

METFORMIN TREATMENT IN INSULIN RESISTANT POLYCYSTIC OVARIES PATIENTS

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ABSTRACT

Objectives : To know the incidence and characters of insulin resistance (IR) in polycystic ovaries (PCO) patients, and the efficacy of metformin treatment for induction of ovulation compared to clomiphene citrate (CC); also the effect of metformin on the clinical, biochemical and hormonal features of the patient would be evaluated.

Design : A prospective, blind, controlled study.

Setting : Outpatient infertility clinic, Benha University Hospital.

Subjects : Sixty infertile PCO patients.

Methods : The body mass index (BMI), the hirsutism and the acne scores, the fasting blood glucose, the fasting serum insulin and serum testosterone levels were measured for every patient. A ratio of fasting blood glucose to fasting serum insulin (G/I) of less than $4.5 \text{ mg}/10^{-4}$ units was considered IR. Insulin resistant patients were randomly divided into three groups and treated for three cycles. The first group was treated with CC + metformin, the second with placebo + metformin and the third with CC + placebo.

Main outcome measures : The ovulation and pregnancy rates with metformin treatment compared to CC.

Results : IR is present in about 86.6% of PCO patients. They are characterized by having higher BMI, fasting serum insulin and serum testosterone levels, than non IR patients. Treatment with CC + metformin results in higher ovulation and pregnancy rates compared to that obtained with CC alone.

Conclusions : IR must be diagnosed in PCO patients. Induction of ovulation with CC + metformin results in higher ovulation and pregnancy rates. In contrast to CC, the longer the duration of metformin treatment, the better are the results.

INTRODUCTION

Polycystic ovaries are a common endocrine disorder affecting up to 10% of women at the reproductive age⁽¹⁾. The manifestations of the disease are variable, but the keystone for diagnosis is a patient complaining of oligomenorrhea and infertility, an ultrasound appearance of polycystic ovaries and an elevated serum LH and LH/FSH ratio. Other findings include obesity, hirsutism, acne, and elevated serum androgen levels.

In recent years, insulin resistance with compensatory hyperinsulinemia and increased risk of glucose intolerance are well recognized abnormal laboratory findings in PCO patients⁽²⁾.

Different investigators showed that hyper-

insulinemia causes increases in serum androgen level by augmenting abnormal ovarian androgen secretion^(3,4).

Clomiphene citrate is the drug of choice for induction of ovulation in PCO patients, however, about 25% of patients are resistant to CC⁽⁵⁾. Hyperinsulinemia and hyperandrogenemia are thought to be causative factors.

Metformin is a biguanide oral anti hyperglycemic drug which improves insulin sensitivity and lowers blood glucose and serum insulin levels⁽⁶⁾. Treatment of insulin resistant PCO patients with metformin combined with CC has been claimed to result in higher ovulation and pregnancy rates.

AIM OF THE WORK

The aims of this work was:

1. To detect the incidence and characters of IR in PCO patients.
2. To compare between metformin and clomiphene citrate treatments for induction of ovulation in PCO cases.
3. To evaluate the effects of metformin treatment on the clinical, biochemical and hormonal features of the patients.

MATERIALS & METHODS

The study was done at the outpatient infertility clinic of Benha university hospital during the period from January 2002 to June 2004, and included sixty PCO patients complaining of infertility and oligomenorrhea. Vaginal US showed enlarged ovaries containing 10 or more sub capsular cysts, 2-8 mm in diameter, arranged around echo dense stroma, and the laboratory investigations revealed elevated serum LH and LH/FSH ratio.

The body mass index (BMI), the hirsutism score⁽⁷⁾ and the acne score⁽⁸⁾ were reported for every patient then the following laboratory investigations were done after an overnight fast:

a- The fasting and the 2-hours post prandial blood glucose level using the glucose oxidase technique. Normal fasting value =70-110 mg/dl and 2-hours post prandial value =140-145 mg/dl. Higher values were further investigated by oral glucose tolerance test. Patients who proved to be diabetic were excluded from the study.

b,c- The fasting serum insulin and serum testosterone levels by the chemiluminescence immunoassay (Elecsys) method using Roche

diagnostics, Gmbh, D. 68298, Mannheim, Germany. Normal value for serum insulin = 2-25 μ IU/ml and for serum testosterone = 0.1-0.8 ng/ml.

A ratio of fasting blood glucose to fasting serum insulin (G/I ratio) of less than 4.5 mg/10⁻⁴ unit was considered insulin resistance (IR)⁽⁹⁾.

