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Review Article

Metformin effects on Polycystic Ovarian Syndrome

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Abstract: Metformin treatment for polycystic ovarian syndrome (PCOS) is gaining popularity and acceptance, although clinical practice still outpaces research in this area. Although non-randomized trials with metformin have shown a broad variety of improvements in metabolic, reproductive, and clinical variables, a detailed examination of the findings from the studies with appropriate controls reveals that the benefits are limited. With a focus on the few randomized controlled trials, our goal in this descriptive review is to increase physicians' awareness of the published clinical data available, not to create practise recommendations. We also draw attention to additional concerns that need to be addressed before definitive therapeutic metformin may be prescribed for PCOS in order to treat different conditions. It also emphasises the possibility for larger gains from improvements in lifestyle alone. We anticipate that the evaluation will encourage more prudent use of metformin in PCOS patients.

Keywords: Metformin, PCOS, acne, ovulation.

INTRODUCTION

Women who are of reproductive age are affected by polycystic ovarian syndrome (PCOS) [1]. Infertility, high androgens, and metabolic issues are all caused by PCOS [2]. Unknown factors may be contributing to the 6-to-15% morbidity rate among women who are fertile. At least 50% of people with PCOS are fat or overweight [3]. Endocrine and metabolic issues are severe in PCOS-obese women [4]. Obesity increases insulin production while decreasing insulin metabolism in the liver, skeletal muscle, and fat. Being overweight may potentially cause insulin resistance and lipodystrophy by lowering adipocyte production of lipid droplet proteins [5, 6]. Patients with syndrome are thought to typically have insulin resistance, increased blood insulin, and altered lipoprotein metabolism [7, 8]. Biguanide insulin sensitizers include metformin [10]. Although it may enhance insulin action, it has no effect on insulin secretion [11]. Type 2 diabetes treatment is a first-line medication [12]. It works by lowering blood lipid levels, lowering hepatic glucose synthesis, inducing insulin-mediated glucose absorption in the liver and skeletal muscles, and lowering the use of gluconeogenic substrates [13]. When it comes to insulin resistance and hyperinsulinemia, obese women with PCOS have metabolic traits that are comparable to those of those with T2 DM [14]. Metformin has been used to treat polycystic ovarian syndrome since 1994 as an insulin sensitizer [15]. Metformin has been demonstrated in studies to not only alleviate endocrine abnormalities in PCOS patients, but also to control ovarian function and even help obese PCOS patients lose weight [16]. According to Heidari *et al*., [17], metformin has only modest benefits on improving glucose metabolism and dyslipidemia, but it can enhance endothelial function with PCOS.

Clinical Therapy:

Metformin was first used clinically in 1996 to treat individuals with polycystic ovary syndrome by lowering insulin levels, ovarian 17,20- lyase activity, and androgen production. Results from most follow-up trials revealed that metformin was effective in reducing fasting insulin and testosterone in PCOS patients, albeit this was not the case for all. Met formin's impact on hirsutism, acne, and androgenetic alopecia has only been the subject of a small number of research. A randomised, placebo-controlled study conducted in 1998 indicated that pretreatment with metformin boosted ovulation following clomiphene medication [18]. The effectiveness of metformin was compared to that of a placebo, metformin alone, metformin with clomiphene, and metformin alone plus clomiphene. Lord *et al*., [19] did a meta-analysis in 2003 that included the most thorough publications. After the

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meta-analysis, three randomised clinical studies [20, 21] were published. Inconclusive were the results of clinical research comparing metformin, metformin + clomiphene, and clomiphene for inducing ovulation in PCOS patients. In terms of short-term ovulation induction and birth outcomes, clomiphene was better than metformin. Metformin lowers the risk of type 2 diabetes in adults with reduced glucose tolerance, according to randomised clinical research 26% and 31% reduction [22]. Metformin's capacity to lower blood glucose levels and hence prevent diabetes remains debatable, despite some evidence to the contrary. Compared to what have been expected if covering were the predominant result, fewer individuals in the DPP developed diabetes when metformin therapy was stopped. Due to the absence of a randomised clinical trial, there are insufficient data about the polycystic ovarian syndrome patients. 50 patients with PSOS were treated metformin for an average of 43 months, and 11 (22.0%) of them had low glucose tolerance to begin with. Only 1.4% of women with polycystic ovarian syndrome who did not use metformin saw an annual shift from normal to impaired glucose tolerance [24, 25].

