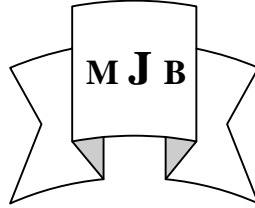


## The Role of Metformin in Women with Polycystic Ovarian Syndrome as a Treatment of Infertility

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### Abstract

This study was conducted to study the therapeutic benefit of metformin in achieving ovulation in women with polycystic ovarian syndrome (PCOS). Twenty eight women received metformin, ovulation rate was (60.2%). While it was (100%) when we add clomiphene citrate to it. So over all ovulation rate was (100%) and overall pregnancy rate was (10.8%) which was with metformin alone.

### الخلاصة

اجريت هذه الدراسة لتحديد مدى كفاءة نواء الميتفورمين في تحريض الاباضة في مريضات العقم اللواتي يعانين من عدم حدوث الاباضة بسبب متلازمة المبيض المتعدد التكيسات تم بحث 28 مريضة ثم اعطائهم هذا الدواء و كانت نسبة حدوث تحريض الاباضة (60.2%) و كانت النسبة (100%) عند اضافة نواء الكلومفين ستريت للبرنامج العلاجي. اما نسبة الحمل كانت (10.8 %) في هذه الدراسة عند استخدام الميتفورمين وحده.

### Introduction

**P**oly cystic ovarian syndrome (PCOS), also known as stein-leventhal syndrome or functional ovarian hyperandrogenism, is characterized by an ovulation, infertility and hyperandrogenism, with clinical manifestation of irregular menstrual cycles, hirsutism and acne [1]. This condition affects about 5-10% of women with reproductive age [2]; although this varies depending on the diagnostic criteria used [3]. These women have increased prevalence of cardiovascular risk factors and insulin resistance [4, 5].

The use of metformin for women with PCOS has aroused a tremendous amount of interest. Metformin is an

insulin sensitizing biguanide commonly used for treatment of type II diabetes mellitus (D.M) [6]. Metformin decreases hyperandrogenism and insulin resistance, also it improves ovulation rate, cervical score and pregnancy rate [7]. This study shows the therapeutic benefit of metformin in achieving ovulation in PCOS women.

### Materials and Method

Twenty eight women were studied in Al-amal center for infertility management from March 2007 until May 2009. These women were diagnosed as having PCOS according to ESHRE/ASRM criteria [8]. Clinical criteria of women involved are listed in table (1).

**Table 1** clinical data of women involved in the study:

Mean age	27.6 years
Mean duration of infertility	2.4 years
Number with primary infertility	26
Number with secondary infertility	2
Percentage with acne	35
Percentage with hirsutism	56
Percentage with irregular menses	65
Mean body weight\kilogram(mean)	78

Tubal patency was proved by HysteroSalpinigioGraphy (HSG), base line Follicular Stimulating Hormone (FSH), Luteizing Hormone (LH) DiHydroEpinadrosteron, (DHEA) or testosterone and serum prolactin was assessed by cycle day 2. Male partner have normal sremiogram according to WHO criteria [9]. Diet management, exercise and life style readjustment were discussed with these patients.

**Treatment protocol:**

All patients under went base line ultrasound (u\s) for ovarian volume, follicular size, numbers and endometrial thickness. Five hundred milligrams (mg) tablet of metformin with meal was started for 1 week, then 2 tablets of 500 mg metformin twice daily for another week. Then after we started the full dose of 1 tablets 3 times daily, by this regimen the women will have less side effects.

How did we monitor the therapy?

Patients will be asked to return 2 months after initial therapy. If she resumes her cycle we monitor her ovulation at cycle day 11 (CD 11) by u\s or cervical score assessment [10]. If the patient ovulated we ask her to have regular intercourse, and to continue therapy for another 3 months to see if she can conceived; if not; we re-

evaluate her by measurement of the laboratory tests that were abnormal at the initial evaluation. If after 9 months no ovulation or pregnancy achieved we add clomiphen citrate (C.C) to the protocol in a dose of 50 mg tablet twice daily from CD2-CD5, and we follow the patients for ovulation, and we check B-subunit of human chronic gonado tropin (B-HCC) for pregnancy.

