

Response to treatment with metformin in patients with polycystic ovarian syndrome: territorial center of care for the infertile couple, Holguín

Summary

Introduction: Approximately 60% of women with polycystic ovarian syndrome are overweight and obese, 70% have insulin resistance and type 2 diabetes mellitus. The global prevalence of gestational diabetes mellitus is estimated at 14%.

Objective: To evaluate the response to metformin treatment in patients with polycystic ovarian syndrome.

Method: A retrospective case series study was conducted, which involved 96 patients diagnosed with polycystic ovarian syndrome treated at the Territorial Center for Infertile Couple Care, selected within a non-probabilistic sample, to which comprehensive evaluation was performed. Initial that included physical examination and complementary, then it was indicated as part of the medical treatment metformin (500mg tablet) in increasing doses of 500 to 1000mg, according to patient tolerances for a period of six months. After this period of time, a humoral clinical evaluation was carried out which allowed determining the group of patients suitable for ovulation stimulation, which coincided with the total sample.

Results: Of 96 patients who formed the sample and received treatment with metformin, more than 50% were between 25 and 34 years old. 78.7% showed a decrease in hyperandrogenism, (66.18%) patients achieved pregnancy and only 48, 89% showed manifestations of gestational diabetes.

Conclusions: Metformin is a useful drug for the treatment of polycystic ovarian syndrome as a cause of female infertility. Its regular use helps to reduce the incidence of gestational diabetes and the complications derived from this disease.

Keywords: polycystic ovary syndrome, gestational diabetes, metformin

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Annis Almenares Garcés,¹ Leandro León Román,² Yisel González Ríos,³ Maurio González Hernández,⁴ Annarelis Pérez Pupo,⁵ Aylene Pérez Almenares⁶

¹Second degree specialist in Comprehensive General Medicine, First Degree in Endocrinology, Assistant teacher, Vladimir Ilich Lenin University General Hospital, Cuba

²Second Degree Specialist in Allergology, Máximo Gómez Báez Polyclinic, Cuba

³First degree specialist in Comprehensive General Medicine and Endocrinology, Assistant teacher, Amalia Simoni Argilagos University General Hospital, Cuba

⁴First degree specialist in Comprehensive General Medicine and Endocrinology, Instructor teacher, Holguín Military Hospital, Cuba

⁵Degree in Health Information Management, Assistant teacher, Vladimir Ilich Lenin University General Hospital, Cuba

⁶General practitioner, Manuel Díaz Legra Polyclinic, Cuba

Correspondence: Annis Almenares Garcés, Second degree specialist in Comprehensive General Medicine, First Degree in Endocrinology, Assistant teacher, Vladimir Ilich Lenin University General Hospital, Holguín, Cuba, Tel 53 55999477, Email annisa@infomed.sld.cu

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Introduction

Polycystic ovary syndrome (PCOS) is a chronic alteration of ovarian function with hyperandrogenism that affects approximately 5-10% of women of childbearing age and is characterized by symptoms such as menstrual disorders (oligomenorrhea), infertility, hirsutism and some cases acne.¹ In 1844, Cheréau described the existence of sclerocystic changes in the human ovary. The first correlation between androgen levels and insulin resistance was published in 1921 by Acheron and Thiers, calling it "bearded woman's diabetes." In 1928 Irving Stein drew attention to a group of patients with hirsutism, sterility, obesity and oligomenorrhea. In 1935 it is called "Stein-Levental syndrome", being determined as ovarian dysfunction. The existence of elevated levels of LH was reported in 1958, setting criteria for the diagnosis of polycystic ovary syndrome. In 1971, the use of radioimmunoassays stimulates the biochemical diagnosis. In 1976, the concept of polycystic ovary with normal levels of LH is accepted; the same year, Kahn reports six patients with insulin resistance, acanthosis nigricans and hyperandrogenism. Swanson, in 1981, describes for the first time the ultrasound findings of the ovarian polycystic; until 1985, Adams defines the sonographic diagnostic criteria, being accepted. Only 50% of women with clinical and biochemical evidence of

PCOS, show abnormalities by ultrasound.^{2,3} According to reports in Greece and Spain there is a prevalence of 4-8% of women who have polycystic ovary. In the United States more than 250,000 women use the ultrasound evaluation, for the diagnosis of the disease, of these between 4% and 7% have ovarian cysts larger than 30 mm in diameter.⁴

PCOS has various consequences on women's health; one of the most important are reproductive problems; the most frequent cause of infertility an ovulatory being considered, 90 to 95% of women who cannot conceive have this history.^{5,6} Studies in young women with PCOS, who were administered 850 mg of metformin for 6 months with contraceptives and meals, showed ovulatory cycles, decreased serum insulin levels, increased sex hormone-linked globulin (SHBG) and decrease in the free androgen index that favored continuing pregnancy and reducing the incidence of abortion (ALI).⁷ It is known that in developed countries, combined therapy (combined oral contraceptives plus metformin) is the one that offers the best results for the treatment of polycystic ovarian syndrome, such treatment is used for six months on average.⁸ In the Territorial Center of Attention to the Infertile Couple, in Holguín this pathology has become a problem, due to its high incidence in patients attended in consultations, so it

motivated the conduct of this research and it is proposed as objective to evaluate the response to treatment with metformin in these patients.

