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Is metformin an effective adjunctive treatment in treating hirsutism in patients with PCOS?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not “Is metformin an effective adjunct treatment in treating hirsutism in patients with PCOS?”

Study Design: A review of three randomized control trials (RCTs) published in English between 2011-2018.

Data Sources: This paper evaluates three RCTs found via PubMed comparing the efficacy of simvastatin, clomiphene citrate and exercise as monotherapies versus each therapy in combination with metformin for the treatment of hirsutism in women with PCOS.

Outcome(s) Measured: Hirsutism was measured using the Ferriman and Gallwey score. This score measures hirsutism based on the quantity and thickness of terminal hair growth in 9 androgen-sensitive areas, including upper lip, chin, chest, upper and lower abdomen, back and upper arm and thigh.

Results: All three studies found that adjunctive metformin did not offer a statistically significant increase in the reduction of hirsutism when compared to monotherapy treatments. The RCT performed by Banaszewska et al. showed a 1.0 point Ferriman and Gallwey score decrease when treated with simvastatin and metformin combination, which is not a statistically significant reduction when compared to the simvastatin only group, a 1.1 point decrease ($p=0.52$). The RCT performed by Roth et al. similarly showed a 1.1 point decrease when treated with clomiphene citrate and metformin combination, which is not a statistically significant reduction when compared to the clomiphene citrate only group, a 0.6 point decrease ($p=0.44$). The RCT performed by Tiwari et al. showed a 1.63 point decrease when treated with exercise and metformin which is also not a statically significant reduction when compared to the exercise only group, a 0.67 point decrease ($p=0.567$).

Conclusions: All three studies demonstrated that the adjunctive metformin accounted for a decrease from the Ferriman and Gallwey score baselines, however, the decrease from baseline was not significantly different from the monotherapy treatment. Future studies should include adolescent populations, incorporate patient self-assessment data and cover a duration of treatment greater than six months.

Keywords: Hirsutism, PCOS, polycystic ovarian syndrome, polycystic ovaries, metformin

INTRODUCTION:

Polycystic ovarian syndrome (PCOS) is a condition caused by hormonal imbalance in which the ovaries produce increased amounts of androgens, responsible for many male secondary sex characteristics. The excess androgens cause many disruptions to the female body, including irregular menstrual cycles, acne, obesity and hirsutism.

Hirsutism is a condition in which females acquire excessive male-pattern terminal hair growth in androgen-dependent areas of the body, such as the face, abdomen and chest. This occurs in 7% of the total female population in the United States, more than 70% of those cases being caused by PCOS.¹ PCOS is commonly diagnosed via the Rotterdam Consensus Criteria that deems a patient to have PCOS if they have at least two of either clinical or chemical hyperandrogenism, oligomenorrhea or amenorrhea, or transvaginal ultrasound evidence of polycystic ovaries.² These manifestations are accompanied by hormonal imbalances that aid in various hormonal changes throughout the body.

The exact etiology of hirsutism in PCOS is unknown, however it is thought to be caused by a combination of insulin resistance, excess serum insulin called hyperinsulinemia and excess free serum androgens called hyperandrogenism. Tissues resistant to insulin cause excess free serum insulin that then stimulates an over production of androgens, such as testosterone. These excess androgens can suppress the sex-hormone binding globulin (SHBG) that is responsible for ridding excess serum androgens in females.⁴ Hirsutism occurs in the estimated fifty percent of women with PCOS that have androgen-sensitive pilosebaceous units, consisting of the hair follicle and sebaceous gland.⁵ These units respond to the excess androgens and stimulate male-pattern hair growth.⁵ Overall, the excess insulin causes hyperandrogenism that stimulates male pattern hair growth, converting small, villus hairs to thicker, darker terminal hairs.^{4,5}

