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The gender-specific clinical pharmacology of statins: an update

Andrea Cignarella

Department of Medicine, University of Padua, Italy. *Received 16 June 2018; accepted 23 July 2018.*

Summary. When overlooked, underrepresentation in clinical trials and the difference in cardiovascular disease (CVD) symptoms in women may lead to worse outcomes and the recurrence of CVD. The efficacy of statins in women with CVD has been established in randomised clinical trials. However, the use of statins should be broadened and not be denied to women with high-risk CVD, in whom the benefits may be greater than those observed in men. There is also a major gender difference in the use of lipid-lowering drugs between men and women with CVD. Statin doses should be adjusted in patients with a high probability of potential side effects, especially with polydrug use. Although the association between statin use and incident diabetes is known, this risk appears to be higher amongst elderly women and shows a dose-response effect. Increasing evidence from observational studies indicates that the use of statins may delay the progression of breast cancer and other malignancies affecting women. Furthermore, interventional studies have shown that statin use may have benefits with regard to prevalent female conditions such as preeclampsia and polycystic ovary syndrome, suggesting novel gender-specific treatment options.

Key words: statins, cardiovascular disease, incident type 2 diabetes, gender, cancer, endocrinological disease.

La farmacologia clinica specifica per sesso delle statine: un aggiornamento

Riassunto. La sottorappresentazione negli studi clinici e le manifestazioni diverse delle malattie cardiovascolari (CVD) nelle donne, se trascurate, possono condurre a esiti sfavorevoli e alla ricorrenza di CVD. L'efficacia delle statine nelle donne con CVD è stata stabilita in studi clinici randomizzati. Tuttavia, l'uso delle statine dovrebbe essere allargato e non essere negato alle donne ad alto rischio di CVD le quali, in effetti, potrebbero avere un beneficio superiore rispetto agli uomini. Inoltre, esiste un'importante differenza di genere nell'uso dei farmaci ipolipidemizzanti fra uomini e donne con CVD. Il dosaggio delle statine dovrebbe essere aggiustato nelle pazienti con un'alta probabilità di potenziali effetti avversi particolarmente a causa della politerapia. Anche se la relazione fra uso di statine e diabete incidente è nota, questo rischio sembra aumentato nelle donne anziane e mostra un effetto di dose-risposta. Prove crescenti dagli studi osservazionali indicano che l'uso delle statine può ritardare la progressione del cancro al seno e di altri tumori che interessano le donne. Ancora, alcuni studi d'intervento mostrano un beneficio potenziale del trattamento con statine in patologie prevalenti nelle donne quali la pre-eclampsia e la sindrome dell'ovaio policistico, suggerendo delle nuove possibili opzioni terapeutiche genere-specifiche.

Parole chiave: statine, malattie cardiovascolari, diabete incidente di tipo 2, genere, cancro, malattie endocrinologiche.

Introduction

When statins first appeared on the market in the late 1980s, the management of vascular risk was a major problem in most patients and the understanding of the benefits of lowering cholesterol was still in its infancy. All of the most commonly-used statins available today seem to achieve a 20-50% reduction in the risk of a cardiovascular event. They decrease the risk of stroke and peripheral vascular disease, are effective in old and young of both sexes[1,2], are effective in patients with concomitant diseases such as hypertension and diabetes and there is growing evidence that the lower the cholesterol level, the better the outcome. Whilst the golden age of statin trials that ended about 10 years ago witnessed their effectiveness in preventing atherothrombotic cardiovascular disease, in several studies women were underrepresented and there was a lack of statistical power for gender stratification[3]. For instance, the landmark WOSCOPS primary prevention trial only enrolled men between 45 and 64 years of age[4]. CVD manifestations and susceptibility to risk factors differ between men and women[5]. The efficacy of statins in women with CVD was well established in recent randomised clinical trials[6]. Yet the use of statins (in particular high intensity statin therapy) should be broadened and not be denied to women with CVD, who, in actual fact, may obtain greater benefits from this kind of therapy than men[7]. The demonstration of a treatment-sex interaction in the SATURN study[8], along with a greater clinical benefit in terms of LDL-C reduction in TESTS IT-TIMI 22[9], points to an inherent biological tendency for women to benefit more from statin treatment. In the prolonged high-intensity statin therapy setting, particularly in those achieving very

low LDL-C levels, plaque regression is more evident in women than in men. Although the incidence of major adverse cardiac events tended to be higher in women than in men on statin treatment following percutaneous coronary intervention (PCI), this difference was no longer present after adjustment by age and gender, suggesting that statin treatment may be equally effective in preventing post-PCI cardiovascular events in both men and women[10]. However, clinical trials regarding CVD prevention enrolling mainly women suggest that more individualised therapeutic strategies are required in order to halt atherothrombotic disease[11].