Material and methods

A case series study was conducted in patients treated at the Territorial Center for Infertile Couple Care with a diagnosis of PCOS, in the period from January-December 2017. The universe was composed of 134 females seen in the endocrinology clinic of said institution, a simple random sampling was carried out and the sample consisted of 96 patients. Patients with a history of: diabetes mellitus, unilateral oophorectomy, peripheral venous insufficiency, heart disease, adverse drug reactions, as well as those who did not agree to participate in the study or did not adequately comply with medical indications were excluded from the study. The variables were studied: age, outcome of treatment at six months, diagnosis of pregnancy after treatment, diagnosis of gestational diabetes (DG) after treatment.

Treatment

The patients studied were evaluated comprehensively: interrogation, physical examination, determination of body mass index (BMI) and complementary to assess biochemical, hormonal and ultrasonographic parameters. Each clinical or complementary data was recorded in the individual clinical history of each of them. Then the administration of Metformin 500 mg tablet was started, at doses of 500 mg per day for two weeks. After this time the dose was increased to 500 mg associated with breakfast and food, to complete six months. The treatment was accompanied during this period of time with Estracip contraceptive tablets, 1 tablet from the fifth day of the menstrual cycle. After six months, the contraceptive tablets were suspended, the first follicular follow-up ultrasound, biochemical and hormonal evaluation were performed, which allowed comparison with insulin resistance and hyperandrogenism parameters before and after treatment and defined the criteria for response to treatment.

The following month they were treated with Merapur, 1 bulb 75 U, intramuscularly, on the second, fourth and sixth day of the menstrual cycle. Follicular follow-up was done again on days ten, fourteen and eighteen of the cycle to evaluate follicle size and endometrial response. When obtaining follicles greater than or equal to 18 mm, the administration was oriented at 9:00 pm of chorionic Gonadotropin (HCG), 5000 U, intramuscularly. Once the treatment was completed, they were directed to perform scheduled intercourse or insemination between 24 and 36 hours, depending on the characteristics of each couple. After the first three months of having started the treatment, a reassessment of each patient was carried out verifying BMI, menstrual calendar, adverse drug reactions due to the presence of clinical manifestations or alterations in complementary biochemical tests. In those that were evidenced adverse reaction the administration of the drug was stopped or did not comply regularly with medical indications, they were excluded from the study.

Results

When analyzing the distribution of patients with treatment according to age, a predominance of the age group of 25 to 29 with 28, 13% was verified, despite there being no significant differences between one group and another (Table 1).

When evaluating the results obtained after six months of treatment, significant improvements were observed in 70.83% of the patients, and within these the most representative group was that of 30 to 34 years with 22 patients, (22.92) (Table 2).

At the end of the six months of treatment, the number of women who had conceived pregnancy was determined. It was observed that more than 50% had achieved it, with a total of 45 pregnant women (66, 18%) and the group most represented was 30-34 years with 19 patients (Table 3).

The DG, is a frequent complication of PCOS, however after the scheme and achieve pregnancy by 45 women, this complication only appeared in 22 (48.89%) (Table 4).

Table 1 Distribution of patients with PCOS diagnosis and treatment with Metformin according to age

Age	No	%
20-24	20	20,83
25-29	27	28,13
30-34	25	26,04
35 +	24	25,00
Total	96	100

Table 2 Results obtained after 6 months of treatment

Age	Improved		They did not improve		Total	
	No	%	No	%	No	%
20-24	12	12,50	8	8,33	20	20,83
25-29	20	20,83	7	7,29	27	28,13
30-34	22	22,92	3	3,13	25	26,04
35 +	14	14,58	10	10,42	24	25,00
Total	68	70,83	28	29,17	96	100

