Association of oral contraceptive and metformin did not improve insulin resistance in women with polycystic ovary syndrome

Margareth Chiharu Iwata[1]*, Livia Porquere[2], Isabel C. Espósito Sorpreso[3], Edmund C. Baracat[4], José Maria Soares Júnior[5]

[1]Specialist in Gynecology and Obstetrics – Graduate student, Department of Gynecological Endocrinology, Gynecology Division, Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil
[2]Graduate student, Human Reproduction, Unifesp, São Paulo, SP, Brazil
[3]Associate professor of Gynecology in the Department of Obstetrics and Gynecology, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo, SP, Brazil
[4]Full professor of Gynecology in the Department of Obstetrics and Gynecology, HC-FMUSP, São Paulo, SP
[5]Associate professor of Gynecology in the Department of Obstetrics and Gynecology, HC-FMUSP, São Paulo, SP, Brazil

Summary

Objective: to compare clinical and laboratory parameters in women with polycystic ovary syndrome (PCOS) using metformin or combined oral contraceptive (COC) after 6 months.

Methods: retrospective study analyzing records of patients with PCOS using the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society criteria. The groups were: I-COC (21 tablets, pause of 7 days; n=16); II-metformin (850mg 12/12h, n=16); III-COC plus metformin (n=9). Body mass index (BMI), acne (% of improvement), modified Ferriman-Gallway index and menstrual cycle index (MCI), luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), androstenedione (A) and homeostasis model assessment: insulin resistance (HOMA-IR) index were assessed.

Results: isolated use of COC compared to metformin was better regarding to acne, Ferriman index, MCI, LH, TT and A levels. On the other hand, metformin was better in the HOMA-IR index (4.44 and 1.67 respectively, p=0.0007). The association COC plus metformin, compared to metformin alone shows the maintenance of improvement of acne, Ferriman index, MCI, and testosterone levels. The HOMA-IR index remained lower in the metformin alone group (4.19 and 1.67, respectively; p=0,046). The comparison between COC plus metformin and COC alone, in turn, shows no difference in the improvement of acne, Ferriman index, MCI, LH, TT and A levels, indicating that the inclusion of metformin did not lead to additional benefits in these parameters. Still, the HOMA-IR index was similar in both groups (4.19 and 4.44 respectively; p=0.75), showing that the use of metformin associated with COC may not improve insulin resistance as much as it does if used alone.

Conclusion: our data suggest that the combination of metformin and contraceptive does not improve insulin resistance as observed with metformin alone.

Keywords: polycystic ovary syndrome, metformin, contraceptives, insulin resistance.

Study conducted at the Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil

Article received: 10/13/2014
Accepted for publication: 10/17/2014

***Correspondence:**
Address: Rua Napoleão de Barros, 608
Vila Clementino
São Paulo, SP – Brazil
Postal code: 04024-002
megiwata@yahoo.com

Financial support: FAPESP – São Paulo State Research Foundation

http://dx.doi.org/10.1590/1806-9282.61.03.215

Conflict of interest: none

Introduction

The polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. It affects 6 to 10% of women, but depending on the diagnostic criteria, up to 15%.[1] Signs and symptoms include anovulation, hyperandrogenism, and ovaries with polycystic appearance, all other causes excluded. The syndrome's pathophysiological mechanism remains unclear, but there is evidence relating it to a decrease in insulin sensitivity with compensatory hyperinsulinemia, an abnormality observed in 30 to 80% of patients with the syndrome, both lean and obese individuals.[2] Obesity in these women is seen as an additional factor, and does not trigger abnormal insulin response.[3-6] Hyperinsulinemia stimulates production of androgens by the ovaries and adrenals, and reduces the production of hepatic globulins, such as sex hormone-binding globulin (SHBG), which increases the androgenic action, culminating in ovarian follicular atresia, anovulatory cycles and amenorrhea, as well as skin effects, including hirsutism and severe worsening of acne.[7]

Women with PCOS are 5 to 10 times more likely to develop *diabetes mellitus*.[8-10] This fact, combined with other diseases commonly found in the syndrome, such as hypertension, dyslipidemia and obesity, increases the risk of metabolic syndrome and cardiovascular events. Moreover, chronic exposure to estrogen not opposed by progesterone due to anovulation increases the risk of endometrial hyperplasia and cancer in these patients.[11,12] Also, these women produce more androgens, and insulin resistance can intensify hyperandrogenism. Therefore, assessing treatments aimed at controlling metabolic and endocrine disorders in these women is very important.

