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The use of Simvastatin Plus Metformin Therapy in Patients With Polycystic Ovarian Syndrome

Erin Carrick
Pacific University

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The use of Simvastatin Plus Metformin Therapy in Patients With Polycystic Ovarian Syndrome

Abstract

Background: Polycystic ovarian syndrome (PCOS) is a common endocrine disorder that affects the fertility of reproductive-aged women due to high levels of testosterone. Metformin is currently used to treat patients with PCOS in order to improve the biochemical markers of the disease. New studies show that statin medications like simvastatin may prove efficacious with reduction of testosterone levels, and therefore, possibly increase fertility.

Methods: An extensive search of MEDLINE, CINAHL, Web of Science, and EBM Multifiles was conducted. Articles that were not written in the English language and duplicate articles were excluded.

Results: Three studies were identified through the search of literature. The studies showed that simvastatin and metformin therapy do reduce testosterone levels in patients with PCOS. The studies used for this review were of low to very low quality.

Conclusion: Based on current research, utilizing simvastatin and metformin as dual therapies for patients with PCOS should not be recommended. Even though there seems to be some significance to the therapy in decreasing testosterone levels and other biochemical markers of the disease, more high-quality research is necessary to determine the effects of simvastatin plus metformin therapy in polycystic ovarian syndrome patients.

Keywords: simvastatin, anticholesteremic agents, hydroxymethylglutaryl-CoA reductase inhibitors, metformin, polycystic ovarian syndrome

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Keywords
simvastatin, anticholesteremic agents, hydroxymethylglutaryl-CoA reductase inhibitors, metformin, polycystic ovarian syndrome

Subject Categories
Medicine and Health Sciences

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The use of Simvastatin Plus Metformin Therapy in Patients With Polycystic Ovarian Syndrome

Erin Carrick, PA-S

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Masters of Science Degree, August 11, 2012

Faculty Advisor: Dr. Robert Rosenow Clinical Graduate Project Coordinator: Annjanette Sommers MS, PA-C
Biography

[Information redacted for privacy]
Abstract

**Background:** Polycystic ovarian syndrome (PCOS) is a common endocrine disorder that affects the fertility of reproductive-aged women due to high levels of testosterone. Metformin is currently used to treat patients with PCOS in order to improve the biochemical markers of the disease. New studies show that statin medications like simvastatin may prove efficacious with reduction of testosterone levels, and therefore, possibly increase fertility.

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**Keywords:** simvastatin, anticholesteremic agents, hydroxymethylglutaryl-CoA reductase inhibitors, metformin, polycystic ovarian syndrome
Acknowledgements

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Table I: Characteristics of Studies
Table II: Summary of Findings

List of Abbreviations

BMI………………………………………………………………………Body Mass Index
FSH………………………………………………………..Follicule Stimulating Hormone
HDL……………………………………………………………High Density Lipoprotein
hMG-CoA……………………………...3-hydroxy-3methylglutaryl coenzyme A (Statins)
LDL...............................................................................................Low Density Lipoprotein
LH…………………………………………………………………… Luteinizing Hormone
OCP...............................................................................Oral Contraceptive Pill
PCOS........................................................................Polycystic Ovarian Syndrome
The use of Simvastatin Plus Metformin Therapy in Patients With Polycystic Ovarian Syndrome

BACKGROUND

Polycystic ovarian syndrome (PCOS) is a common gynecologic endocrine disorder that affects approximately 6.6% of the reproductive-aged female population.1 This syndrome is often diagnosed using the Rotterdam criteria which state that the patient must have two of the following three conditions: 1) chronic oligo- or anovulation, 2) hyperandrogenism as signified by biochemical or clinical signs, and/or 3) polycystic ovaries for which there is no other diagnosis.2 Many females exhibit clinical signs of PCOS such as hirsutism, acne, oligomenorrhea, and infertility caused by increased levels of testosterone. Therefore, therapy in PCOS patients usually targets testosterone level decreases in order to decrease the clinical signs of the disease.

Traditionally, metformin has been prescribed for the treatment of PCOS in order to improve the patient’s hormone profile with the ultimate goal of gaining increased fertility. Metformin is proven to decrease testosterone levels, decrease insulin resistance, and reverse menstrual cycle changes independent of weight loss.3 Effecting these changes hopefully results in the PCOS patient gaining some degree of fertility.