IR patients were randomly allocated for induction of ovulation with one of the following regimens for three cycles:

1. CC 100mg daily from cycle day 5-9+ metformin 1500 mg daily through out the cycle.
2. Placebo from cycle day 5-9 + metformin 1500 mg daily through out the cycle.
3. CC 100 mg daily from cycle day 5-9 + placebo through out the cycle.

Vaginal US was done on cycle day 12, if the diameter of the leading follicle was 18 mm or more, ovulation was considered impending and 10.000 IU hCG was given IM, and sexual intercourse advised in next days. If the follicle diameter was less than 18 mm, vaginal US was repeated on cycle days 14,16 and 18. If the diameter was still below 18 mm the cycle was considered a failure of ovulation and hCG was not given.

After three treatment cycles, the ovulation and pregnancy rates were calculated, and the effect of metformin treatment on the BMI, the hirsutism and the acne scores, the fasting blood glucose, the fasting serum insulin and serum testosterone levels were recorded.

Statistical Methods :

Results were statistically analyzed using the mean, the standard deviation, the student-t test and the paired-t test. The result was considered significant if its P value was < 0.05.

RESULTS

Sixty PCO patients were studied, 52 patients (86.6%) had a fasting blood glucose level / fasting serum insulin level less than $4.5 \text{ mg}/10^{-4}$, which is consistent with IR, while 8 patients were non IR (13.4%).

Table I: shows that the mean BMI, fasting serum insulin, and serum testosterone levels were significantly higher in IR patients ($P < 0.05-0.001$).

Table II, III and IV: show that the ovulation and pregnancy rates increase in the second and third treatment cycles in patients who received metformin with CC or metformin alone, while both parameters decreased in patients who received CC alone.

Table V: shows that the highest ovulation and pregnancy rates were in the CC + metformin group, followed with metformin + placebo group, while the lowest were in the CC + placebo group.

Table VI: shows that after metformin treatment there was a significant decrease in fasting serum insulin and serum testosterone levels ($P < 0.01$), while there was no change in the BMI, hirsutism and acne scores and the fasting blood glucose level.

DISCUSSION

Insulin resistance (IR) is defined as a clinical state in which a normal or elevated insulin level produces an impaired biological response⁽¹⁰⁾. There are different tests to diagnose IR, but the easiest and mostly used is the ratio of fasting blood glucose to fasting serum insulin level (G/I)⁽⁹⁾ of less than $4.5 \text{ mg}/10^{-4}$.

Not all PCO patients have IR. In our study 86.6% of patients had IR due to the increase in serum insulin. The exact pathogenesis of hyperinsulinemia in PCO patients remains

undetermined. Some authors⁽¹¹⁾ found that there was no decrease in insulin receptors number or affinity in PCO patients. Others⁽¹²⁾ mentioned that IR may be a consequence of obesity, as adipose tissue produces tumor necrosis factor α (TNF α) which exerts inhibitory effects on insulin action. A post receptor defect in insulin action which is manifested by decrease in insulin receptors phosphorylation following insulin binding was proposed⁽¹³⁾.

Other causes of hyperinsulinemia in PCO patients could be increased pancreatic secretion of insulin resulting from genetic mutation⁽¹⁴⁾ or a defect in glucose transport⁽¹⁵⁾.

In our study, serum testosterone level was significantly higher in IR, PCO patients ($P < 0.05$). This result agrees with that reported by most authors^(16,17). Hyperinsulinemia causes increased ovarian androgen secretion through different mechanisms :

Insulin by acting via its own receptors⁽¹⁸⁾ or via insulin like growth factor-1 (IGF-1) receptors⁽¹⁹⁾ stimulates ovarian production of androgens. Others⁽²⁰⁾ suggested that insulin by increasing IGF-1 increases the effect of luteinizing hormone on ovarian androgen production. An association between hyperinsulinemia and increased adrenal androgen secretion was suggested⁽²¹⁾ while other authors⁽²²⁾ found that insulin inhibit hepatic production of sex hormone binding globulin, thus increasing free androgen level.

Hirsutism and acne are markers for increased androgen production, but it does not occur in all hyperandrogenic PCO patients. In our study, there was no significant difference between the incidence of either hirsutism or acne in IR and non IR patients.

In the present study, the BMI was significantly higher in IR than in non IR patients ($P < 0.05$); this

result agrees with that reported by prelevic (23) who found that IR was present in 30% of slim and in 75% of obese women with PCO.

In our study, the highest ovulation and pregnancy rates were in patients treated with CC + metformin followed by metformin then by CC. This result agrees with that reported by several authors (24,25,26,27). On the other hand, some authors(28,29) failed to find any beneficial effect of metformin treatment. An interesting result in our study was that the ovulation and pregnancy rates increased with longer duration of metformin treatment, in contrast with CC alone treatment, where both parameters decreased. This result was not reported in previous studies.