Hirsutism is often associated with social stigmas that may cause patients to have a negative self-image and poor connection with their feminine identity leading to emotional distress.⁶ In a 2018 study, women reported a decreased quality of life due to the unwanted hair, causing limitations at work, social dysfunction and marital sexual dysfunction.⁶ The women with PCOS reported a higher presence of decreased quality of life caused by hirsutism when compared to idiopathic hirsutism.⁶ In addition to the emotional and psychological toll, a financial burden often becomes an issue for women that seek treatment. Most patients require a multi-disciplinary team and a variety of both medication and procedural trials.⁷ A 2005 study suggests that \$620 million is spent annually on treatment for hirsutism in women suffering from PCOS.⁸

The initial suggested course of action in treating hirsutism in patients with PCOS is pharmacotherapy, starting with combined estrogen-progestin contraceptives.^{1,9} If response is not satisfactory, antiandrogen therapy, such as spironolactone, cyproterone acetate, drospirenone and finasteride may be added.⁹ Lifestyle changes are suggested in obese patients and have shown effectiveness in reducing hirsutism when an average of 5-10% body weight is lost.^{1,3}

The current regimens and treatments for hirsutism in PCOS patients are limited and the efficacy of them has not shown drastic decreases in the already formed terminal hairs, but instead limit the formation of new terminal hair growth, decrease coarseness of the hairs and decrease the rate of hair growth.⁹ Laser hair removal and electrolysis offer potential permanent removal of the terminal hair follicles and are deemed more effective for long-term treatment of hirsutism. Unfortunately, both options are considered more painful and typically more expensive for patients since they fall under cosmetic procedures and are not covered by most insurance companies.^{1,9} This results in many women resorting to temporary fixes such as tweezing, waxing

and shaving that can be time consuming, painful and may have a negative impact on the woman's self-body image and feeling of femininity.⁶

Since hirsutism in PCOS patients is thought to be caused by hyperinsulinemia and insulin resistance, metformin has been suggested as an adjunctive treatment for hirsutism.^{2,4} Metformin is a medication that works by reducing glucose production from the liver and decrease intestinal absorption of glucose while also improving peripheral glucose uptake.⁴ This causes a reduction in hyperinsulinemia, reducing the free serum insulin that leads to the formation of excess androgens thought to cause hirsutism. Although metformin has been proven non-efficacious as monotherapy for hirsutism, it is being hypothesized that when added as adjunctive therapy, it may aide in the decrease of excess serum insulin and androgens, potentially further benefiting the patient.^{2,3,9}

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “Is metformin an effective adjunct treatment in treating hirsutism in patients with PCOS?”

METHODS:

The studies used in this review were found by searching PUBMED database with the keywords “hirsutism”, “PCOS”, “polycystic ovarian syndrome”, “polycystic ovaries” and “metformin” used in the search. The studies were then selected based on their relevance to my question and if they included patient-oriented evidence that matters (POEM). The inclusion criteria restricted to only randomized control trials published after 2009. The exclusion criteria consisted of studies using combination treatments with oral contraceptives or insulin. Table 1 offers additional inclusion and exclusion criteria within each individual study. All three of the selected studies were published peer-reviewed articles in English between the years 2011-2018.

The statistics used to compare and contrast the data within this review are mean change from baseline, standard deviation and p-value.

This review evaluates three randomized control trials (RCTs) comparing the efficacy of simvastatin, clomiphene citrate and exercise as monotherapies versus each therapy in combination with metformin for the treatment of hirsutism. This review's focused population is women over the age of 18 years old that meet PCOS diagnostic criteria. Banaszewska et al. study used Simvastatin 20mg daily for the control group, adding metformin 850mg twice daily as the intervention.² Roth et al. study used standard clomiphene citrate treatment daily for the control group and added metformin 1000mg twice daily as the intervention.¹⁰ Tiwari et al. study used marching for 30 minutes three times weekly plus a placebo as the control group, replacing the placebo with metformin 850mg twice daily as the intervention.³ Both Banaszewska et al. and Roth et al. included a metformin only group for their comparative measures, however, that data was not incorporated into the interpretation of this review since metformin is being researched as an adjunctive therapy rather than monotherapy.^{2,10}

