

## Finasteride (plus Oral Contraceptive pill) vs Metformin in Treatment of Polycystic Ovary Syndrome-Related Infertility: a Prospective Randomized Trial

Entisar J Al-Mukhtar<sup>1</sup> MBChB MSc, Adeb A Al-Zubaidy<sup>2</sup> MSc PhD, Liqaa M Al-Khuzae<sup>3</sup> FIDOG

<sup>1</sup>Dept. of Pharmacology, College of Medicine, University of Babylon, Babylon, <sup>2</sup>College of Pharmacy, University of Kerbala, Kerbala, <sup>3</sup>Dept. of Gynecology & Obstetrics, College of Medicine, Al-Nahrain University, Baghdad, Iraq

### Abstract

**Background** Polycystic ovary syndrome (PCOS) is a common endocrinopathy characterized by oligo-ovulation or anovulation, signs of androgen excess, and multiple small ovarian cysts. PCOS is thought to be one of the leading causes of female subfertility.

**Objective** To evaluate and compare the effects of finasteride vs metformin in treatment of PCOS related infertility.

**Methods** Seventy seven infertile married women with an age range between 18 and 35 years were studied complaining from infertility due to PCOS. They were divided into group 1 treated with finasteride (5 mg daily concomitantly with an oral contraceptive pill "OCP" continuously for 2 months) and group 2 was treated continuously for 3 months with metformin (500 mg three times daily).

**Results** The percentage of patients responded to metformin treatment was 35.89%, whereas 26.32% of patients were responded to the treatment with finasteride-OCP combination. There were no significant difference between metformin and finasteride in regard to the mean number of mature follicles ( $1.21 \pm 0.43$  vs  $1.2 \pm 0.42$ ) and endometrial thickness ( $7.26 \pm 1.1$  vs  $7.80 \pm 2.25$  mm) respectively. The pregnancy rate per patient was higher in metformin treated group in comparison to finasteride treated group (60% vs 21.42%); however, this difference was insignificant ( $P > 0.05$ ).

**Conclusion** Finasteride has a good promising effect in the treatment of infertility due to PCOS, as more patients responded to an oral finasteride-OCP combination in comparison to those responded to an oral metformin monotherapy and the difference in the pregnancy rate of the two groups was not significant.

**Keywords** Finasteride, Metformin, Polycystic ovary syndrome, Infertility

### Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders that affects approximately 5-10% of pre-menstrual women<sup>(1,2)</sup>, and it a leading cause of infertility in these women<sup>(3,4)</sup>. PCOS is a syndrome with unknown etiology, characterized by hyperandrogenism which may be clinical (particularly hirsutism and acne) and/or biochemical (hyperandrogenemia), and chronic anovulation<sup>(2,5)</sup>. However, PCOS includes a wide spectrum of

signs and symptoms (obesity, polycystic ovary), pathology, and laboratory findings. Studies have shown that women with PCOS are frequently insulin resistant and at increased risk of developing glucose intolerance or non-insulin-dependant diabetes mellitus in the third and fourth decades of their life<sup>(2,6)</sup>.

Hyperinsulinemia lead to hyper production of ovarian androgens because insulin like Luteinizing hormone (LH) stimulates directly the ovarian biosynthesis of steroid hormones, in

particular, of ovarian androgens<sup>(7)</sup>. Furthermore, insulin decreases the sex-hormone-binding globulin (SHBG) production in the liver, thus, further elevating free androgen levels<sup>(8-10)</sup>. Therefore, both pathways end in the stimulation of ovarian theca cells with elevated ovarian androgen production, resulting in disturbed folliculogenesis, cycle disorders and chronic anovulation<sup>(11)</sup>. It is therefore probable that women develop PCOS because of a hypersensitivity of their intra-ovarian insulin androgen signaling pathway<sup>(12)</sup>.

Metformin is one of insulin-sensitizing agents, its an oral biguanide used for type 2 diabetes mellitus, is a safe and effective drug that can be used for the treatment of PCOS patients<sup>(10,13,14)</sup>, to induce ovulation in anovulatory PCOS patients<sup>(15,16)</sup>. In-vitro culture had shown that metformin has a significant inhibitory effect on androgen production by ovarian cells<sup>(17,18)</sup> also it lowers LH concentration, reduces total testosterone and raises SHBG levels, producing a decrease in the free testosterone index<sup>(19,20)</sup>.