**Results**

Seventeen women of the twenty eight (17/28) achieved ovulation within a period from 3-9 months (60.2%) with metformin alone. Three of them (3/28) have conceived and have live birth baby within the span of treatment. Pregnancy rate (10.8%) the other 11 patients succeeded to have ovulation when we add C.C to the protocol and ovulation rate was 100% within a period of 12 months; but no pregnancy achieved in this group (0%).

**Discussion**

although PCOS is heterogeneous syndrome, the final common pathway seems to involve a dysregulation of enzyme responsible for androgen biosynthesis, possibly influenced by insulin growth factor and L.H. A single gene defect, inherited as an autosomal

dominant pattern has been proposed [11]. Since 1999 national institute of health sponsored a conference on PCOS, it has been appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria. The 2003 Rotterdam Consensus Workshop concluded that PCOS is a syndrome of ovarian dysfunction along the cardinal features of hyperandrogenism and PCOS morphology [8]. PCOS remains a syndrome and as such no single diagnostic criteria is sufficient for clinical diagnosis. Its clinical manifestation may include menstrual irregularities, a sign of androgen excess and obesity. Insulin resistance which is thought to be a key factor in the development of the metabolic syndrome [12]; elevated LH levels are also a common feature in PCOS. PCOS is associated with increased risk of type II DM and cardiovascular events [13], and it may represent a major risk factor for psychological problems [14]. Endometrial and breast cancer are also common in these patients so seeking treatment is critical [13]. Treatment of PCOS depends on symptoms, age, whether or not patients want to get pregnant, and the degree of ovarian-adrenal excess. First line management includes diet modification, weight loss and stress reduction, since obesity and stress can contribute to androgen excess [15]. Other management and treatment are directed at addressing specific symptoms. Infertility treatment includes in addition to ovarian stimulation medication, an ongoing increasing evidence that endocrine abnormalities can be reversed by the widely available standard medication used for treatment of adult onset DM. "Metformin" and results can be seen within 2 months. By six months over 90% women will resume regular

manse [16]. Metformin is a biguanide insulin sensitizer which is not used only for the treatment of all PCOS related disturbances, but also for the prevention of the syndromes [16, 17]. This study conclusively points out the beneficial effect of metformin in case of PCOS. Seventeen of 28 patients (60.2%) achieved ovulation with metformin alone with a period of 3-9 months, this result is better than those of Hague, et al; who achieved 46% ovulation rate with metformin in a period of 6 months [18]. This difference in the result may be due to the longer duration of the study of our patients and the mean weight which was lower than those of Hague, et al; (78 kg vs. 90 kg); since non obese patients respond better than obese ones to metformin [19]. The 100% ovulation rate gained by combination of metformin and clomiphene citrate was surprising result accomplished within 12 months of the treatment, since no previous research had such result. Hague, et al; [18]; found that ovulation rate was 76% when they use metformin and C.C, but the duration of the treatment was shorter than those of our study group (4 months vs. 12 months), while castello et al; [20]; achieved 57% ovulation rate with metformin and C.C when they used this protocol but for shorter duration, and their study group was larger. Other researcher achieved ovulation rate of 75% [21]. The 100% ovulation rate we have was the outcome (harvest) of the complete cooperation between the patients and our staff, since they were sincere in losing weight by diet restriction, and taking the medication as it was prescribed and they were aware that metformin is not "weight losing drug" [16]. Other reviews have described ovulation rate of 40-85% with C.C alone [22]. Although resistance to C.C is more in women who are overweight, which common

situation with PCOS [23, 24]. The pregnancy rate achieved with metformin alone in a period of three months (10.8%) was achieved in 3 women who weren't obese but they have PAO by u/s so the response to metformin treatment was dramatic. In conclusion metformin is an effective treatment for ovulation induction in women with PCOS and can be the choice as first line agent seems justified, and there's some evidence of benefit on variable metabolic syndrome [7, 25] and there's no report of abnormal babies in women who conceived using metformin and all resulting babies were normal. It should be used as adjuvant treatment and not a replacement for exercise and improved diet. The additional benefits are relatively low cost of therapy and diminished hazard associated with surgical interventions such as ovarian drilling and InVitro Fertilization (IVF) [26].

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