OUTCOMES MEASURED:

The focused outcome measured in all three studies was hirsutism via Ferriman and Gallwey score performed by investigators.^{2,3,9} This is the most common method used to quantify hair growth in 9 androgen-sensitive areas, including upper lip, chin, chest, upper and lower abdomen and back, upper arm and thigh.¹ These sites are each individually scored from 0-4, with 0 being no hair growth and 4 being frankly virile hair growth, following male sex characteristics.^{1,9} A total score 8 or higher is deemed abnormal for female hair growth pattern in the United States, with lower variations for Asian populations and higher variations for Mediterranean populations.^{1,9}

Table 1. Demographics & Characteristics of Included Studies.

Study	Type	# pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Banaszewska ² (2011)	RCT	64	25-27	Met PCOS criteria via Rotterdam consensus with at least 2/3 of the following: 1) clinical or chemical hyperandrogenism 2) oligo- or amenorrhea 3) polycystic ovaries via transvaginal ultrasound	Elevated prolactin, thyroid disease, Cushing ds or DM. OCP, steroids or other treatments affecting ovarian function, insulin sensitivity or lipid levels within last 3 months.	28 ^A	-Simvastatin 20mg/d QD PO only -Combination of Simvastatin 20mg/d QD PO <i>and</i> metformin 850mg BID PO
Roth ¹⁰ (2012)	RCT	333	24-32	Met criteria for PCOS. Women must be infertile.	Fertile women	0 ^{A,B}	-“standard clomiphene citrate treatment” - Combination of “standard clomiphene citrate treatment” <i>and</i> Metformin XR 1000mg BID
Tiwari ³ (2018)	RCT	66	19-29	Met PCOS criteria via Rotterdam consensus. Follow exercise schedule and not on any other regimen.	Medical illnesses that CI exercise. Untreated hyperprolactinemia or hyperthyroidism, smoker, being treated with hormones that affect insulin metabolism. Pts who received metformin 3 months prior. Pts who have renal or hepatic disorders.	0	Marching in place for 30 minutes TIW with placebo vs. marching in place for 30 minutes TIW with Metformin 850 mg BID

^A Losses include those from a third group not included in this review as the primary authors did not list data of withdraws by individual groups^{2,10}

^B variation of study duration due to pregnancy, dropout or completing 6 weeks – not all losses accounted for¹⁰

RESULTS:

Banaszewska et al. (2011) conducted a randomized control trial comparing the use of simvastatin, metformin and the combination of the two to evaluate the long-term effectiveness on PCOS prominent features.² Blinding was used for randomization, however, there was not investigator or patient blinding of treatment due to the use of commercially marked simvastatin and metformin pills.² All patients in this study fulfilled the Rotterdam consensus criteria, with additional inclusion and exclusion criteria data for this study is located in Table 1.² Sixty-four patients were randomly assigned to either the control simvastatin only group (n=28) or experimental simvastatin and metformin group (n=36).² Over the 6-month duration of this study, 82% of patients completed the first 3 months and 70% completed the full 6 months.² Hirsutism was noted in 79% of the total patients at baseline and was measured via the Ferriman and Gallwey scoring system at baseline, and again after 3 and 6 months of treatment.² The simvastatin only treatment had a decrease in Ferriman and Gallwey score by roughly 1.1 points (12%) whereas the combination of simvastatin and metformin saw a decrease of 1.0 point (11.7%), as noted in Table 2.² Both groups had a statistically significant decrease in hirsutism from their baselines, having p-values less than 0.001, however there was not a statistically significant difference when comparing p-values, with p-value of 0.52.²

Table 2. Ferriman and Gallwey Score as Mean \pm SD Before and After Treatment.²

	Before treatment	After treatment	p-value
Control group Simvastatin alone	9.1 \pm 0.3	-1.1 \pm 0.1 (-12%)	<0.001*
Experimental group Simvastatin and metformin	8.7 \pm 0.3	-1.0 \pm 0.15 (-11.7%)	<0.001*