Drugs that block male hormones can protect women with PCOS from developing diabetes, heart attacks, obesity and masculinizing traits such as hirsutism, acne, and large muscles and bones and that progesterone can protect them from uterine cancer<sup>(21-23)</sup>, also lower cholesterol<sup>(24)</sup> and help the eggs to pop from the ovaries<sup>(25,26)</sup>. Reduction of ovarian androgen production not only improves ovulation and pregnancy rates, but also reduces spontaneous abortion rates<sup>(27)</sup>.

Finasteride, is a potent 5 $\alpha$ -reductase (5 $\alpha$ -R) inhibitor, has been approved by Food and Drug Administration (FDA) for treatment of androgenetic alopecia in men<sup>(28)</sup>. The largest application of finasteride consists in treating benign prostate hyperplasia, in women finasteride has been used in some control trials for treatment of hirsutism<sup>(29)</sup>, because of its teratogenicity<sup>(30)</sup> finasteride should be used a contraceptive. Finasteride is a preferential, competitive inhibitor of the intracellular, 5 $\alpha$ -R isoenzyme type II which converts testosterone into dihydrotestosterone (DHT), a more potent

androgen. The high loss rate experienced by women with PCOS is partly due to compromised oocyte quality, but may also be due to the compromised uterine perfusion that occurs as a result of elevated androgen levels. Correction of androgen status clearly results in a decrease in the spontaneous abortion rate in these individuals<sup>(27)</sup>.

The intention of the study is to evaluate and compare the effects of finasteride vs metformin in treatment of PCOS related infertility.

## Methods

Women included in this study had been assessed clinically regarding regularity of the menstrual cycle, body mass index (BMI) [calculated using the equation: [weight (kilograms)/height (meters)<sup>2</sup>], duration and type of infertility and presence or absence of hirsutism.

Luteinizing hormone, Follicle stimulating hormone (FSH), LH:FSH ratio, total testosterone, Thyroid stimulating hormone (TSH), prolactin and fasting blood sugar levels were measured at day 2 (early follicular phase) of cycle. Diagnosis of PCOS was based on the revised 2003 consensus on diagnostic criteria and long-term health risks related to PCOS.

All patients enrolled in the study fulfilled the following criteria:

Inclusion criteria: (1) patients who had diagnosed as PCOS in the presence of at least 2 of Rotterdam criteria, based on Rotterdam consensus meeting 2003<sup>(23)</sup>. (2) The patients were unable to achieve pregnancy in a period of last 12 months or more despite regular unprotected intercourse. (3) The patients had patent Fallopian tubes proved by hysterosalpingography. (4) The husband infertility evaluation by an urologist doctor revealed no abnormalities in the male side. (5) No history of heart, liver, or kidney disease, and unsuspected pregnancy.

Exclusion criteria: (1) Patient aged more than 35 years. (2) History of recent administration of hormonal therapy. (3) Male factor infertility.

Seventy seven married women in the reproductive age (18-35 years), who had diagnosed to have a PCOS, were included in this prospective study, all were complain infertility due to PCOS. For the amenorrhoeic women among those included in this study, 10 mg dydrogesterone oral tablets daily for 10 days was used to induce withdrawal bleeding. Two months washout period was used to eliminate the effect of any post-treatment in women who had received any treatment before enrolment in this study.

Women included in this study were classified into two groups, 38 women received 500 mg metformin oral tablets three times daily for 3 months and 39 women received 5 mg finasteride oral tablets daily continuously for 2 months, finasteride has been received concomitantly with an OCP consisting of 2 mg cyproterone acetate + 0.035 mg ethinyloestradiol oral tablets, OCP was received daily starting from day 5 of the menses. TVS examination has done at day 12 of the menstrual cycle after 3 months of treatment with metformin, regarding finasteride US has done at day 12 of the third menstrual cycle in which finasteride and OCP have been withdrawn (drug free cycle).

Post treatment the primary outcome measures were the number and size of the growing and mature follicles and endometrial thickness (ET) by monitoring with TVU at day 12 of the menstrual cycle.

Good response was achieved when at least one mature follicle becomes 17 mm in diameter and the patients were advised to have timed intercourse every other day, starting at least 24 hours after the leading follicular diameter reached 17 mm in size.

