

The benefits of statins as adjunct therapy for non-pregnant and non-lactating women diagnosed with PCOS

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Abstract

Polycystic ovary syndrome (PCOS) is a hormonal disorder affecting 20% of women in their reproductive years. PCOS is associated with many health complications, including insulin resistance, diabetes, and obesity. These health complications pose as major risk factors for cardiometabolic diseases. The mainstay treatment plan includes lifestyle changes, oral contraceptive pills (OCP), and metformin. This review analyzes the potential benefit of adding statins as an adjunct therapy (I) to decrease the risk of cardiometabolic disease (O) in women diagnosed with PCOS (P) compared to the current recommended treatment management.

Introduction

PCOS Overview:

- Hormonal disorder that causes abnormal levels of luteinizing hormone (LH) and follicular stimulating hormone (FSH) in women of reproductive age.
- Causes irregular periods, excess androgen, and polycystic ovaries.
- Associated with insulin resistance, diabetes, obesity, metabolic syndrome, and cardiovascular disease.

Diagnosis:

- Rotterdam criteria requires at least 2 of 3 major manifestations: oligomenorrhea or amenorrhea, elevated androgen hormones, and enlarged ovaries with at least 12 follicles each.
 - Found 19.9% of women diagnosed with PCOS.

Treatment management:

- Lifestyle changes, OCP, metformin are
- Statins have been studied as possible adjunct therapy
- Side effects include myalgias, increased liver enzymes, and abnormal discomfort. Serious side effects include rhabdomyolysis, acute renal failure, and pancreatitis. In addition, it is a category X drug.

Methods

Literature search

- PubMed
- Science Direct

Search terms:

- "PCOS statin intervention OR PCOS statin cardiovascular risk"

Inclusion Criteria:

- Published in 2010 or later in peer reviewed journals written in English
- Based on case studies, clinical trials, or randomized control trials
- Subjects were women of reproductive age
- Article title includes statin medication

Exclusion Criteria:

- Systemic meta-analysis reviews or clinical research involving animals
- Subjects were pregnant or lactating

Results

The evidence collected by each study showed that statins brought a significant improvement on the patients' lipid profiles, as well as a significant decrease in the patients' serum C-reactive protein (CRP) levels, while showing no significant difference in the patients' insulin resistance (IR). Most studies looked at statins as a monotherapy and saw significant effects on CRP levels and the lipid profiles. One study saw that statins used in addition to metformin brought significant change to the patients' lipid profiles. Another study found that most of the benefits from statin occurred in the first three months, and at six months, there was no significant change to the lipid profile.

Appendix 1

Study	Design	Total N (all female)	Age Range	Duration of intervention	Statin used	Control	Other interventions used	Outcome measure
Kazerooni T et al (2010)	RCT	84 with PCOS	17-29 years	12 weeks	Sim 20 mg	P	Metformin 500 mg qd	BMI, TC, LDL, TG, HDL, OGTT
Puurunen J et al (2013)	RCT	28 with PCOS	Pre-men.	6 months	Ator 20 mg	P	None	OGTT, IVGTT, CRP, TC, LDL, TG
Kaya C et al (2009)	RCT	104 (52 with PCOS)	17-34 years	12 weeks	Sim 20 mg vs. Ator. 20 mg	None	None (52 without PCOS)	TC, LDL, HDL, TG, Hey
Seyam E et al (2018)	RCT	200 with PCOS	Pre-men.	6 months	Sim 20 mg	P	None	TC, HDL, LDL, TG, IR, BMI
Bozdag G et al (2013)	Cohort	N/A	N/A	N/A	N/A	N/A	Lifestyle, OCP, Metformin	TC, LDL, EH
Kaya C et al (2010)	RCT	64 with PCOS	pre-men.	3 months	Sim 20 mg vs. Ator 20 mg	None	None	FI, IR, CRP, TC, LDL, HDL
Raja-Khan N et al (2011)	RCT	20 with PCOS	21-46 years	6 weeks	Ator 40 mg	P	None	FMD, TC, LDL, TG, IR, CRP

Key:
RCT: Randomized Control Trial, Pre-men: pre-menopausal, Sim: Simvastatin, Ator: Atorvastatin, TC: total cholesterol, TG: triglycerides, OGTT: Oral Glucose Tolerance Test, CRP: C-reactive protein, IR: Insulin Resistance, Hey: Homocysteine levels, EH: endothelial hyperplasia, FI: fasting insulin, FMD: Brachial Artery Flow-Mediated Dilatation.