Different diagnostic criteria for PCOS have been described, and the most used are those of the Rotterdam consensus (2003) and the Androgen Excess Society (2006). We used in this study the Androgen Excess and PCOS (AE-PCOS) Society criteria, which imply two main points for the diagnosis of the syndrome: hyperandrogenism (with hirsutism and/or increased androgen levels) and ovarian dysfunction (anovulation and/or ovaries with polycystic appearance). Other causes such as hyperprolactinemia, adrenal enzyme deficiency, thyroid dysfunction, androgen-producing tumors, Cushing's syndrome, and hypo- or hypergonadotropic hypogonadism should be excluded.[13]

Treatment of patients with polycystic ovary syndrome is traditionally based on the use combined of oral contraceptives (COC), which promote endometrial protection, regulation of the menstrual flow and improvement of signs of hyperandrogenism. However, the possibility of worsening glucose tolerance is questioned in this case.[14] Currently, insulin sensitizing agents are also used to treat such patients based on their main pathophysiological substrate, hyperinsulinemia. The most commonly used of these drugs is metformin (dimethylbiguanide), a biguanide that increases the sensitivity of peripheral tissues (muscle and fat) to insulin, increases the translocation of GLUT-1 and GLUT-4 glucose transporters, and reduces the production of glucose in the liver.[15] Metformin causes a reduction in blood pressure, fasting blood glucose and *serum* androgens, with little improvement in hirsutism, particularly in non-obese patients with PCOS.[16] In a recent review, hormonal contraceptives were considered the treatment of choice in PCOS and metformin was reserved for women with impaired glucose tolerance or associated type 2 diabetes mellitus who did not respond to changes in lifestyle. However, the impact of contraceptives on carbohydrate metabolism, as well as the impact of metformin on hirsutism, the regulation of the menstrual cycle and the improvement of fertility, is not well defined.[17]

Evaluating the response of women with PCOS to these medications is very important, aiming not only at improving menstrual cycles and hirsutism but also at reducing cardiovascular risk by improving risk factors such as insulin resistance, dyslipidemia and obesity.

Thus, the aim of this study was to compare patients with PCOS treated with metformin and oral contraceptive, alone or combined, after 6 months.

Methods

Retrospective study conducted based on the analysis of medical records of patients diagnosed with PCOS, according to the criteria of the AE-PCOS Society (2006). All patients received general nutritional guidance and were encouraged to practice physical activity before and during treatment. Patients were divided in the following groups:

- Group 1: combined oral contraceptive (21 tablets of ethinyl estradiol 35 μg, cyproterone 2mg, plus seven day break; n=16);
- Group 2: metformin (850mg 12/12h; n=16);
- Group 3: contraceptive combined with metformin (n=9).

Clinical parameters

Body mass index (BMI – calculated as weight in kilograms divided by height in meters squared), presence of acne (% improvement), modified Ferriman-Gallway index and menstrual cycle index (MCI).

Laboratory parameters

Levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), androstenedione (A), blood glucose and fasting insulin (homeostasis model assessment: insulin resistance – HOMA-IR), at baseline and after 6 months of medication.

Statistical analysis

Unpaired Student's t-test and Mann–Whitney test were used, as well as Holm-Sidak method to determine significance, with alpha = 5%.

Results

This study included the records of 41 patients: 16 in group I, 16 in group II and 9 in group III (Tables 1 and 2).

The authors found that, after six months, the isolated use of COC compared to metformin was statistically significantly better with regard to acne (89 and 17% improvement; p=0.0011), Ferriman index (8.7 and 11.9; p=0.01), MCI (0.94 and 0.47; p=0.0004), LH (4.31 and 9.22; p=0.002),

TABLE 1 Clinical parameters of the three groups at baseline (0) and after use of medications (6m).

