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Therapeutic Roles of Statins in Gynecology and Obstetrics: The Current Evidence

Burak Zeybek, MD[1], Maged Costantine, MD[1], Gokhan S. Kilic, MD[1], and Mostafa A. Borahay, MD, PhD[2]

Abstract

Introduction: Statins are a class of drugs, which act by inhibiting the rate-limiting enzyme of cholesterol biosynthesis (3-hydroxy-3-methyl-glutaryl-CoA reductase). The inhibition of mevalonate synthesis leads to subsequent inhibition of downstream products of this pathway, which explains the pleiotropic effects of these agents in addition to their well-known lipid-lowering effects. Accumulating evidence suggests that statins might be beneficial in various obstetric and gynecologic conditions. **Methods:** Literature searches were performed in PubMed and EMBASE for articles with content related to statins in obstetrics and gynecology. The findings are hereby reviewed and discussed. **Results:** Inhibition of mevalonate pathway leads to subsequent inhibition of downstream products such as geranyl pyrophosphate, farnesyl pyrophosphate, and geranylgeranyl pyrophosphate. These products are required for proper intracellular localization of several proteins, which play important roles in signaling pathways by regulating membrane trafficking, motility, proliferation, differentiation, and cytoskeletal organization. The pleiotropic effects of statins can be summarized in 4 categories: antiproliferative, anti-invasive, anti-inflammatory, and antiangiogenic. The growing body of evidence is promising for these agents to be beneficial in endometriosis, polycystic ovary syndrome, adhesion prevention, ovarian cancer, preeclampsia, and antiphospholipid syndrome. Although in vivo studies showed varying degrees of benefit on fibroids and preterm birth, appropriately designed clinical trials are needed to make definitive conclusions. **Conclusion:** Statins might play a role in the treatment of endometriosis, polycystic ovary syndrome, adhesion prevention, ovarian cancer, preeclampsia, and antiphospholipid syndrome.

Keywords

statins, endometriosis, fibroids, leiomyoma, polycystic ovary syndrome, adhesion prevention, gynecologic cancers, preeclampsia, antiphospholipid syndrome, preterm birth

Introduction

Statins are a class of drugs primarily used for the treatment of hypercholesterolemia and coronary artery disease. They act by inhibiting the rate-limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, which catalyzes the conversion of HMG to mevalonate.[1] The inhibition of mevalonate synthesis leads to subsequent inhibition of downstream products of this pathway, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), which are required for intracellular localization of several proteins (Figure 1).[2] These intracellular proteins play important roles in signaling pathways by regulating membrane trafficking, motility, proliferation, differentiation, and cytoskeletal organization,[3] which explain the pleiotropic effects of these agents in addition to their well-known lipid-lowering effects. Many of these effects were shown to be beneficial in certain female reproductive problems. In this article, we will review and analyze the current literature regarding the beneficial effects of statins in various gynecologic and obstetric conditions.

Statins in Gynecology

Endometriosis

Endometriosis is a common estrogen-dependent gynecologic condition, which is defined as the presence of the endometrial glands and/or stroma outside the uterine cavity. It is an important health issue of reproductive aged women, as its incidence is reported to be 6% to10%.[4] The potential effects of statins on endometriosis have been studied widely and have been attributed to 4 main pleiotropic effects (Figure 2).

[1] Department of Obstetrics & Gynecology, The University of Texas Medical Branch, Galveston, TX, USA
[2] Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Corresponding Author:
Mostafa A. Borahay, Department of Obstetrics & Gynecology, Johns Hopkins University School of Medicine, 4940 Eastern Ave, Baltimore, MD 21224-2780, USA.
Email: mboraha1@jhmi.edu

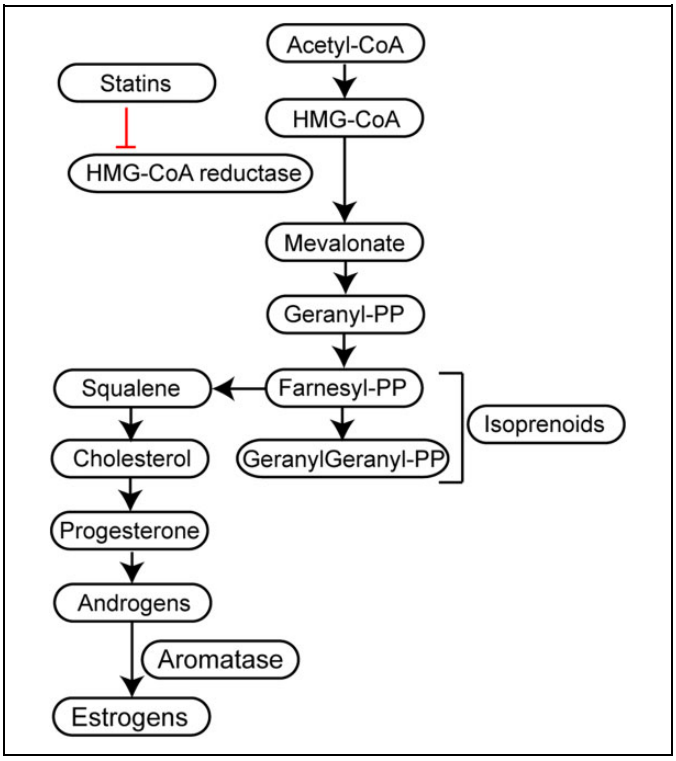

Figure 1. Mevalonate pathway demonstrating effects of statins. Farnesyl-PP and geranylgeranyl-PP (known as isoprenoids) are involved in posttranscriptional modification of proteins and their intracellular localization. In addition to ovaries, aromatase is expressed by uterine fibroids and endometriosis tissues. Farnesyl-PP indicates farnesyl pyrophosphate; geranyl-PP, geranyl pyrophosphate; geranylgeranyl-PP, geranylgeranyl pyrophosphate; HMG-CoA, hydroxy-methyl-glutaryl-CoA. Red line denotes inhibition.

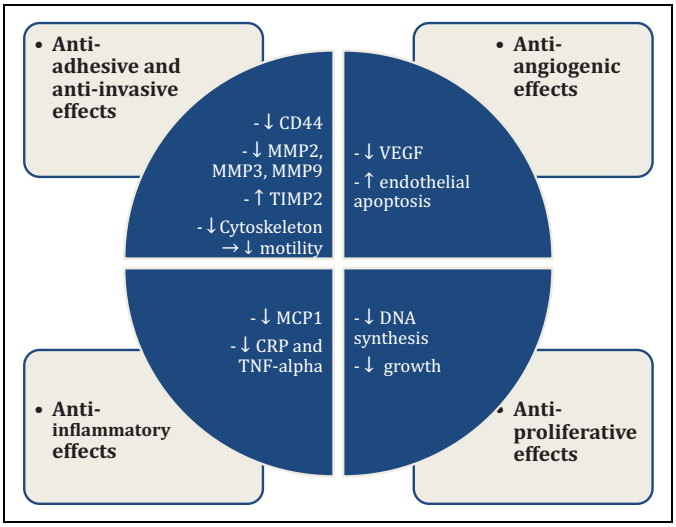

Figure 2. Mechanisms of statin effects in endometriosis. ↑ and ↓ denote increased or decreased expression or function, respectively. CRP indicates C-reactive protein; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinases; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Antiadhesive and anti-invasive properties. The formation of endometriotic implants requires complex interactions between ectopic endometrial cells and the peritoneum. The initial step of these interactions is "adhesion," which was demonstrated to be stronger in endometriotic stromal cells.[5] This enhanced adhesive properties was mainly attributed to increased concentrations and higher expressions of CD44 in peritoneal fluid and endometrial stromal cells of patients with endometriosis.[6,7] CD44 is a transmembrane protein that plays a significant role during initiation of the attachment between endometriotic cells and the peritoneum.[8] Simvastatin was found to be effective in decreasing this adhesiveness by downregulating CD44 expression.[9] In another study, simvastatin was demonstrated to suppress the attachment of endometriotic stromal cells to collagen fibers in a 3-dimensional collagen gel culture system.[10]