*= Statistically significant (P<0.05)

Roth et al. (2012) conducted a double-blinded randomized control trial comparing the use of clomiphene citrate, metformin and a combination of the two to evaluate the effectiveness of

these treatments on improving hirsutism in PCOS patients.¹⁰ All the subjects of this study met the criteria for PCOS and were infertile.¹⁰ Hirsutism was noted in 81% of the patients at baseline and was measured via the Ferriman and Gallwey scoring system at baseline and at the completion of the study, whether it was ended by drop-out, pregnancy or completion of 6 cycles of treatment.¹⁰ Both the patients and investigators were blinded to the randomization of the groups and the treatment the patients were receiving.¹⁰ Three-hundred and thirty three patients were randomly assigned to either the control clomiphene citrate group (n=165) or experimental combination group (n=168).¹⁰ The clomiphene citrate only treatment decreased the Ferriman-Gallwey score by 0.6 points while the combination of clomiphene citrate and metformin treatment decreased the Ferriman-Gallwey score by 1.1 points, as noted in Table 3.¹⁰ Although the combination of clomiphene citrate and metformin together had a statistically significant decrease from baseline ($p < 0.001$), there was not a statistically significant difference when compared to the clomiphene alone group ($p < 0.024$), with a p-value of 0.44.¹⁰

Table 3. Ferriman and Gallwey Score as Mean \pm SD Before and After Treatment.¹⁰

	Before treatment	Mean change after treatment	p-value
Control group Clomiphene citrate alone	17.3 \pm 7.1	-0.6 \pm 3.3	<0.024*
Experimental group Clomiphene citrate and metformin	16.8 \pm 6.1	-1.1 \pm 4.0	<0.001*

*= Statistically significant ($P < 0.05$)

Tiwari et al. assessed the efficacy of exercise and metformin in treating hirsutism in patients with PCOS by conducting a double-blind placebo controlled randomized control trial.³ All of the women in this study diagnosed with PCOS via the Rotterdam criteria, were not currently on an exercise regimen and had the willingness to forego 48-week long exercise plan.³ Other further inclusion and exclusion data are listed in Table 1. Sixty-six women were divided into two groups of 33 women, one group receiving a placebo and the other receiving metformin

while both were doing the same exercise regime of 30 minutes of marching 3 times a week for 3 months.³ Hirsutism was measured via the Ferriman and Gallwey scoring system at baseline and again after 3 and 6 months of treatment.³ Exercise alone decreased the Ferriman-Gallwey score by 0.67 points while the combination of exercise and metformin decreased the Ferriman-Gallwey score by 1.63 points, as noted in Table 4.³ Although the combination of exercise and metformin together had a significant decrease from baseline ($p < 0.001$), it was not a statistically significant difference from one another when comparing their p-values ($p = 0.567$).³

Table 4. Ferriman and Gallwey Score as Mean \pm SD Before and After Treatment.³

	Before treatment	Mean change after treatment	p-value
Control group Exercise alone	4.67 \pm 3.43	4.0 \pm 3.34 (-0.67)	<0.005*
Experimental group Exercise and metformin	5.09 \pm 3.43	3.46 \pm 2.66 (-1.63)	<0.0001*

*= Statistically significant ($P < 0.05$)

DISCUSSION:

This review evaluates adjunctively using metformin with currently studied treatments for hirsutism in PCOS patients. Each study within this review contained limitations. All three studies used the Ferriman and Gallwey scale which measures hirsutism in a subjective manner.^{2,3,10} Even though investigators may have been trained on proper use of the scale before the studies began, this method allows for human variation due to the perception and visual estimation of each individual patient's hair growth. In addition, both Roth et al. and Tiwari et al. investigators knew that all subjects were receiving at least one type of treatment, only being blinded and concealed to which treatment they were receiving.^{3,10} Banaszewska et al. investigators and patients were aware of the treatment individual patients were receiving due to the use of commercially used pills that are identifiable to the public.² This poses the concern for study bias amongst all three studies.