The secondary outcome measure was the occurrence of pregnancy. Chemical pregnancy was assessed by measurement of  $\beta$ -HCG (human chorionic gonadotropin) in blood after at least 3 days of miss period and clinical pregnancy by detection of fetal heart beat on sonography after 6-7 weeks of missed period.

Miscarriage rate was determined only in finasteride group because follow up for some women in metformin group had been lost.

### **Statistical Analysis**

SPSS version 17.0 was used for the statistical analysis. ANOVA, chi-square and Fisher exact tests were use when appropriate. P- Values less than 0.05 were considered as statistically significant.

### **Results**

Table 1 shows number of women and their clinical and hormonal characteristics on which the diagnosis of PCOS was determined according to Rotterdam criteria.

Table 2 shows post treatment results with finasteride and metformin including number of women responded to the treatment, means of number and size of mature follicles, number of mature follicles (1 or 2) per women, also value of endometrial thickness and pregnancy rate per patient.

### **Discussion**

#### **Effect of Metformin**

Metformin is a very important component of the PCOS treatment <sup>(32)</sup>. The low percentage of responded patients (26.31%) in the present study disagrees with that found by Palomba *et al* <sup>(33)</sup> study in which it was (55%) and with that found by Ashrafi *et al* study <sup>(34)</sup> in which ovulation had occurred in (65.7%) patients after 8 weeks of treatment with metformin. This disagreement may be related to the period of therapy used by the present study which was relatively short or it may be attributed to the presence of clomiphene (CC)-resistance since it had been shown that metformin cause no improvement in insulin resistance in CC-resistant PCOS patients with normal glucose tolerance, and also has no significant effect on ovarian response <sup>(35)</sup>. Regarding the percentage of patients in whom mono-follicle had developed (80%) and those in whom 2 mature follicles had developed (20%) among patients treated with metformin, up to knowledge studies that deal

with number of mature follicles after treatment with metformin were unavailable.

**Table 1. Clinical and hormonal characteristics of the patients pretreatment with finasteride and metformin**

| Variable                        | Finasteride<br>N = 39  | Metformin<br>N = 38    | P value |
|---------------------------------|------------------------|------------------------|---------|
| Age (years)                     | 25.10 ± 5.25 (18 - 35) | 24.41 ± 4.06 (18 - 35) | > 0.05  |
| Duration of infertility (Years) | 2.64 ± 0.44            | 3.34 ± 0.54            | > 0.05  |
| Primary infertility No. (%)     | 24/36 (66.66)          | 26/35 (74.28)          | > 0.05  |
| Secondary infertility No. (%)   | 12/36 (33.33)          | 9/35 (25.71)           | > 0.05  |
| Irregular cycle No. (%)         | 39/39 (100)            | 36/37 (97.29)          | > 0.05  |
| Regular cycle No. (%)           | 0/39 (0)               | 1/37 (2.70)            | > 0.05  |
| BMI                             | 30.4 ± 5.2             | 32.2 ± 6.4             | > 0.05  |
| Present Hirsutism No. (%)       | 35/37 (94.6)           | 29/35 (82.9)           | > 0.05  |
| Absent Hirsutism No. (%)        | 2/37 (5.4)             | 6/35 (17.1)            | > 0.05  |
| Positive US No. (%)             | 36/38 (94.73)          | 35/37 (94.59)          | > 0.05  |
| Negative US No. (%)             | 2/38 (5.26)            | 2/37 (5.40)            | > 0.05  |
| LH (mIU/ml)                     | 6.90 ± 4.24            | 6.63 ± 4.57            | > 0.05  |
| FSH (mIU/ml)                    | 5.60 ± 1.43            | 4.67 ± 1.73            | > 0.05  |
| LH/FSH ratio                    | 1.28 ± 0.772           | 1.52 ± 1.014           | > 0.05  |
| Testosterone (ng/ml)            | 0.99 ± 0.95            | 0.99 ± 0.95            | > 0.05  |
| PRL (ng/ml)                     | 23.38 ± 10.49          | 19.45 ± 12.33          | > 0.05  |
| TSH (mIU/ml)                    | 1.67 ± 0.83            | 2.46 ± 1.21            | > 0.05  |
| FBS (mmol/L)                    | 4.56 ± 0.4             | 4.82 ± 0.9             | > 0.05  |