Besides adhesion, the second step of interaction is invasion in the pathogenesis of the disease. Invasion requires degradation of basement membrane, which is achieved by increased expressions of matrix metalloproteinases (MMPs). Statins have been shown to be effective in downregulating MMP-2, MMP-3,[9] MMP-9[11] and upregulating tissue inhibitor of MMP-2 expression,[9] as well as impairing cell motility by disrupting the cell cytoskeleton.[12] The latter was demonstrated to be enhanced by disorganizing F-actin fibers, altering cell shape, and inducing cell shrinkage. The disrupted cytoskeleton decreases the invasiveness of the disease; this is suggested to be mediated by inhibition of geranylgeranylation.

Antiangiogenic properties. One of the reasons statins are of great interest for treating endometriosis has been their impact on angiogenesis, independent from their lipid lowering effects.[13] So far, studies have shown that statins' effect on angiogenesis is biphasic and dose dependent.[13,14] Weis et al[14] reported that low concentrations of statins (0.005-0.01 µmol/L) enhanced endothelial cell proliferation, migration, and differentiation; however, high statin concentrations (0.05-1 µmol/L) significantly inhibited angiogenesis. Antiangiogenic effects at high concentrations were associated with decreased endothelial release of vascular endothelial growth factor (VEGF) and increased endothelial apoptosis, which were reversed by GGPP, again supporting "inhibition of geranylgeranylation" as a potential mechanism. Similar findings were reported by Oktem et al,[15] who reported that low dose of atorvastatin (0.5 mg/kg/d orally) induced proangiogenic effects through endothelial nitric oxide synthesis in Wistar-albino rats, whereas high-dose atorvastatin (2.5 mg/kg/d orally) inhibited angiogenesis. In another study, Esfandiari et al[16] examined the inhibitory effects of lovastatin on angiogenesis in a 3-dimensional culture of human endometrial fragments and demonstrated that angiogenesis was abolished in a dose-dependent manner. Sharma et al[17] confirmed these findings by showing a significant time- and dose-dependent downregulation of VEGF expression in an atorvastatin exposed culture.

Anti-inflammatory and antioxidative properties. Endometriosis is known to be a pro-inflammatory condition, and few studies

investigated the anti-inflammatory effects of statins on this disease. Sharma et al[17] first demonstrated that atorvastatin attenuated gene expression profiles of inflammation in a time- and dose-dependent manner in endometriotic cells. In a very recent study by Taylor et al,[18] simvastatin not only reduced the volume of endometriotic lesions in a baboon model of endometriosis, but it also reduced the expression of neopterin, which is a marker of inflammation. Another possible mechanism of "anti-inflammatory" action was reported by Cakmak et al,[19] who showed decreased monocyte chemotactic protein 1 expressions by atorvastatin and mevastatin in cultured endometriotic cells. In another study by Simsek et al,[20] atorvastatin was found to decrease serum levels of high-sensitivity C-reactive protein (HS-CRP) and tumor necrosis factor (TNF) α in a rat endometriosis model.

Antiproliferative properties. Statins also show antiproliferative effects and decrease growth in endometriosis. In the study by Piotrowski et al,[21] a concentration-dependent decrease of DNA synthesis and cell count of endometrial stromal cells were demonstrated with simvastatin and mevastatin, and these effects were independent of cholesterol availability. The mechanism of antiproliferative effect in this study was mainly attributed to decreased mitogen-activated protein kinase 3/1 (MAPK3/1) activation, which is important in the pathogenesis of the disease. Mitogen-activated protein kinases regulate cell function including proliferation, differentiation, and mitosis, and their activation requires isoprenylation of small guanosine triphosphateses, which is reduced by statins' inhibitory effect on HMG-CoA reductase; thus, this leads to decreased MAPK pathway activity including MAPK3/1. Similar antiproliferative findings were also reported by Esfandiari et al,[16] who showed a lovastatin-induced, concentration-dependent inhibitory effect on cell growth in an in vitro endometriosis model. In this study, high statin concentrations (5-10 μM) significantly decreased cell proliferation compared to controls. However, the same effect could not be observed in the setting of low statin concentration (1 μM).

Clinical evidence. Currently, there is only 1 published clinical trial for statin use in endometriosis. Almassinokiani et al[22] compared the efficacy of a statin with a gonadotropin-releasing hormone agonist on endometriosis-related pain after surgery. In this study, patients were assigned into 2 groups (30 in each) to receive either simvastatin (20 mg, orally, daily, for 16 weeks) or decapeptyl (3.75 mg, intramuscular, monthly, for 4 doses) after laparoscopic surgery for endometriosis-related pelvic pain. Visual analog scores for dyspareunia, dysmenorrhea, and pelvic pain 6 months after laparoscopic surgery declined significantly in both groups; however, the difference between 2 groups was not statistically significant. Although authors concluded that both treatments showed comparable effectiveness, it is impossible to make firm conclusions due to significant limitations. One of them is the selection bias in the simvastatin group, for which the major reason for surgery was reported to be infertility rather than pain. Second and the most important one is that there was no control group, which would have helped to discriminate the effects of surgery for pain in both study groups.

Despite the growing evidence supporting the use of statins in the treatment of endometriosis, more well-designed clinical trials are needed, especially those which investigate safe and effective doses, as animal studies suggest higher than standard doses for achievement of aforementioned pleiotropic effects.

Uterine Fibroids

Uterine fibroids are the most common tumors of female reproductive tract with a lifetime incidence of 50% to 70%.[23] Although treatment options exist such as contraceptive steroids, gonadotropin-releasing agonists, progesterone modulators, uterine artery embolization, and radiofrequency ablation, they mostly provide partial relief and some are associated with significant side effects. Currently fibroid uterus is the main indication for more than half of the 400 000 hysterectomies that are being performed in the United States annually.

