



Published in final edited form as:

*Fertil Steril.* 2011 April ; 95(5): 1849–1852. doi:10.1016/j.fertnstert.2010.11.040.

## Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovary syndrome: a double-blind, randomized placebo-controlled trial

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### Abstract

In order to determine the effects of statins on vascular function, inflammation and androgen levels in women with polycystic ovary syndrome (PCOS), we randomized 20 women with PCOS who had LDL-cholesterol levels >100 mg/dl to atorvastatin (40 mg/day) or placebo for six weeks and found that atorvastatin reduced androgen levels, biomarkers of inflammation, and blood pressure, increased insulin levels and brachial artery conductance during reactive hyperemia, and failed to improve brachial artery flow-mediated dilation. We conclude that until additional studies demonstrate a clear risk-to-benefit ratio favoring statin therapy in PCOS, statins should only be used in PCOS women who meet current indications for statin treatment.

### Keywords

statin; PCOS; hyperandrogenemia; vascular function; hyperinsulinemia

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As LDL-cholesterol is the primary precursor for sex steroid biosynthesis, dyslipidemia may play a central role in the pathogenesis of polycystic ovary syndrome (PCOS), contributing to hyperandrogenemia and increased cardiovascular risk. Although many women with PCOS

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ClinicalTrials.gov Identifier: NCT00529542

**Presented in part at:** NIH Annual Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Scholars Meeting, November 2008, Bethesda, Maryland and 92<sup>nd</sup> Annual Endocrine Society Meeting, June 2010, San Diego, CA.

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have dyslipidemia (1,2), they usually do not meet the National Cholesterol Education Program (NCEP) indications for statin therapy (3).

Beyond their LDL-lowering effects, statins inhibit ovarian theca-interstitial cell proliferation and steroidogenesis in vitro (4,5) and reduce T levels in women with PCOS (6–10). In non-PCOS populations, statins have been shown to reduce inflammation and cardiovascular events (11–13). In normocholesterolemic middle-aged men and patients with hypercholesterolemia, statins improve flow-mediated dilation (FMD), a non-invasive measure of endothelial function and early indicator of atherosclerosis (14–16). However, the effects of statins on FMD and other parameters of vascular function have not been investigated in PCOS.

The objective of this double-blind, randomized placebo-controlled trial was to determine whether atorvastatin improves brachial artery FMD and conductance, inflammation and hyperandrogenemia in PCOS. Brachial artery FMD, the percent change in brachial artery diameter following release of transient occlusion, was selected as the primary outcome because it is the most widely used research tool for evaluating the effects of interventions on endothelial function (17,18). FMD is currently not suitable for use in clinical practice due to lack of standardization and normative data (18,19). FMD has been shown to predict long-term cardiovascular events, even in patients with no apparent heart disease (20–22).

The Institutional Review Board of Pennsylvania State University approved the study. Written informed consent was obtained from all participants. Participants were recruited through the clinics of the Departments of Medicine and Obstetrics and Gynecology at Penn State Hershey Medical Center from October 20, 2006 to September 8, 2008. Women with PCOS and LDL-cholesterol >100 mg/dl were eligible to participate in the study. This LDL cutoff was selected because NCEP guidelines recommend LDL reduction to <100 mg/dl in high-risk patients (3). PCOS was defined using the 1990 National Institutes of Health criteria (23). Evaluation for secondary causes of hyperandrogenism and anovulation were carried out, including measurement of TSH, PRL, and 17-hydroxyprogesterone.

Participants presented for their baseline evaluation in a 12-hour fasting state and had abstained from caffeine and chocolate for at least 24 hours. Blood pressure (BP), pulse, anthropometrics and modified Ferriman-Gallwey hirsutism scores were recorded (24). Pelvic ultrasound was performed using the 6.5 MHz probe of an ATL 400 machine to characterize ovarian size and morphology.