Who will benefit from metformin and ovulation is predicted

This important subject is understudied. Metformin increases ovulation in insulin-resistant infertile women (provided the dosing schedule is satisfactory). Uncertainty remains. Moghetti *et al.*, [23] found that BMI, insulin levels and less severe monthly anomalies predicted clinical efficacy. Fleming and colleagues [26] observed that high SHBG and a low free androgen index indicated normal ovarian function. As a result, we draw the conclusion that there is presently insufficient evidence to restrict metformin therapy research to a particular unit of women through PCOS. The relationship between dose and body weight is one issue that needs to be resolved at this time. There is no reason to think that therapy with metformin won't help even if a woman with PCOS is underweight. Only those receiving active therapy saw a reduction in their waist-to-hip ratio.

Metformin may help women regulate their cycles if they do not want to get pregnant.

However, not all PCOS patients will have instant success with metformin alone in restoring normal menstrual periods. Even at the recommended dosage, fewer than half of women will have normal ovarian function while using metformin. Therefore, women who do not want to get pregnant may find that oral contraceptives are a more effective method of period management. However, the therapeutic importance of these effects from oral contraceptives on PCOS women is still unclear [27]. There are norms that must be followed while addressing this issue. Diseases of the liver and metformin

Metformin (1.5–7 g/day) was used to treat hirsutism in six studies. Only in one case [9] was hirsutism the predominant outcome. While three research [26] found no difference in Ferriman-Gallwey scores following metformin treatment, the other three studies found a small but statistically significant reduction. Most studies lasted only 3-6 months and included only a few women. Additionally, there was no division by anatomical location. The average hair growth cycle is around six months long, thus seeing results from treatment might take a while. To far, studies have shown only minor hirsutism, as measured by a mean Ferriman-Gallwey score prior to treatment (between 8 and 17).

The Effects of Metformin on Acne

To date, there is just one research that has looked at acne as an outcome specifically. Kolodziejczyk *et al.*, [28] found that the acne score dropped from 145 to 114. (p 0.001). It is uncertain whether the decrease has any therapeutic effect, given the investigation was not placebo controlled.

Metformin in young people

Recent findings from a short (n=11) non-randomized experiment suggest that metformin (150-255 g/day) may help teenage women lose weight and achieve regular menstrual cycles by lowering testosterone levels. However, additional strong, randomised studies are required to confirm these discoveries in the adult women with PCOS.

Use of metformin over time and its capacity to protect women from developing polycystic ovary syndrome

Metformin and other ISDs have garnered a lot of attention because of the common opinion polycystic ovarian syndrome is greatly influenced by insulin resistance (PCOS) and that treatment regimens should concentrate on lowering IR and hyperinsulinemia. Furthermore, PCOS is garnering significant attention as a disease with long-term repercussions and problems rather than only a reproductive condition, owing to the high morbidity and mortality linked with it. Obesity and IR are not required for the diagnosis of PCOS; nonetheless, they have been related to type 2 diabetes, metabolic syndrome, diseases of the heart, blood vessels, and blood lipids and other conditions that might have long-term effects of the syndrome [29]. Metformin is being studied as a potential preventative strategy, however it is unclear whether it will really lower patients' long-term illness risk. Still, we must find a solution to this issue.

Diseases of the heart, blood vessels, and blood lipids.

PCOS is linked to obesity, insulin resistance, dyslipidemia, and high blood pressure [30]. High androgen levels are linked to an increased risk of heart disease [31]. Polycystic ovarian syndrome individuals with elevated insulin levels consume an amplified risk

of heart disease, self-governing of weight. Obesity and PCOS influence endothelium cells differently, according to Mancini et al. [32] found that PCOS women had different lipid profiles than women of the same age and weight. High triglycerides and low HDL-C are predictive of cardiovascular disease and myocardial infarction. Metformin may help treat dyslipidemia by reducing hyperinsulinemia, according to some data. Changing the liver's fatty acid metabolism may cause this. Metformin benefits PCOS women with dyslipidemia, according to many studies. LDL-C reduced but total cholesterol remained stable [33].

Total cholesterol levels did not vary significantly between those on metformin and those on the COC pill in a separate meta-analysis. Total LDL-C levels are said to rise once metformin is stopped, and then quickly recover to their pre-treatment levels. In addition to helping PCOS patients, an unselected sample of obese and overweight people has had their dyslipidemia improve while using metformin [34]. As a result, it seems that metformin's potential advantages in IR and dyslipidemia may help lower CVD risk. Its significance in a genetically diverse population like that with PCOS is, however, yet unknown. There is some debate regarding how best to treat hypertension in PCOS.