The idea of investigating the effects of statins on fibroid growth arose from the studies that were previously performed in a number of neoplasms including breast,[24] gynecologic,[25] prostate,[26] colon,[27] and leukemia.[28] Borahay et al[29] published the first study of the effects of these agents on fibroids, which demonstrated that simvastatin had dual effect on human leiomyoma cells. First effect was the inhibition of proliferation via inhibition of extracellular signal-regulated kinases (ERK) phosphorylation, which is a common pathway for growth factor signaling. As human leiomyoma cells are dependent upon the presence of autocrine production of steroids and continuous stimulation of a variety of growth factors, such as insulin-like growth factor 1,[30,31] platelet-derived growth factor,[32] and epidermal growth factor,[33] this inhibition of ERK phosphorylation signaling pathway might have impact on leiomyoma growth. Second effect was cell cycle arrest, which was induced by activation of high, voltage-activated L-type calcium channels, leading to mitochondrial calcium influx and release of proapoptotic factors such as cytochrome c. Addition of nimodipine, a calcium channel blocker, blocked the calcium-dependent apoptosis induced by simvastatin, supporting the role of L-type calcium channels in cell cycle arrest. In another study of a patient-derived xenograft mouse model, simvastatin was shown to inhibit phosphorylation of growth factor signaling pathway, AKT.[34] This inhibition increased the levels of apoptotic Bcl-2 family member protein, Bim that led to enhanced apoptosis and inhibition of proliferation. Figure 3 presents proposed mechanism of action of simvastatin in fibroid cells.

The only human study for the effects of statins on fibroids is a nested case control study, in which the association between statin use and risk of uterine fibroids and fibroid-related symptoms were investigated.[35] From a cohort of women aged 18 to 65 years diagnosed with hyperlipidemia, 47 713 women with a diagnosis of uterine fibroids were matched with 143 139 controls. Exposure to statins within 2 years before the event/index date was found to be associated with a decreased risk of

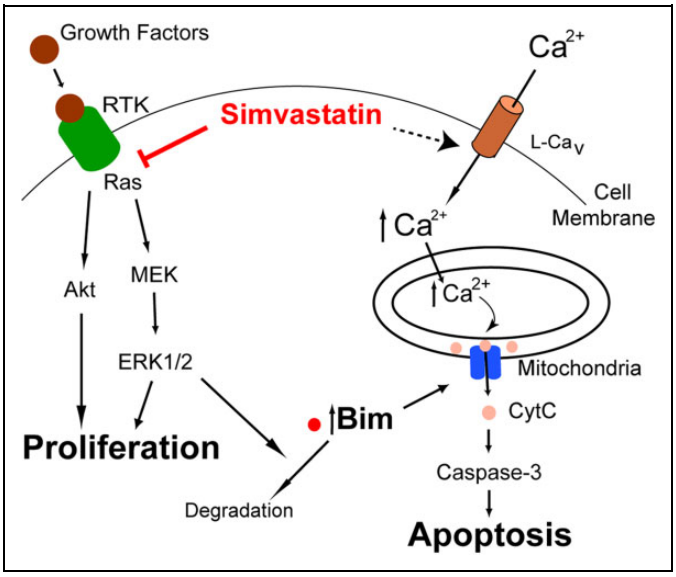

Figure 3. Proposed mechanisms of simvastatin effects in fibroid cells. Effects include inhibition of growth factors signaling and increased expression of the proapoptotic Bcl-2 family member protein Bim through decreased ERK-mediated degradation. This leads to mitochondrial leakage of cytochrome c and caspase-3 activation. This also requires activation of L-Ca_V and intramitochondiral calcium influx. CytC indicates cytochrome C; ERK, extracellular signal-regulated kinases; L-Ca_V, L-type voltage-gated calcium channels; RTK, receptor tyrosine kinase. Adapted from Borahay et al.[29]

fibroids (odds ratio: 0.85; 95% confidence interval [CI]: 0.83-0.87). Statin users also had a lower likelihood of having menorrhagia (odds ratio: 0.88; 95% CI: 0.84-0.91), anemia (odds ratio: 0.84; 95% CI: 0.79-0.88), pelvic pain (odds ratio: 0.85; 95% CI: 0.81-0.91), and lower likelihood of undergoing myomectomy (odds ratio: 0.76; 95% CI: 0.66-0.87).

Although initial reports are promising, it should be mentioned that there is no clinical trial yet investigating the effects of these agents specifically on fibroids. Future studies are needed especially to find the most efficacious dose without side effects. Development of targeted drug delivery technologies might be considered.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among reproductive aged women with a varying prevalence of 6% to 20% depending on the diagnostic criteria used.[36,37] The use of statins in the management of this challenging disease has been of great interest due to the fact that the pleiotropic effects of these drugs could be implemented in the treatment. Initial reports of in vitro studies suggested that statins might alter ovarian steroidogenesis in 2 ways: first, by reducing steroid hormone synthesis[38] and, second, by decreasing the growth of theca-interstitial cells in ovaries.[39] The mechanism of reduced steroid hormone synthesis, at least in part, was attributed to decreased expression of CYP17A1 gene, which encodes the enzyme 17α-hydroxylase/17,20 lyase.[40] This enzyme has a dual effect and is responsible for conversions of pregnenolone to 17-hydroxyprognenolone and dehydroepiandrosterone, progesterone to 17-hydroxyprogesterone and androstenedione. Another possible mechanism could be the decrease in isoprenylation substrates (GPP, FPP, GGPP) in mevalonate pathway that leads to decreased steroid synthesis. In the study by Ortega et al,[40] this mechanism is supported by the fact that addition of FPP and GGPP in vitro significantly reversed simvastatin-induced suppression of CYP17A1 messenger RNA (mRNA) expression and androgen levels. The effect of decreased theca cell growth might be due to blockade of farnesylation by these drugs, which leads to reduction of posttranslational modifications of several rat sarcoma (RAS) family proteins and a subsequent decrease in the activity of RAS-MAPK signaling pathway.[39,41]

These aforementioned findings from in vitro trials were further evaluated in clinical studies so far; 3 meta-analyses have investigated the effects of statins on endocrine profile of women with PCOS. A Cochrane review and meta-analysis included 4 randomized controlled trials (RCTs), comprising a total of 244 women with PCOS, who received 6 or 12 weeks of treatment.[42] Two of the 4 studies investigated statin monotherapy (atorvastatin) versus placebo, and 2 other studies evaluated the combination of statin (simvastatin) with other agents versus a comparable combination. As a result, although statins were found to improve lipid profiles and reduce testosterone levels in women with PCOS, there was no evidence that statins improved resumption of menstrual regularity or spontaneous ovulation, or there was any improvement of hirsutism or acne. There was also no evidence of effect of statins either alone or combination with oral contraceptive pills on high-density lipoprotein (HDL), fasting insulin, HS-CRP, or insulin resistance. Another meta-analysis, which included 4 RCTs, investigated the effects of statins on serum total testosterone levels and lipid profiles in patients with PCOS.[43] Three of these studies compared the effect of a statin (either simvastatin or atorvastatin) with placebo, and the fourth one was a multi-arm study comparing simvastatin, metformin, and simvastatin plus metformin. The decline in serum total testosterone was found to be statistically significant when statin was used either alone or in combination with metformin when compared to controls. Also, statins were found to significantly improve serum total cholesterol, triglyceride, and low-density lipoprotein levels as expected; however, there was no improvement in HDL, fasting blood glucose, or fasting insulin levels. In a more recent meta-analysis, Sun et al[44] investigated the therapeutic effects of statins with metformin on PCOS. Data from 4 RCTs comparing statin and metformin with metformin alone concluded that although combined statin and metformin therapy could improve lipid and inflammation parameters, it did not effectively improve insulin sensitivity. There was also no improvement in hyperandrogenism, which was inconsistent with the previous 2 meta-analyses.

