THE JOURNAL OF
Obstetrics and Gynaecology Research

The official Journal of Asia and Oceania Federation of Obstetrics and Gynaecology
Japan Society of Obstetrics and Gynecology

doi:10.1111/j.1447-0756.2009.01166.x J. Obstet. Gynaecol. Res. Vol. 36, No. 1: 218, February 2010

Retraction

The following article from *The Journal of Obstetrics and Gynaecology Research*, 'Effects of metformin on insulin resistance, androgen concentration, ovulation and pregnancy rates in women with polycystic ovary syndrome following laparoscopic ovarian drilling' by Idris Kocak and Cazip Üstün, published in Volume 32, Issue 3, June 2006, pages 292–298, and online on 5 June 2006 in Wiley InterScience (http://www.interscience.wiley.com), has been retracted by agreement between the journal Editor in Chief, Takashi Okai, and Blackwell Publishing Asia Pty Ltd. The retraction has been agreed due to plagiarism between this article and the following articles published in the *European Journal of Obstetrics & Gynecology and Reproductive Biology*; 'The effects of metformin on insulin resistance, clomiphene-induced ovulation and pregnancy rates in women with polycystic ovary syndrome' by Yılmaz Sahina, Unal Yirmibes, Fahrettin Kelestimurb and Ercan Aygena. Volume 113, Issue 2, 2004, pages 214–220, and in *Acta Obstetricia et Gynecologica Scandinavica*, 'Review of non-surgical and surgical treatment and the role of insulin-sensitizing agents in the management of infertile women with polycystic ovary syndrome' by Ahmed M. Saleh and Hala S. Khalil, Volume 83, Issue 7, 2004, pages 614–621.

doi:10.1111/j.1447-0756.2006.00401.x J. Obstet. Gynaecol. Res. Vol. 32, No. 3: 292–298, June 2006

Effects of metformin on insulin resistance, androgen concentration, ovulation and pregnancy rates in women with polycystic ovary syndrome following laparoscopic ovarian drilling

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Abstract

Aim: To evaluate the effects of metformin on insulin resistance, androgen concentration, ovulation rates and pregnancy rates in infertile women with polycystic ovary syndrome (PCOS).

Methods: Forty-two infertile women with PCOS were selected in this randomized clinical study. Basal steroid and gonadotropin levels were measured, and oral glucose tolerance test (OGTT) was performed. The patients were randomly divided into group 1 ($n = 21$) and group 2 ($n = 21$). Group 1 patients were treated with laparoscopic ovarian drilling (LOD). Group 2 patients underwent laparoscopic ovarian drilling (LOD) and received 1700 mg per day of metformin for 6 months. LOD was performed in women with PCOS using a unipolar electrode. Serum progesterone (P) level > 5 ng/mL was considered as a confirmation of ovulation. Ovulation and pregnancy rates were determined after six cycles.

Results: Serum androgens and insulin response to OGTT decreased significantly after metformin therapy. Mean serum P levels and endometrial thickness were significantly higher in cycles treated with metformin plus LOD (34.6 ± 25.4 ng/mL, 8.4 ± 1.1 mm) than in those treated with LOD alone (26.2 ± 24.7 ng/mL, 7.9 ± 2.8 mm) ($P < 0.05$). The ovulation (56 of 65 cycles, 86.1% vs 29 of 65 cycles, 44.6%) and pregnancy rates (nine of 21 women, 47.6% vs four of 21 women, 19.1%) were significantly higher in group 2 than in group I.

Conclusions: Metformin improves insulin resistance, reduces androgen levels and significantly increases the ovulation and pregnancy rates in infertile women, following LOD.

Key words: metformin, polycystic ovary syndrome, pregnancy, surgically induced.

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent and heterogeneous condition affecting 6–10% of reproductive-aged women and 35–40% of infertile women.[1,2] It is the most common cause of chronic anovulation.[1,3,4] Patients may also present with menstrual irregularities (usually oligo- or amenorrhea), hirsutism, acne or a combination of these. Treatment of this condition has generally been prescribed to alleviate symptoms that bring these women to further medical attention, such as infertility or hirsutism. The association between PCOS-related hyperandrogenemia, insulin resistance and hyperinsulinemia has been recognized as an important factor in reproductive abnormality.[1,5,6] Women with PCOS have an increased prevalence of impaired glucose tolerance (35–40%) and a prevalence of type 2 diabetes mellitus (7.5–10%).[7,8] Furthermore, long-term risks of metabolic consequences in women with PCOS who are characterized by insulin resistance

