Metformin : The Treatment of Choise in Polycystic Ovary Disease

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Abstract

Aim of study: Was to determine wheather metformin , which reduces hyperinsulinemia , would reverse the endocrinopathy of PCOS, allowing resumption of regular , normal menses.

Subjects and Methods:A study included 29 patients with PCOS were treated with metformin for 3-6 months and effects on regulation of menstrual cycles, weight reduction, improvement in endocrinopathy was assessed after treatment.

Results: Of 29 patients with PCOS,with menstual irregulation, the analysis showed that 20 patients resume normal menses after metformin therapy, 14 patients loss weight , and there was reduction in level of blood insulin and testosterone after treatment .

Conclusion: Safe and effective therapy with metformin in PCOS reverses endocrinopathy , restores normal menstrual cycles , and restores fertility, allowing pregnancy.

الخلاصة

دراسة تفصيلية أجريت في مستشفى بابل للولادة والاطفال والعيادات الخاصة للفترة من كانون الثاني عام ٢٠٠٤ لغاية تشرين الثانى عام ٢٠٠٤ .

تضمنت دراسة ٢٩ مريضة مصابة بعضال المبيض المتعدد الاكياس يعانين من اضطرابات فى الدورة الشهرية (بهييئة قلة أوانعدام الدورة الشهرية).

وقد تم معالجة المصابات بدواء المتفورمين بجرعة تتراوح من ١،٥–١غم يوميا لفترة تتراوح من ٣– ٦أشهر

تم اجراء التحاليل التالية للمصابات:

قياس هرمون الانسولين في الدم ، الهرمون الذكري .

أظهرت الدراسة ان ٢٠ مريضة من ضمن ٢٩ مريضة من المصابات بعضال المبيض المتعدد الاكياس واللواتي يعانين من اضطرابات فى الدورة الشهرية ، قد استعدن دورات شهرية تعتبر طبيعية بعد العلاج بدواء المتفورمين .

وان ١٤ مرييضة قد فقدن الوزن ، وكذلك قد حصل هبوط فى مستوى هرموني الانسولين فى الدم والهرمون الذكرى بعد العلاج .

Introduction

Polycystic ovary syndrome (PCOS) is common, affecting 5-10% of the population, and is characterized by chronic anovulation with oligo - amenorrhea and infertility, and by clinical (hirsutism, acne) and biochemical hyperandrogenism [1,2].

Commonly insulin resistance with resultant hyperinsulinemia leads to abnormal ovarian and adrenal androgen secretion which, in turn, leads to abnormal LH and FSH release and subsequent oligo- amenorrhea.

Women with PCOS have at least seven times the risk of myocardial infarction and ischemic heart disease of other women , and by the age of 40 years up to 40% will have type 2 diabetes or impaired glucose tolerance [3] .

Metformin (an insulin sensitizing drug) induced reduction of insulin resistance and reduction of

hyperinsulinemia and subsequent reduction of hyperandrogenemia appears to be central to reversal of endocrinopathy in PCOS [1,4].

Many (probably most) women with PCOS are now able to conceive while taking metformin .

The mechanisms underlying the beneficial effects of metformin in the treatment of PCOS remain incompletely understood. Improvement of insulin resistance (IR) by metformin may not only result from the well – known reduction of hepatic glucose production and increase of peripheral glucose utilization but also from a direct effect on ovarian steroidogenesis , as demonstrated by in vitro studies [5-7].

Since not all PCOS patients are obese or insulin resistant , it is not clear whether PCOS patients without IR also benefit from a therapy with insulin sensitizers .

Goldenberg et al. [8] demonstrated an equal improvement of menstrual irregularities both in insulin – resistant and insulin – sensitive PCOS patients .

Metformin usually normalizes high PAI.FX (plasminogen activator inhibitor) in women with PCOS (causes thrombosis and placental insufficiency) , and as such , should be protective against the high rate of first trimester
miscarriage in PCOS [9] .

Metformin now shown to reduce first trimester miscarriage 3- folds , to reduce development of gestational diabetes 7- folds , to prevent fetal macrosomia , without any adverse effects on mothers or their newborn infants.