Despite being more controversial, there is also evidence to support the use of statin therapy for primary prevention in women at higher CVD risk[12]. However, in premature myocardial infarction patients (<50 years), risk prediction is insufficiently addressed by the standard CVD risk scoring tools. Retrospective analysis of a cohort from two US academic centres revealed that significantly more women (184; 63%) would not be eligible for statin treatment than men (549; 46%, p <0.001). Thus, current risk assessment tools are inadequate for preventing early manifestations of coronary artery disease (CAD), and improved strategies are urgently needed to identify premature CAD patients in a primary prevention setting[13].

Gender and age issues in appropriate statin use

There is a major difference in the use of lipid-lowering therapy between men and women with coronary artery disease. Women are at a higher risk of statin noncompliance than men and are more likely to stop or switch their statin therapy because of side effects than men are[14]. Although women are less likely to be prescribed a nonstatin lipid-lowering drug than men[15], females were less likely to start an appropriate statin before and after the release of the ACC/AHA cholesterol management guidelines in November 2013[16]. The retrospective analyses of electronic outpatient health records showed that women with coronary artery disease are prescribed inadequate doses of statins and combination lipid-lowering therapy and are less likely to achieve their optimal LDL and non-high-density lipoprotein cholesterol goals[17]. Amongst individuals with a statin prescription, women are less likely than men to be prescribed a statin, get up-titrated or even initiate a high-intensity statin therapy following hospital discharge for myocardial infarction[18]. A retrospective cohort study also showed that use of statins and other pharmacological agents following myocardial infarction was significantly higher amongst male patients than amongst female ones[19]. Similarly, the management of the dyslipidaemia that is often found in HIV-seropositive women should be more aggressive[20].

The lipid management of elderly patients has been insufficiently addressed in large randomised clinical trials. Data from observational studies may assist clinicians in their quest for reliable evidence on how to manage this growing category of patients. In a retrospective analysis of data collected from 216 elderly patients (>80 years) for 1 year, of which 122 (56.5%) were women, 53% of the women and 47% of the men used statins for ≥3 years after hospital admission. Over 3 years, 39% of the women and 51% of the men died. Statins were seen to have a protective effect in the women only. Of the women not using statins, 57.1% died vs. 24.2% of those who used statins (p <0.0001). Clinical benefit was significant in women on statin treatment for both primary and secondary prevention. For elderly men, no benefits were observed, due perhaps to the fact that life expectancy is higher for women than for men[21].

The gender-specific incremental benefit of add-on therapy: the IMPROVE-IT study

The IMPROVE-IT study included 18,144 post-acute coronary syndrome (ACS) patients, of whom 4416 (24%) were women. Based on a recent sub-analysis of the trial[22], the cardiovascular protection action of ezetimibe on top of simvastatin in secondary prevention would appear to be comparable for the two sexes, in line with previous metanalyses[23]. However, despite similar reductions in LDL-C, the absolute reduction of both primary and total events with the addition of ezetimibe was greater in women than men[22]. Thus, aggressively addressing CVD risk factors may have a significant impact on women's health. In secondary prevention, lowering LDL-C in women provides comparable relative risk reductions, but the impact on absolute risk is more striking. In the IMPROVE-IT trial, women had a relative risk reduction of 12% vs 5% in men. The number of events was reduced by 18% in women vs 6% in men. In high-risk women, efficacy of statin + ezetimibe started early, leading to a 27% relative risk and a 7.4% absolute risk reduction for the primary endpoint[22].