Received: November 4 2004.
Accepted: January 20 2006.
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are also increased, including dyslipidemia, hypertension, coronary artery disease and endometrial carcinoma.[1,7–9]

Several theories explain these changes after laparoscopic destruction of androgen-producing stroma of the ovaries: (i) the amount of substrate available for peripheral aromatization to estrogen may be decreased, thus restoring the feedback mechanism to the hypothalamic-pituitary ovarian axis, allowing appropriate gonadotropin stimulation of follicular maturation and ovulation; (ii) at the ovarian level, reduction in intra-ovarian androgen allows follicular maturation and ovulation; (iii) the levels of inhibin may be reduced, allowing a secondary rise in the follicle-stimulating hormone (FSH) level, and in combination with the reduction in local androgen levels may facilitate follicular growth and ovulation; and (iv) in response to thermal injury the ovary produces a number of growth factors, such as insulin growth factor-I (IGF-I), which sensitize the ovary to circulating FSH, resulting in stimulation of follicular growth and maturation.[10,11]

The number of studies that evaluate the effect of metformin on insulin resistance, ovulation and pregnancy rates among infertile women with PCOS are limited and have short-term treatment periods. Also, their results are conflicting. While metformin improved the fasting insulin or the insulin response to an oral glucose challenge in some studies,[1,8,12,13] it did not alter the baseline or oral glucose-challenged levels of insulin in women with PCOS in some other studies.[1,13] Numerous studies have shown that the administration of metformin 500 mg three times per day or 850 mg twice daily for 4–8 weeks (1.5 g/day) to insulin-resistant and/or hyperinsulinemic obese and lean PCOS women restores menstrual cycle and ovulation responses to clomiphene citrate (CC) and ultimately improves pregnancy rates.[14–17]

The aim of the present study was to evaluate the effect of metformin on insulin resistance, androgen concentration, ovulation rates and pregnancy rates in infertile women with PCOS following laparoscopic ovarian drilling (LOD).

Methods

Forty-two infertile patients with PCOS were included in the study. Prospective case record analysis of 42 cases of polycystic ovary syndrome were reported between December 1998 And July 2004. All patients had primary infertility. All patients used clomiphene citrate for three cycles before this study. Male factor and tubal-uterine factor infertility were excluded with semen analyses and hysterosalpingography and/or laparoscopy. The diagnosis of PCOS was made on the basis of three or more of the following criteria: oligomenorrhea/amenorrhea, infertility, hirsutism, obesity, hyperandrogenism, chronic anovulation, and ovarian cortical multiple follicles (≥10, 2–10 mm diameter).

Of the patients, 71% in group 1 and 68% in group 2 were obese (BMI 25 kg/m^2) A complete clinical and laboratory evaluation was performed to exclude the patients with androgen secreting tumors of ovarian or adrenal origin, Cushing's syndrome, thyroid dysfunctions, non-classic adrenal hyperplasia and hyperprolactinemia. For at least 12 weeks before the study, none of the subjects in both groups had received any medication known to affect pituitary-gonadal function or carbohydrate metabolism. They did not have a history of diabetes mellitus. All patients in the study groups had normal renal and liver function tests. The tests were conducted during the first 10 days after the onset of vaginal bleeding or after medroxyprogesterone-induced vaginal bleeding.

Laboratory tests

After an overnight fasting, blood samples were obtained for the determination of fasting blood glucose (FBG), insulin, FSH, luteinizing hormone (LH), estradiol (E_2), total and free testosterone (T), androstenedione (A), dehydroepiandrostenedione sulfate (D-HEAS), prolactin (PRL), and sex hormone-binding globulin (SHBG) levels. Before the treatment, the patients were given a 3-day 2000 calorie standardized diet (300 g carbohydrate/day) before an oral glucose tolerance test (OGTT) was performed after ingestion of a 75 g glucose load. Blood samples were obtained at 30 min intervals for 2 h between 09.00 and 11.00 hours in both groups for the measurement of glucose and insulin after 10–12 h of fasting.

Metformin was given at a dose of 850 mg two times a day for 6 months after LOD. At that time the pretreatment studies including OGTT were repeated in both groups. The glucose and insulin responses to OGTT were also expressed as the area under the curve (AUC) estimated by the trapezoidal rule. The ratio of fasting glucose to insulin was calculated. Glucose tolerance was assayed by the WHO criteria.[18] The serum samples were stored at –20°C until they were assayed.