**Table 2. Post treatment results with finasteride and metformin**

| Variables                         | Treatment Groups      |                     | P value |
|-----------------------------------|-----------------------|---------------------|---------|
|                                   | Finasteride<br>N = 39 | Metformin<br>N = 38 |         |
| *Responded patients No. (%)       | 14 (35.89)            | 10 (26.31)          | > 0.05  |
| No. (%) of patients with 1 MF     | 11 (78.57)            | 8 (80)              | > 0.05  |
| No. (%) of patient with 2 MF      | 3 (21.42)             | 2 (20)              | > 0.05  |
| Mean No. of mature follicle ± SD  | 1.21 ± 0.43           | 1.2 ± 0.42          | > 0.05  |
| Mean size of mature follicle ± SD | 20.26 ± 3.66          | 18.75 ± 1.82        | > 0.05  |
| ET Mean ± SD (mm)                 | 7.26 ± 1.1            | 7.80 ± 2.25         | > 0.05  |
| Pregnancy Rate / Patient (%)      | 3/14 (21.42)          | 6/10 (60.0)         | > 0.05  |

\* = Resulted in one or more mature follicles ≥ 17 mm; ET = endometrial thickness

Endometrial thickness measured at day 12 of menstrual cycle after 3 months of treatment with metformin was (7.8±2.25) in the present study and was comparable to (8.2 mm) that found by Sohrabvand *et al* <sup>(36)</sup> who measured endometrial thickness (ET) at the day of hCG administration in women received letrozole (2.5 mg) after an initial treatment for 6-8 weeks with metformin, while it disagrees with (5.5 mm) found by the same study when CC was combined

with metformin instate of letrozole. Up to our knowledge there were no enough studies to which result of ET in the present study could be compared.

In the present study the pregnancy rate per patient in metformin group is in agreement with Heard *et al* and Palomba *et al* studies <sup>(17,37)</sup> which were (69%) and (69%) respectively, also it goes with a meta-analysis of more than a dozen

randomized clinical trials that found metformin superior to placebo<sup>(38)</sup>.

The high rate of pregnancy in metformin group may be attributed to the small number of patients responded to metformin treatment, or the PCOS was less severe, thus these patients became pregnant despite short term of therapy. While it disagrees with that found by Tang *et al* and Palomba *et al* studies<sup>(39,40)</sup> which were (23%) and (20%) respectively, and with that found by Ashrafi *et al*<sup>(34)</sup> study which was (20%) despite high ovulation rate (65.7%) after 8 weeks of treatment with metformin the disagreement with Ashrafi *et al* may be due to large number of the responded patients (since ovulation rate in Ashrafi *et al* was 65.7% while the percentage of the responded patients (produced at least one mature follicle) in the present study was small (26.31%). Also it disagrees with that found by Palomba *et al* and Ortega *et al* studies<sup>(33,41)</sup> which were (19%) and (16.7%) respectively over 6 months of treatment with metformin, this disagreement may be attributed to the differences in numbers of total patients and that of the responded patients, as ovulation rate was (55%) in Palomba *et al*<sup>(33)</sup> study and number of total patients was 18 in Ortega *et al.* study<sup>(41)</sup>. Also it disagrees with Legro *et al* study<sup>(42)</sup> in which pregnancy rate was (8.7%) over 6 months of treatment with metformin.

The high pregnancy rate (60%) of the present study population is consistent with the hypothesis that insulin resistance and/or hyperandrogenism play an important role in the pathogenesis of anovulation in patients with PCOS<sup>(17-19,34)</sup>.

An evidence of decreased insulin sensitivity is seen in both lean (30%) and obese (75%) women<sup>(6,43)</sup>. It had been confirmed that metformin does not act on BMI but does appear to act on hirsutism and acne and induce the onset of regular cycles<sup>(18,38, 44,45)</sup>.

What have been found by the above studies is in agreement with our study. In the present study the mean of BMI of 4 out of 6 (66.66%) patients who were became pregnant on metformin was 25.68 (range 21.66-27.89),

while it was 32.95 for the other 2 (33.33%) patients, this result agrees with other previous studies<sup>(18,38,44,45)</sup>, and this proves the activity of metformin in obese as well as in non obese women which agrees with Ashrafi *et al*<sup>(34)</sup> who found that BMI and LH level had no significant effect on response to metformin and it's comparable to that of Baillargeon<sup>(32)</sup> who found that up to 90% of thin women with PCOS ovulated in the six months after initiating metformin treatment.