Table 1. Randomized Controlled Trials of Statins in Patients With Polycystic Ovary Syndrome.

Authors	PCOS diagnosis Criteria	Intervention	Duration of Treatment	Outcome
Duleba et al[47]	ESHRE/ ASRM	Simvastatin, 20 mg/d plus OCP (n = 24) vs OCP alone (n = 24)	12 weeks	- Testosterone levels declined by 41% in the statin group and by 14% in the OCP group. - There was a greater decrease of LH (43% decrease vs 9% in the OCP group) and a greater decline of LH/FSH ratio (44% vs 12%). In the statin group, total cholesterol declined by 10% and LDL by 24%. In the OCP group, total cholesterol increased by 8%, and LDL was unchanged.
Banaszewska et al[48]	ESHRE/ ASRM	Simvastatin plus OCP (n = 24) for 12 weeks followed by OCP alone for an additional 12 weeks or to OCP alone (n = 24) for 12 weeks and subsequently simvastatin plus OCP for an additional 12 weeks	24 weeks	- Total testosterone decreased by 38% after Statin + OCP, whereas OCP alone led to a 26% decrease. - Free testosterone declined by 58% after Statin + OCP, significantly more than the 35% decline after OCP alone. - Hirsutism decreased by 8.1% after Statin + OCP, a greater effect than the 4.7% decrease after OCP alone. - Statin decreased LH, but not FSH or prolactin. - Statin + OCP decreased total and LDL cholesterol by 7.5% and 20%, respectively. OCP alone led to a 5% increase of total cholesterol without effect on LDL cholesterol. - Statin prevented OCP induced increase of triglycerides. - CRP decreased by 45% after Statin + OCP, a significantly different effect than a 6% increase after OCP alone. - Soluble VCAM-1 decreased by 18% after Statin + OCP, a greater decline than the 10% decrease after OCP alone
Sathyapalan et al[49]	ESHRE/ ASRM	Atorvastatin 20 mg daily (n = 19) vs placebo (n = 18)	12 weeks	Significant reduction in atorvastatin group - CRP - Free androgen index - Testosterone - Insulin resistance Significant increase - Sex hormone binding globulin
Sathyapalan et al[50]	ESHRE/ ASRM	Atorvastatin 20 mg daily (n = 19) vs placebo (n = 18)	3-month period of atorvastatin vs placebo, which was followed by addition of metformin 1500 mg daily to be completed to a 6-month treatment	Significant increase in atorvastatin group - 25 OHD
Kazerooni et al[51]	ESHRE/ ASRM	Simvastatin 20 mg/d plus metformin (500 mg 3 times a day; n = 42) vs metformin (500 mg 3 times a day) plus placebo (n = 42)	12 weeks	Significantly greater decrease in simvastatin plus metformin group - Testosterone - LH - LH/FSH ratio
Rashidi et al[52]	ESHRE/ ASRM	Simvastatin 20 mg/d (n = 32) vs placebo (n = 32) in patients before they underwent IVF + ICSI for a male factor indication	8 weeks	Significantly greater decrease in simvastatin group - Testosterone level - CRP - Vascular cell adhesion protein 1 No statistically significant difference between groups - Mean DHEAS reduction - Fasting insulin nor quantitative insulin sensitivity check index - Median number of retrieved oocytes during IVF - Fertilization rates - Clinical pregnancy rates

(continued)

Table 1. (continued)

Authors	PCOS diagnosis Criteria	Intervention	Duration of Treatment	Outcome
Navali et al[53]	ESHRE/ ASRM	Simvastatin 20 mg/d (n = 200) vs metformin 500 mg 3 times daily (n = 200)	3 months	- In the statin group the lipid profile status (abnormal total cholesterol, high- and LDLs), CRP, serum DHEAS, hyperinsulinemia, severity of acne, and menstrual abnormalities improved significantly after treatment. - Comparing the 2 groups, the improvements in fasting blood sugar and serum insulin levels were significantly better in the biguanide group, whereas the improvements in serum total cholesterol, LDL, CRP (P <.001), and acne status were significantly superior in the statin receivers
Raja-Khan et al[54]	NIH	Atorvastatin 40 mg/d (n = 20) vs placebo (n = 20)	6 weeks	Significant reduction in atorvastatin group - Androstenedione - DHEAS No difference between groups - Fasting glucose - Insulin resistance
Banaszewska et al[55]	ESHRE/ ASRM	Simvastatin 20 mg/d (n = 41 at 3 months; n = 28 at 6 months) vs metformin 850 mg twice a day (n = 36 at 3 months; n = 33 at 6 months) vs simvastatin plus metformin (20 mg/d and 850 mg twice a day) (n = 37 at 3 months; n = 36 at 6 months)	Assessments were done at 3 and 6 months	- Total testosterone decreased significantly and comparably in all groups: by 25.6, 25.6, and 20.1%, respectively. - Both simvastatin and metformin improved menstrual cyclicity and decreased hirsutism, acne, ovarian volume, BMI, CRP, and soluble VCAM-1 -DHEAS declined significantly only in the simvastatin group
Sathyapalan et al[56]	ESHRE/ ASRM	Atorvastatin 20 mg daily (n = 19) vs placebo (n = 18)	3-month period of atorvastatin vs placebo, which was followed by addition of metformin 1500 mg daily to be completed to a 6-month treatment	Significant decrease of Malondialdehyde concentrations with atorvastatin
Sathyapalan et al[57]	ESHRE/ ASRM	Atorvastatin 20 mg daily (n = 19) vs placebo (n = 18)	3-month period of atorvastatin vs placebo, which was followed by addition of metformin 1500 mg daily to be completed to a 6-month treatment	Significant reductions in atorvastatin group - Androstenedione - DHEAS
Puurunen et al[58]	ESHRE/ ASRM	Atorvastatin 20 mg/d (n = 15) vs placebo (n = 13)	6 months	- Impaired insulin sensitivity in atorvastatin group - Decreased DHEAS and CRP levels in atorvastatin group - No differences in serum testosterone levels
Karakas et al[59]	ESHRE/ ASRM	Simvastatin 20 mg/d (n = 24) vs metformin 850 mg twice daily (n = 20) vs simvastatin plus metformin (n = 18)	3 months	Simvastatin alone or with metformin did not affect serum-free fatty acid binding protein 4 or retinol binding protein 4

(continued)

Table 1. (continued)

Authors	PCOS diagnosis Criteria	Intervention	Duration of Treatment	Outcome
Ghazeeri et al[60]		Rosuvastatin 10 mg/d plus metformin 850 mg twice daily (n = 18) vs rosuvastatin 10 mg/d plus placebo (n = 19)	Patients received rosuvastatin (10 mg/d) for a period of 3 months, then they were randomly allocated to 1 of 2 groups: rosuvastatin (10 mg/d) plus metformin (850 mg twice daily after meals) vs rosuvastatin (10 mg/d) plus placebo for a period of 3 months	No significant differences between groups at 3 and 6 months - CRP - Homocysteine - DHEAS - Testosterone - Insulin

Abbreviations: 25-OHD, 25-hydroxyvitamin D; ASRM, American Society of Reproductive Medicine; BMI, body mass index; CRP, C-reactive protein; DHEAS, dehydroepiandrosterone sulfate; ESHRE, European Society of Human Reproduction and Embryology; FSH, follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; LDL, low-density lipoprotein; LH, luteinizing hormone; NIH, National Institute of Health; OCP, oral contraceptive pill; PCOS, polycystic ovary syndrome; VCAM-1, vascular cell adhesion molecule-1.