As shown in Table 1, there were no statistically significant differences in age, duration of infertility, body

Table 1 Results of induction of ovulation with LOD in both groups

	LOD plus metformin $n = 21$	LOD $n = 21$	*P*-value
No. cycles	65	65	
Cycles with ovulation	56 (86.1%)	29 (44.6%)	<0.05
No. pregnancy rates	9 (47.6%)	4 (19.1%)	<0.05
No. abortion	2	0	
No. pre-term deliveries	2	0	
Delivered full-term healthy babies	5	4	
Mean serum *P* level	34.6 ± 25.4 ng/mL	26.2 ± 24.7 ng/mL	<0.05
Endometrial thickness	8.4 ± 1.1 mm	7.9 ± 2.8 mm	<0.05

LOD, laparoscopic ovarian drilling.

mass index, and hormonal data between the two groups. Serum insulin, glucose, AUC glucose, AUC insulin, AUC glucose : AUC insulin ratio, and fasting glucose (G) : fasting insulin (I) ratio values were also similar in both groups.

The technique of LOD is performed under general anesthesia by using three abdominal puncture ports. A 10-mm video laparoscope is introduced through the subumbilical port and two 5-mm punctures at the right and left lower abdominal sides are used for grasping forceps and the diathermy needle Ovarian diathermy is performed by using an insulated monopolar needle and electrocoagulation at a setting of 30–40 W, to a standard depth of 8 mm. Pure cutting of 30–40 W is used to pierce the ovarian capsule followed by a coagulation current for 2–4 s at each point.

Transvaginal ultrasound was performed and endometrium was observed during midluteal phases on the 22nd day of cycles. Endometrial thickness was measured at the thickest part of the midsagittal plane. Spontaneous ovulation was checked by blood samples taken on the 21st day. If no spontaneous menstruation occurred, they were taken every 2 weeks for 3 months during the metformin therapy. A progesterone (P) level > 5.0 ng/mL was considered as confirmation of ovulation. No subject ovulated in response to metformin only. PCOS women were instructed not to alter their usual eating habits and lifestyle during the study protocol. Group 2 patients were subjected to LOD. Metformin was given at a dose of 850 mg two times a day after LOD for six months. The same treatment regimen was repeated until either a pregnancy occurred, or a maximum of six cycles occurred. Follicular development was monitored by serial ultrasound scanning. The serum P level was measured on the 21st day of the cycle. Pregnancy was defined by ultrasound evidence of a gestational sac and the presence of fetal heart motion.

Data analysis

Plasma glucose level was determined by a glucose oxidase method (Konelab, Espoo, Finland). Serum insulin, total and free T, P, A, SHBG, DHEAS, and PRL levels were determined by radioimmune assay (RIA), using commercial kits (insulin, DPC, Los Angeles, CA, USA; total and free T, Diagnostic Systems Laboratories, Webster, TX, USA; SHBG, Euro-Diagnostica, Malmö, Sweden; P, DHEAS and A, Immunotech, Marseille, France; PRL, ICN Biomedicals, Costa Mesa, CA, USA). Serum FSH, LH (Bayer, Tarrytown, NY, USA), and E_2 (Chiron Diagnostics, East Walpole, MA, USA) levels were measured with specific automated chemiluminescence system, using commercial kits. The intra-assay and interassay precision coefficients of variation were 9.3 and 10.0% for insulin; 8.1 and 9.1% for total T; 3.7 and 7.9% for free T; 4.7 and 7.6% for A; 3.1 and 3.1% for P; 4.1 and 6.5–8.3% for SHBG; 3.2–7.4 and 4.1–10.6% for DHEAS; 14.8 and 15.3% for E_2; 4.8 and 8.2% for PRL, respectively. The intra-assay coefficients of variation were 2.8 and 5% for FSH and LH, respectively. All samples from the same patients were assayed in the same assay.

The results were reported as means ± SEM or median and range. The Wilcoxon signed-rank test was used to evaluate the effect of metformin on hormones and glucose levels. The χ^2 test was used to evaluate ordinal variables, and Mann–Whitney *U*-test and the unpaired Student's *t*-test were used to evaluate continuous numeric variables. A *P*-value of <0.05 was considered as statistically significant.

