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Role of Metformin in PCOS – A Prospective Observational Randomized Control Trial

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Abstract

Aim

To assess the effect of metformin in the management of PCOS

Objective

The objective of the study is to evaluate the potential effects of metformin in women with PCOS.

Methods

Metformin is an important component of PCOS treatment. The use of metformin had proven beneficial in the population of women with PCOS.The combination of severe insulin resistance and LH stimulation results in increased ovarian secretion of testosterone, leading to the virilizing features of PCOS. The syndrome should be suspected in women with hirsutism, irregular menstruation, or infertility. Therefore randomized control trial of 30 patients is conducted to determine the effects of metformin in PCOS patients.

Result

The results show that, in all studies, overweight women with polycystic ovary syndrome treated with metformin had significantly improved metabolic indicators, including insulin resistance, ovulatory cycles, estradiol and menstrual cycle.

Conclusion

Compared to placebo, metformin appears to be more effective intervention in PCOS.

Keywords

Metformin, PCOS, Obesity, Insulin Resistance

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinological disorder affecting 4-12% of women. It was also called as Polycystic Ovarian Syndrome which implying that primary pathology lies in ovary. It is a disorder associated with combination of metabolic and reproductive characteristics (1). Although the first description of polycystic ovary syndrome (PCOS) is generally credited to Stein and Leventhal in 1935 (2). Polycystic ovary syndrome (PCOS) is characterized by elevated circulating androgen levels and/or clinical signs of hyperandrogenism, chronic oligo- or anovulation and the presence of polycystic ovaries in ultrasound (3). PCOS is also associated with overweight or obesity, mainly abdominal adiposity (4).In PCOS, there is relative increase in LH pulsatile secretion from the pituitary gland leading to altered high LH to FSH ratio (5).

Incidence of PCOS

Depending on the diagnostic criteria used, prevalence in the population as a whole varies from 10% to 20%. Studies since then suggest a greater than 20% incidence and prevalence of PCOS in overweight and obese women (6). Around 30–75% of PCOS women are obese and many PCOS women show evidence of insulin resistance and hyperandrogenism (7).

Obesity and PCOS

Reproductive disturbances are more common in obese women regardless of the diagnosis of PCOS. In reproductive-age women, the relative risk of anovulatory infertility increases at a BMI of 24 kg/m2 and continues to rise with increasing BMI (8). Obesity is associated with an increase in the risk for developing impaired glucose tolerance. Obesity may affect peripheral metabolism of sex steroids. This is associated with suppression of SHBG, causes decreased binding of Testosterone. This leads to development of masculinization (9).

Insulin Resistance and PCOS

Failure of the target cells to respond to normal or ordinary levels of insulin is regarded as insulin resistance (10). The most of the women with PCOS are insulin Resistant. Insulin stimulates ovarian theca cell androgen production and secretion, and suppresses the hepatic production of sex hormone-binding globulin (11).Insulin produce steroid genic effects through MAP Kinase Pathway. The hyperinsulinemia in PCOS stimulate the MAP Kinase Pathway. This enhance the steroid genic effects and insulin resistance. Obesity worsens the insulin resistance and hyper androgenic features of PCOS (12).

Metformin as treatment for obesity

Metformin is a member of the biguanide family with proven safety and efficacy. Metformin has long been used in the management of Type-2 diabetes mellitus and it is one of the insulin sensitising agents commonly used in the treatment of PCOS (13). Metformin lowers serum insulin and androgen levels and promotes resolution of cyclicity abnormalities inducing ovulation by normalizing pulsatile production of GNRH and gonadotropins (14). In addition, potentially through a direct effect, it inhibits ovarian gluconeogenesis and thus reduces ovarian androgen production (15). Obese women with PCOS exhibit metabolic characteristics similar to those with T2 DM in terms of insulin resistance and hyperinsulinemia. Studies have shown that metformin can not only improve endocrine disorders in patients with PCOS but

also regulate ovarian function and even reduce the weight of overweight women with PCOS (16).

Subjects and Methods

Inclusion Criteria

1. Women with PCOS (n =30), aged 21–36 years, whose chief complaints were menstrual disturbances and infertility and/or clinical signs of hyperandrogenism (e.g. hirsutism and acne)

2. The diagnosis of PCOS was based on at least two of the three following abnormalities

- ✓ Disturbed ovulatory function with chronic oligomenorrhea (cycle length 35 days; less than nine cycles per year)
- ✓ Amenorrhea (cycle length 12 weeks)
- ✓ Typical appearance of polycystic ovaries by ultrasound

3. Patients could have clinical and/or biochemical signs of hyperandrogenism

- ✓ Serum total testosterone concentration 60 ng/dl or greater (2.1 nmol/litre)
- ✓ Serum Androstenedione concentration greater than 2.9 ng/ml (10.1 nmol/litre).

Exclusion Criteria

The presence of the following disorders was excluded

- ✓ Impaired glucose tolerance test (fasting glucose 5.6 mmol/litre and/or 2-h glucose 7.8 mmol/litre)
- ✓ Patient with any form of diabetes mellitus, hyperprolactinemia, thyroid disorders, late onset congenital adrenal hyperplasia.
- ✓ Patient with absence of heart, liver, or kidney diseases (predisposing lactic acidosis) and unsuspected pregnancy in all participants before inclusion in the study.

