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Metformin Therapy in Infertile Women with Polycystic Ovary Syndrome

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ABSTRACT

Background: Polycystic ovary syndrome is a common cause of infertility and can occur at any age during reproductive life. Metformin is an insulin sensitizer medication widely used for the treatment of patients affected by type 2 diabetes mellitus. It was introduced in clinical practice to treat women with polycystic ovary syndrome because many of them are insulin resistant

The aim: To assess the effectiveness of 6 months therapy of metformin in improving clinical and biochemical indices of infertile women with polycystic ovary syndrome

Study Design and Methods: This uncontrolled clinical trial study included all women who were registered in Infertility and In Vetro Fertilization Center in Al- Batool Maternity and Teaching Hospital in Mosul city during the period from 1st Jan. 2010- 30th Nov. 2010 and who were diagnosed as polycystic ovary syndrome according to certain criteria were considered as the study population. One hundred and twenty seven infertile women with polycystic ovary syndrome were enrolled and comprehensively assessed by gynecologist through history, physical examination and hormonal assays. Metformin was provided for all participants at the 3rd day of their cycle. No control women were included in this study because most of the participants were overweight and obese and they want to get benefit from the therapy. After this baseline assessments which include menstrual pattern, body mass index, and serum level of gonadotropins, testosterone and prolactin hormone, the patients were given 1500-1700 mg of Metformin for 6 months period and then revaluated so that the study period was from 1st Jan. 2010-31st May 2011.

Results: Out of 127 enrolled women, 111 (87.4%) who completed the study with 6 months Metformin therapy and their follow up, showed significant improvement in body mass index and 71. 2% of the sample resumed regular menstrual cycle with ovulation rate of 66.6% while the conception rate was 10.8%. The hormonal assays of the study sample revealed a statistically significant decrease in testosterone, luteinizing hormones and with a statistically significant increase in follicular stimulating hormone and progesterone

Conclusion: A six month course of Metformin therapy improves menstrual cycli city and fertility in women with polycystic ovary syndrome. It is recommended to be considered as an important component to support a preventive health care among anovulatory women with PCOS.

Keywords: Metformin, Pregnancy, PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is not a disease of ovary but it is considered as a multisystem disease, and a significant cause of infertility worldwide affects approximately 5%–8% of all reproductive-age women that can occur at any age during reproductive life of women [(1-2)].

Much has been changed over the past 80 years in the way to diagnose, and treat polycystic ovary syndrome. The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome of ovarian dysfunction, with the cardinal features of

hyperandrogenism and polycystic ovary morphology [3], thus no single diagnostic criterion is sufficient for clinical diagnosis. The clinical manifestations of PCOS include menstrual irregularities, signs of androgen excess, and obesity. Insulin resistance and elevated serum luteinizing hormone levels are also common features in PCOS [4-6].

The pathogenesis of PCOS is still unclear, and a complex of genetic and environmental factors may be involved, [7] where family studies demonstrated that PCOS is significantly more prevalent among family members than in the general population [8,9].

The rationale for the use of an insulin sensitizer drug, such as metformin, which was introduced in clinical practice to treat women with PCOS, arises from the knowledge that insulin resistance with compensatory hyperinsulinemia has a role in the pathogenesis of PCOS and affects approximately 65-70% of PCOS women [7,10]. It is a major trigger of metabolic and reproductive abnormalities as it leads to thecal thickening in the ovary, which in turn leads to anovulation and infertility [11]. PCOS may account for > 75% of the anovulatory infertility [12]. Evidences indicate that hyperinsulinemia precedes and in fact give rise to hyperandrogenism in PCOS and places them at high risk of type 2 diabetes mellitus, cardiovascular disease, endometrial cancer and obstructive sleep apnoea cancer [4,13].