Results

In group 2, there were significant changes in the hirsutism score, BMI, mean LH, total testosterone, free testosterone, androstenedione, DHEAS, fasting insulin

Table 2 Clinical and metabolic characteristics of patient in both group

	Group 1	Group 2
Age (years)	28.4 ± 2.6	27.6 ± 2.4
Duration of infertility (years)	4 ± 2.1	5 ± 3.6
FGS	7 ± 2.2	8 ± 5.4
BMI (kg/m^2)	31.9 ± 4.5	26.9 ± 1.3
FSH (2.5–12.5 mIU/mL)	5.4 ± 2.6	5.3 ± 4.2
LH (1.9–12.5 mIU/mL)	10.9 ± 3.6	11.2 ± 6.8
Estradiol E_2 (11–69 pg/mL)	39.2 ± 2.8	33.9 ± 2.2
Prolactin (ng/mL)	8.9 ± 3.4	7.9 ± 3.2
Total testosterone (10–80 ng/dL)	112 ± 7.4	105 ± 6.5
Free testosterone (0.21–3.08 pg/mL)	4.1 ± 5.2	2.11 ± 1.3
Androstenedione (0.21–3.08 ng/mL)	3.2 ± 2.3	4.4 ± 1.7
SHBG (20–40 μmol/L)	23.9 ± 1.4	23.1 ± 2.1
DHEAS (30–333 μg/dL)	242 ± 33.5	210 ± 11.4
Fasting glucose (70–110 mg/dL)	90 ± 1.7	86 ± 7.9
Fasting insulin (2–25 μU/mL)	10.2 ± 2.7.1	9.9 ± 7.6
AUC insulin (μUmin/mL)	12 121 ± 467.3	1 216 ± 160.8
AUC glucose (mgmin/mL)	18 812 ± 336.1	17 986 ± 235.4
Fasting glucose : insulin	3.8 ± 0.2.5	5.2 ± 3.7
AUC glucose : AUC insulin	1.4 ± 1.3	1.35 ± 4.1

AUC, area under the curve; BMI, body mass index; DHEAS, dehydroepiandrostenedione sulfate; FGS, Ferriman–Gallwey score; FSH, follicle stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin. Values are median and range.

Table 3 Clinical, hormonal, and metabolic parameters before and after 6 months of treatment with metformin plus LOD group

	Before treatment	After treatment	*P*-value
FGS	8 ± 5.4	5.9 ± 2.8	<0.05
BMI (kg/m^2)	26.9 ± 1.3	6.1 ± 4.6	<0.05
FSH (2.5–12.5 mIU/mL)	5.3 ± 4.2	19.8 ± 12.1	NS
LH (1.9–12.5 mIU/mL)	11.2 ± 6.8	79.8 ± 9.4	<0.05
Estradiol E_2 (11–69 pg/mL)	33.9 ± 2.2	35.9 ± 2.4	NS
Prolactin (ng/mL)	7.9 ± 3.2	8.7 ± 4.2	NS
Total testosterone (10–80 ng/dL)	105 ± 6.5	2.4 ± 2.5	<0.05
Free testosterone (0.21–3.08 pg/mL)	2.11 ± 1.3	32.9 ± 17	<0.05
Androstenedione (0.21–3.08 ng/mL)	4.4 ± 1.7	154.1 ± 9.2	<0.05
SHBG (20–40 nmol/L)	23.1 ± 2.1	10.9 ± 5.2	<0.05
DHEAS (30–333 μg/dL)	210 ± 11.4	74 ± 7.1	<0.05
Fasting glucose (70–110 mg/dL)	86 ± 7.9	86 ± 5.9	NS
Fasting insulin (2–25 μU/mL)	9.9 ± 7.6	17 112 ± 216.8	<0.05
AUC glucose (mgmin/mL)	17 986 ± 235.4	17 986 ± 116.7	NS
AUC insulin (μUmin/mL)	12 161 ± 160.8	7 123 ± 541.8	
Fasting glucose : insulin	5.2 ± 3.7	8.6 ± 5.2	<0.05
AUC glucose : AUC insulin	1.35 ± 4.1	2.4 ± 3.2	NS

AUC, area under the curve; BMI, body mass index; DHEAS, dehydroepiandrostenedione sulfate; FGS, Ferriman–Gallwey score; FSH, follicle stimulating hormone; LH, luteinizing hormone; NS, not significant; SHBG, sex hormone-binding globulin. Values are median and range.

levels, and AUC insulin. Fasting glucose (G) : insulin (I) ratio values decreased significantly after metformin therapy ($P < 0.05$). SHBG levels increased significantly ($P < 0.05$). The mean basal serum FSH, E_2, PRL and fasting G levels, AUC-G and AUC-G : AUC-I ratio values did not change significantly.