Safety issues and pharmacokinetics: back to basics

Plasma statin concentrations are pivotal in many of the adverse effects observed. Statin doses should be adjusted in patients with a high probability of potential side effects due to e.g. age, co-morbidities, genetic disposition and, last but not least, co-medications. Knowledge regarding the enzymes that are responsible for statin elimination and are targeted by other pharmacological interventions is also important. All statins except pravas-

tatin are metabolised by hepatic cytochrome P450 (CYP). Simvastatin, lovastatin and atorvastatin are predominantly metabolised by CYP 3A4. Because in women the expression of CYP 3A4 is twice than seen in men, faster and more extensive statin metabolism may result in lower activity than in men[24]. By contrast, fluvastatin, pitavastatin, rosuvastatin and pravastatin pose a lower risk for interaction with drugs inhibiting or increasing CYP 3A4 activity. CYP 2E9 is targeted by different concomitant drugs and in this case fluvastatin, pitavastatin and rosuvastatin are more likely to lead to interactions. Alternatively, statin transporters such as OATP1B1, OATP1B3 and P-glycoprotein can also impact plasma concentrations[25]. In general, women have (a) a lower body mass index and thereby increased risk of myopathy; (b) more adipose tissue and, therefore, a greater volume of distribution for lipophilic statins (e.g. simvastatin) and increased half-life; and (c) a lower glomerular filtration rate than men. Overall, although there are metabolic differences and the % LDL-C change may not be the same as in men, a high-risk woman will still benefit from statin therapy[24].

Increased risk of statin-related incident diabetes

The pro-diabetogenic effects of statins were recently brought to light[26]. The increased cholesterol uptake in the pancreatic islet Beta-cells via the LDL-receptor may have a damaging effect on insulin secretion and even Beta-cell apoptosis[27]. Older women taking statins face a significantly higher risk of developing diabetes. More specifically, Australian women over 75 faced a 33% higher chance of developing diabetes if they were taking statins, and the risk increased with the dose of statins[28]. Indeed, of almost 8400 women aged between 76 and 82 years, the risk of new-onset diabetes ranged from 17% with the lowest statin doses to 51% with the highest doses. The impact of statins on incident diabetes in the context of hypertension and gender was recently evaluated in a relatively healthy Korean population[29]. Over a period of 7-8 years about 40,000 participants from the National Health Insurance System with elevated LDL-C were evaluated. Of over 22,000 statin users, 7.63% developed new-onset diabetes vs. 5.68% amongst statin non-users. For unclear reasons, the association between statin use and incident diabetes was found in normotensive patients only. However, women showed a higher risk of diabetes with continuous statin use regardless of hypertension status, whereas increased risk was observed in normotensive males only[29]. This suggests that the risk of diabetes associated with statin therapy in the management of patients with dyslipidaemia is higher amongst women.

Emerging evidence of statin benefit in cancer

Because breast cancer expression of the statin target (3-hydroxy-3-methylglutaryl coenzyme-A reductase) is associated with lymph-node negative cancer[30], pre-diagnostic statin use may be associated with reduced breast cancer-specific mortality. One cohort study showed that pre-diagnostic statin use in women with breast cancer is associated with a significant reduction in both breast cancer-specific and all-cause mortality, particularly in those with oestrogen receptor-positive breast cancer[31]. In a population of women with newly diagnosed breast cancer, although black women have a worse prognosis than white women, this racial disparity is not accounted for by differences in pre-diagnosis statin use[32]. However, no SNPs across the genome were identified for a significant interaction with baseline statin use in breast cancer risk[33].

Statins may afford protection for other cancer types as well. For instance, use of statins, in particular lipophilic statins, is associated with a borderline lower risk of non-Hodgkin's lymphoma and with a significantly lower risk of diffuse large B-cell lymphoma in the large Women's Health Initiative cohort study[34]. In one retrospective cohort of women diagnosed with ovarian cancer, statin therapy was found to be associated with better overall survival amongst elderly patients[35]. Consistently, a systematic review and meta-analysis based on relevant studies that together included nearly 20,000 patients with ovarian cancer provides significant evidence of an overall protective effect of post-diagnostic statin use on all-cause and cancer-specific mortality[36].

Finally, on a slightly different note, one retrospective study showed that uninterrupted use of statins in women suffering from breast cancer before and during anthracycline chemotherapy is associated with a lower risk of new-onset incident heart failure[37]. Of the proposed mechanisms, it is conceivable that statin pre-treatment attenuates anthracycline-induced oxidant stress by inhibiting isoprenoid synthesis or microRNAs in cardiomyocyes[38].