Metformin is the only remaining member of the biguanide family that has been used as an anti-hyperglycemic agent for the treatment of type 2 diabetes for a long time and improves glucose intolerance [14]. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. It increases the number of insulin receptor but not insulin concentration and therefore does not cause hypoglycemia in normoglycemic patients. The most common side effects associated with metformin are gastrointestinal in nature however; it is contraindicated in patients with significant renal dysfunction [3, 15, 16].

The Androgen Excess and PCOS Society (AEPS) [17], suggests that metformin could be used to treat and prevent progression to impaired glucose tolerance (IGT) in PCOS patients and the American Association of Clinical Endocrinologists' guidelines [18] recommend metformin as an initial intervention in overweight and obese patients with PCOS.

The available evidence supports the use of metformin from the earliest stages of treatment in women with PCOS to reduce symptoms of hyperandrogenism and promote fertility [3,19]; although the beneficial effect of metformin might vary according to the clinical characteristics of the patient to be treated [20].

In our locality the data regarding the role of metformin in PCOS is scarce thus the present study was conducted to assess the effectiveness of 6 months therapy of metformin in improving biochemical and hormonal indices as well as ultrasonographic profile of infertile PCOS women.

The present study aimed to assess the effectiveness of six months of metformin therapy in improving clinical and biochemical indices of infertile women with polycystic ovary syndrome.

PATIENTS AND METHODS

The present study was conducted in Infertility and In Vitro Fertilization (Infertility and IVF) Center in Al-Batool Maternity and Teaching Hospital in Mosul city and all infertile women with PCOS who were registered in this center during the period from 1st Jan. 2010 - 30th Nov. 2010 were considered as the study population.

The diagnosis of the cases was based on Rotterdam criteria (2003) and European Society for Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) guidelines [3], that PCOS could be diagnosed, even after the exclusion of related disorders, by at least two of the following features: 1) oligo- or anovulation; 2) clinical and/or biochemical signs of hyperandrogenism; and 3) polycystic ovarian morphology on ultrasound examination which is defined as the presence of ≥ 12 follicles measuring 2-9 mm in diameter (within one ovary sufficient for diagnosis). While women with related ovulatory or other androgen excess disorders such as; hypothyroidism, idiopathic hyperprolactinamia, Cushing syndrome and non-classic congenital adrenal hyperplasia were excluded by appropriate investigations. Other specific exclusion criteria include bilateral tubal obstruction or male factor infertility diagnosed by hysterosapingogram and semen analyses; in addition, cases with diabetes and abnormal renal function tests were also excluded.

After applying the inclusion and exclusion criteria; the purpose of the study was carefully explained to each infertile woman with PCOS who was eligible to participate, so 127 PCOS infertile women from those eligible were willing to participate in this study. A written consent was obtained from them and they were interviewed according to especially designed

questionnaire form which gathered information regarding socio-demographic characteristics such as; age, type of infertility with its duration, menstrual history and miscarriages.

Each participant was assessed thoroughly at the beginning of the study by gynecologist through history and physical examination including general and pelvic examination as well as laboratory tests. As part of baseline assessment, the participants underwent clinical evaluation of menstrual pattern. Anthropometric measurements using World Health Organization (WHO) recommendations were performed [21]. The weight was measured in kilogram (kg) with light clothes to within 100 gm and the height was measured with bare feet to within 0.5 cm to calculate the body mass index (BMI) in kg/m^2. All overweight and obese participants were advised to have life style modifications including healthy diet and physical exercise. On the other hand their male partners were assessed accordingly by the urologist and each registered couple was provided by special return card.

For hormonal assays, peripheral blood samples were obtained during the early proliferative phase; day 2-3 of progesterone-induced withdrawal uterine bleeding. Measurements of serum follicular-stimulating hormone (FSH), luteinizing hormone (LH), testosterone and prolactin were carried out; while progesterone hormone was performed on the day 21-22 of the cycle (mid luteal phase) or one week before the expected onset of the menstrual period. All hormonal assays were done by Enzyme-Linked-Fluorescent-Assay method [3]. Transvaginal ultrasonographic examination on day 13 was performed to evaluate the size of ovaries and the number of follicles.