The participants were placed supine in a quiet, dimly lit room. Electrocardiogram electrodes were attached to the chest to continuously monitor heart rate (HR) and rhythm. Blood pressure was measured beat-by-beat by finger photoplethysmography of the nonexperimental arm using a Finapres device (Ohmeda, Madison, WI) and the data was collected electronically using a MacLab system (ADI Instruments, Castle Hill, Australia). Pneumatic cuffs were positioned on the upper arm and wrist of the experimental arm. The brachial artery was imaged using an ATL Doppler ultrasound probe (5–12MHz linear array scanhead, HDI 5000, Advanced Technology Laboratories, Bothell, WA). Mean blood flow velocity (MBV) and brachial artery diameter (BAD) were recorded at baseline. Then the wrist cuff was inflated to 200–250 mmHg. After a minute, with the wrist cuff still inflated, the arm cuff was inflated to 200–250 mmHg. After 10 minutes the arm cuff was released. Upon release of the arm cuff, we continuously measured BP, HR, and MBV, and intermittently measured BAD in the experimental arm. Brachial artery conductance (BAC) was calculated as MBV/MAP and FMD was calculated as percent change in BAD from baseline. Some of the baseline data was used as part of a case-control study (25).

Fasting blood was obtained to measure hormonal and metabolic parameters. A 75 gram oral glucose tolerance test was performed with blood draws at 0, 30, 60, 90 and 120 minutes. All blood samples were analyzed in either the General Clinical Research Center or Core Endocrine Laboratory at the Penn State Hershey Medical Center using validated assays.

Following the above baseline evaluation, subjects were randomized in a double-blind fashion to receive either atorvastatin 40 mg or placebo once daily for six weeks. At the end of the 6 weeks, measurements were repeated to assess change from baseline.

Randomization was performed according to Consolidated Standard of Reporting Trials (CONSORT) guidelines. The biostatistician generated a permuted block randomization scheme for the allocation sequence and provided it to the pharmacist. The atorvastatin and placebo were over-encapsulated by the pharmacist so that the participants, research coordinator who administered the intervention, and investigators who assessed the outcomes were blinded to group assignment. Whether over-encapsulation of atorvastatin affects absorption has not been reported. Over-encapsulation is a standard practice for blinding medication and does not affect absorption of the antibiotic moxifloxacin (26).

This study was initiated as a pilot study with the goal of enrolling 19 women in each group, which we hypothesized would provide 80% power to detect an absolute difference in the change in FMD between the two groups of 3.75%, assuming a common SD of 4%, using a two-sided, two-sample t-test with  $\alpha=0.05$ . Recruitment was slow due to strict inclusion/exclusion criteria so we analyzed our data after the first 20 women completed the study. This analysis revealed that the required sample size was 235 subjects per group for 80% power to detect an absolute 2% increase in FMD with Atorvastatin compared to Placebo. A 2% increase in FMD is the minimum improvement required to detect a treatment benefit in clinical trials (17,27,28). We stopped the trial early because we had insufficient funds for the required sample size.

Linear mixed-effects models, extensions of regression that account for within-subject correlation inherent in pre-post designs, were fit to continuous outcomes to assess the change from baseline to 6 weeks within and between treatment groups. All hypotheses tests were two-sided. All analyses were performed by intention-to-treat using SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

Twenty eligible women were randomized and started the allocated treatment. Eighteen women completed their treatment. One woman was on oral contraceptives during the study. She was randomized to the placebo group. The remaining women were instructed to use non-hormonal contraception during the study. Two women, one in each group, were on anti-hypertensives. None of the women were on metformin or any other medications known to affect any of the outcomes.

At baseline, the two groups were similar in age, BMI and other cardiometabolic and reproductive characteristics (Table 1). Compared to placebo, atorvastatin significantly reduced diastolic BP, total and LDL-cholesterol, triglycerides, androstenedione and DHEAS levels (Table 1). Atorvastatin appeared to worsen FMD by reducing it by 1.5% whereas in the placebo group FMD increased by 0.4%. These differences were not statistically significant in the within or between-group comparisons. Compared to baseline, the peak BAC during reactive hyperemia and area under the curve (AUC) for insulin during OGTT were significantly increased while systolic BP and high sensitive C-reactive protein (hsCRP) were significantly decreased after atorvastatin, but not after placebo; these differences did not reach statistical significance in the between-group comparisons. There were no differences in AUC for glucose, fasting glucose or insulin, HOMA-IR, T, E<sub>2</sub>, estrone or P levels.