Table 2 shows clinical, hormonal, and metabolic parameters of patients before therapy in both groups. There were no statistically significant differences in age, duration infertility, BMI or hormones between the two groups. Serum I, G, and fasting G : I ratio values were also similar in both groups. Table 3 shows clinical, hormonal, and metabolic parameters of patients before and after metformin therapy in group 2. Hirsutism, BMI, mean LH, total T, free T, A, DHEAS, fasting I levels, AUC I and fasting G : I ratio, SHBG level,

Table 4 Fasting glucose : fasting insulin ratio value and pregnancy response to treatment with metformin plus LOD and LOD alone

Metformin plus LOD Fasting G:I				LOD		
Before metformin	After metformin	Ovulatory cycle	Pregnancy	Fasting G:I	Ovulatory cycle	Pregnancy
3.4	8.2	3	+	5.2	1	–
4.2	7.1	1	–	5.6	2	+
3.6	7.5	2	+	5.3	1	–
3.2	8.7	2	–	4.1	2	–
3.1	7.9	4	+	5.1	3	+
4.3	6.2	2	–	4.2	1	–
3.9	8.4	2	+	4.8	1	–
3.6	5.9	5	–	4.1	2	–
3.8	6.2	5	–	3.9	1	–
3.4	10.2	2	+	3.2	1	–
3.2	8.4	3	+	4.5	1	–
3.4	7.2	2	–	6.4	1	–
5.1	6.9	2	–	7.2	2	–
3.6	5.9	4	–	6.8	1	+
2.7	7.2	6	+	4.3	1	–
3.1	8.3	2	–	3.8	1	–
3.2	9.2	1	–	5.2	2	+
3.8	7.1	2	+	4.9	1	–
3.6	6.8	3	–	4.1	1	–
3.8	5.9	2	–	4.9	1	–
3.4	9.2	1	+	5.2	2	–

G, glucose; I, insulin; LOD, laparoscopic ovarian drilling.

mean basal serum FSH, E_2, PRL and fasting G levels, AUC-G and AUC-G : AUC-I ratio values did not change significantly after LOD in group 1.

Mean serum P level and endometrial thickness were significantly higher in cycles treated with metformin plus LOD (34.6 ± 25.4 ng/mL, 8.4 ± 1.1 mm) than in those treated with LOD alone (26.2 ± 24.7 ng/mL, 7.9 ± 2.8 mm), respectively ($P < 0.05$). The ovulation (56 of 65 cycles, 86.1% vs 29 of 65 cycles, 44.6%) and pregnancy rates (nine of 21 women, 47.6% vs 4 of 21 women 19.1%) were higher significantly, in the metformin plus LOD group than in the LOD alone group (Table 1).

Fourteen of 21 patients had insulin resistance (fasting G : I ratio value <4.5) in the metformin plus surgical treatment group, and 11 of 21 patients in the surgical treatment only group. Nine pregnancies (47.6%) occurred in 21 women treated with metformin plus LOD, all the patients who conceived had insulin resistance (fasting G : I ratio value <4.5) in the metformin plus LOD group. Four pregnancies (19.1%) occurred in those treated with LOD alone. Four women who conceived were non-insulin resistance. Two pregnancies in group 2 ended in first trimester spontaneous abortion and two in pre-term delivery, the other five have delivered full-term healthy babies (Table 4).

Discussion

In the present study, we examined the effects of metformin on insulin resistance and ovarian androgen concentration and ovulation and pregnancy rates in women with PCOD following LOD. We have shown that metformin significantly reduces hyperinsulinemia and hyperandrogenemia in women with PCOS.