A distillation from these studies suggests that, although statins seem to be effective regarding improvement of lipid profile and inflammation parameters, the results for improvement of insulin sensitivity and reduction of hyperandrogenism are conflicting at this time. This might be due to several reasons. First, studies exhibit significant heterogeneity regarding diagnostic criteria that were used to diagnose PCOS, body mass index of patients, serum insulin levels at baseline, and methods that were used to measure androgens. Second, the sample sizes of these studies are very small. Third, 6 to 12 weeks of therapy duration is not long enough to expect an improvement in hirsutism. Fourth, the pleiotropic potency of different types of statins varies greatly based on that statin's lipophilic chemical structure. While hydrophilicity requires organic anion transporters, lipophilicity gives the advantage to that specific statin to traverse cell membrane via passive diffusion. A direct comparison of relative lipophilicity of several statins has been previously studied and following rank order was demonstrated: simvastatin > lovastatin > atorvastatin >> pravastatin.[45] Sokalska et al[46] showed that higher the lipophilicity, higher the potency of that specific statin on both growth and steroidogenesis of theca-interstitial cells. This finding could partly explain the results in the meta-analysis by Sun et al,[44] as different statins (atorvastatin and simvastatin) are pooled and analyzed together. Finally, study selection criteria were different across these meta-analyses, which might explain the discrepancy in improvement of serum androgen levels. Randomized controlled trials of statins in patients with PCOS are summarized in Table 1.

In summary, although initial in vitro trials and some clinical studies were promising, larger scale appropriately designed RCTs are needed to further clarify the long-term benefits and the effects of these agents on serum hormone levels and clinical outcomes, such as hirsutism, acne, ovulatory function, and infertility, in patients with PCOS.

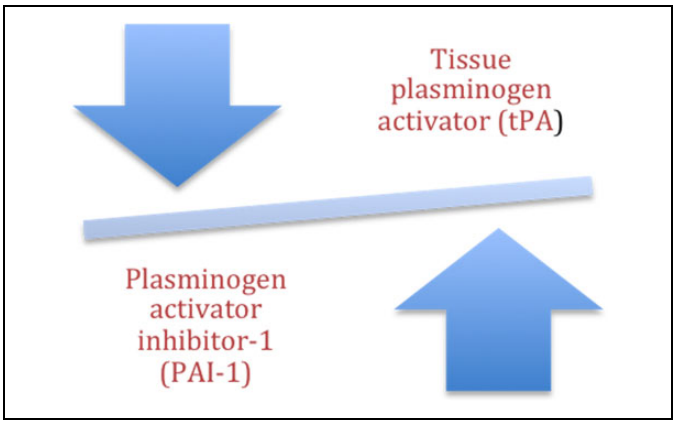

Figure 4. Proposed mechanism of statins in adhesion formation prevention. Statins reverse the process by increasing tPA and decreasing PAI-1. PAI-1 indicates plasminogen activator inhibitor-1; tPA, tissue plasminogen activator.

Adhesion Prevention

Intraperitoneal adhesion formation is one of the most important causes of long-term sequelae after surgeries. It is related to increased morbidity due to consequences such as intestinal obstruction, pelvic pain, dyspareunia, infertility, and also related to higher health-care costs due to readmissions and reoperations.[61,62] The pathophysiology of adhesion formation has been studied widely and 2 of the mechanisms have been attributed to increased levels of Transforming growth factor beta 1 (TGF-b1)[63] and an imbalance between tissue plasminogen activator (tPA)/plasminogen activator inhibitor-1 (PAI-1; Figure 4).[64]

The first study, evaluating the effects of statins on prevention of postoperative adhesion formation, was reported in 2007. Aaron et al,[65] in their study, demonstrated that intraperitoneal

administration of lovastatin and atorvastatin could reduce intra-abdominal adhesion formation if they were given within 6 hours of initial peritoneal insult. The mechanism of this effect was attributed to effects of these statins on fibrinolytic pathway as both lovastatin and atorvastatin was shown to increase tPA and decrease PAI-1 in vitro.

In another study, Lalountas et al[66] compared the effectiveness of a statin containing antiadhesive film with sodium hyaluronate–carboxymethylcellulose (Seprafilm^{TM},Genzyme Corporation, Cambridge, MA)) for prevention of postoperative adhesions. In this study, 100 Wistar rats were allocated into 5 groups: a control group with no adhesion barrier, sodium hyaluronate–carboxymethylcellulose group, a placebo group with a film containing carboxymethylcellulose without atorvastatin, a low-dose atorvastatin group with a film containing carboxymethylcellulose and atorvastatin of 0.125 mg per kg bodyweight, and a high-dose atorvastatin group with a film containing carboxymethylcellulose and atorvastatin of 1 mg per kg bodyweight. All antiadhesive film groups (Seprafilm, low- and high-dose atorvastatin) had significant adhesion reduction when compared to control. The atorvastatin groups were similar when compared to each other, but they were superior to Seprafilm in terms of adhesion prevention. Adhesions were present in 75% of rats in Seprafilm group; however, only 25% of rats had adhesions in low-dose atorvastatin group. In this study, the authors used the lowest (0.125 mg/kg to 10 mg per 80 kg) and highest (1 mg/kg to 80 mg per 80 kg) oral doses indicated for antilipid therapy, to test safe and clinically applicable doses of atorvastatin.

A more recent study by Arslan et al[67] investigated the effects of lovastatin on postsurgical adhesions and compared its effectiveness with hyaluronic acid and carboxymethyl cellulose (Seprafilm). Thirty-two Wistar-albino rats were used in this study and 4 groups were created as sham, control, lovastatin, and Seprafilm, each of which included 8 rats. In the lovastatin group, adhesion formation was significantly lower when compared to the control group. Lovastatin was also found to increase tPA and decrease PAI-1 production by human mesothelial cells. There was no significant difference between lovastatin and Seprafilm groups regarding postoperative adhesion formation.

Currently, there are no human studies investigating the efficacy, safety, and side effects of topical statins for prevention of postoperative adhesion formation. Thus, proper studies are needed to make definitive conclusions. Also, theoretical concern for increased risk of bleeding due to activated fibrinolytic pathway should be further investigated.