In addition to the clinical indications, females diagnosed with PCOS can be at risk for other diseases including type II diabetes mellitus, cardiovascular disease, insulin resistance, and dyslipidemia.4-8 Therefore, polycystic ovarian syndrome patients may necessitate additional therapeutic interventions, such as statin medications, which are prescribed for patients with cardiovascular disease.

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (hMG-CoA reductase inhibitors), are commonly used as treatment for
hyperlipidemia in order to reduce the risk of cardiovascular disease. Since PCOS patients have an increased cardiovascular risk and incidence of dyslipidemia, they may also benefit from the use of statin medications such as simvastatin. The statin drugs are known to be efficacious in lowering cholesterol and LDLs, but they may also prove to be beneficial in lowering other metabolic parameters.9,10

Current research is studying the effects of simvastatin and atorvastatin on the endocrinology profile of females with PCOS.9-11 The statins have been studied singly and in combination with OCP. In both the single and OCP trials, the statin medications were shown to decreased testosterone levels, insulin resistance, and ameliorate the lipid profile.11 However, studies involving metformin and simvastatin are few and far between, but new interest in the topic seems to be emerging.

This review evaluates the three studies that address the validity of metformin plus simvastatin therapy in PCOS patients. The clinical question that guides the assessment of studies asks if simvastatin plus metformin therapy is more effective, in comparison to monotherapy with simvastatin or metformin, for reducing total testosterone in patients with polycystic ovarian syndrome.

METHODS

Search Strategy

An extensive electronic search for articles was conducted using MEDLINE (Ovid), CINAHL, EBM Multifiles, and Web of Science databases. The keywords simvastatin, anticholesteremic agents, hydroxymethylglutaryl-CoA reductase inhibitors, metformin, and polycystic ovarian syndrome were utilized as search terms. Duplicate
articles were excluded. Articles were required to be in the English language and were not excluded based on date of publication. The articles cited by the included studies were also evaluated in addition to searching reputable websites and news articles for any additional studies that might meet the inclusion criteria.

**Assessment of Quality**

The studies were assessed for validity and quality using the GRADE criteria. The appraisal comprises evaluation of the studies’ randomization, blindness, and precision. Each study was categorized into high, medium, low, or very low quality of evidence as seen in Table I.

**RESULTS**

The literature search identified thirty studies, but only three remained after duplicate and irrelevant articles were removed (see Table I). The studies were performed in Iran and Poland at universities and associated clinics. All studies were randomized controlled trials, but the *Kazerooni et al*\(^{12}\) study was the only study that was also double-blinded. In the other two studies,\(^ {13,14}\) the participants and researchers were not blinded to the allocation of therapy. Those two studies (*Banaszewska et al (2009)*\(^ {13}\) and *Banaszewska et al (2011)*\(^ {14}\)) were performed on the same patient population with the most recent of the two studies being supplementary to the primary study in 2009. *Banaszewska et al (2011)*\(^ {14}\) had three extra participants and extended follow-up for three more months. In addition, all the studies used sealed envelopes to allocate the treatments. The *Kazerooni et al*\(^ {12}\) study blinded the practitioners that were giving the patients their randomly assigned medication.
whereas Banaszewska et al (2009)\textsuperscript{13} and (2011)\textsuperscript{14} chose to give the participants the allocated medications unconcealed, so only the randomization was a concealed process.

\textit{Kazerooni et al}\textsuperscript{12}

Eighty four females were identified at an infertility clinic that was associated with Shiraz University of Medical Sciences in Iran. Patients from 17-29 years old were involved. Participants in this study were randomized into therapy groups using sealed envelopes, and the researchers that handled the envelopes were blinded to the patient’s randomization. The therapy groups received either simvastatin and metformin (treatment group) or metformin and placebo (control group) oral pills. The patients in the study groups were fairly similar with respect to prognostic factors. Additionally, no patients were lost to follow-up during the study. The simvastatin and metformin group took 20mg per day of simvastatin and 500mg three times per day of metformin. In the control group, metformin was dosed at 500mg three times a day and delivered with a placebo pill.\textsuperscript{12}