Metformin therapy was started at the third day of menstrual cycle using a dose of 500 mg daily which was increased in a stepwise manner during the first 3 weeks to accommodate the side effects until the patients were taking a total of 1500 - 1700 mg daily for 6 months period. The participants were followed up by serial transvaginal ultrasonographic examinations on day 13 of every cycle for monitoring of ovulation and once the follicle reached a size of 18 mm-20 mm in diameter; an injection of human chorionic gonadotropin (HCG) 5000 IU was given intramuscularly and timed intercourse was advised. Any conception during the period of the therapy was recorded.

At the end of the six months therapy; BMI, menstrual pattern and serum hormonal levels on day 3 for FSH, LH, testosterone & prolactin were reassessed.

Data of all the study participants were entered into a computer and analysis was performed using the Statistical Package of Social Science (SPSS) software version 16. Chi square test was used to test the differences between data of the participants who were initially enrolled at the beginning of this study and those who completed the 6 months Metformin therapy and follow up period. The significance between pre- and post-therapy parameters was assessed by paired Student's t-test. Correlations were calculated using Pearson's correlation coefficient and the level of significance was considered at $P< 0.05$.

RESULTS

A total of 127 infertile PCOS women were initially included in the study sample during the period from 1st Jan, 2010 - 30th Nov, 2010. A complete baseline and post therapy information was available for only 111 participants (87.4 %) who received the six months Metformin therapy and were followed up; thus their results were analyzed. The remaining 16 (12.6 %) participants were excluded because five of them couldn't tolerate Metformin therapy and developed severe gastrointestinal side effects; while the remainders (11) were dropped out due to either incomplete investigations or lost site off.

(Table 1) indicates that the prominent age group was 20-29 years old and constituted 59.5% of the study sample with mean age 27.51 ± 5.12 years. More than two thirds 72.2 % of the sample were obese with mean duration of infertility of 5.04 ± 2.72 years. More than half (55.0%) of the participants suffered from primary infertility while only a minority (7.2%) had regular menstrual cycle. The table also showed that about one third (30.6%) had miscarriages.

The results of this study showed no significant differences between initially enrolled participants (127) and who completed the 6 months metformin therapy and follow up period (111) in term of age distribution, BMI and obstetric and gynecological history including; types and duration of infertility in addition to the history of miscarriages and their menstrual pattern, (Table 1).

Table 1: Basal characteristics of the study participants (initially enrolled with those of completed the metformin therapy)

Characteristics	Study Sample (n=111) No. (%)	Total Enrolled (n=127) No. (%)	P-Value*
Age (years)			
< 20	4 (3.6)	5 (3.9)	0.931
20 -29	66 (59.5)	78 (61.4)	
30 - 40	41 (36.9)	44 (34.6)	
Mean ± SD	27.51 ± 5.12	27.37 ± 5.04	
Range (min- max)	(17 – 39)	(17 – 39)	
Body Mass Index (BMI) kg/ m²			
18.5-24.9 kg/ m²	2 (1.8)	3 (2.4)	0.956
25.0 -29.9 kg/ m²	30 (27.0)	44 (39.6)	
≥ 30 kg/ m²	79 (72.2)	90 (70.9)	
Type of Infertility			
Primary	61 (55.0)	69 (54.3)	0.923
Secondary	50 (45.0)	58 (45.7)	
Duration of infertility (years)			
< 5	65 (58.6)	73 (57.5)	0.972
5-9	36 (32.4)	43 (33.9)	
10 -15	10 (9.0)	11 (8.6)	
Mean ± SD	5.04 ± 2.72	5.04 ± 2.64	
Range (min- max)	(2 – 16)	(2 – 16)	
Miscarriage(Abortion)			
Nil (0)	77 (69.4)	90 (70.9)	0.987
1	21 (18.9)	24 (18.9)	
2	7 (6.3)	7 (5.5)	
3	6 (5.4)	6 (4.7)	
Mean ± SD	0.46 ± 0.83	0.43 ± 0.79	
Range (min- max)	(0 - 3)	(0 - 3)	
Menstrual cycle pattern			
Amenorrhea	12 (10.8)	13 (10.2)	0.962
Polymenorrhea (DUB)	11 (9.9)	15 (11.8)	
Oligomenorrhea	80 (72.1)	91 (71.7)	
Regular	8 (7.2)	8 (6.3)	