Gynecologic Malignancies

The potential benefit of statin use in treating various malignancies has been reported,[26-28] and their potential additive effect when used with standard chemotherapy regimens has been investigated in specific cancer types with promising results.[68] In gynecological cancers, statins have demonstrated several antitumor effects in vitro, such as enhanced apoptosis, decreased adhesiveness, and inhibition of proliferation (Table 2). Enhanced apoptosis was shown to be mediated via activation of caspase cascade.[77] Decreased adhesiveness achieved by decreased expressions of different adhesion molecules such as vascular cell adhesion molecule-1, annexin V, and β1 integrin.[78] Schointuch et al[73] reported the inhibitory effect of simvastatin on proliferation in endometrial cancer cell lines, which was achieved via inhibition of the MAPK pathway and induction of apoptosis. Stine et al[74] demonstrated significantly increased mitochondrial DNA damage, leading to apoptosis and significantly reduced cell adhesion/invasion in an ovarian cancer model. Inhibition of proliferation in this study was achieved by reduction of MAPK and AKT/mammalian target of rapamycin pathways, and decreased invasion was attributed to reduced VEGF production in tumor cells. A recent study demonstrated that statins' antiproliferative activity was especially strong in cancer cells with p53 mutations.[76] This information suggests that statins might be effective in high-grade serous ovarian cancers, as TP53 mutations occur in majority of these cases.

Despite these in vitro trials, human data have shown conflicting results. In a recent meta-analysis,[25] the use of statins was associated with a 21% risk reduction (RR: 0.79; 95% CI: 0.64-0.98) in the incidence of ovarian cancer; however, no association was found for endometrial cancer (RR: 0.90; 95% CI: 0.75-1.07). Elmore et al[79] reported improved overall survival for women with epithelial ovarian cancer who were statin users compared with nonusers ($P = .04$). Lavie et al[80] found improved survival for ovarian (hazard ratio: 0.45; 95% CI: 0.23-0.87) and a trend toward improved survival for patients with endometrial cancer receiving statin therapy. In a Danish nationwide registry including 4103 epithelial ovarian cancer patients, no difference was found in ovarian cancer incidence among statin users.[81]

These inconsistencies might be due to several reasons. First, the majority of these studies included small samples. Second, antitumor effects of these agents were demonstrated at supratherapeutic doses compared to hypercholesterolemia patients.[74,82] For example, while the maximum recommended clinical dose of simvastatin is 80 mg/d, Stine et al[74] used a dose of 3 mg/kg/d and Fang et al[82] used a dose of 5 mg/kg/d with no significant side effects. Third, instead of investigating the individual effects of different statins, all classes of statins are included and analyzed together in large database studies and meta-analyses. Kato et al[77] demonstrated that ovarian, endometrial, and cervical cancer cells undergo apoptosis in the presence of lipophilic, but not hydrophilic, statins. Due to their lipophilic structure, lovastatin and simvastatin easily pass the cellular membrane via passive diffusion and are metabolized to their active forms by cytochrome p450 3A4 inside the cell.[83,84] Contrarily, hydrophilic statins do not have the ability to pass through the cellular membrane directly and require membrane transporters, which are known to mediate not only the cellular entrance but also cellular excretion of these agents.[85,86] One of those transport protein, the multidrug resistance–associated protein-2, was suggested to be responsible for the absence of

Table 2. Evidence for Potential Antitumor Effects of Statins.

Author	Study Design	Malignancy	Statin	Mechanism of Action
Horiuchi et al [69]	Cultured cell line	Ovarian cancer	Lovastatin	- RhoA suppression
Liu et al[70]	Cultured cell line	Ovarian cancer	Lovastatin, atorvastatin	- Induction of apoptosis through activation of JNK and enhancement of Bim expression
Taylor-Harding et al[68]	Cultured cell line	Ovarian cancer	Fluvastatin	- Induction of apoptosis and cell cycle arrest
Matsuura et al[71]	Cultured cell line	Ovarian clear cell carcinoma	Simvastatin	- Induction of apoptosis and cell growth arrest by reducing osteopontin expression
Martirosyan et al[72]	Cultured cell line	Ovarian cancer	Lovastatin	- Induction of apoptosis - Sensitization of multidrug resistant cells to doxorubicin by inhibition of drug transport likely through inhibition of P-glycoprotein
Schointuch et al[73]	Cultured cell line	Endometrial cancer	Simvastatin	- Antiproliferative and antimetastatic effects by modulation of the mitogen activated protein kinase and AKT/mammalian target of rapamycin pathways
Stine et al[74]	Cultured cell line and mouse model	Ovarian cancer	Simvastatin	- Inhibition of proliferation, induction of cell cycle G1 arrest and apoptosis - Induction of DNA damage and reduce cell adhesion and invasion - Inhibition of MAPK and mTOR pathways
Karlic et al[75]	Cultured cell line	Breast cancer, prostate carcinoma, osteosarcoma	Simvastatin	-Downregulation of DNA methyltransferase and histone deacetylase - Regulation of micro RNAs - Downregulation of folate metabolism genes - Upregulation of vitamin D metabolism
Kobayashi et al[76]	Mouse model	Serous tubal intraepithelial carcinoma	Lovastatin	- Inhibition of tumor growth - Effects on the expression of genes associated with DNA replication, Rho/PLC signaling, glycolysis pathway

Abbreviations: mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; JKN, c-Jun N-terminal kinase; PLC, Phospholipase C.

effect of pravastatin on ovarian cancer cell lines due to high amounts of drug excretion from the cell.[86]

More studies, especially clinical trials, which particularly investigate the effects of lipophilic statins on different gynecologic cancer types, are needed for conclusive results.

Statins in Obstetrics

Preeclampsia

Preeclampsia, a pregnancy-specific multisystem disorder, remains a major cause of maternal/neonatal morbidity and mortality worldwide. Due to recent advances in understanding the pathogenesis of the disease, extensive research have focused on developing a novel preventive and therapeutic option. Statins have been suggested to be a good candidate due to the similarities between preeclampsia and cardiovascular disease and the confirmed role of these agents in prevention of cardiovascular morbidity and mortality.

Pravastatin is the specific statin that has been used in most of the studies for prevention and treatment of the disease, due to its several favorable structural characteristics to be used during pregnancy. First, it is one of the least potent inhibitors of HMG-CoA reductase, which makes it more advantageous for its pleiotropic effects to be applied instead of lipid-lowering effects.[87] Second, pravastatin has a short elimination half-life, that is, estimated to be 2.1 and 3 hours during the second and third trimesters, respectively, which helps to minimize fetal exposure.[88] Third, there is a dual clearing system for the drug via both hepatic and renal routes, which reduces the need for dose reduction in cases of renal or hepatic impairment. Fourth, it is the most polar hydrophilic statin among the current HMG-CoA reductase inhibitors, which minimizes the transfer of this drug to the fetus.[89,90] In an ex vivo study investigating the bidirectional transfer of pravastatin across human term placenta, Nanovskaya et al[89] concluded that not only fetal exposure to pravastatin is limited ($18\% \pm 4\%$), but that clearance in the fetal-to-maternal direction was higher than maternal-to-fetal direction, strongly suggesting the involvement of efflux transporters in decreasing its transfer in the placenta.