	Group 1		Group 2		Group 3	
	COC (0)	COC (6m)	Met (0)	Met (6m)	COC Met (0)	COC Met (6m)
BMI	28.8 ± 4.5	26.6± 3.7	31.1± 3.62	28.4± 5.71	29.15± 6.34	29.32± 6.56
Acne (%)	30	3.3	20	16.6	55.5	22.2
Ferriman	11.9± 4.3	8.7± 3.6	12.2± 5.7	11.9± 2.9	8± 2.91	4.78± 4.68
MCI	0.26± 0.18	0.94± 0.15	0.21± 0.21	0.47± 0.45	0.21± 0.19	0.98± 0.003

COC: combined oral contraceptive; Met: metformin; LH: luteinizing hormone; FSH: follicle stimulating hormone; HOMA-IR: homeostasic model assessment: insulin resistance.

TABLE 2 Laboratory parameters of the three groups at baseline (0) and after use of medications (6m).

	Group 1		Group 2		Group 3	
	COC (0)	COC (6m)	Met (0)	Met (6m)	COC Met (0)	COC Met (6m)
LH	13.47± 2.57	4.31± 2.96	12.87± 3.46	9.22± 5.01	7.91± 1.09	6.31± 2.18
FSH	5.42± 2.41	6.95± 1.93	4.98± 2.27	8.58± 2.98	4.71± 5.07	3.59± 5.64
TT	88.33± 17.55	29.44± 11.81	79.56± 11.34	61.34± 17.33	43.91± 15.01	31.25± 23.29
A	4.77± 1.45	2.45± 0.43	5.23± 2.78	3.98± 2.45	2.6± 0.78	2.69± 1.58
HOMA-IR	5.88± 0.78	4.44± 0.89	4.93± 0.87	1.67± 2.83	4.05± 3.36	4.19± 2.94

COC: combined oral contraceptive; Met: metformin; LH: luteinizing hormone; FSH: follicle stimulating hormone; HOMA-IR: homeostasic model assessment: insulin resistance.

TT (29.44 and 61.34) and A (2.45 and 3.98; p=0.019) levels. By contrast, metformin did better in relation to the HOMA-IR index (4.44 and 1.67; p=0.0007).

The COC combined with metformin group showed continued improvement of acne compared with metformin alone (60 and 17% improvement; p=0.0015), Ferriman index (4.78 and 11.9), MCI (0.98 and 0.47; p=0.002) and levels of TT (31.25 and 61.34; p=0,001). The HOMA-IR index remained statistically significantly lower in the metformin alone group (4.19 and 1.67; p=0.046).

Comparison between COC combined with metformin and COC alone, in turn, does not show any statistically significantly difference in terms of improvement of acne, Ferriman index, MCI, levels of LH, TT and A, leading to the conclusion that probably the addition of metformin does not produce additional benefit in these parameters. Still, the HOMA-IR index was similar in both groups (4.19 and 4.44; p=0.75), showing that the use of metformin associated with COC may not improve insulin resistance as much as it does if used alone.

Discussion

The effect of hormonal contraceptives on glucose metabolism has been widely studied, but with mixed results. It is known that both the estrogen dose and the type of progestogen present in the contraceptive composition, especially norderivatives can influence this response.[18] In a recent meta-analysis, it was concluded that hormonal contraceptives can alter carbohydrate metabolism in women without *diabetes mellitus*, but not significantly.[19] In patients with PCOS, contraceptives are considered first-line treatment because they regulate the menstrual cycle, improve hyperandrogenism and decrease ovarian volume, which are the main signs of the syndrome,[17] despite doubts about the drug's effects on glucose metabolism in case of long-term use, and the important role of hyperinsulinemia in the syndrome.

Many studies investigate the use of metformin in PCOS, as it appears to contribute to the improvement of common metabolic and cardiovascular risk parameters in these women, such as decreased waist circumference (decreased abdominal fat), and lowering of insulin and triglyceride levels.[20-22]

These medications appear to be beneficial in the treatment of various aspects of the syndrome, and therefore, combined treatment could be better than using either drug alone. However, there are few studies that corroborate this claim.