*χ^2 test was used.

(Table 2) showed that all parameters of study sample showed very high significant improvement after 6 months of metformin therapy, where the participants' mean weight pre-and post-metformin therapy was 79.10±9.83 kg and 73.81±10.24 kg respectively where the mean weight loss ± SD was 5.29±4.19 kg; this difference was highly significant (p=0.000). This reflect the highly significant (P=0.000) reduction in the mean BMI (2.12 ±1.87 kg/m^2) of the participants at post- therapy assessment. The same table also indicates a very high significant reductions in the level of LH hormone (p=0.000), FSH hormone (p=0.000), LH/FSH ratio (p=0.000) and Testosterone (p=0.000). On the other hand the progesterone level increased significantly (p=0.000) at post therapy assessment, (Table 2).

Table 2: Hormonal assays and physical measurements of the participants at baseline pre and post-metformin therapy.

Parameters	Pre- therapy (n=111)	Post- therapy (n=111)	P-value*
	Mean ± SD	Mean ± SD	
Weight (kg) Range (min- max)	79.10 ± 9.83 (60 - 109)	73.81 ± 10.24 (55 - 105)	0.000
BMI (kg/m^2) Range (min- max)	32.32 ± 4.07 (22.3 - 43.75)	30.11 ± 4.28 (20.52 - 42.50)	0.000
LH (µIU/ml) Range (min- max)	7.53 ± 4.30 (2.04 - 32.10)	3.89 ± 1.38 (1.34 - 10.20)	0.000
FSH (µIU/ml) Range (min- max)	4.28 ± 1.34 (1.10 - 7.41)	5.35 ± 1.42 (1.70 - 9.69)	0.000
LH / FSH ratio Range (min- max)	1.89 ± 1.02 (0.34 - 6.20)	0.77 ± 0.36 (0.27 - 2.17)	0.000
Testosterone (µIU/ml) Range (min- max)	1.01 ± 0.47 (0.23 - 2.70)	0.48 ± 0.25 (0.14 - 1.45)	0.000
Progesterone D 21 (ng/ml) Range (min- max)	1.68 ± 0.77 (0.25 - 4.50)	6.66 ± 4.40 (1.70 - 18.90)	0.000

*Paired Student's t-test was used.

The overall improvements in the pattern of menstrual cycle post- metformin therapy was seen in 71.2% of patients who resumed regular menstruation including; 73.8% of those with oligomenorrhea, 42.7% of patients had secondary amenorrhea and 9.9% of patients presented with polymenorrhea, (Table 3).

Table 3: The effect of the six months metformin therapy on the participants' menstrual cycle pattern.

Menstrual cycle Pattern		Post - Therapy			
		Oligomenorrhea	Polymenorrhea (DUB)	Spontaneous Regular	Total
		No. (%)	No. (%)	No. (%)	No. (%)
Pre -Therapy	Secondary Amenorrhea	7 (58.3)	-----	5 (42.7)	12 (10.8)
	Oligomenorrhea	21 (26.2)	-----	59 (73.8)	80 (72.1)
	Polymenorrhea (DUB)	-----	4 (36.4)	7 (63.6)	11 (9.9)
	Regular	-----	-----	8 (100.0)	8 (7.2)
	Total	28 (25.2)	4 (3.6)	79 (71.2)	111 (100.0)

Data of the results showed very high significant improvement (P=0.000) in ovulation rate of anovulatory PCOS women between pre- and post- metformin therapy through 6 months period (7.2% and 66.6 % respectively). Moreover the result of the present study also indicates that the conception rate was 10.8%. (Figure 1) illustrates that 33.4% of patients had no ovulation at all, while 25.2% had one ovulatory cycle only and 23.4% have been ovulated twice, 15.3% have been ovulated thrice, while the remainders 2.7% have been ovulated four times.