In the present study, there were a significant decrease in fasting serum insulin and serum testosterone levels after metformin treatment compared to pre treatment levels. These results agreed with that reported by several studies (30,31,32,33). On the other hand, some authors did not find any decrease in serum insulin and serum testosterone levels after metformin therapy(34,25). This discrepancy in results may be due to inclusion of both IR and non IR, PCO patients in other studies, or due to different dose and duration of metformin treatment.

In our study there was no change in the BMI after metformin treatment, a result which agrees with that reported by Morin-papunen et al and Ehrmann et al(35,34). However, other authors reported a significant decrease in the BMI after metformin treatment(32,25). This discrepancy in results may be due to differences in the duration and dose of metformin treatment or in the definition of obesity of either a BMI > 25 or 27.

the mechanisms by which metformin affect weight, are not fully established. A decrease in serum insulin with consequent decrease in appetite and lipogenesis, or the decrease in the dietary

intake associated with the gastrointestinal effect of the drug was suggested(36).

In our study, hirsutism and acne were not improved after metformin treatment in spite of significant decrease in serum testosterone level, a result which agreed with that reported by other (34,32). On the other hand a decrease in hirsutism and acne scores after 12 weeks of metformin treatment was reported by Kolodziejczyk et al (8). The degree of hirsutism associated with PCO does not correlate only with the concentration of circulating androgens but also on the genetic sensitivity of the hair follicle(37).

CONCLUSIONS

Insulin resistance must be diagnosed in PCO patients. treatment with metformin decreases serum insulin and serum testosterone levels. Combined CC + metformin results in higher ovulation and pregnancy rates. In contrast with CC, the longer the duration of metformin treatment, the better are the results.

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Table I : Clinical, biochemical and hormonal features of IR and non-IR PCO patients.

Features	IR n = 52		non IR n = 8		t	P
	Mean	± S.D	Mean	± S.D		
BMI	30.20	3.30	27.90	2.88	1.42	< 0.05
Hirsutism score	8.66	0.26	7.98	1.77	1.08	N.S
Acne score	1.34	0.20	1.32	0.03	0.70	N.S
Fasting blood glucose	86.36	4.64	85.16	2.44	1.12	N.S
Fasting serum insulin	25.60	3.32	16.17	2.52	9.40	< 0.001
G/I ratio	3.38	0.31	5.27	0.51	10.6	< 0.001
Serum testosterone	1.98	0.06	1.88	0.03	7.70	< 0.001

Table II : Ovulation and pregnancy rates with CC + metformin in the three treatment cycles.

Cycle	No.	Ovulation		Pregnancy	
		No.	%	No.	%
1 st	18	12	66.7	4	22.2
2 nd	14	10	71.4	4	28.6
3 rd	10	8	80.0	3	30.0
Total	42	30	71.4	11	26.2

Table III : Ovulation and pregnancy rates with placebo + metformin in the three treatment cycles.

Cycle	No.	Ovulation		Pregnancy	
		No.	%	No.	%
1 st	17	6	35.3	1	5.9
2 nd	16	6	37.5	2	12.5
3 rd	14	6	42.9	2	14.3
Total	47	18	38.3	5	10.6

Table IV : Ovulation and pregnancy rates with CC + placebo in the three treatment cycles.

Cycle	No.	Ovulation		Pregnancy	
		No.	%	No.	%
1 st	17	9	29.4	1	5.9
2 nd	16	4	25.0	0	0
3 rd	16	3	18.8	0	0
Total	16	12	26.1	1	2.2

Table V : Cumulative ovulation and pregnancy rates per cycle in the three treatment groups of IR, PCO patients.

Cycle	No.	Ovulation		Pregnancy	
		No.	%	No.	%
CC + metformin.	42	30	71.4	11	26.2
Placebo + metformin.	47	18	38.3	5	10.6
CC + placebo	46	12	26.1	1	2.2

Table VI : Effects of metformin treatment on clinical, biochemical and hormonal features of IR, PCO patients (n = 35).

Features	before ttt		After ttt		Paired-t	P
	Mean	± S.D	Mean	± S.D		
BMI	29.16	2.16	28.87	1.18	1.71	N.S
Hirsutism score	8.33	0.66	8.16	0.41	1.82	N.S
Acne score	1.16	0.44	1.26	0.63	1.91	N.S
Fasting blood glucose	84.98	3.18	82.77	3.22	1.78	N.S
Fasting serum insulin	25.33	2.19	18.17	1.85	2.75	<0.01
G/I ratio	3.35	0.38	5.12	0.53	2.60	<0.01
Serum testosterone	1.30	0.30	0.99	0.20	2.88	<0.01

ttt = treatment