Appendix 2

Study	TC	LDL	HDL	TG	CRP	OGTT	IR
Kazerooni T et al (2010)	S	S	S	S	N/A	NS	N/A
Puurunen J et al (2013)	S	S	N/A	S	S	NS	N/A
Kaya C et al (2009)	S	S	S	S	N/A	S (Ator.) NS (sim.)	N/A
Seyam E et al (2018)	S	S	S	S	N/A	N/A	NS
Bozdag G et al (2013)	S	S	N/A	N/A	N/A	N/A	N/A
Kaya C et al (2010)	S	S	S	N/A	S	S (Ator.) NS (Sim.)	S (Ator.) NS (Sim.)
Raja-Khan N et al (2011)	S	S	N/A	S	S	N/A	NS

Key: S- Significant, NS- Not Significant

Lipid Profile (TC, LDL, HDL, TG)	CRP	OGTT	IR
S- increase in HDL & decrease in TC, LDL, and TG with the addition of statins, or p<0.05 NS- no change (or worsening) in lipid profile after statin intervention, or p<0.05	S- decrease in circulating C-reactive protein with statin intervention, or p<0.05 NS- no decrease, or p<0.05	S- decrease in OGTT score with the statin intervention, or p<0.05 NS- no decrease, or p<0.05	S- decrease in insulin resistance with statin intervention, or p<0.05 NS- no decrease in insulin resistance, or p<0.05

Discussion

The seven studies in the results section address the potential effect of statins as a therapy to decrease the risk of cardiometabolic diseases based on statins' effect on lipid profile, CRP, and insulin resistance.

Appendix 1 shows a comparison of the 7 chosen studies, looking at their designs and methods. The majority of RCT look at statin intervention as singular therapy, where one looked at the effect of statin in conjunction with metformin. It also looks at the outcome measures of each study. All the RCT studies look at the subjects' lipid profiles, CRP, and insulin resistance, which are linked to cardiometabolic disease.

Appendix 2 shows the result summaries of those 7 studies. **7 out of 7 articles showed that the statin intervention led to a significant improvement to the patients' lipid profile.** The 3 studies that measured CRP levels showed significant decrease in serum CRP with statin medication, which demonstrates that statins also decrease chronic inflammation in women diagnosed with PCOS. Lastly, the studies showed mixed results about the effect of statins on insulin resistance and insulin sensitivity. The statin's positive effect on the subjects' lipid profiles are seen predominantly in the first 3 months. By 6 months, there is minimal improvement

Limitations:

- No long-term studies beyond 3 months
- No studies comparing the use of statins as an adjuvant treatment

Future studies:

- RCT studies that research current interventions vs. current interventions plus statins
- RCT studies that look at the potential benefits of using statins intermittently as adjunct therapy to current interventions

Conclusion

Statins have been recommended as first line treatments for hyperlipidemia, which has been shown to decrease cardiovascular disease (CVD). The RCT studies showed that statins as a monotherapy improved CRP levels and lipid profiles, while one showed statin in addition to metformin added further benefits to the lipid profile. There are not enough studies that show the benefits of statins as adjunct therapy, but more research is warranted to further investigate this topic.

Overall, results of the meta-analysis results are positive, but there is not sufficient evidence to change the current therapeutic management of women with PCOS, especially when they are of child-bearing age. The risks must be weighted carefully with the benefits of statin therapy as an adjuvant treatment.

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