The response obtained by the present study during the short-moderate term therapy (3 months) with metformin goes with Nestler *et al*<sup>(46)</sup> who found that by day 35, 34% of women received metformin had ovulated, compared with only 4% of the placebo-treated women, also it goes with Ashrafi *et al*<sup>(34)</sup> who found that after 8 weeks of metformin monotherapy, ovulation occurred in (65.7%) patients and (20%) patients became pregnant, in regard to the present study 3 pregnant women among those who got pregnancy on metformin they became pregnant after 1.5-2 months of treatment with metformin. Result of the present study in regard to metformin confirms what have been found by Ehrmann<sup>(47)</sup> who appeared that normal menstrual cycles achieved within 3 months of starting treatment in some groups of patients.

High pregnancy rate (60%) after 3 months of treatment with metformin may be attributed to the reduction in serum insulin level<sup>(34)</sup>. The correlation between hyperandrogenism and insulin resistance had been recognized in both obese and nonobese anovulatory PCOS women<sup>(48,49)</sup>. Acien *et al* and Meirou *et al* reported that approximately 10% of non obese PCOS patients could present with insulin resistance<sup>(50,51)</sup>.

Result of the present study agrees with the United Kingdom's National Institute for Health and Clinical Excellence which recommended metformin's usage for PCOS women those whom BMI was above 25 when other therapy had failed<sup>(52)</sup>, while it disagrees with the subsequent randomized control trials<sup>(53,54)</sup> which in general

not shown the promise suggested by the early observational studies.

### Effect of Finasteride

Testosterone is converted into DHT by the enzyme 5 $\alpha$ -R. DHT is a more powerful androgen than testosterone as it has a much higher affinity for the androgen receptor<sup>(55,56)</sup>. Finasteride is an inhibitor of 5 $\alpha$ -R by being an aza analog of testosterone, thereby initially binding to 5 $\alpha$ -R similarly to testosterone<sup>(57)</sup>. Up to knowledge the role of finasteride in the treatment of PCOS related infertility had been investigated only by one study done by Tartagni *et al*<sup>(58)</sup>, who add finasteride to conventional protocol of ovarian stimulation with gonadotropin and found that finasteride can improve ovarian follicular growth and ovulation in PCOS women who did not respond to previous stimulation with gonadotropin alone. In regard to finasteride activity in the treatment of PCOS related infertility, result of the present study confirms what had been found by Tartagni *et al*<sup>(58)</sup>.

In comparison to metformin treated group the pregnancy rate in finasteride treated group was low (60% vs 21.43%) that may be explained by higher activity of metformin due to its ability to decrease insulin resistant which in turn decrease androgen production, while finasteride is an inhibitor of steroid 5 $\alpha$ -R, the enzyme that converts testosterone to the more potent androgen DHT<sup>(55,56)</sup>.

The higher percentage of patients who responded to finasteride comparing to those responded to metformin (35.89% vs 26.31%) may be related to the time needed by the mechanism through which metformin decrease androgen production as it first should decrease insulin resistance for which more time may be needed, while finasteride decreases androgenic activity through direct inhibition of 5 $\alpha$ -R.

Finasteride has well-documented risk for teratogenicity in male fetuses, and adequate contraception should be used<sup>(30)</sup>. Thus the lower rate of pregnancy in finasteride group in comparison to that in metformin group (21.43% vs 60%), may be related to the

presence of OCP which necessarily had received concomitantly with finasteride.

Reduction of ovarian androgen production not only improves ovulation and pregnancy rates, but also reduces spontaneous abortion rates. The high loss rate experienced by women with PCOS is partly due to compromised oocyte quality, but it may also be due to the compromised uterine perfusion that occurs as a result of elevated androgen levels<sup>(27)</sup> and this may explain why there were no any miscarriage in finasteride group as the correction of androgen status is clearly results in a decrease in the spontaneous abortion rate in PCOS pregnant women<sup>(30)</sup>.

