCOS.

Anthropometric, clinical, and biochemical baseline data were recorded, including age, body mass index (BMI), infertility duration, frequency of oligomenorrhea, number of children before therapy, levels of cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, fasting serum insulin (FSI), fasting plasma glucose (FPG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone (DHEA), testosterone, estradiol, and prolactin. As outcome measures, we determined the ovulation and clinical pregnancy rates. In addition, pre-existing comorbidities included hypertension (HTN), diabetes, hyperprolactinemia, hypercholesterolemia, hypothyroidism, and mental health disorders (e.g., depression, anxiety) were recorded. The previous use of other drugs including clomiphene and/or leuprolide with metformin was also recorded.

3. Statistical analysis

Descriptive statistical analysis was conducted by *t*-test and Chi-square test. Multiple logistic regression analysis was conducted to examine the relationship between the adjunctive use of metformin among women undergoing IVF therapy and the rates of successful pregnancy. Statistical significance was defined as $P < 0.05$. All analyses were performed using statistical software (SAS, version 9.2; SAS Institute Inc., Cary, NC, USA).

4. Results

A total of 210 women with PCOS, with mean age and BMI of 27.49 ± 5.35 years and 30.74 ± 6.08 kg/m^2; respectively, were included in the final analysis in which 109 of them received metformin in addition to gonadotropins (Fig. 1). The anthropometric, clinical, and biochemical baseline data of patients are shown in Table 1. The patient characteristics of the control and metformin treated groups are shown in Table 2. The majority of patients had a history of 4–7 years of infertility in both the metformin and control groups (51.4% vs. 58.4%; $P = 0.37$; respectively). Oligomenorrhea was observed in 63 patients (57.8%) in the metformin group compared to 35 patients (34.31%) in the control group ($P = 0.02$). In addition, 70 patients (64.2%) in the metformin group did not have any children before therapy compared to 68 patients (66.7%) in the control group ($P = 0.63$). Ovulation was recorded in 92 patients (84.40%) in the metformin group compared to 86 patients (85.15%) in the control group ($P = 0.88$). Clinical pregnancy was found in 50 patients (45.87%) in the metformin group compared to 49 patients (48.51%) in the control group ($P = 0.70$). The mean BMI of patients on metformin was almost similar to that of those who were not on metformin (30.96 kg/m^2 vs. 30.5 kg/m^2, respectively). The pre-existing comorbidities among patients in the metformin and control groups are shown in Table 3. The use of clomiphene and leuprolide in the metformin and control groups is shown in Table 4. Patients who received metformin were 16% less likely to be pregnant in comparison with those who did not receive metformin (OR = 0.840; 95% CI = 0.710–0.993; $P = 0.0415$), when controlled for baseline prolactin and testosterone levels, lipid panel, FSI and FPG concentrations, comorbidities, duration of infertility, daily metformin dosage, and use of clomiphene and/or leuprolide.

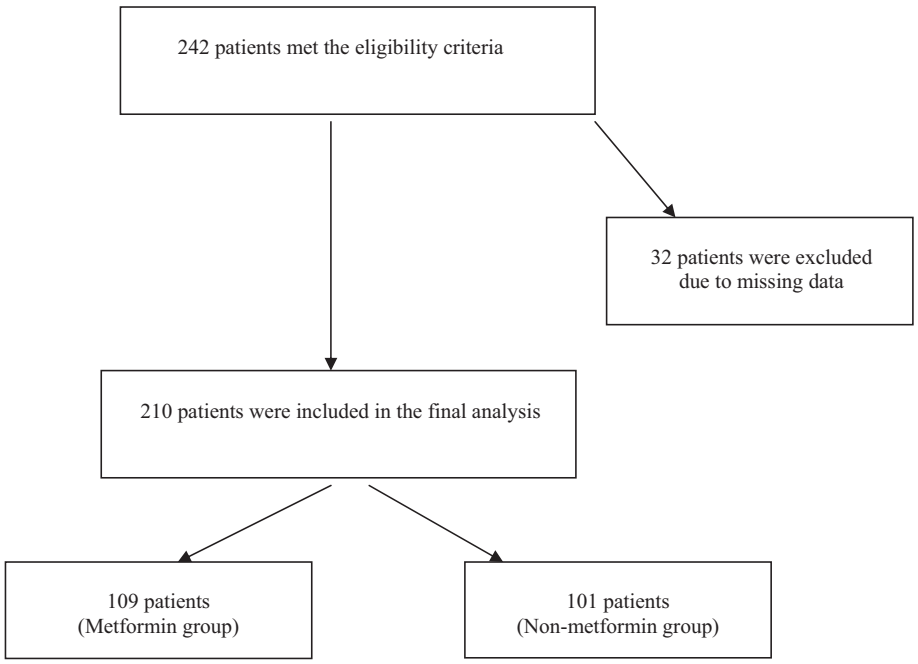

Fig. 1. Flow chart of the inclusion criteria.

Table 1
Anthropometric, clinical, and biochemical baseline data.