Table 3 Distribution of patients who managed to get pregnant after treatment

Age	No	%
20-24	2	2,94
25-29	17	25
30-34	19	27,94
35 +	7	10,29
Total	45	66,18

Table 4 Distribution of patients that triggered DG

Age	No	%
20-24	0	0,00
25-29	6	13,33
30-34	11	24,44
35 +	5	11,11
Total	22	48,89

Discussion

PCOS is one of the most frequent endocrine pathologies in women of childbearing age. This syndrome is characterized by

oligoamenorrhea, hyperandrogenism and classical ultrasound imaging of multiple ovarian cysts. To the above is added insulin resistance in approximately two thirds of patients. In addition, PCOS patients have a higher incidence of obstetric pathology, such as abortion, infertility, premature delivery, preeclampsia and gestational diabetes. 8 Peña Cordero reported that the average age of his study was 36 years, and the most representative group were <40 years of age.⁹ Ledesma and collaborators in their research found that the most affected age group were adolescents between 16 and 19 years of age, who occupy 31% of the population studied.¹⁰ Polished and collaborators also reported that this pathology affects 4% -8% of women of reproductive age.¹¹ In a review of 1,042 patients, the prevalence was 23%, and practically half of the women between 15 and 25 years had ovaries with polycystic morphology.¹²

Regarding the results obtained after treatment Nestler and collaborators in an experimental study reported that 35 patients received 1 tablet of 500 mg of metformin and 26 in the control group. From the study group ovulation was documented by determination of serum progesterone >8ng/ml in 12 (34%), versus 1 in the control group (4%). 21 patients in the metformin group and 25 in the control group were added clomiphene because they did not spontaneously ovulate in the first phase of the study. In the study group there was a decrease in the area under the insulin curve, after oral glucose administration, without change in the control group. There was ovulation in 19 patients in the study group (90%) versus 2 (8%) in the control group. The authors' conclusion is that their findings show that the decrease in insulin secretion facilitates spontaneous ovulation and the induction of clomiphene ovulation.¹³

Heard and collaborators analyze a series of 48 anovulatory patients over a period of 15 months. All were started with metformin 1000 mg per day, for 6 weeks. If ovulation did not occur, the dose was increased to 1500 mg per day, for 6 weeks. If the lack of ovulatory response persists, clomiphene citrate was added. Nineteen patients of the total studied resume spontaneous ovulations with metformin alone (40%), which is documented by baseline temperature and luteinizing hormone monitoring, while 31% required association with clomiphene citrate.¹⁴

Costello and Eden, in their systematic review, point out that 9 studies evaluate the effectiveness of metformin alone in restoring ovulation in patients not selected with PCOS. Seven of the investigations involve a small number of patients (<50) with a duration of 1 to 26 months of treatment. The combined data from 5 observational and uncontrolled studies show that 61% of women with PCOS ovulate with metformin alone. Four randomized studies compare metformin with placebo. 56% of patients ovulate compared to 35% with placebo.¹⁵

Bordewijk and colleagues point out that metformin is 50% better than placebo when inducing ovulation in infertile women with PCOS, however, no benefit for pregnancy achievement has been confirmed. Metformin associated with clomiphene citrate is superior to clomiphene alone, in terms of ovulation and fertility achievement.¹⁶ The use of metformin in infertility does not require intensive monitoring and available evidence, indicates an almost non-existent risk of ovarian hyperstimulation and multiple gestation, so this drug could be a first-line treatment for ovulation induction in women with PCOS, although the results in relation to the prevention of DG are still not very encouraging. In the case of our investigation, more than half of the patients managed to get pregnant after treatment similar results to those reported by Rosa and collaborators reported that after a minimum follow-up of 3 months after the end of the treatment 11 patients became pregnant, with metformin being suspended in 9 of

them once the pregnancy was diagnosed, in another one at 17 weeks and in the remaining one at 35 weeks of gestation.¹⁷

In accordance with the improvement in ovulation rates, an increase in the pregnancy rate has been observed in several clinical trials with the use of metformin. This drug has a category B of the FDA and although the conservative practice in this case consists in withdrawing this treatment once the pregnancy is established, in two retrospective analyzes,¹⁸ it was observed that the continuation of the treatment during the first trimester of the pregnancy reduced the rates of pregnancy loss, a fact that could not be supported in a more recent prospective study. The apparent beneficial effect of metformin is due to an improvement in the development potential of the oocyte or embryo or an improvement in implantation.¹⁹ López states that the effectiveness of metformin treatment during pregnancy to prevent DG. And although it is true we cannot draw conclusions about it either, 2 patients who discontinued metformin presented DG and fetal macrosomia, and the only patient who continued the treatment until week 35, did not present DG or fetal macrosomia despite having a history of this Pathology in previous pregnancy.²⁰ Other authors also postulate that one of the greatest benefits of continuing treatment during pregnancy is to avoid weight gain in patients who are already obese or morbidly obese if necessary, in the 3 morbidly obese patients who became pregnant and metformin was discontinued, they had macrosomic newborns and 2 presented DG.¹⁶

Conclusions

Metformin is a useful drug for the treatment of polycystic ovarian syndrome as a cause of female infertility. Its regular use helps to reduce the incidence of gestational diabetes and the complications derived from this disease.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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