The effectiviness of metformin has been best demonstrated in obese women and it is likely that women with normal weight would benefit very little from this drug.

Weight loss in obese women with PCOS leads to a reduction of hyperinsulinaemia (Kiddy et al. 1992) .

Although metformin is known to cross the placenta , there is , as yet , no evidence of teratogenicity [11] .

Patients on metformin should take folic acid and B12 supplements since metformin slightly decreases these [12].

Subjects and Methods

A prospective study was done from January 2004 to November 2004 , included 29 patients with PCOS , their age range from 15 – 34 years presented with menstrual abnormalities (oligomenorrhea or amenorrhea) with a duration of primary infertility ranging from 1- 7 years when attending the infertility department at Babylon Hospital For Maternity and Children and at a privid clinic .

PCOS was diagnosed by transvaginal ultrasonography using a 5 MHZ vaginal probe i.e > 10 follicles of 2-10 mm in diameter and increasing density of ovarian stroma , irregular cycles (oligomenorrhea or amenorrhea), clinical or biochemical signs of hyperandrogenism.

Bilateral patent fallopian tubes were confirmed in all women by hysterosalpingography or laproscopy and dye test .

Husbands of subjects all had normal semen variables .

Exclusion criteria were smokers , or those suffering from renal impairment or taking sex hormones within the last 3 months .

All patients in the study kept on metformin therapy 1- 1.5gm/day for 3-6 months.

Investigations were done to them included :
Serum insulin hormone and serum testosterone , and results compared before and after treatment .

These hormones were measured by radioimmunoassay Diagnostic Products Corporation , Los Angles ,

CA , USA .

Body mass index (BMI) was calculated as weight /(height)2 in Kg/m2.

We follow the effects of metformin on regulation of menstrual cycles , and effects on weight reduction.

We also assess the side effects of metformin in these patients such as nausea , vomiting and diarrhea .

Stastical analysis

Significance was assessed by chi-square test.

A difference between values was considered significant * when $p < 0.05$, and very significant ** when $p < 0.01$.

Results

In 29 amenorrheic women with PCOS , metformin (1 - 1.5 gm / day) was given for 3 - 6 months .

On metformin 20 of 29 patients (68.96%) previously with oligomenorrhea - amenorrhea , resume normal menses .

Of 29 patients , 14 patients (48.27%) lose weight (5 - 34 pounds) .

Mean serum insulin fell from 46 _+37 uU / ml to 22+_17 on metformin .

Testosterone fell from 62_+34 ng /dl to 44 _+25 on metformin .

About side effects of metformin , 9 of 29 patients develop nausea , headache , tiredness (31.03%).

4 patients of 29 develop vomiting (13.79%) during treatment , and they stop the drug (metformin) for 1-2 months and then resume treatment .

No patient develop lactic acidosis during treatment .

Table 1 Showed serum insulin Concentrations in Women Treated with Metformin.

Serum insulin before treatment (uU/ ml)	Serum insulin before treatment (uU/ ml)
75	39
71	38
69	62
68	36
65	36
61	61
58	29
55	30
53	28
42	41
40	25
39	24
35	23
36	33
33	19
29	18
28	17
26	26
24	15
21	20
20	14
19	13
18	13
16	15
15	12
13	10
11	8
10	6
8	5

Before treatment X= 37.056

21.515 (SD)

After treatment X = 22.33

10.375 (SD)

P < 0.001 ** (very significant)

Table 2 Showed serum testosterone Concentrations in Women Treated with Metformin.

Serum testosterone before treatment (ng/ dl)	Serum testosterone after treatment (ng/ dl)
92	69
90	68
86	86
83	62
81	80
80	80
77	59
75	58
74	74
73	55
71	54
70	53
69	67
67	65
65	49
62	62
60	48
59	59
58	46
56	56
55	42
52	52
51	39
46	35
40	39
35	34
29	29
26	23
24	21

Before treatment X= 58.421

20.633 (SD)

After treatment X = 45.053

15.215 (SD)

P < 0.001 ** (very significant)

Table 3 Showed distribution of patients according to B. M. I (Body mass index) in women treated with metformin.