The three pregnancies obtained by finasteride treatment were ended with full term deliveries, this result may be attributed to the reduction in androgen level as found by Ajoss *et al.* (2002)<sup>(27)</sup> study which had demonstrated that reduction of ovarian androgen production not only improves ovulation and pregnancy rates, but also reduces spontaneous abortion rates and the high loss rate experienced by women with PCOS is partly due to compromised oocyte quality, but may also be due to the compromised uterine perfusion that occurs as a result of elevated androgen levels.

Up to knowledge at least one miscarriage had occurred among the 6 patients who became pregnant on meformin therapy, the usefulness of metformin in reducing miscarriages and improving pregnancy outcome is in doubt<sup>(59)</sup>. No occurrence of any miscarriage among the patients who became pregnant on finasteride may be attributed to the higher activity of finasteride in comparison to meformin to improve the compromised uterine perfusion rather than to its activity to improve the compromised oocyte quality which occurs as a result of elevated androgen levels<sup>(27)</sup>.

In conclusion, treatment with finasteride combined with an OCP for 2 months had a good promising effect in the treatment of PCOS related infertility in comparison to metformin as the responded patients were higher in finasteride group and although the rate of

pregnancy was higher in metformin group the difference was not significant ( $p > 0.05$ ).

### **Acknowledgment**

Special gratefulness to the Assistant Professor Dr. Bushra J Al-Rubaie a consultant at the Department of Gynecology and Obstetrics, College of Medicine in Babylon university for her great support and to the members of Infertility center at Babylon Maternity and Pediatric teaching hospital particularly Dr. Suhaila for her great cooperation.

### **References:**

1. Polson DW, Worth WJ, Adams J, et al. Polycystic ovarian a common finding in normal woman. *Lancet*. 1988; 1: 870-2.
2. Franks S. Polycystic ovarian syndrome. *N Engl J Med*. 1995; 333: 853-61.
3. Goldenberg N, Glueck C. Medical therapy in women with polycystic ovarian syndrome before and during pregnancy and lactation. *Minerva Ginecol*. 2008; 60(1): 63-75.
4. Boomsma CM, Fauser BC, Macklon NS. Pregnancy complications in women with polycystic ovary syndrome. *Semin Reprod Med*. 2008; 26(1): 72-84.
5. Dunaif A. Insulin resistance and ovarian dysfunction. *The Endocrinologist*. 1992; 2: 248-60.
6. Dunaif A, Graf M. Insulin administration alters gonadal steroid metabolism independent of changes in gonadotropin secretion in insulin-resistant women with polycystic ovary syndrome. *J Clin Invest*. 1989; 83: 23-9.
7. Eisenhardt S, Schwarzmann N, Henschel V, et al. Early Effects of Metformin in Women with Polycystic Ovary Syndrome: A Prospective Randomized, Double-Blind, Placebo-Controlled Trial. *J Clin Endocrinol Metab*. 2006; 91: 946-952.
8. Barbieri RL, Smith S, Ryan KJ. The role of hyperinsulinemia in the pathogenesis of ovarian hyperandrogenism. *Fertil Steril*. 1988; 50: 197-212.
9. Plymate Sr, Matej La, Jones Re. Inhibition of sex hormone-binding globulin production in human hepatoma (Hep G2) cell line by insulin and prolactin. *J Clin Endocrinol Metab*. 1988; 67: 460-4.
10. Paquali R, Gambineri A, Biscotti D, et al. Effect of long term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2000; 85: 2767-2774.
11. Cleemann L, Lauszus FF, Trolle B. Laparoscopic ovarian drilling as first line of treatment in infertile women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2004; 18: 138-43.
12. Baillargeon J, Nestler J. Polycystic ovary syndrome: a syndrome of ovarian, hypersensitivity to insulin? *J Clin Endocrinol Metab*. 2006; 91(1): 22-4.
13. Kashyap S, Wells GA, Rosenwaks Z. Insulinsensitizing agents as primary therapy for patients with polycystic ovarian syndrome. *Hum Reprod*. 2004; 19: 2474-83.
14. Costello MF, Eden JA. A systematic review of the reproductive system effects of metformin in patients with polycystic ovary syndrome. *Fertil Steril*. 2003; 79: 1-13.
15. DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean non-insulin dependent diabetic subjects. *J Clin Endocrinol Metab*. 1991; 73: 1294-301.
16. Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effect of metformin in non- insulin dependent diabetes mellitus. *N Engl J Med*. 1995; 333: 550-4.
17. Heard MJ, PierceA, CarsonSA, et al. Pregnancies following use of metformin for ovulation induction in patients with polycystic ovary syndrome. *Fertil Steril*. 2002; 77(4): 669-73.
18. Mansfield R, Galea R, Brincat M, et al. Metformin has direct effects on human ovarian steroidogenesis. *Fertil Steril*. 2003; 79: 956-62.
19. Barbieri RL. Metformin for the treatment of polycystic ovary syndrome. *Obstet Gynecol*. 2003; 101: 785-93.
20. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450C17-alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med*. 1996; 335: 617-23.
21. Berga SL. The obstetrician-gynecologist's role in the practical management of polycystic ovary syndrome. *Am J Obst Gynecol*. 1998; 179(6) Part 2: S109-S113.
22. Guzick D. Polycystic ovary syndrome: Symptomatology, pathophysiology, and epidemiology. *Am J Obst Gynecol* 1998; 179(6) Part 2: S89-S93.
23. Taylor AE. Understanding the underlying metabolic abnormalities of polycystic ovary syndrome and their implications. *Am J Obst Gynecol*. 1998 Dec; 179(6) Part 2: S94-S100.
24. Diamantikandarakis E, Mitrakou A, Raptis S, et al. The effect of a pure antiandrogen receptor blocker, flutamide, on the lipid profile in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 1998; 83(8): 2699-705.
25. Falsetti L, Defusco D, Eleftheriou G, et al. Finasteride (5 mg daily) or flutamide (259 mg twice daily) for 6 consecutive months. Treatment of hirsutism by finasteride and flutamide in women with polycystic ovary syndrome. *Gynecol Endocrinol*. 1997 Aug; 11(4): 251-7.
26. Deleo V, Lanzetta D, Dantona D, Lamarca A, Morgante G. Hormonal effects of flutamide in young women with