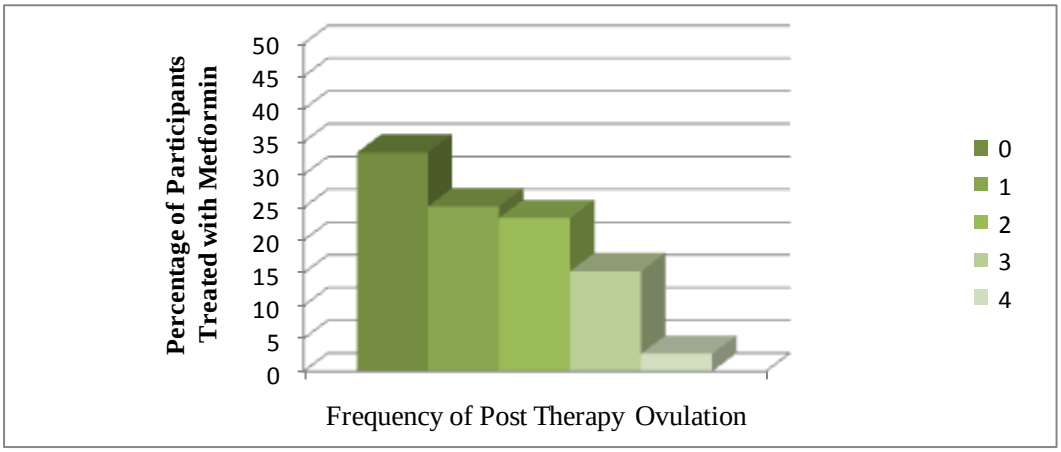

Figure-1 Distribution of participants post Metformin therapy according to the frequency of ovulation.

DISCUSSION

The prevailing concept is that PCOS is a polygenic trait that may result from interaction of predisposing and protective factors under the influence of environmental factors. It is now recognized as a female subtype of metabolic syndrome [(22)].
The results of the present study showed that the mean age of the study sample was 27.51±5.12 years and majority (92.8%) had menstrual irregularities. Similar findings were reported earlier in 2004 in India by Aruna et al [(23)]. Menstrual dysfunctions affect a high number of PCOS patients, where 60-80% of patients present with menstrual irregularities with fewer than nine menstrual periods per year [(24)]. In some patients, menses occur very infrequently or not at all, while 5-10% of PCOS women, more frequent bleeding and menorrhagia may occur. Anovulatory bleeding has been reported in up to 20% of women who report normal menstrual cycles [(25)]. Several pathogenic mechanisms were proposed, although hyperinsulinemia could play a central role [(26)]. Evidence indicated that the coexistence between PCOS and obesity have important clinical and pathological implications [(27)]. The present study found that obesity is prevalent in the study participants constituting 72.2%, this is in agreement with the findings of other studies which reported that the frequencies of obesity in the PCOS cohort varied from 30%-75% [(28, 29)]. Moreover, recent study conducted in Russia in 2017 showed a lower rate of patients with normal BMI was found predominantly in the PCOS group than their control group with a significantly higher mean BMI among Asian infertile women with PCOS [(30)].