Data	Metformin			Total (n = 210)
	Treatment (n = 109)	Control (n = 101)	P-value	
Age (year)	27.66 ± 4.99	27.3 ± 5.72	0.7075	27.49 ± 5.35
BMI (kg/m^2)	30.96 ± 6.07	30.5 ± 6.12	0.5179	30.74 ± 6.08
Total cholesterol (mmol/L)	4.38 ± 1.56	4.40 ± 0.65	0.9572	4.38 ± 1.28
LDL (mmol/L)	3.20 ± 0.69	2.99 ± 0.46	0.4408	3.13 ± 0.63
HDL (mmol/L)	1.14 ± 0.22	1.16 ± 0.20	0.7845	1.15 ± 0.21
Triglyceride (mmol/L)	1.06 ± 0.38	1.03 ± 0.58	0.8878	1.05 ± 0.47
FSI (mIU/L)	17.7 ± 6.69	17.65 ± 5.51	0.9682	17.42 ± 3.79
FPG (mmol/L)	5.06 ± 0.87	5.06 ± 0.49	0.9866	5.07 ± 0.73
FSH (IU/L)	5.24 ± 1.46	5.77 ± 3.08	0.1119	5.49 ± 2.39
LH (mIU/mL)	7.72 ± 4.54	8.25 ± 5.68	0.3938	7.98 ± 5.11
DHEA (nmol/L)	5.13 ± 3.04	5.06 ± 2.63	0.9152	5.1 ± 2.86
Testosterone (ng/dL)	1.39 ± 0.74	1.52 ± 0.75	0.4382	1.45 ± 0.75
Estradiol (ng/dL)	15.7 ± 7.13	16.3 ± 5.03	0.5560	15.9 ± 6.21
Prolactin (ng/mL)	3.73 ± 2.59	3.58 ± 2.74	0.6015	3.65 ± 2.66

Note: Data are expressed as the mean ± standard deviation. BMI: body mass index, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FSI: fasting serum insulin, FPG: fasting plasma glucose, FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEA: dehydroepiandrosterone.
[*] Significant difference ($P < 0.05$).

5. Discussion

The present study aimed to evaluate the efficacy of metformin in improving the rates of successful pregnancy among women with PCOS undergoing IVF. PCOS is a heterogeneous condition with varying characteristic features in diverse subgroups of patients. Since insulin resistance and the accompanying hyperinsulinemia are hallmarks of PCOS, treatment with insulin sensitizers such as metformin is commonly used in the management of PCOS (Legro and Myers, 2004; Dunaif et al., 1989; Velazquez et al., 1994). In a previously published study, Caliskan et al. reported a 24% prevalence of insulin resistance among a population sample of Turkish women with PCOS (Caliskan et al., 2007). Although metformin is not a fertility drug, it has been shown to affect the metabolism of glucose, insulin, and lipid metabolism, resulting in diminished plasma concentrations of glucose, insulin, and free fatty acids and thereby inducing ovulation (Ehrmann et al., 1997; Morin-Papunen et al., 1998; Nestler and Jakubowicz, 1997). Furthermore, metformin has been shown to reduce circulating concentrations of insulin, testosterone, and LH among women with PCOS (Ehrmann et al., 1997; Morin-Papunen et al., 1998; Nestler and Jakubowicz, 1997). Although metformin is not recommended for all women with PCOS, it has been proposed for patients with PCOS who have insulin resistance and/or obesity (Checa et al., 2005).

This study failed to demonstrate any clinical benefits of metformin in improving ovulation and pregnancy rates in patients with PCOS who underwent IVF treatment. In the present study, patients who received metformin were 16% less likely to be pregnant in comparison with the control group who did not receive metformin. In a previous study, Onalan et al. reported that metformin had no beneficial effects on IVF outcomes including the total and clinical pregnancy rates in patients with PCOS (Onalan et al., 2005). Similarly, Kjotrod et al. reported that metformin co-treatment with IVF did not yield favorable outcomes in women with PCOS (Kjotrod et al., 2004). In a systematic review and meta-analysis of 10 randomized controlled trials, Palomba et al. revealed that metformin administration had no effect on clinical pregnancy rate (OR 1.2, 95% CI 0.90–1.61) or live birth rate (OR

Table 2
Patient characteristics of the metformin treated and control groups.