- polycystic ovary syndrome. *J Clin Endocrinol Metab.* 1998 Jan; 83(1): 99-102.
27. Ajoss S, Guerriero S, Paoletti AM, et al. The antiandrogenic effect of flutamide improves uterine perfusion in women with polycystic ovary syndrome. *Fertil Steril.* 2002; 77: 1136-40.
  28. Sinclair R: Male pattern androgenic alopecia. *BMJ.* 1998; 317: 865-9.
  29. Cilotti A, Danza G, Serio M. Clinical application of 5 $\alpha$ -reductase inhibitors. *J Endocrinol Invest.* 2001; 24: 199-203.
  30. Swiglo BA, Cosma M, Flynn DN, et al. Clinical review: Antiandrogens for the treatment of hirsutism: a systematic review and meta analyses of randomized controlled trials. *J Clin Endocrinol Metab.* 2008; 93: 1153-60.
  31. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod.* 2004; 19: 41.
  32. Baillargeon J-P. Oral presentation. The Endocrine Society. San Francisco 2002.
  33. Palomba S, Orio F, Nardoo L et al. Metformin Administration versus Laparoscopic Ovarian Diathermy in Clomiphene Citrate-Resistant Women with Polycystic Ovary Syndrome: a Prospective Parallel Randomized Double-Blind Placebo-Controlled Trial. *J Clin Endoc Metab.* 2004; 89(10):4801-4809.
  34. Mahnaz A, Fatemeh Z, Reza BA. Effects of Metformin on Ovulation and Pregnancy Rate in Women with Clomiphene Resistant Poly Cystic Ovary Syndrome. *Royal Inst Iranian J Fertil Steril.* 2007; 1(1): 39-42.
  35. Yarali H, Yildiz BO, Demiroglu A, et al. Coadministration of metformin during rFSH treatment in patients with clomiphene citrate-resistant polycystic ovarian syndrome: a prospective randomized trial. *Hum Reprod.* 2002; 17(2): 289-94.
  36. Sohrabvand F, Ansari S, Bagheri M. Efficacy of combined metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. *Hum Reprod.* 2006; 21: 1432-5.
  37. Palomba S, Orio F Jr, Falbo A, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2005; 90: 4068-74.
  38. Lord JM, Flight IHK, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ.* 2003; 327(7421): 951-6.
  39. Tang T, Lord JM, Norman RJ, et al. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. In: *The Cochrane Library*, Issue 4. Chichester, UK: John Wiley & Sons Ltd. 2009.
  40. Palomba S, Pasquali R, Orio F, et al. Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head-to-head randomized controlled studies and meta-analysis. *Clin Endocrinol (Oxf).* 2009; 70: 311-21.
  41. Ortega-Gonzalez C, Luna S, et al. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. *Clin Endocrinol Metab.* 2005; 90(3): 1360-5.
  42. Legro RS, Barnhart HX, Schlaff WD. Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome. *N Engl J Med.* 2007; 356 (6): 551-66.
  43. Conway GS, Jacobs HS, Holly JMP, et al. Effects of luteinizing hormone, insulin, insulin-like growth factor-1 and insulin-like growth factor small binding protein-1 in the polycystic ovary syndrome. *Clin Endocrinol.* 1990; 33: 593-603.
  44. Gerard C. The use of metformin in the polycystic ovary syndrome. The Middlesex Hospital, Mortimer Street London W1N 8AA January 2000.
  45. Genazzani AD, Battaglia C, Malvasi B, et al. Metformin administration modulates and restores luteinizing hormone spontaneous episodic secretion and ovarian function in non-obese patients with polycystic ovary syndrome. *Fertil Steril.* 2004; 81: 114-9.
  46. Nestler JE, Jakubowicz DJ, Evans WS, et al. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med.* 1998; 338: 1876-80.
  47. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med* 2005; 352(12):1223-1236.
  48. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2005; 81: 19-25.
  49. González F, Rote N, Minium J, et al. Reactive oxygen species-induced oxidative stress in the development of insulin resistance and hyperandrogenism in polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2006; 91(1): 336-40.
  50. Acien P, Querada F, Matallin P, et al. Insulin, androgens, and obesity in women with and without polycystic ovary syndrome: a heterogeneous group of disorders. *Fertil Steril.* 1999; 72:32-40.
  51. Meirrow D, Yossepowitch O, Rosler A, et al. Insulin resistant and non-resistant polycystic ovary syndrome represent two clinical and endocrinological subgroups. *Hum Reprod.* 1995; 10: 1951-6.
  52. National Institute for Health and Clinical Excellence. Clinical guideline 11: Fertility: assessment and treatment for people with fertility problems. London 2004.