The rate of miscarriages among the study participants was 30.6%. Similarly, earlier studies showed that the risk of miscarriage in PCOS patients after spontaneous or assisted conception was reported in 30-50% [(31)] and the miscarriage rate seems to be 3-fold higher in PCOS subjects than in healthy women [(32)]. Thus high LH levels, hyperinsulinemia, hyperandrogenism, and hypofibrinolysis mediated by plasminogen activator inhibitor activity could be involved alone or in combination is the mechanism underlying the increased risk of miscarriage in the PCOS population [(7, 33)].

The realization of the major defect of insulin action in PCOS patients which is probably decrease in insulin sensitivity with compensatory hyperinsulinemia has resulted in the use of Metformin to ameliorate the biochemical profile and improve reproductive function [(7)]. The present study found a significant reduction (p= 0.000) in the participants' body weight and their BMI after 6 months therapy with metformin. This reflects the fact that metformin could act to improve body weight in obese PCOS patients both directly and indirectly, where it stimulates catabolic processes in the peripheral organs and modulates appetite in the hypothalamus [(34)]. Similar findings were reported by Tan et al,[(34)] where they found that metformin use was significantly associated with decreased body weight and BMI in the overweight and obese PCOS patients. On the other hand, other researchers observed that Metformin reduced BMI in PCOS patients both with and without insulin resistance [(35)]. Moreover, earlier study compared the efficacy of a lifestyle modification program combined with metformin or placebo in PCOS patients, showed that reduction of body weight, BMI, and visceral fat mass was greater in the metformin group than the placebo group [(36)].

The main complaints about menstrual disorders from PCOS patients are absence or infrequency of menstrual bleeding [(7)]. The result of this study illustrated that metformin is effective in restoring regular menses even within the first 3 months from the beginning of the therapy and at the end of the study more than two thirds (71.2 %) of the PCOS patients with menstrual disturbances resumed regular menstrual cycle. This is in agreement with the findings of a similar study conducted earlier in India by Aruna et al [(23)]. While findings obtained from uncontrolled studies carried out in different

countries all over the world [37-39] demonstrated that metformin was effective in restoring regular menses in approximately 62% of PCOS women with oligoamenorrhea.

In a randomized, double-blind controlled trial patient with PCOS were treated with 6-month course of metformin showed a significant improvement in menses frequency, whereas no change was observed in those receiving placebo. In a long-term follow-up of the same study, the frequency of menses per month per patient continued to improve significantly over time during the metformin administration [40]. The beneficial effect of metformin on menstrual cycle is commonly attributed to its effectiveness on ovulatory function [7].

Polycystic ovary syndrome is the most common cause of anovulatory infertility, the present study demonstrates a significant improvement (p=0.000) in the ovulation rate with 10.8% conception rate. A similar achievement was obtained by Aruna etal (23) in their study in India, where they reported an ovulation rate of 66% and pregnancy rate 28% among their patients (23). Other study reported that metformin alone in a dose of 500mg three times daily will restore ovulation in 40% of anovulatory women with PCOS (41). Furthermore, a large review using 27 clinical trials found that metformin enhanced ovulation rates, but not the number of live births especially when it was used in combination with clomiphene 42 The mechanism by which metformin restores ovulation is still controversial some studies have suggested that metformin induced menstrual regularization is a consequence of a decrease in androgens and LH levels secondary to a decrease in insulin levels [43,44]; while other study found that metformin directly inhibited androgen production in the human ovarian thecal cells [45].

The highly significant reduction (p=0.000) in the circulating androgen and LH observed in this study is comparable with the findings of earlier studies [43,44]. Moreover, other study reported a similar result within one week of commencing metformin [46]. A study on overweight PCOS patients confirmed that the combination of metformin plus lifestyle intervention was more effective in weight and androgen reduction than placebo plus lifestyle intervention [47].

CONCLUSION

Metformin is an effective therapy for initial intervention in infertile women with polycystic ovary syndrome as insulin sensitizing agents and its benefit goes beyond the achievement of ovulation and pregnancy so it is recommended to be considered as an important component to create and support a preventive health care in anovulatory women with PCOS.

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