The authors of this study evaluated the primary outcome, testosterone levels, at baseline and 12 weeks later. The study showed that serum testosterone decreased by approximately 25.5\% in the treatment group versus only 16.8\% in the control group. Both measures were significant with $P$ values less than or equal to 0.002.\textsuperscript{12}

Besides testosterone levels, the Kazerooni et al\textsuperscript{12} study also measured secondary outcomes that were similar to those in the other two studies. Total cholesterol, LDL, triglycerides, and hirsutism scores were significantly lower, and HDL was higher, in the simvastatin plus metformin group than in the control group. In addition, the LH to FSH ratio was studied and was shown to be lower in the treatment group. None of the other secondary outcomes changed significantly.\textsuperscript{12}
Banaszewska et al (2009)\textsuperscript{13} and (2011)\textsuperscript{14}

Both of these randomized controlled trials looked at the same patient population. The study\textsuperscript{14} that was published in 2011 included three extra participants and an extended follow-up period. Patients were recruited at the Poznan University of Medical Sciences in Poznan, Poland over a 27 month period between December 2006 and March 2009. The 2009 study\textsuperscript{13} randomized 136 females with PCOS into three different therapeutic groups whereas the 2011 study\textsuperscript{14} randomized 139 females into the same groups. The females either received oral simvastatin at a dose of 20mg once a day, oral metformin at a dose of 850mg twice a day, or oral simvastatin plus oral metformin therapy at a dose of 20mg once per day and 850mg twice per day, respectively.\textsuperscript{13,14}

The patients were randomized into the three separate study groups (simvastatin only, metformin only, and simvastatin plus metformin) using random number tables to set the blocks used to allocate patients in a 1:1:1 ratio. The randomization was concealed until the patient actually received the allocated medication. The patients in the study groups were similar in respect to some important prognostic factors such as age, BMI, and total testosterone. However, the patients were not similar in respect to other important prognostic factors such as their lipid profiles (primarily in the total cholesterol and triglycerides).\textsuperscript{13,14}

The initial study\textsuperscript{13} lost twenty three subjects during the three month follow-up period. Also, no significant adverse events were reported by the patients. Only three patients in the metformin only group described minor gastrointestinal discomfort while taking the medication, but they did not discontinue the study.\textsuperscript{13}
Banaszewska et al (2009)\textsuperscript{13} measured various parameters at baseline and then after three months of treatment with metformin and/or simvastatin. The primary outcome measured was the change in total testosterone levels. As displayed in Table II, this study found that total testosterone levels decreased in each of the therapy groups. Testosterone decreased by 15.1\% in the combined therapy group compared with 17.1\% in the simvastatin group and 13.6\% in the metformin group. The effects were considered significant due to the $P$ values of less than 0.01. Moreover, simvastatin, when taken alone, was found to decrease testosterone levels more than simvastatin and metformin combined.\textsuperscript{13}

Secondary outcomes of the 2009 study\textsuperscript{13} included reductions in luteinizing hormone (LH), follicle stimulating hormone (FSH), fasting glucose (or fasting blood sugars), fasting insulin, insulin sensitivity index, total cholesterol, LDL, triglycerides, hirsutism (measured using the Ferriman/Gallwey score), BMI, and increases in HDL. Table II showcases the change in biochemical markers that was measured. Of those measurements, only total cholesterol, LDL, and triglycerides decreased significantly in the simvastatin plus metformin group over either of the monotherapies.\textsuperscript{13}

The 2011 study by Banaszewska et al (2011)\textsuperscript{14} had an additional three participants and the follow-up was extended to six months with continued medication use. Forty two subjects were lost to follow-up over the extended time period and six patients on metformin reported gastrointestinal side effects. However, the side effects did not affect the six patients’ continued participation. This study measured the same outcomes as the original study, but evaluated the outcomes primarily from the three to six month extended follow-up period. The testosterone levels kept significantly decreasing from the three
month follow-up mark (see Table II), but the total cholesterol and LDL did not continue decreasing after three months. This study also found that simvastatin alone actually decreased testosterone levels more than in combination with metformin.\textsuperscript{14}

**DISCUSSION**

This systematic review indicates a greater decrease in testosterone levels in patients with PCOS with the use of simvastatin and metformin over just metformin therapy alone. Of the secondary outcomes that were evaluated, simvastatin plus metformin reduced total cholesterol, LDL, and triglycerides across the studies. Other secondary outcomes were not significant or were not assessed in some of the reviewed studies.