Characteristics	Metformin			Total (n = 210)
	Treatment (n = 109)	Control (n = 101)	P-value	
Duration of infertility (year)				
1	6 (5.50%)	1 (0.9%)	0.3734	7 (3.33%)
2–3	18 (16.51%)	13 (12.8%)		31 (14.76%)
4–5	31 (28.44%)	28 (27.72%)		59 (28.1%)
6–7	25 (22.94%)	31 (30.69%)		56 (26.67%)
8–10	15 (13.76%)	17 (16.83%)		32 (15.24%)
>10	14 (12.84%)	11 (10.89%)		25 (11.9%)
Oligomenorrhea				
Yes	63 (57.80%)	35 (34.31%)	0.0221*	104 (49.52%)
No	31 (28.44%)	41 (40.20%)		65 (30.95%)
Unknown	15 (13.76%)	26 (25.49%)		41 (19.52%)
Number of children before therapy				
0	70 (64.22%)	68 (66.67%)	0.6286	137 (65.24%)
1	21 (19.27%)	17 (16.67%)		38 (18.10%)
2	9 (8.26%)	11 (10.78%)		20 (9.52%)
3	7 (6.42%)	3 (2.94%)		10 (4.76%)
4	1 (0.92%)	2 (1.96%)		3 (1.43%)
5	1 (0.92%)	0 (0%)		1 (0.48%)
6	0 (0%)	1 (0.98%)		1 (0.48%)
Ovulation				
Yes	92 (84.40%)	86 (85.15%)	0.8807	178 (84.76%)
No	17 (15.60%)	15 (14.85%)		32 (15.23%)
Clinical pregnancy				
Yes	50 (45.87%)	49 (48.51%)	0.7014	111 (52.86%)
No	59 (54.13%)	52 (51.49%)		99 (47.14%)

Note: Data are expressed in frequency and percentage.
* Significant difference (P < 0.05).

Table 3
Patient comorbidities of the metformin treated and control groups.

Comorbidity	Metformin			Total (n = 210)
	Treatment (n = 109)	Control (n = 101)	P-value	
Hypertension (HTN)	3 (1.42%)	2 (0.95%)	0.3254	5 (2.38%)
Diabetes	3 (1.42%)	2 (0.95%)	0.3254	5 (2.38%)
Hyperprolactinemia	10 (4.76%)	7 (3.33%)	0.5376	17 (8.095%)
Hypercholesterolemia	2 (0.95%)	0 (0%)	0.4982	2 (0.95%)
Hypothyroidism	14 (6.66%)	11 (5.23%)	0.6436	25 (11.90%)
Mental illness (e.g., depression, anxiety)	3 (1.43%)	1 (0.47%)	0.6222	4 (1.90%)

Note: Data are expressed in frequency and percentage.
*Significant difference (P < 0.05).

Table 4
The use of clomiphene and leuprolide in the metformin treated and control groups.

Medication	Metformin			Total (n = 210)
	Treatment (n = 109)	Control (n = 101)	P-value	
Clomiphene	17 (8.095%)	2 (0.95%)	0.0005*	19 (9.05%)
Leuprolide	14 (6.66%)	8 (3.81%)	0.2349	22 (10.48%)

Note: Data are expressed in frequency and percentage.
* Significant difference (P < 0.05).

1.7, 95% CI 0.85–3.34) (Palomba et al., 2013). In another systematic review, Costello et al. reported the insignificant effect of metformin co-treatment on ovulation and pregnancy or live birth rates in patients with PCOS undergoing gonadotropin ovulation induction or IVF (Costello et al., 2006). However, in a Cochrane review, Tso et al. reported that the use of metformin increased the rates of clinical pregnancy and decreased the risk of ovarian hyperstimulation syndrome; however, evidence on metformin treatment before or during IVF for improving the live birth rates in women with PCOS was inconclusive (Tso et al., 2014).

In contrast, few studies have reported the beneficial effects of metformin co-treatment on IVF outcomes in women with PCOS (Tang et al., 2010; Palomba et al., 2014; Stadtmauer et al., 2002). Stadtmauer et al. revealed the benefits of metformin in improving IVF outcomes in women with clomiphene citrate-resistant PCOS (Stadtmauer et al., 2002). In a systematic review, Palomba et al. reported increased live birth and pregnancy rates following metformin co-treatment in addition to gonadotropins for ovulation induction in patients with PCOS (Palomba et al., 2014). In a Cochrane review, Tang et al. reported that the administration of

metformin was associated with improved clinical pregnancy rates but failed to demonstrate beneficial effects in improving live birth rates (Tang et al., 2010). Recently, Christianson et al. conducted a worldwide web-based survey among IVF centers to evaluate the effects of metformin administration in patients undergoing IVF treatment. In this survey, use of metformin was reported to increase the clinical pregnancy rates in 70% of IVF cycles, however, 75% of IVF cycles reported that the data was not sufficient to reach a definitive conclusion concerning the use of metformin among patients undergoing IVF (Christianson et al., 2015).

The present study had some potential limitations. Similar to other retrospective cohort studies, inaccuracies due to incorrect or incomplete documentation may occur in the medical files of patients and/or data transcription. Furthermore, this was a single-center study, thus limiting the generalizability of our findings. In addition, the sample size of the study was small relative to that of other published studies in the same field, however, the results were still significant. Moreover, we did not control for treatment duration and the number of administered doses of gonadotropins.

In conclusion, the present study demonstrates that metformin co-treatment during IVF may negatively affect pregnancy rates. Further well-designed, randomized, double-blind placebo-control clinical trials are needed to confirm the findings of this study.

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Conflict of interest: Authors of this study have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this study.

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