Another limitation is the duration of time the patients were receiving treatment. Roth et al. reported the study ended for patients by either pregnancy, drop out or after six consecutive cycles.¹⁰ Data from this study includes patient's parameters after just one cycle of treatment while others received six consecutive cycles.¹⁰ Literature suggests that all initial trials of treatment for hirsutism should be continued for a minimum of six months before a true evaluation for effectiveness is completed.⁹ This is because six months is the approximate length of time of the hair follicle growth phase, offering a more accurate representation of the effects the treatment is having on the hair follicles themselves.⁹ Both Banaszewska et al. and Tiwari et al. completed their study after 6 months of treatment, meeting the minimum suggested time.^{2,3}

The patient's satisfaction with the clinical treatment they received was not evaluated within any of the studies. The patient's own assessment and perception on the effectiveness of their treatment would have offered an insight to the psychological impact the results had, or didn't have, on the patient. In addition, between all three studies, the age demographics only included patients from ages 19 to 32 years old.^{2,3,10} Available treatments have shown positive effects of reducing the formation of new terminal hairs rather than ridding the ones that already exist.⁴ Thus, treatments used for reducing quantity and thickness of hirsutism may be more effective when started at adolescent ages, closer to the initial appearance of terminal hair and before the progression of the condition.

Metformin is a relatively safe drug commonly used for type II diabetes mellitus but has not been approved for the use of treating hirsutism.⁴ There are studies that support the use of metformin for the treatment of other clinical manifestations in patients with PCOS, such as oligomenorrhea and obesity, although it is not recommended as first-line therapy due to collectively being less effective than current regimes.^{4,11} Due to the overall lack of evidence that

supports metformin being a superior treatment in hirsutism and other PCOS manifestations, the drug has not been FDA approved and any use of it clinically is considered off-label.¹¹

Metformin does pose some risks when taking the medication, although rare. Decreased B12 absorption was noted in 5-10% of patients.¹¹ When used long term, it is suggested to perform annual serum B12 concentration and complete blood counts to monitor for megaloblastic anemia, although rare.¹¹ Another extremely rare risk of metformin is lactic acidosis so consequently should be avoided in patients with a history of sepsis, congestive heart failure or renal insufficiency.¹¹ It is also common for metformin to cause gastrointestinal side effects, such as diarrhea, abdominal pain, nausea and vomiting. Although mild and transient in nature, it is a frequent reason for noncompliance and/ or discontinuation of therapy.¹¹

CONCLUSIONS:

All three randomized control trials in this evidence-based review did not offer supporting evidence that metformin is an effective adjunct treatment in treating hirsutism in patients with PCOS. Although all three studies demonstrated that the adjunctive metformin accounted for a decrease from the Ferriman and Gallwey score baselines, the decrease from baseline was not significantly different from the treatment groups without adjunctive metformin. Therefore, it would not be advised to add metformin to current regimens due to the risk side effects and increased pill burden without offering additional effectiveness for treatment.

Due to the lack of grossly effective treatments for hirsutism in PCOS patient populations, it is encouraged to continue further research. Although metformin has not been significantly successful in reducing hirsutism in women with PCOS, there are recently published studies that assess the effectiveness of various newly considered therapies to treat hirsutism, such as vitamin D, prebiotics and ketogenic dieting.^{12,13,14} For future studies, it would be beneficial to have the

subjects perform self-assessments using Ferriman and Gallwey scale, in addition to the investigator's, as well as having the subjects monitor their own psychological state to incorporate psychological measures. This would offer results on both the physical treatment of hirsutism and the effectiveness the treatment has on the patients' self-image, femininity and overall quality of life. Also, future studies including adolescent populations may offer insight to a greater impact on preventative progression of hirsutism and reducing the number of patients attaining FG scores over 8.

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