The Kazerooni *et al*\textsuperscript{12} study does not have any major limitations to methodology as the study was randomized and blinded. No patients were lost to follow-up in this study, nor were there any considerable side effects of the medications. Additionally, there were no inconsistent results evident. However, because of the use of surrogate outcomes, there is some indirectness of evidence present. Lack of precision is also exhibited by the variability of testosterone measurements and biochemical markers in general. All of these factors were taken into consideration to rank the level of evidence of this study as low.

The limitations of the studies by Banaszewska *et al* (2009)\textsuperscript{13} and (2011)\textsuperscript{14} are lack of allocation concealment once patients received the medications, not having a strict control group with two pills given for blinding purposes, loss to follow-up that was not addressed, and some unequal prognostic factors between groups. Therefore, the studies\textsuperscript{13,14} prove to have some serious limitations to methodology. Furthermore, there
was strong use of surrogate outcomes as demonstrated by the lengthy list of secondary outcomes previously mentioned. Plus, there was a lack of precision in the results since not all of the $P$ values were less than 0.05. Nonetheless, these studies were evaluated with the GRADE criteria to have a very low level of evidence.

Another noteworthy aspect of the *Banaszewska et al (2011)* study was that three people were added to the studied patient population in the most recent report of the results. There is no mention of three subjects being added, but the numbers in the results section of the 2011 study differ from that of the 2009 study. This brings up the question of why the authors chose to include three additional subjects and why they would not mention the reasons for their inclusion. In addition, there is no discussion in either of the published studies as to the original intention to follow-up for three or six months. Therefore, it is difficult to judge whether the authors published results prematurely or extended the study based on the preliminary results. Consequently, the study’s methodology is intrinsically flawed.

All of the studies used envelopes as a concealment method which is not very reliable if the envelopes are not opaque. The studies were well-focused on the efficacy of a combination therapy of simvastatin plus metformin, but overall, the evidence presented was seriously faulted which decreases the validity of the results. Due to limitations in the methodology, precision, and indirectness of evidence these studies are not of high enough quality to definitively answer the review question. The weakness of study quality suggests that more studies are needed to evaluate the effectiveness of simvastatin plus metformin therapy in patients with PCOS. However, a clinician should take the results into account if working with patients that may have dyslipidemia and PCOS or maybe are
not responding as well to standard metformin only treatment. Even though using simvastatin alone or with metformin would be considered off-label, the medication could possibly be prescribed as an adjunct treatment for PCOS.

It is particularly important that further studies include control groups and treatment groups that are blinded to the treatment allocation. Including a dose response gradient in further studies should also be considered as varied dosages of both simvastatin and metformin could possibly improve or decrease the treatment effect. Other patient-important outcomes, such as fertility, should also be directly addressed. Moreover, other statin medications like atorvastatin could be researched in conjunction with metformin to see if the observed effects are similar.

Interestingly, Banaszewska et al (2009)\textsuperscript{13} and (2011)\textsuperscript{14} also showed that simvastatin monotherapy may decrease serum testosterone even more than simvastatin in combination with metformin. Without further studies addressing the result of simvastatin only, the effectiveness of simvastatin in patients with PCOS cannot be determined.

Other aspects of statin use that were only briefly addressed in the studies are the adverse effects of statin medications and the fact that they are not generally used in pregnant patients.\textsuperscript{16} Statins are known for increasing liver enzymes and causing rhabdomyolysis in some users. This can be a potentially fatal side effect so statin use must be closely monitored. For patients with PCOS that are interested in a return to fertility as their primary reason for using therapeutic medications, a statin medication may not be the best choice due to the teratogenicity and incidence of possible side effects of the drug class.
CONCLUSION

In conclusion, simvastatin therapy for patients with PCOS appears to possibly result in significant decreases in testosterone levels, and therefore reduce the clinical signs of PCOS. However, simvastatin plus metformin therapy does not provide much, if any, additional reduction in metabolic parameters. More research in this area needs to be accomplished before simvastatin therapy becomes a widely used medication recommendation for patients with PCOS.
REFERENCES