Study Design

Treatments

The patients were randomly assigned to one of two groups: group 1 (n = 15) received metformin and group 2 (n = 15) received placebo. The metformin dose is 3 x500 mg per day, but only 500 mg is given twice daily for the first week of treatment to reduce the incidence and severity of gastrointestinal side effects. Randomization was performed prospectively andplacebo-controlled for the stratification of insulin resistance. The patientswere treatedwith metformin or placebo according to computer-generated codes andwere randomly dividedinto six groups.

Assessment program

All patients underwent clinical, metabolic, and hormonal evaluations at baseline and throughout the 12-week treatment period after randomization. Clinical evaluation includes menstrual cycle frequency, height, basal body temperature, weight, BMI and hirsutism. The following study was conducted on days 2-5: After a 12-hour fast overnight, a non-heparinized venous blood sample was collected between 8 and 9 hours to measure prolactin, LH, FSH, estradiol, progesterone, and TSH , Total T3, free T4, cortisol, fasting blood glucose and insulin, total cholesterol (TC), triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol.

After obtaining a baseline blood sample, immediately perform a 2-hour oral glucose tolerance test (OGTT) with an oral glucose load of 75 g, and obtain non-heparinized blood samples at 30, 60, 90, and 120 minutes to measure serum glucose and insulin concentrations.

Results and Discussion

In women with insulin resistance, insulin sensitivity improved after 4 weeks of treatment. Based on this finding, the level of glucose to insulin ratio increased. Although the improvement in insulin

sensitivity in this group is moderate, the impact of main outcome criterion, menstrual disorders, was only successfully improved in the metformin group, but not in the placebo group.

metformin on the menstrual cycle is fascinating. The

Parameter	Placebo (n=15)		Metformin (n=15)	
	Baseline	12 weeks	Baseline	12 weeks
Age, Years		30.7(27.8-33.4)		28(25.9-31.7)
Weight, Kg	86.7(77.3-92.4)	86.4(78.1-92.9)	82.3(73.1-87.3)	79.3(71-88.2)
BMI, kg/m	32.4(27.9-37.5)	32.4(26.7-37.1)	31.1(22.9-34.2)	28.9(23.34.1)
Ovarian Volume (ml)	10.3(8.8-12.2)	9.8(8.5-12.0)	10.1(8.5-12.3)	9.2(7.9-11.8)
PAO (%)	100	95	100	92

Table 1: Clinical Characteristics of Patients

In this study, 80% of insulin resistant women treated with metformin (mainly with severe oligomenorrhea at baseline) reported an improvement in their menstrual cycle, compared to only 18% in the placebo group. With a significant increase in estradiol concentration, 67% of women had at least one ovulation during the 12-week treatment period receiving metformin, compared with only 45% in the placebo group, as shown by the biphasic body temperature curve.

Parameter	Placebo		Metformin	
	Baseline	12 weeks	Baseline	12 weeks
Fasting glucose(mg/dl)	83.0 (78–90)	83.0 (78–90)	86.0 (74–101)	84.0 (77–88)
Fasting insulin (µU/ml)	22.0 (16–24)	22.0 (18–30)	22.2 (15-30)	20.0 (14–28)
βCell function	84.5 (71.0–114.7)	84.2 (67.9-111.4)	86.4(64.9-99.5)	72.1(58.115.5)

Table 2: Metabolic Parameters

In addition, during the entire study period, only patients treated with metformin had three ovulation cycles, indicating a significant improvement in ovulation function. The periodicity and reproductive abnormalities improved significantly after treatment.

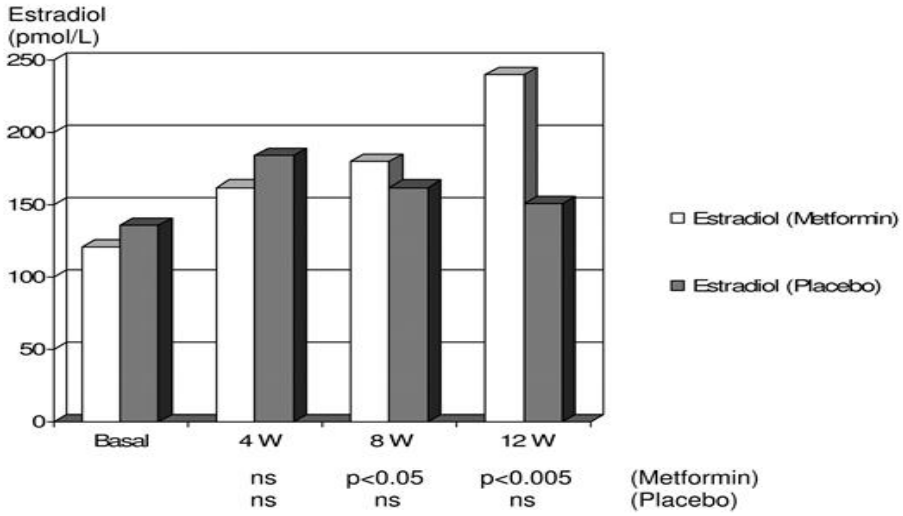

Figure 1: Estradiol development during study treatment in both groups.

Conclusion

This is the prospective randomized placebo-controlled trial of sufficient patient number to address the efficacy of metformin in the treatment of cycle disorders as a primary outcome measure depending on insulin resistance in PCOS.

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