Statins as a novel therapeutic option for preeclampsia and polycystic ovary syndrome

Preeclampsia (PE) is a serious systemic vascular complication affecting 3-5% of all pregnancies[39], and is a risk factor for future CVD[40]. All stages of PE are characterised by vascular changes that, theoretically, could benefit from pharmacological treatments targeting inflammation, cytokines and pro-thrombotic factors. Statin use during the final two trimesters of pregnancy appears to be beneficial in preventing and managing PE patients[41-44] at least in part via anti-inflammatory effects, in view of the increased levels of inflammatory markers (hs CRP) observed in preeclamptic women. Alternatively, gesta-

Table 1. Emerging gender-specific considerations for statin treatment: the highlights.

Conditions	Comment	HR/OR	Reference
Post-acute coronary syndrome	Add-on therapy with ezetimibe more beneficial in high-risk women than men	Primary composite endpoint in women: HR 0.88; 95% CI 0.79-0.99; in men: HR 0.95; 95% CI 0.90-1.01 Total number of primary events in women: HR 0.81; 95% CI 0.71-0.94; in men: HR 0.94; 95% CI 0.87-1.02	22
New-onset type 2 diabetes	Increased dose-dependent risk due to statin treatment in elderly women	HR 1.33; 95% CI 1.04-1.70	28
Breast cancer	Statin use is associated with improved survival	All-cause mortality: HR 0.78; 95% CI 0.69-0.89 Breast cancer-specific mortality: HR 0.81; 95% CI 0.68-0.96	31
Ovarian cancer	As above	HR 0.66; 95% CI 0.55-0.81 All-cause mortality: HR 0.74; 95% CI 0.63-0.87 Cancer-specific mortality: HR 0.87; 95% CI 0.80-0.95	35, 36
Preeclampsia	Pravastatin appears to be effective and safe for the mother and the newborn	Case reports and small-scale phase I trials	41-44
PCOS	Small intervention studies show endocrinological and metabolic benefit of statin treatment	Improvement in surrogate endpoints and significant reduction in HOMA-β	45, 46

HR: hazard ratio; CI: confidence interval; HOMA: homeostasis model assessment.

tional dyslipidaemia could play an important role in accelerated atherosclerosis in the mother as well as in the newborn. Because of its pharmacokinetic profile, a hydrophilic statin, like pravastatin, is less likely to cross the placental barrier and no serious birth defects effects have been noted thus far. The observed safety of pravastatin, in terms of teratogenicity, should be of interest when managing pregnant high-risk women with (very) high LDL-C plasma levels, due e.g. to familial hypercholesterolemia, plus clinical manifestations of atherosclerotic cardiovascular disease, where interrupting statin treatment could be potentially life-threatening. However, data from ongoing randomised clinical trials are needed to determine efficacy and safety in pregnant women and their offspring.

Finally, two recent randomised, double-blind, placebo-controlled studies highlighted the benefit of statin treatment in women with polycystic ovary syndrome (PCOS). In the first, the experimental group received 20 mg simvastatin for 6 months, resulting in improved metabolic and endocrinological endpoints[45]. In the second, treatment with atorvastatin for 12 weeks significantly reduced HOMA-β and improved insulin resistance without inducing hyperglycaemia or hyperinsulinemia[46].

Conclusions

Although the benefits of statins outweigh the risks, these medications should be used responsibly, paying greater attention to the hazard posed by e.g. age and polypharmacy. Statins should be used carefully in elderly women, who are more susceptible to new-onset type 2 diabetes. On the other hand, high-risk women appear to benefit more than men from statin treatment and should be considered for this kind of treatment. Accumulating evidence also suggests that statins may be beneficial in non-cardiovascular settings such as cancer and endocrinological disease that are prevalent in women (Table 1). Thus, novel opportunities are emerging and further studies are awaited to confirm the clinical effectiveness of statins outside the CVD field.

Key messages

- Statin use should be widened and not be denied to women with cardiovascular disease, who may, in actual fact, achieve greater benefits than men.
- Recommended high-intensity statins are still underused in women after myocardial infarction.
- Several studies suggest that statin use substantially increases the risk of type 2 diabetes in both men and women. Elderly women should not be exposed to higher doses of statins.
- Statins appear to increase breast- and ovarian cancer–specific as well as overall survival as compared to no statin use.
- Indications such as preeclampsia and polycystic ovary syndrome are emerging for statin use in younger women.