In the present study we demonstrate that atorvastatin significantly reduces BP, androstenedione and DHEAS and may increase BAC during reactive hyperemia. These are novel effects that to the best of our knowledge have not been previously reported. Our finding that atorvastatin may reduce hsCRP in PCOS confirms the findings of an earlier study (9). Our finding of worsening hyperinsulinemia in atorvastatin-treated PCOS women is consistent with the JUPITER study and two meta-analyses demonstrating a small increased risk of diabetes with statin therapy (29–31). We found no difference in T levels, although previous studies have demonstrated that statins reduce T in women with PCOS (6–10). Since in vitro studies demonstrate that statins inhibit ovarian theca-interstitial cell proliferation (4,5), we hypothesized that statins might reduce ovarian volume in PCOS. However, we found no significant effects of atorvastatin on ovarian volume. The nonsignificant weight loss observed in both groups might be due to the subjects behaving differently while participating in a trial. Lifestyle modification was not part of the study. Conclusions for these secondary outcomes are exploratory in nature as they were not formally powered.

Although statins have been shown to improve FMD in other patient populations (14–16), the present study suggests that atorvastatin does not significantly affect FMD in women with PCOS. We acknowledge that our study is underpowered and a small difference in FMD might be present. Despite this, we believe our study adds to the existing literature as it is the first study, to the best of our knowledge, to explore the effect of a statin on FMD in women with PCOS.

In conclusion, until additional studies demonstrate a clear risk-to-benefit ratio favoring statin therapy in PCOS, statins should only be used in PCOS women who meet current indications for statin treatment (32). Appropriate contraception is required when statins are used in PCOS women with reproductive potential.

## Acknowledgments

Supported by National Institutes of Health (NIH) Grant Number K12HD055882 “Career Development Program in Women’s Health Research at Penn State” from the National Institute of Child Health and Human Development (NICHD), GCRC grant M01 RR10732 and construction grant C06 RR016499 to Pennsylvania State University, and a research grant from Pfizer. Pfizer also provided the atorvastatin. Dr. Legro has received speaker honorarium from Merck-Serono and study support from Solvay. Mr. Kunselman reports ownership of Merck stock. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NICHD or the NIH.

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**Table 1**  
Cardiometabolic and reproductive profiles of both groups before and after treatment.

	Atorvastatin (n=9)			Placebo (n=11)			Atorvastatin vs. Placebo	
	Before Mean (SD)	After Mean (SD)	Within-group Mean Difference(95% CI) [p-value]	Before Mean(SD)	After Mean(SD)	Within-group Mean Difference(95% CI) [p-value]	Mean Difference(95% CI)	Mean Difference(95% CI) [p-value]
<b>Cardiometabolic profile</b>								
Age (years)	33.8 (4.3)	-	-	29.4 (5.8)	-	-	-	-
BMI (kg/m <sup>2</sup> )	40.1 (11.8)	38.2 (8.4)	0.2 (-0.4,0.9) [0.43]	36.0 (10.4)	35.8 (10.8)	0.05 (-0.47,0.56) [0.85]	0.2 (-0.6,1.0) [0.63]	
Systolic BP(mm Hg)	119.8 (15.8)	112.0 (13.2)	-8.5 (-16.6,-0.4) [0.04]	114.5 (14.4)	111.4 (8.8)	-2.5 (-9.9,4.8) [0.47]	-5.9 (-16.9,5.0) [0.27]	
Diastolic BP(mm Hg)	70.8 (14.8)	64.3 (12.3)	-6.7 (-12.7,-0.8) [0.03]	64.6 (8.0)	65.4 (8.1)	1.1 (-4.2,6.4) [0.67]	-7.8 (-15.8,0.1) [0.05]	
Total Cholesterol(mg/dl)	215.8 (39.0)	132.0 (19.7)	-82.5 (-100.7,-64.4) [<.001]	202.8 (28.3)	192.1 (33.6)	-11.7 (-28.0,4.6) [0.15]	-70.8 (-95.2,-46.4) [<.001]	
HDL-Cholesterol(mg/dl)	44.4 (14.6)	47.8 (11.8)	3.2 (-1.4,7.7) [0.16]	46.5 (8.6)	46.8 (8.4)	-0.2 (-4.3,3.9) [0.92]	3.4 (-2.7,9.5) [0.26]	
LDL-Cholesterol(mg/dl)	140.7(24.6)	68.5 (19.3)	-70.2 (-86.3,-54.0) [<.001]	131.3(21.6)	118.8(26.8)	-12.6 (-27.1,1.9) [0.08]	-57.6 (-79.3,-35.9) [<.001]	
Triglycerides(mg/dl)	153.3(84.9)	78.5 (24.8)	-77.1 (-109.8,-44.5) [<.001]	125.5(54.2)	132.5(45.7)	5.0 (-24.5,34.5) [0.72]	-82.2 (-126.2,-38.1) [<.001]	
hsCRP (mg/L)	8.0 (9.6)	4.3 (5.4)	-3.6 (-6.5,-0.6) [0.02]	7.2 (7.7)	6.0 (7.3)	-1.1 (-3.8,1.5) [0.39]	-2.4 (-6.4,1.5) [0.21]	
Fasting Glucose(mg/dl)	87.7 (9.0)	87.8 (8.5)	0.2 (-6.5,7.0) [0.94]	85.3 (8.0)	88.9(10.7)	3.6 (-2.5,9.6) [0.23]	-3.3 (-12.4,5.8) [0.45]	
Fasting Insulin(µU/ml)	18.6 (10.1)	21.0 (11.8)	1.4 (-2.6,5.4) [0.47]	16.8 (9.5)	15.9 (6.7)	-1.1 (-4.7,2.4) [0.51]	2.5 (-2.8,7.9) [0.33]	
AUC Glucose	15693(2162)	16136(2569)	709 (-1044,2462) [0.40]	15309(3692)	15448(3165)	123 (-1513,1758) [0.88]	586 (-1811,2983) [0.61]	