Four randomized controlled trials have compared metformin with placebo, showing that 56% of PCOS patients ovulated with metformin compared with 35% on placebo (relative risk (RR) 1.5; 95% confidential interval (CI) 1.2–2.0). In CC-resistant PCOS women, two randomized controlled trials compared ovulation and pregnancy rates of additional metformin to CC versus CC to placebo.[19,20] In a total of 82 CC-resistant PCOS women, the ovulation rate was 70% versus 19% (RR 4.1; 95% CI 2.2–7.9) and the pregnancy rate was 23% versus 2.3% (RR 10.0; 95% CI 1.3–74.8).[19,20] These

data demonstrate that metformin augments the effect of CC, resulting in significantly higher ovulation and pregnancy rates.[1,3,21]

In the present study, the ovulation and pregnancy rates in cycles were significantly higher, in the women given metformin plus LOD than in those given LOD alone. The pregnancy rate in ovulatory cycles was also significantly higher in the metformin plus LOD group. Nine pregnancies (47.6%) occurred in 21 women treated with metformin plus LOD and four pregnancies (19.1%) occurred in those treated with LOD alone. The mild increased frequency of ovulation may be accompanied by an increased pregnancy rate or birth rate. We found that the mean serum progesterone level and endometrial thickness were significantly higher in the cycles of women treated with metformin plus LOD than those treated with LOD alone.

De Leo *et al*. have demonstrated that metformin-induced insulin reduction is associated with an increase in IGF binding protein-1 (IFGBP-I) and a reduced IGF-I/IGFBP-1 ratio.[22] Hyperinsulinism and free IGF-1 levels in PCOS women may inhibit normal endometrial maturation and it seems that treatment of hyperinsulinism with metformin could increase ovulation and pregnancy rates. Ideally, for obese PCOS women a combination of dietary restriction and exercise remains the best form of treatment. Several investigators have shown that weight loss of more than 5% of pretreatment weight had a beneficial effect in terms of reducing LH (45% decrease), fasting insulin (40% decrease), T (35% decrease) and progression to type 2 diabetes mellitus (by 58%).[23–25] Weight loss also improved diabetes control and serum lipid profiles and restored menstrual function regularity in 89% of women tested, of whom 30% achieved spontaneous pregnancy.[18,21,26–28] Ovarian wedge resection was the first surgical treatment proposed by Stein and Leventhal for ovulation induction.[1,29] This procedure was largely abandoned because of the greater risk of post-surgical formation of adhesions.[29] Lack of etiology of PCOS has led to symptom-oriented therapy.

Surgical ovulation induction in the form of LOD using unipolar cautery or a laser is a common approach presently used for CC-resistant PCOS women. Retrospective studies have shown no statistically significant difference in ovulation rates following LOD with electrocoagulation and laser (83% vs 77.5%), although there is a significantly higher cumulative pregnancy rate in the 12 months (65% vs 54.5%) following the procedure. Deep penetration to 8 mm using an insulated unipolar diathermy needle with thermal energy 450–900 J produced by three to six punctures per ovary has a significantly higher ovulation rate (58–62%) and pregnancy rate (45–60%) than the thermal energy of 300 J produced by two punctures per ovary (ovulation rate of 27% and pregnancy rate of 13%). The application of seven punctures per ovary (thermal energy of >1000 J) offered no improvement in the results.[1,30]

In the present study, 14 of 21 patients had insulin resistance (fasting G : I ratio value <4.5) in the metformin plus LOD group and 11 of 21 patients in the LOD only group. All of the patients who conceived had insulin resistance (fasting G : I ratio <4.5) in the metformin plus LOD group. Four women who conceived were non-insulin-resistant in group 1. This means that metformin therapy may increase the pregnancy rate in women with insulin resistance. Surgical treatment-induced ovulation and pregnancy rates may be increased in hyperinsulinemic women with PCOS by decreasing serum insulin and androgen levels with metformin. Metformin significantly increased the ovulation and pregnancy rates. Metformin therapy can be recommended in PCOS patients with insulin resistance. In conclusion, metformin therapy was effective in reducing insulin resistance and hyperandrogenism in women with PCOS. More randomized, controlled studies in a larger population are needed to determine the effect of metformin.

References

1. Saleh AM, Khalil HS. Review of nonsurgical and surgical treatment and the role of insulin-sensitizing agents in the management of infertile women with polycystic ovary syndrome. *Acta Obstet Gynecol Scand* 2004; **83**: 614.
2. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* 1998; **83**: 3078–3082.
3. Kocak M, Caliskan E, Simsir C, Haberal A. Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. *Fertil Steril* 2002; **77**: 101–106.
4. Frank S, Adams J, Mason H. Ovulatory disorders in women with polycystic ovarian syndrome. *Clin Obstet Gynecol* 1985; **12**: 605–632.
5. Nestler JE. Insulin and ovarian androgen excess. In: Azziz R, Nestler JE, Dewailly D (eds). *Androgen Excess Disorders in Women*. Philadelphia: Lippincott-Raven, 1997; 473–483.
6. Dunaif A. Insulin resistance and the polycystic ovary syndrome. Mechanisms and implications for pathogenesis. *Endocr Rev* 1997; **18**: 774–800.
7. Talbott E, Clerici A, Berga SL *et al.* Adverse lipid and coronary heart disease risk profiles in young women with polycystic