In our study, contraceptive use has led to regularization the menstrual cycle and improvement of hyperandrogenism (acne, hirsutism and TT levels), which has been observed in previous studies.[20,21,23,24] We have also seen that the use of metformin alone improves insulin sensitivity with reduction of the HOMA-IR index, which is also in accordance with other studies.[24-26] However, non-improved insulin sensitivity when metformin is used in combination with an oral contraceptive differs from some literature data. Elter et al.[21] showed in a randomized pro-

spective study that the combination of metformin and a contraceptive (35mcg ethinyl estradiol 2mg cyproterone acetate) in non-obese women with PCOS is better than the contraceptive alone compared to A, waist-hip ratio, blood insulin and total cholesterol levels at the end of 4 months. Ibañez et al.[27] noted that combining flutamide-metformin and an oral contraceptive containing drospirenone reduces the levels of adipocytokines, triglycerides and abdominal fat, suggesting that adding metformin to the therapy is beneficial compared to using a contraceptive alone. Cibula et al.,[28] in turn, comparing the use of oral contraceptives combined or not with metformin, failed to demonstrate a significant additional benefit regarding lipids, insulin sensitivity, SHBG and testosterone when the medications were combined.

The mechanism through which metformin reduces insulin levels in PCOS seems to be related to an increase in insulin uptake by the liver.[20] It is possible that the contraceptive may negatively influence this mechanism. On the other hand, being a retrospective study in which factors such as diet, physical activity and proper use of medications could not be controlled, the results observed in our study can be questioned.

To date, there are insufficient data to demonstrate that the use of metformin combined with contraceptives in patients with PCOS is beneficial compared to the use of either of these drugs alone. Further studies are, therefore, required to assist the choice of the best approach for treating this syndrome.

Conclusion

Our data suggest that the combination of metformin and contraceptives does not improve insulin resistance as much as treatment with metformin alone.

Resumo

A associação de contraceptivo hormonal oral e metformina não melhora a resistência insulínica em mulheres com síndrome dos ovários policísticos.

Objetivo: comparar parâmetros clínicos e laboratoriais de mulheres com síndrome dos ovários policísticos (SOP) em uso de metformina ou contraceptivo hormonal oral (CHO) após 6 meses.

Casuística e métodos: estudo retrospectivo com análise do prontuário de pacientes com SOP (pelos critérios da Androgen Excess and Polycystic Ovary Syndrome Society [AE-PCOS Society]), divididos em 3 grupos: (I) CHO (21 comprimidos e pausa de 7 dias; n=16), (II) metformina (850 mg a cada 12 horas; n=16) e (III) CHO associado com metformina (n=9). Foram avaliados: índice de massa corpórea (IMC), acne (% de melhora), índice de Ferriman-Gallway modificado, índice de ciclos menstruais (ICM), LH, FSH, testosterona total (TT), androstenediona (A) e resistência a insulina (HOMA-IR, do inglês *homeostatic model assessment: insulin resistance*).

Resultados: o uso isolado de CHO comparado ao de metformina foi melhor em relação a acne, índice de Ferriman, ICM, níveis de LH, TT e A. Por outro lado, a metformina foi melhor para HOMA-IR (4,44 e 1,67; p=0,0007). O uso do CHO e metformina, em comparação com o de metformina isolada, manteve a melhora da acne, do índice de Ferriman, do ICM e dos níveis da TT. O índice de HOMA-IR manteve-se menor no grupo metformina isolada (4,19 e 1,67; p=0,046). Por sua vez, a melhora na acne, Ferriman, ICM, LH, TT e A são semelhantes nos grupos CHO associado com metformina e CHO isolado, indicando que a adição de metformina não trouxe benefícios nesses parâmetros. Ainda, o HOMA-IR foi semelhante nos dois grupos (4,19 e 4,44; p=0,75), mostrando que o uso de metformina em associação com o contraceptivo pode não melhorar a resistência insulínica como ocorre no uso isolado.

Conclusão: os dados sugerem que a associação de metformina e contraceptivo não melhora a resistência insulínica como ocorre no uso da metformina isolada.

Palavras-chave: síndrome do ovário policístico, metformina, anticoncepcionais, resistência à insulina.