	Atorvastatin (n=9)			Placebo (n=11)			Atorvastatin vs. Placebo		
	Before Mean (SD)	After Mean (SD)	Within-group Mean Difference(95% CI) [p-value]	Before Mean(SD)	After Mean(SD)	Within-group Mean Difference(95% CI) [p-value]	Before Mean(SD)	After Mean(SD)	Between-group Mean Difference(95% CI) [p-value]
AUC Insulin	12738(10010)	17479(11929)	3074 (387,5762) [0.03]	9338(5208)	9132(4466)	-311 (-2812,2191) [0.79]	9338(5208)	9132(4466)	3385 (-287,7056) [0.07]
Peak BAC(ml/sec/mmHg)	5.4 (2.9)	6.9 (2.8)	1.2 (0.0,2.4) [0.05]	3.6(3.0)	4.3(3.3)	0.5 (-0.5,1.6) [0.30]	3.6(3.0)	4.3(3.3)	0.7 (-0.9,2.3) [0.39]
FMD (%)	12.0 (7.3)	10.4 (4.6)	-1.5 (-7.0,3.9) [0.56]	9.8 (5.8)	10.2(2.9)	0.4 (-4.5,5.3) [0.85]	9.8 (5.8)	10.2(2.9)	-2.0 (-9.3,5.3) [0.58]
<b>Reproductive profile</b>									
Ferriman-Gallwey hirsutism score	14.4 (6.2)	-	-	15.7 (6.5)	-	-	15.7 (6.5)	-	-
Free T (ng/dl)	18.1 (4.9)	-	-	20.2 (8.7)	-	-	20.2 (8.7)	-	-
Total T (ng/dl)	61.3 (16.9)	47.1 (21.4)	-14.9 (-34.2,4.4) [0.12]	92.3(49.8)	75.7(43.6)	-16.7 (-34.0,0.6) [0.06]	92.3(49.8)	75.7(43.6)	1.8 (-24.1,27.8) [0.88]
Androstenedione(ng/ml)	3.4 (0.8)	2.5 (0.9)	-0.9 (-1.3,-0.5) [ $<.001$ ]	3.8 (1.2)	4.1 (1.2)	0.2 (-0.2,0.5) [0.36]	3.8 (1.2)	4.1 (1.2)	-1.1 (-1.6,-0.5) [ $<.001$ ]
DHEAS (ng/ml)	1630.0(873.1)	1326.4(854.3)	-296.5 (-513.5,-79.5) [0.01]	1701.5(681.3)	1739.5(781.8)	67.8 (-126.2,261.7) [0.47]	1701.5(681.3)	1739.5(781.8)	-364.3 (-655.3,-73.2) [0.02]
Mean Ovarian Volume (mm <sup>3</sup> )	15.1 (8.8)	19.2 (7.0)	0.9 (-7.2,9.1) [0.81]	25.4(13.7)	25.2 (9.9)	-2.5 (-8.8,3.7) [0.39]	25.4(13.7)	25.2 (9.9)	3.5 (-6.8,13.7) [0.48]

Note: Data are presented as mean (SD).

AUC, area under the curve; BAC, brachial artery conductance; BMI, body mass index; BP, blood pressure; hsCRP, high sensitive C-reactive protein; FMD, flow-mediated dilation.