CONCLUSION

Women using metformin had one extra ovulation and period every five months, up from one before treatment. Not all metformin-using women have normal ovulation. Metformin helps PCOS-affected women lose 4% of their body weight, according to data. Metformin dose and its link to body mass, as well as pregnancy problems and outcomes in obese women, are unresolved challenges in ovulation induction and infertility treatment. Insufficient evidence on hirsutism and acne consequences prevents any recommendations. A large multicenter research of metformin in PCOS-affected women would answer many concerns. A fertility and pregnancy study is starting in the US. This investigation won't look at hirsutism, acne, metabolic or cardiovascular risk factors. More PCOS patients want metformin treatment. They obtain unapproved treatment outside of research. Except for ovulation induction, these activities lack proof. Since all trials mentioned thus far were investigator-led, pharmaceutical companies can't use the available data for licencing. Doctors must advise women before taking metformin.

REFERENCE

1. Legro, R. S., Arslanian, S. A., Ehrmann, D. A., Hoeger, K. M., Murad, M. H., Pasquali, R., & Welt, C. K. (2013). Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *98*(12), 4565-4592.
2. Norman, R. J., Dewailly, D., Legro, R. S., & Hickey, T. E. (2007). Polycystic ovary syndrome. *The Lancet*, *370*(9588), 685-697.
3. Mu, L., Zhao, Y., Li, R., Lai, Y., & Qiao, J. (2018). Metabolic characteristics of normal weight central obesity phenotype polycystic ovary syndrome women: a large-scale national epidemiological survey. *Reproductive Biomedicine Online*, *37*(4), 498-504.
4. Arya, S., Hansen, K. R., & Wild, R. A. (2020). Metformin, rosiglitazone, or both for obese women with polycystic ovary syndrome?. *Fertility and Sterility*, *113*(1), 87-88.
5. Shi, B., Feng, D., Sagnelli, M., Jiao, J., Sun, X., Wang, X., & Li, D. (2020). Fructose levels are elevated in women with polycystic ovary syndrome with obesity and hyperinsulinemia. *Human Reproduction*, *35*(1), 187-194.
6. Czech, M. P. (2017). Insulin action and resistance in obesity and type 2 diabetes. *Nature medicine*, *23*(7), 804-814.
7. Karimi, E., Heshmati, J., Shirzad, N., Vesali, S., Hosseinzadeh-Attar, M. J., Moini, A., & Sepidarkish, M. (2020). The effect of synbiotics supplementation on anthropometric indicators and lipid profiles in women with polycystic ovary syndrome: a randomized controlled trial. *Lipids in health and disease*, *19*, 1-9.
8. Heshmati, J., Farsi, F., Yosaee, S., Razavi, M., Rezaeinejad, M., Karimie, E., & Sepidarkish, M. (2019). The effects of probiotics or synbiotics supplementation in women with polycystic ovarian syndrome: a systematic review and meta-analysis of randomized clinical trials. *Probiotics and Antimicrobial Proteins*, *11*, 1236-1247.
9. Glueck, C. J., Wang, P., Fontaine, R., Tracy, T., & Sieve-Smith, L. (2001). Metformin to restore normal menses in oligo-amenorrheic teenage girls with polycystic ovary syndrome (PCOS). *Journal of Adolescent Health*, *29*(3), 160-169.
10. Bennett, W. L., Aschmann, H. E., Puhan, M. A., Robbins, C. W., Bayliss, E. A., Wilson, R., ... & Boyd, C. M. (2019). A benefit–harm analysis of adding basal insulin vs. sulfonylurea to metformin to manage type II diabetes mellitus in people with multiple chronic conditions. *Journal of clinical epidemiology*, *113*, 92-100.
11. Moghetti, P., Castello, R., Negri, C., Tosi, F., Perrone, F., Caputo, M., ... & Muggeo, M. (2000). Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *The Journal of Clinical Endocrinology & Metabolism*, *85*(1), 139-146.
12. Viollet, B., Guigas, B., Garcia, N. S., Leclerc, J., Foretz, M., & Andreelli, F. (2012). Cellular and molecular mechanisms of metformin: an overview. *Clinical science*, *122*(6), 253-270.
13. Goodarzi, M. O., & Bryer-Ash, M. (2005). Metformin revisited: re-evaluation of its properties and role in the pharmacopoeia of modern antidiabetic