TABLES

Table I: Characteristics of Studies

<table>
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<tr>
<th>Study</th>
<th>Number of Participants Randomized</th>
<th>Age Range</th>
<th>Therapy Groups</th>
<th>Randomization</th>
<th>Allocation Concealment</th>
<th>Similar Prognostic Factors</th>
<th>Blindness</th>
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<tr>
<td>Banaszewska et al (2009)</td>
<td>136 (113 after 23 lost to follow-up)</td>
<td>not specified</td>
<td>Simvastatin plus metformin, simvastatin only, metformin only</td>
<td>Adequate</td>
<td>Not Adequate</td>
<td>Not Adequate</td>
<td>Some</td>
</tr>
<tr>
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<td>Adequate</td>
<td>Not Adequate</td>
<td>Not Adequate</td>
<td>Some</td>
</tr>
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<td>84 (42 in each study group)</td>
<td>17-29</td>
<td>Simvastatin plus metformin, metformin plus placebo</td>
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<td>Adequate</td>
<td>Adequate</td>
<td>Double</td>
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</table>

Table I Continued

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<tr>
<th>Study</th>
<th>Complete Follow-up</th>
<th>Loss to Follow-up</th>
<th>Mean time of Follow-up</th>
<th>Preciseness (CI, p-values)</th>
<th>Other Considerations</th>
<th>GRADE</th>
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<td>Yes</td>
<td>Yes- 23 patients</td>
<td>3 months</td>
<td>some p-values &lt;0.05</td>
<td>None</td>
<td>Very low</td>
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<tr>
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<td>6 months</td>
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<td>Yes</td>
<td>No</td>
<td>3 months</td>
<td>95% CI and some p-values &lt;0.05</td>
<td>None</td>
<td>Low</td>
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<tr>
<td>Study</td>
<td>Group</td>
<td>Number of Participants at End</td>
<td>Age Range</td>
<td>Total Testosterone</td>
<td>Testosterone Percent Change</td>
<td>LH:FSH ratio</td>
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<tr>
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<td>------------------------------</td>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Banaszewska et al (2009)</td>
<td>Simvastatin plus Metformin</td>
<td>37</td>
<td>24.7 ± 0.6</td>
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<td>-15.1%</td>
<td>n/a</td>
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<td>Banaszewska et al (2009)</td>
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<td>40</td>
<td>26.1 ± 0.6</td>
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<td>-16.3%</td>
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<td>36</td>
<td>25.3 ± 0.6</td>
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<td>-20.1%</td>
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<td>28</td>
<td>26.3 ± 0.6</td>
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<td>33</td>
<td>26.0 ± 0.6</td>
<td>-0.15 ± 0.04</td>
<td>-25.6%</td>
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<td>Simvastatin plus Metformin</td>
<td>42</td>
<td>25.6 ± 4.32</td>
<td>-0.22 ± 0.06</td>
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<table>
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<tr>
<th>Study</th>
<th>Group</th>
<th>Number of Participants at End</th>
<th>Total Cholesterol</th>
<th>LDL</th>
<th>Triglycerides</th>
<th>HDL</th>
<th>Hirsutism</th>
<th>BMI</th>
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<td>37</td>
<td>-44 ± 6</td>
<td>-40 ± 4</td>
<td>-20 ± 6</td>
<td>0.2 ± 1.9</td>
<td>-0.16 ± 0.06</td>
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<td>-4.4 ± 4.2</td>
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<td>36</td>
<td>3.4 ± 4.4</td>
<td>2.0 ± 4.1</td>
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<td>12.8 ± 7.5</td>
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<td>Simvastatin plus Metformin</td>
<td>42</td>
<td>-64.8 ± 26.27</td>
<td>-24.52 ± 20.21</td>
<td>-34.28 ± 15.18</td>
<td>6.92 ± 7.13</td>
<td>-1.1 ± 1.2</td>
<td>-2.21 ± 1.51</td>
</tr>
<tr>
<td>Kazerooni et al</td>
<td>Metformin plus Placebo</td>
<td>42</td>
<td>-9.32 ± 24.23</td>
<td>-2.06 ± 5.36</td>
<td>-5.82 ± 17.68</td>
<td>-0.43 ± 4.74</td>
<td>-0.6 ± 1.9</td>
<td>-2.17 ± 1.02</td>
</tr>
</tbody>
</table>