References

1. The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). Hum Reprod. 2012; 27(1):14-24.
2. Conway GS, Jacobs HS, Holly JMP, Wass JA. Effects of luteinizing hormone, insulin, insulin-like growth factor-1 and insulin growth factor small binding protein-1 in the polycystic ovary syndrome. Clin Endocrinol (Oxf). 1990; 33(5): 593-603.
3. Nestler JE. Metformin for the treatment of the polycystic ovarian syndrome. N Engl J Med. 2008; 358(1):47-54.
4. Tao MF, Zhu JP, Zhou J, Lu VW, Qin W, Teng YC, et al. [Insulin release and daily glucose change in polycystic ovary syndrome women with normal glucose tolerance]. Zhonghua Yi Xue Za Zhi. 2009; 89(10):659-63.
5. Svendsen PF, Madsbad S, Nilas L. The insulin-resistant phenotype of polycystic ovary syndrome. Fertil Steril. 2010; 94(3):1052-8.
6. Kulshreshtha B, Ganie MA, Praveen EP, Grupta N, Lal Khurana M, Seith A, et al. Insulin response to oral glucose in healthy, lean young women and patients with polycystic ovary syndrome. Gynecol Endocrinol. 2008; 24(11):637-43.
7. Utiger R. Insulin and polycystic ovary syndrome. N Engl J Med. 1996; 335(9):657-8.
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(1):165-9.
9. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care. 1999; 22(1):141-6.

10. Palmert MR, Gordon CM, Kartashov AL, Legro RS, Emans SJ, Dunaif A. Screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome. J Clin Endocrinol Metab. 2002; 87(3):1017-23.
11. Ovalle F, Azziz R. Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus. Fertil Steril. 2002; 77(6):1095-105.
12. Hardiman P, Pillay OS, Atiomo W. Polycystic ovary syndrome and endometrial carcinoma. Lancet. 2003; 361(9371):1810-2.
13. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al.; Task Force on the Phenotype of the Polycystic Ovary Syndrome of the Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009; 91(2):456–88.
14. Diamanti-Kandakaris E, Baillargeon JP, Iuorno MJ, Jakubowicz DJ, Nestler JE. A modern medical quandary: polycystic ovary syndrome, insulin resistance, and oral contraceptive pills. J Clin Endocrinol Metab. 2003; 88(5):1927-32.
15. Bailey CJ, Path MRC, Turner RC. Metformin. N Engl J Med. 1996; 334(9):574-9.
16. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome (Cochrane Review). Cochrane Database Syst Rev. 2003; (3):CD003053.
17. Legro R, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013; 98(12):4565-92.
18. Wynn V, Godsland I, Niththyananthan R, Adams PW, Melrose J, Oakley NW, et al. Comparison of effects of different combined oral contraceptive formulations on carbohydrate and lipid metabolism. Lancet. 1979; 1(8125):1045-9.
19. Lopez LM, Grimes DA, Schulz KF. Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. Cochrane Database Syst Rev. 2009; 4:CD006133.
20. Morin-Papunen L, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen H, Tapanainen JS. Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of non-obese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab. 2003; 88(1):148-56.
21. Elter K, Imir G, Durmusoglu F. Clinical, endocrine and metabolic effects of metformin added to ethinyl estradiol-cyproterone acetate in non-obese women with polycystic ovary syndrome: a randomized controlled study. Hum Reprod. 2002; 17(7):1729-32.
22. Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC. Effects of metformin and ethinyl estradiol-cyproterone acetate on lipid levels in obese and non-obese women with polycystic ovary syndrome. Eur J Endocrinol. 2005; 152(2):269-75.
23. Lord JM, Flight IHK, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome (Cochrane Review). Cochrane Database Syst Rev. 2003; (3):CD003053.
24. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen JS. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab. 2000; 85(9):3161-8.
25. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ. 2003; 327(7421):951-3.
26. Arslanian SA, Lewy V, Kapriel D, Saad R. Metformin therapy in obese adolescents with polycytic ovary syndrome and impaired glucose tolerance: amelioration of exaggerates adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab. 2002; 87(4):1555-9.
27. Ibañez L, de Zegher F. Ethinyl estradiol-drospirenone, flutamide-metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity. J Clin Endocrinol Metab. 2004; 89(4):1592-97.
28. Cibula D, Fanta M, Vrbikova J, Stanicka S, Dvorakova K, Hill M, et al. The effect of combination therapy with metformin and combined oral contraceptives (COC) versus COC alone on insulin sensitivity, hyperandrogenemia, SHBG and lipids in PCOS patients. Hum Reprod. 2005; 20(1):180-4.