B. M. I Before treatment	B. M. I after treatment
44.3	42.6
43.8	42.3
40.6	40.6
39.5	37.5
37.9	36.7
36.2	35.1
35.8	34.8
35.2	34.3
34.6	33.9
34.1	32.3
33.8	32.1
33.3	31.9
33.1	31.7
32.9	31.3
32.6	30.6
32.5	30.2
32.1	30.1
31.8	29.8
30.3	29.6
29.2	29.1
28.8	28.1
28.5	28.3
27.9	27.2
27.2	27.1
26.9	26.1
26.3	25.5
26.1	26
25.7	25.6
25.5	25.1

Before treatment X= 35.495
3.996 (SD)
After treatment X = 34.074
4.147 (SD)
$P < 0.001$ ** (very significant)

Table 4 Showed side effects of women treated with metformin.

Side effects	No.	%
Nausea	9	31.5
Headache	9	31.5
Vomiting	4	10.5
Lactic acidosis	Zero	Zero
Diarrhea	Zero	Zero

Discussion

PCO is one of the most common endocrine disorders of women of reproductive age .

Metformin , a biguanide , has been used to treat insulin resistance and infertility in women diagnosed with PCOS [13].

Metformin decreases glucose production in the liver , threby decreasing intestinal absorption of glucose and improving insulin sensitivity by increasing peripheral glucose uptake and utilization . It dose not cause low blood sugars except in special rare circumstances.

Metformin , by reduding insulin , insulin resistance , PAI-FX , weight , triglycerides, and blood pressure , should also reduce the increased C.H.D (coronary heart disease) risk which characterizes PCOS patients in later adulthood (1,2,14,15) .

By restoring normal menstrual cycles , metformin may also reduce the likelihood of endometrial hyperplasia and carcinoma associated with PCOS [16].

Metformin has been shown to induce the resumption of regular menses and ovulation in PCOS patients by reducing levels of LH , sex hormone - binding globulin,and circulating androgens .

Metformin - induced improvements in ovarian function have been associated with restoration of normal menstrual cycles in 91 % of 43 previously amenorrheic American women with PCOS [1].

Twenty - one of 22 (96 %) previously oligo - amenorrheic obese Venezuelan Mestizo women with PCOS had restoration of menstrual cyclicity on metformin (1, 500 mg /day) for 6 months [17].

In 20 obese Finnish women with PCOS 11 (69 %) of those with menstrual disturbances experienced more regular cycles during therapy with metformin, 1,500mg /day for 6 months [18].

Diamanti - Kanarakis et al. reported resumption of normal menses in 44 % of 16 Greek women with PCOS on metformin (1,700 mg / day) for 6 months (19).

In our study 20 of 29 patients (68.9 %) previously with oligomenorrhea - amenorrhea resume normal menses.

Metformin is used in doses of 1,500 to 2000 mg / day . The most common side - effects of metformin is diarrhea which occured in 41 % of patients on metformin versus placebo in one study (in our study no patient develops diarrhea during treatment) .
Nausea and vomitting (17 %) , and indigestion (3%) . The one severe side -effect of metformin which occurs only very rarely , is lactic acidoses , but has a 50 % fatality rate if it occurs . So the drug is contraindicated in women with hepatic or renal impairment.
One case of encephalopathy reported , this case did not have lactic acidoses [20].

In our study , of the 29 patients , 9 patients (31.03%) develop nausea , and only 4 patients (13.79%) develop vomiting. .
No patient develop lactic acidosis .

A second insulin - sensitizing drug Rezulin , although now withdrawn because of hepatotoxicity , was also effective in adult women with PCOS [21,22].

Moghetti et al. (2000) reported a significant increase in the ovulation rate , decrease in serum testosterone concentration and fasting insulin concentration , and an increase in HDL after taking metformin [23].

This is in consistent with results of our study , we reported a significant decrease in serum testosterone and fasting insulin concentrations after taking metformin .

Hahn et al. [24] pointed out a

positive effect of metformin on hyperandrogenism , chronic anovulation , and IR in a German PCOS cohort.

Many metformin intervention studies from Itally , Finland , UK , United States demonstrated a positive effect of metformin on body weight and / or BMI [25-29].

In accordance with these studies , metformin caused a significant weight reduction in our PCOS cohort of overweight and obese patients.

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