agents. *Diabetes, Obesity and Metabolism*, *7*(6), 654-665.
14. Cirillo, F., Catellani, C., Lazzeroni, P., Sartori, C., Nicoli, A., Amarri, S., ... & Street, M. E. (2019). MiRNAs regulating insulin sensitivity are dysregulated in polycystic ovary syndrome (PCOS) ovaries and are associated with markers of inflammation and insulin sensitivity. *Frontiers in Endocrinology*, *10*, 879.
15. Velazquez, E. M., Mendoza, S., Hamer, T., Sosa, F., & Glueck, C. J. (1994). Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism*, *43*(5), 647-654.
16. Blomquist, K. K., Milsom, V. A., Barnes, R. D., Boeka, A. G., White, M. A., Masheb, R. M., & Grilo, C. M. (2012). Metabolic syndrome in obese men and women with binge eating disorder: developmental trajectories of eating and weight-related behaviors. *Comprehensive Psychiatry*, *53*(7), 1021-1027.
17. Heidari, B., Lerman, A., Lalia, A. Z., Lerman, L. O., & Chang, A. Y. (2019, December). Effect of metformin on microvascular endothelial function in polycystic ovary syndrome. In *Mayo Clinic Proceedings* (Vol. 94, No. 12, pp. 2455-2466). Elsevier.
18. Nestler, J. E., Jakubowicz, D. J., Evans, W. S., & Pasquali, R. (1998). Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *New England Journal of Medicine*, *338*(26), 1876-1880.
19. Lord, J. M., Flight, I. H., & Norman, R. J. (2003). Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *Bmj*, *327*(7421), 951-953.
20. Legro, R. S., Barnhart, H. X., Schlaff, W. D., Carr, B. R., Diamond, M. P., Carson, S. A., ... & Myers, E. R. (2007). Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *New England Journal of Medicine*, *356*(6), 551-566.
21. Moll, E., Bossuyt, P. M., Korevaar, J. C., Lambalk, C. B., & van der Veen, F. (2006). Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. *Bmj*, *332*(7556), 1485-1490.
22. Ramachandran, A., Snehalatha, C., Mary, S., Mukesh, B., Bhaskar, A. D., Vijay, V., & Indian Diabetes Prevention Programme (IDPP). (2006). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia*, *49*, 289-297.
23. Moghetti, P., Castello, R., Negri, C., Tosi, F., Perrone, F., Caputo, M., ... & Muggeo, M. (2000). Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *The Journal of Clinical Endocrinology & Metabolism*, *85*(1), 139-146.
24. Ehrmann, D. A., Barnes, R. B., Rosenfield, R. L., Cavaghan, M. K., & Imperial, J. (1999). Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes care*, *22*(1), 141-146.
25. Legro, R. S., Gnatuk, C. L., Kunselman, A. R., & Dunaif, A. (2005). Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. *The Journal of Clinical Endocrinology & Metabolism*, *90*(6), 3236-3242.
26. Fleming, R., Hopkinson, Z. E., Wallace, A. M., Greer, I. A., & Sattar, N. (2002). Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *The Journal of Clinical Endocrinology & Metabolism*, *87*(2), 569-574.
27. Korytkowski, M. T., Mokan, M. A. R. I. O. N., Horwitz, M. J., & Berga, S. L. (1995). Metabolic effects of oral contraceptives in women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism*, *80*(11), 3327-3334.
28. Kolodziejczyk, B., Duleba, A. J., Spaczynski, R. Z., & Pawelczyk, L. (2000). Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. *Fertility and sterility*, *73*(6), 1149-1154.
29. Kelly, C. J., & Gordon, D. (2002). The effect of metformin on hirsutism in polycystic ovary syndrome. *European journal of endocrinology*, *147*(2), 217-221.
30. Guzick, D. S. (1996, February). Cardiovascular risk in women with polycystic ovarian syndrome. In *Seminars in reproductive endocrinology* (Vol. 14, No. 01, pp. 45-49). Copyright© 1996 by Thieme Medical Publishers, Inc..
31. Barrett-Connor, E., & Goodman-Gruen, D. (1995). Prospective study of endogenous sex hormones and fatal cardiovascular disease in postmenopausal women. *Bmj*, *311*(7014), 1193-1196.
32. Mancini, F., Cianciosi, A., Reggiani, G. M., Facchinetti, F., Battaglia, C., & de Aloysio, D. (2009). Endothelial function and its relationship to leptin, homocysteine, and insulin resistance in lean and overweight eumenorrheic women and PCOS patients: a pilot study. *Fertility and sterility*, *91*(6), 2537-2544.
33. LordJM, F. I., & Norman, R. J. (2003). Insulin-sensitizing drugs (met? formin, trogletazone, rosigliotazone, pioglitazone, D-chiroinos-itol) for polycystic ovary syndrome. *Cochrane Database Syst Rev*, *3*, CD003053.
34. Salpeter, S. R., Buckley, N. S., Kahn, J. A., & Salpeter, E. E. (2008). Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. *The American journal of medicine*, *121*(2), 149-157.

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