The mechanisms how statins could be beneficial in preeclampsia have been studied in animal models and these mechanisms could be classified as follows (Figure 5):

1. Restoration of angiogenic imbalance (decrease in sFlt-1 and soluble endoglin serum concentrations and increase in placental growth factor (PlGF) and VEGF expression).[91]
2. Decrease in blood pressure possibly through upregulation of endothelial nitric oxide synthase in the

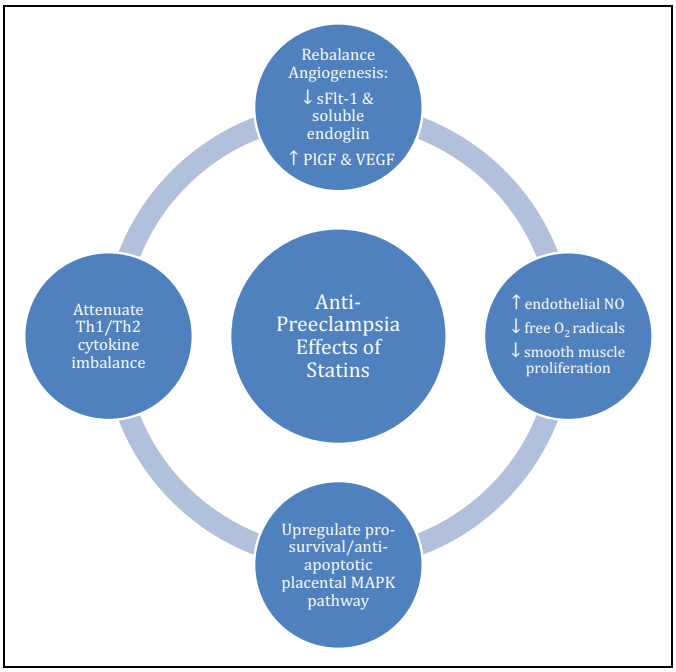

Figure 5. Anti-preeclampsia effects of statins. PlGF indicates placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; VEGF, vascular endothelial growth factor.

vasculature leading to improvement in vascular relaxation.[88,92]

3. Attenuation of imbalance in Th1/Th2 cytokine responses.[93]
4. Decrease in oxidative stress due to reduced free oxygen radicals, smooth muscle cell proliferation, upregulation of heme-oxygenase-1 expression.[88,92,94-98]
5. Improvement in placental blood flow due to restoration of trophoblast invasiveness and upregulation of prosurvival/antiapoptotic MAPK pathway in the placenta.[99]

Other than animal studies,[100,101] 2 clinical trials evaluated the effects of pravastatin on preeclampsia. Statins to Ameliorate early onset Preeclampsia (www.contolled-trials.com; ISRCTN23410175) trial aimed to evaluate whether pravastatin ameliorates angiogenic imbalance in women with severe preeclampsia before 32 weeks of gestation. The results of this trial have not been reported yet. The second trial is a pilot, multicenter, double-blind, placebo-controlled, randomized trial by *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network (www.cliniclatrials.gov. NCT01717586). In this study, women at high risk for preeclampsia (defined as a history of prior pregnancy requiring delivery less than 34 weeks of gestation due to preeclampsia with severe features) are randomized between 12 weeks 0 days and 16 weeks 6 days to receive either placebo or pravastatin 10 mg daily until delivery.[88] The results of this pilot trial showed that women who received pravastatin (n = 10) had lower rates of preeclampsia (0/10 vs 4/10) and indicated preterm delivery (1/10 vs 5/10) compared with women in the placebo group (n = 10). There were no differences in rates of drug side effects or congenital anomalies. The concentrations of PlGF were shown to be higher, and concentrations of sFlt-1 and soluble endoglin were lower in patients receiving pravastatin; however, the differences for these markers did not reach statistical significance. Although maternal serum cholesterol concentrations were lower in pravastatin group, umbilical cord cholesterol concentrations and infant birth weights were not different between 2 groups. The maternal and cord blood concentrations of liver (alanine and aspartate transaminases) and muscle (creatine kinase) enzymes were not increased with pravastatin therapy. Regarding neonatal outcomes, 5 infants born to women in the placebo group were admitted either to an intermediate nursery (n = 2) or the neonatal intensive care unit (NICU, n = 3) compared with 2 infants in the pravastatin group (intermediate nursery [n = 1], NICU [n = 1]). None of the newborns in either group failed their auditory brainstem response-evoked potential or similar hearing screening tests. Although the results of this trial are promising, it is still preliminary. The study is still enrolling patients using at a higher pravastatin dose.

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by arterial/venous thromboembolic events and obstetrical complications such as recurrent/spontaneous pregnancy losses, preterm preeclampsia, and growth restriction necessitating preterm birth. In women, who have APS secondary to recurrent early pregnancy losses, current standard therapy during pregnancy consists of low-dose aspirin in addition to heparin. This regimen has been shown to improve live birth rates, however, fails to prevent other pregnancy complications such as preeclampsia or growth restriction. The pathogenesis of these adverse pregnancy outcomes was initially thought to be due to a pure thrombotic process; however, more recent evidence in the light of partial success of anticoagulation therapy showed that exaggerated inflammation plays the major role.[102,103] The key mediator in this exaggerated inflammation was identified to be the tissue factor, which is known to be a major cellular activator of coagulation cascade, and increased tissue factor expression in neutrophils was shown to contribute to trophoblast injury, leading to pregnancy loss.[104,105] This pathologic mechanism in combination with data from previous studies, which demonstrated suppression of tissue factor expression by statins in various cell types,[106,107] encouraged researchers to focus on the anti-inflammatory properties of statins in the management of APS during pregnancy. In a mouse model of recurrent pregnancy loss induced by antiphospholipid (aPL) antibodies, Redecha et al[105] demonstrated that simvastatin and pravastatin prevented pregnancy loss. In this study, simvastatin and pravastatin were also shown to prevent tissue factor expression on neutrophils from aPL antibody–treated mice and reduced the aPL-associated increase in free radical-mediated lipid peroxidation in decidual tissue. However, not all of the in vitro trials showed similar beneficial

effects. In an aPL modulation of human trophoblastic cell line, pravastatin showed no impact on the secretion of pro-inflammatory cytokines and angiogenic factors indicating the need of more research for clarification.[108]

One clinical trial investigated the effects of statins on APS during pregnancy.[109] In a small observational prospective cohort study, 21 women with APS due to history of adverse pregnancy outcomes, who developed preeclampsia and/or intrauterine growth restriction, were divided into 2 groups. Ten patients were maintained on standard therapy of low-dose aspiring and heparin and were considered as the control group, whereas 11 patients were started on pravastatin (20 mg once daily) in addition to standard therapy and considered as the study group. When compared to the control group, the patients who received pravastatin had improved blood pressure and uterine artery blood flow. Time from initial diagnosis to delivery was significantly longer (13 weeks, interquartile range [IQR]: 8-14 weeks vs 4.5 weeks, IQR: 2-5), and gestational age at birth was significantly higher (36 weeks, IQR: 35-36 weeks vs 26.5 weeks, IQR: 26-32) in the pravastatin group. Although the results of this study are promising, significant limitations should be taken into account such as lack of placebo arm, small number of participants, and lack of blinding and randomization.

Preterm Birth

Preterm birth is a major cause of perinatal morbidity and mortality, as it affects more than 12% of pregnancies in the United States.[110] Although the exact initiating factors are still unknown, the growing body of evidence indicates inflammation as a major pathway. So far, several inflammatory cytokines (especially interleukin-1β [IL-1β], IL-6, IL-10, TNF-α, and MMP-9) were shown to play significant roles in the pathologic process of spontaneous preterm birth, which led to the hypothesis of using the anti-inflammatory properties of statins to prevent/control the inflammation.