ovary syndrome: results of a case-control study. *J Clin Epidemiol* 1998; **51**: 415–422.
8. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999; **84**: 165–169.
9. Fagan TO. The cardiovascular dysmetabolic syndrome. *Am J Med* 1998; **105**: 77S–82S.
10. Felemban A, Tan SL, Tulandi T. Laparoscopic treatment of polycystic ovaries with insulated needle cautery: a reappraisal. *Fertil Steril* 2000; **73**: 266–269.
11. Kovacs G, Buckler H, Gangah M *et al.* Treatment of anovulation due to polycystic ovarian syndrome by laparoscopic ovarian cautery. *Br J Obstet Gynaecol* 1991; **98**: 30–35.
12. Kolodziejczyk B, Duleb JA, Spaczynski RZ, Pawelczyk L. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. *Fertil Steril* 2000; **73**: 1149–1154.
13. Crave JC, Fimbel S, Lejeune H, Cugnardey N, Dechaud H, Pugeat M. Effects of diet and metformine administration on sex hormone-binding globulin, androgens, and insulin in hirsute and obese women. *J Clin Endocrinol Metab* 2005; **80**: 2057–2062.
14. Diamanti-Kandarakis E, Kouli C, Tsianateil T, Bergiele A. Therapeutic effects of metformin on insulin resistance and hyperandrogenism in polycystic ovary syndrome. *Eur J Endocrinol* 1998; **138**: 269–274.
15. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998; **338**: 1876–1880.
16. Vandermolen DT, Patts VS, Evans WS. Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. *Fertil Steril* 2001; **75**: 310–315.
17. Yu Ng EH, Sun Wat NM, Ho PC. Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double-blinded placebo-controlled trial. *Hum Reprod* 2001; **16**: 1625–1631.
18. Holte J, Bergh T, Berne C, Wide L, Lithell H. Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic syndrome. *J Clin Endocrinol Metab* 1995; **80**: 2586–2593.
19. Farquhar C, Vandekerckhove P, Lilford R. Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. *The Cochrane Library*, Issue 4. Oxford: Update Software, 2001.
20. Franks S. Polycystic ovary syndrome. *N Engl J Med* 1995; **333**: 853–861.
21. Anderson P, Seljeflot I, Abdelnoor M *et al.* Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome. *Metabolism* 1995; **44**: 611–616.
22. De Leo W, Marca A, Orvieto R, Morgante G. Effect of metformin on insulin-like growth factor (IGF) I and IGF-binding protein I in polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000; **85**: 1598–1600.
23. Futterweit W. An endocrine approach to obesity. In: Simopoulos AP, Vanltallie TB, Gullo SP, Futterweit W (eds). *Obesity: New Directions in Assessment and Management*. New York: Charles Press, 1994; 96–121.
24. Kiddy DS, Hamilton-Fairley D, Bush A *et al.* Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 1992; **36**: 105–111.
25. Pasquali R, Antenucci D, Casimirri F *et al.* Clinical and hormonal characteristics of obese and amenorrheic hyperandrogenic women before and after weight loss. *J Clin Endocrinol Metab* 1989; **68**: 173–189.
26. Lobo RA, Paul L, Granger L. Clomiphene and dexamethasone in women unresponsive to clomiphene alone. *Obstet Gynecol* 1982; **60**: 497–501.
27. Garcia J, Jones GS, Wentz AC. The use of clomiphene citrate. *Fertil Steril* 1977; **28**: 707–717.
28. Tan SL, Farhi J, Homburg R, Jacobs HS. Induction of ovulation in clomiphene–resistant polycystic ovary syndrome with pulsatile GnRH. *Obstet Gynecol* 1996; **88**: 221–226.
29. Kistner RW. Peritubal and periovarian adhesions subsequent to wedge resection of the ovaries. *Fertil Steril* 1969; **20**: 35–42.
30. Gjonnaess H. Polycystic ovarian syndrome treated by ovarian electrocautery through the laparoscope. *Fertil Steril* 1984; **4**: 20–25.