53. Balen A. Metformin therapy for the management of infertility in women with polycystic ovary syndrome (PDF). Scientific Advisory Committee Opinion Paper 13. Royal College of Obstetricians and Gynaecologists 2008. [http://www.rcog.org.uk/files/rcog-corp/uploaded-files/SAC13metformin\\_inorrevison.pdf](http://www.rcog.org.uk/files/rcog-corp/uploaded-files/SAC13metformin_inorrevison.pdf). Retrieved 2009-12-13.
54. Leeman L, Acharya U. The use of metformin in the management of polycystic ovary syndrome and associated anovulatory infertility: the current evidence. *J Obstet Gynaecol.* 2009; 29(6):467-72.
55. Snyder PJ. Androgens. In: Brunton LL, Lazo JS, Parker KL (eds). *Goodman and Gilman's - The pharmacological basis of therapeutics.* 11<sup>th</sup> ed. USA: McGraw-Hill Companies, Inc.; 2006. p. 1573-85.
56. George P. The Gonadal Hormones and Inhibitors. In: Katzung BG, Masters SB, Trevor AJ (eds). *Basic and Clinical Pharmacology* 11<sup>th</sup> ed. McGraw-Hill; 2009. p. 699-726.
57. Robaire B, Henderson N. Actions of 5 $\alpha$ -reductase inhibitors on the epididymis. *Mol Cell Endocrinol.* 2006; 250(1-2): 190-5.
58. Tartagni M, Cicinelli E, De Pergola G, et al. Effect of finasteride on ovulation induction in nonresponder (hyperandrogenic) polycystic ovary syndrome (PCOS) women. *Fertil Steril.* 2010; 94(1): 247-9.
59. Mathur R, Alexander CJ, Yano J, et al. Use of metformin in polycystic ovary syndrome. *Am J Obstet Gynecol.* 2008; 199(6): 596-609.

---

**Address Correspondence to Entisar J Al-Mukhtar**

**E-mail: ejhas28@yahoo.com**

**Received 8<sup>th</sup> Apr. 2012: Accepted 31<sup>st</sup> Dec. 2012**