References

1. Gutierrez J, Ramirez G, Rundek T, Sacco RL. Statin therapy in the prevention of recurrent cardiovascular events: a sex-based meta-analysis. Arch Intern Med 2012; 172: 909-18.
2. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. J Am Coll Cardiol 2012; 59: 572-82.
3. Tziomalos K, Kakafika AI, Athyros VG, Karagiannis A, Mikhailidis DP. The role of statins for the primary and secondary prevention of coronary heart disease in women. Curr Pharm Des 2009; 15: 1054-62.
4. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia: the West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333: 1301-7.
5. Benjamin EJ, Virani SS, Callaway CW, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018; 137: e67-e492.
6. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation 2016; 133: 916-47.
7. Puri R, Nissen SE, Nicholls SJ. Statin-induced coronary artery disease regression rates differ in men and women. Curr Opin Lipidol 2015; 26: 276-81.
8. Puri R, Nissen SE, Shao M, et al. Sex-related differences of coronary atherosclerosis regression following maximally intensive statin therapy: insights from SATURN. J Am Coll Cardiol Cardiovasc Imaging 2014; 7:1013-22.
9. Truong QA, Murphy SA, McCabe CH, et al. Benefit of intensive statin therapy in women: results from PROVE IT-TIMI 22. Circ Cardiovasc Qual Outcomes 2011; 4: 328-36.
10. Wada H, Ogita M, Miyauchi K, et al. Impact of gender difference on long-term outcomes of percutaneous coronary intervention for coronary artery disease in patients under statin treatment. Heart Vessels 2017; 32: 16.
11. Raparelli V, Pannitteri G, Todisco T, et al. Treatment and response to statins: gender-related differences. Curr Med Chem 2017; 24: 2628-38.
12. McKibben RA, Al Rifai M, Mathews LM, Michos ED. Primary prevention of atherosclerotic cardiovascular disease in women. Curr Cardiovasc Risk Rep 2016; 10.
13. Singh A, Collins BL, Gupta A, et al. Cardiovascular risk and statin eligibility of young adults after an MI: Partners YOUNG-MI Registry. J Am Coll Cardiol 2018; 71: 292-302.
14. Karalis DG, Wild RA, Maki KC, et al. Gender differences in side effects and attitudes regarding statin use in the understanding statin use in America and gaps in patient education (USAGE) study. J Clin Lipidol 2016; 10: 833-41.
15. Salami JA, Warraich HJ, Valero-Elizondo J, et al. National trends in nonstatin use and expenditures among the US adult population from 2002 to 2013: insights from Medical Expenditure Panel Survey. J Am Heart Assoc 2018; 7: e007132.
16. Olufade T, Zhou S, Anzalone D, et al. Initiation patterns of statins in the 2 years after release of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol management guideline in a large US health plan. J Am Heart Assoc 2017; 6.
17. Victor BM, Teal V, Ahedor L, Karalis DG. Gender differences in achieving optimal lipid goals in patients with coronary artery disease. Am J Cardiol 2014; 113: 1611-15.
18. Peters SA, Colantonio LD, Zhao H, et al. Sex differences in high-intensity statin use following myocardial infarction in the United States. J Am Coll Cardiol 2018; 71: 1729-37.
19. Eindhoven DC, Hilt AD, Zwaan TC et al. Age and gender differences in medical adherence after myocardial infarction: women do not receive optimal treatment: the Netherlands claims database. Eur J Prev Cardiol 2018: 25: 181-89.
20. Todd JV, Cole SR, Wohl DA, et al. Underutilization of statins when indicated in HIV-seropositive and seronegative women. AIDS Patient Care STDS 2017; 31: 447-54.
21. Justo D, Tchernichovsky M, Kremer A, et al. Gender differences in mortality among statin users aged 80 years or more. Z Gerontol Geriatr 2017; doi: 10.1007/s00391-017-1335-y.
22. Kato ET, Cannon CP, Blazing MA, et al. Efficacy and safety of adding ezetimibe to statin therapy among women and men: insight from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). J Am Heart Assoc 2017; 6.
23. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015; 385: 1397-405.
24. Mombelli G, Bosisio R, Calabresi L, et al. Gender-related lipid and/or lipoprotein responses to statins in subjects in primary and secondary prevention. J Clin Lipidol 2015; 9: 226-33.
25. Wooten JM. A brief drug class review: considerations for statin use, toxicity, and drug interactions. South Med J 2018; 111: 39-44.
26. Carter AA, Gomes T, Camacho X, et al. Risk of incident diabetes among patients treated with statins: population based study. BMJ 2013; 346: f2610.
27. Yu Q, Chen Y, Xu CB. Statins and new-onset diabetes mellitus: LDL receptor may provide a key link. Front Pharmacol 2017; 8: 372.
28. Jones M, Tett S, Peeters GM, et al. New-onset diabetes after statin exposure in elderly women: the Australian Longitudinal Study on Women's Health. Drugs Aging 2017; 34: 203-09.
29. Lee SE, Sung JM, Cho IJ, et al. Risk of new-onset diabetes among patients treated with statins according to hypertension and gender: results from a nationwide health-screening cohort. PLoS One 2018; 13: e0195459.
30. Brennan DJ, Laursen H, O'Connor DP, et al. Tumor-specific HMG-CoA reductase expression in primary premenopausal breast cancer predicts response to tamoxifen. Breast Cancer Res BCR 2011; 13: R12.
31. Smith A, Murphy L, Zgaga L, et al. Pre-diagnostic statin use, lymph node status and mortality in women with stages I-III breast cancer. Br J Cancer 2017; 117: 588-96.
32. Leiter A, Bickell NA, LeRoith D, et al. Statin use and breast cancer prognosis in black and white women. Horm Cancer 2018; 9: 55-61.