In a mouse model of lipopolysaccharide (LPS)-induced inflammation, pretreatment with pravastatin resulted in decreased IL-1β mRNA expression in the uterus, IL-6 mRNA expression in the cervix, and decreased IL-1β and granulocyte-macrophage colony-stimulating factor concentrations in the serum.[111] In the same study, pretreatment with simvastatin was found to reduce IL-1β and IL-6 mRNA expressions in the uterus, TNF-α and IL-6 expressions in the cervix, and IL-6 levels in amniotic fluid. In another mouse model of LPS-induced inflammation, Gonzalez et al[112] showed that pravastatin and simvastatin prevented cervical remodeling and inhibited myometrial contractions and complement activation. The mechanism of action for decreased myometrial contraction was attributed to increased expression and activity of heme oxygenase 1 enzyme, an antioxidant enzyme that is essential in heme degradation by releasing carbon monoxide. The heme oxygenase/carbon monoxide pathway was previously shown in another study to decrease myometrial contractility.[113] Inhibition of complement activation also alleviates uterine activity, as C5a is known to be a significant uterotonic molecule.[114] This inhibition was attributed to increased expression of complement inhibitor decay-accelerating factor.[115]

The major limitation of the aforementioned studies is that statins were given prior to administration of the inflammatory stimulus (LPS), calling into question whether the inflammation would be reduced if they were given after the initiation of the inflammatory cascade. Using an ex vivo model of human fetal membrane explants, Basraon et al[116] investigated the anti-inflammatory properties of simvastatin. Human fetal membrane explants from 11 term pregnant women were randomly allocated into 6 study groups: control, LPS only, simvastatin only, simvastatin given 6 hours prior to LPS, simvastatin given 6 hours post-LPS, and simvastatin and LPS given simultaneously. Pretreatment with simvastatin significantly reduced LPS-induced IL-6, TNF-α, and MMP-9 concentrations, which is known to be responsible for proteolysis of collagen in the extracellular matrix of the membranes leading to rupture.[117] Pretreatment with simvastatin also attenuated the cytokine imbalance created by LPS. Posttreatment group showed similar results as pretreatment group with the exception of no significant difference in IL-6 and MMP concentrations.

Safety of Statins in Pregnancy

Lovastatin, the first statin introduced in the United States in 1987 for treatment of hypercholesterolemia, was designated by the Food and Drug Administration (FDA) as pregnancy category X, which was defined as: "Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits." The classification of statins as category X was mainly due to the fact that there were no clear indications to warrant statin use during pregnancy and there was a theoretical concern for inhibiting cholesterol synthesis, as it is essential for embryogenesis. The FDA recently removed the 5-letter classification system (A, B, C, D, X) of safety of drugs during pregnancy in 2015; however, statins are still considered contraindicated.

Initial animal studies showed conflicting results, possibly due to the fact that dosage used in these studies were excessive when compared to commonly prescribed human doses[118,119]; however, human data from postmarketing surveillance and epidemiological studies have been more consistent. A report from the Merck pharmacological vigilance database identified 477 reports of simvastatin or lovastatin exposure during pregnancy, 225 of which had a documented outcome.[120] The rate of congenital anomalies was 3.8%, which was similar to the 3% background population rate. An epidemiologic study conducted in Quebec compared 3 groups of women in terms of teratogenicity of statins[121]; group A included women who received a statin during the first trimester of pregnancy, group B included women who received a fibrate or nicotinic acid in the first trimester of pregnancy, and group C consists of women

who received a statin in the period between 1 year before conception and 1 month before conception. The rates of congenital anomalies in groups A, B, and C were 4.69%, 21.4%, and 10.45%, respectively, suggesting that statin exposure during the first trimester did not increase the risk of malformations. A systematic review and meta-analysis by Kusters et al,[122] including 13 human studies and 10 animal studies, investigated the teratogenic effects of statins during pregnancy. Even the statin exposure was during the first trimester in these observational human studies, there was a similar prevalence of congenital anomalies between statin-exposed pregnancies and controls.

There are also 3 cohort studies in the literature about the safety of statins during pregnancy. In a prospective, observational cohort study, 64 pregnant women who were exposed to statins during first trimester of their pregnancies were compared with a control group.[123] No statistically significant difference was found in the rate of major malformations between the statin group (2.2%) and controls (1.9%). There were also no differences in terms of live birth rates (71.9% vs 81.2%), spontaneous abortions (21.9% vs 17.2%), or stillbirths (1.5% vs 1.6%). However gestational age at birth (38.4 $\pm$ 2.8 vs 39.3 $\pm$ 1.3) and birth weights (3140 $\pm$ 680 g vs 3450 $\pm$ 420 g) were lower in the statin group. In the study by Winterfield et al,[124] 249 pregnant women who were exposed to statins during first trimester were compared with 249 matched controls. The rate of major birth defects was 4.1% in statin users, whereas it was 2.7% in the control group. This difference was not statistically significant. The difference in miscarriage rates was also not statistically significant after adjustment for confounding variables. Although median gestational age at birth (39 weeks, IQR: 37-40 vs 39 weeks, IQR: 38-40) and birth weight (3280 g, IQR: 2835-3590 g vs 3250 g, IQR: 2880-3630 g) was not statistically different, premature birth was more frequent in statin-exposed pregnancies (16.1% vs 8.5%). In a more recent cohort study, 886 996 completed pregnancies were reviewed, out of which 1152 were noted to use a statin during first trimester of their pregnancies.[125] After controlling for confounding variables, particularly for preexisting diabetes, there was no statistically significant difference in terms of major congenital malformations.

When assessing the teratogenicity of statins, we should keep in mind that the majority of mothers who are receiving statin therapy have diagnoses of pregestational diabetes and/or obesity, which are known to be strongly associated with major congenital anomalies and spontaneous abortion.[126,127] Also the "reporting bias" in retrospective drug exposure studies should also be taken into account, as the birth of a malformed child is several times more likely to be reported than pregnancies with a healthy outcome. A very recent and the largest systematic review to date, including 16 human studies, concluded that there was no clear relationship between statin use and congenital anomalies.[128] Long-term follow-up on newborns is needed to draw definitive conclusions regarding the safety of statins during pregnancy. Data from animal studies so far are reassuring.[101,102,129]

Conclusion

The growing evidence is promising for the use of statins in different gynecologic and obstetric conditions. However, a common theme is the need for well-designed, adequately powered clinical trials to investigate the efficacy, safety, and appropriate dosage of different statins. Also, further basic and translational studies are warranted to understand the mechanisms of action of these agents in these conditions.

Authors' Note

B. Zeybek designed the study, reviewed literature, and identified relevant papers and wrote the manuscript. Both G. S. Kilic and M. Constantine edited the manuscript. M. A. Borahay designed the study, discussed content, and revised and edited the manuscript. All authors discussed and approved the final manuscript.

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ORCID iD

Mostafa A. Borahay, MD, PhD http://orcid.org/0000-0002-0554-132X

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