33. Bock CH, Jay AM, Dyson G, et al. The effect of genetic variants on the relationship between statins and breast cancer in postmenopausal women in the Women's Health Initiative observational study. Breast Cancer Res Treat 2018; 167: 741-49.
34. Desai P, Wallace R, Anderson ML, et al. An analysis of the effect of statins on the risk of Non-Hodgkin's Lymphoma in the Women's Health Initiative cohort. Cancer Med 2018; 7: 2121-30.
35. Vogel TJ, Goodman MT, Li AJ, Jeon CY. Statin treatment is associated with survival in a nationally representative population of elderly women with epithelial ovarian cancer. Gynecol Oncol 2017; 146: 340-45.
36. Li X, Zhou J. Impact of postdiagnostic statin use on ovarian cancer mortality: a systematic review and meta-analysis of observational studies. Br J Clin Pharmacol 2018; 84: 1109-20.
37. Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: an observational clinical cohort study. J Am Coll Cardiol 2012; 60: 2384-90.
38. Tian S, Zhao W, Yang D, et al. Atorvastatin inhibits miR-143 expression: a protective mechanism against oxidative stress in cardiomyocytes. Int J Cardiol 2016; 211: 115-18.
39. American College of Obstetricians and Gynecologists. Hypertension in pregnancy: report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122: 1122-31.
40. Lee G, Tubby J. Preeclampsia and the risk of cardiovascular disease later in life – a review of the evidence. Midwifery 2015; 31: 1127-34.
41. Gajzlerska-Majewska W, Bomba-Opon DA, Wielgos M. Is pravastatin a milestone in the prevention and treatment of preeclampsia? J Perinat Med 2018; Mar 23. doi:10.1515/jpm-2017-0109.
42. Esteve-Valverde E, Ferrer-Oliveras R, Gil-Aliberas N, et al. Pravastatin for preventing and treating preeclampsia: a systematic review. Obstet Gynecol Surv 2018; 73: 40-55.
43. Maierean SM, Mikhailidis DP, Toth PP, et al. The potential role of statins in preeclampsia and dyslipidemia during gestation: a narrative review. Expert Opin Investig Drugs 2018; 27: 427-35.
44. Costantine MM, Cleary K, Hebert MF, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. Am J Obstet Gynecol 2016; 214: 720.e1-17.
45. Seyam E, Al Gelany S, Abd Al Ghaney A, et al. Evaluation of prolonged use of statins on the clinical and biochemical abnormalities and ovulation dysfunction in single young women with polycystic ovary syndrome. Gynecol Endocrinol 2017; 1-8.
46. Sathyapalan T, Coady AM, Kilpatrick ES, Atkin SL. The effect of atorvastatin on pancreatic beta cell requirement in women with polycystic ovary syndrome. Endocr Connect 2017; 6: 811-16.

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Correspondence to:
Andrea Cignarella
Department of Medicine
University of Padua
Pharmacology Building
Largo Meneghetti 2
35131 Padova
email andrea.cignarella@unipd.it