HHS Public Access

Author manuscript

Semin Perinatol. Author manuscript; available in PMC 2021 June 30.

Published in final edited form as:

Semin Perinatol. 2014 December ; 38(8): 523–527. doi:10.1053/j.semperi.2014.08.019.

Challenges of studying drugs in pregnancy for off-label indications: Pravastatin for preeclampsia prevention

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Abstract

Statins (3 hydroxy-3 methyl-glutaryl coenzyme-A reductase inhibitors) are the most commonly prescribed cholesterol lowering medications due to their efficacy in reducing cardiovascular mortality and morbidities, tolerability and safety profiles. Based on pathophysiologic similarities between cardiovascular disease and preeclampsia, a common and dangerous complication of pregnancy, there is increasing interest in studying this class of medications during pregnancy to prevent and/or treat preeclampsia. Undergoing such a study, which entails the use of a pregnancy class X medication for an off label indication in pregnancy, requires intensive multidisciplinary involvement of a group of experts in basic and clinical pharmacology, research methods, pregnancy physiology and maternal fetal medicine, as well as U.S. Food and Drug Administration (FDA) regulatory guidelines and practice. Issues of potential fetal risk, altered maternal-fetal pharmacokinetics and pharmacodynamics and regulatory challenges are real, and must be carefully considered in the process of research in this arena.

Introduction

Preeclampsia complicates approximately 3% to 5% of pregnancies and remains a major cause of maternal and neonatal morbidity and mortality. It shares many risk factors with adult cardiovascular disease as well as pathogenic similarities. Whereas, attempts at prevention of preeclampsia have had limited success; primary and secondary prevention of cardiovascular mortality and other cardiovascular events in non-pregnant patients using 3 hydroxy-3 methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, is widely accepted.[1] Statins are effective in the long-term prevention of cardiovascular morbidities and mortality, not only through their lipid lowering mechanisms, but more significantly through their modulation of inflammation, oxidative and endothelial vascular homeostasis, as well as other pleiotropic actions.[2] Given these protective properties and the pathophysiologic similarities between preeclampsia and adult atherosclerotic cardiovascular

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Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

disease;[3–4] statins have attracted interest as a potential preventive therapy for preeclampsia. However, despite their widespread use among adults at risk for cardiovascular disease, and although, statins have a favorable safety profile and known pharmacokinetic properties, the data on their maternal and fetal safety after exposure during pregnancy are limited. Given statins' potential therapeutic effect in prevention and/or treatment of a life threatening pregnancy complication, a thorough examination of maternal and fetal safety profile is warranted.

Characteristics of pravastatin

Pravastatin is one of two hydrophilic statins currently available for clinical use. Pravastatin's biochemical properties make it theoretically safer in pregnancy than other statins. Pravastatin (C23H35NaO7 & 446.52 kd) is rapidly absorbed after oral administration (time to achieve maximal plasma levels is 1 to 1.5 hours), and has a short elimination half-life (1.77 hours) in non-pregnant individuals.[5] It is the most polar hydrophilic compound among the current HMG-CoA reductase inhibitors.[5] Transplacental transfer of pravastatin is minimal, and higher in the fetal-to-maternal direction than the maternal-to-fetal-direction because of its low passive diffusion, hydrophilicity, and because it is subject to placental efflux transporters.[5–7] Pravastatin is actively taken up into hepatocytes via a carrier mediated active transport mechanism that is shared by the sodium-independent bile acid uptake system, and has limited access to non-hepatic cells that do not express this transporter. For example, the potency of HMG-CoA reductase inhibition in fibroblasts is at least 1000-fold lower than in hepatocytes.[8] This hepatoselectivity of pravastatin was also demonstrated in cell culture studies where radiolabelled pravastatin was hardly taken up by non-hepatic cells such as umbilical vascular endothelial cells, retinal pigment epithelial cells, cornea fibroblasts, and others.[9] Compared to other statins, pravastatin is one of the least potent inhibitors of HMG-CoA reductase enzyme. In addition, the intact drug and metabolites are cleared through both hepatic and renal routes, and CYP3A-dependent metabolism represents only a minor pathway in pravastatin elimination, which is relevant in pregnancy since CYP-3A activity increases during gestation. The dual elimination reduces the need for dose reduction in cases of liver or renal impairment and makes pravastatin safe in a variety of conditions that may affect liver or kidneys.

Assessing pravastatin safety and teratogenicity concerns

The safety of a pharmaceutical agent is a relative term. The safety concerns for therapies designed for long term use to treat chronic diseases obviously differ from those used acutely to treat life threatening illnesses. For treatments used during pregnancy, the safety of both the mother and the fetus must be considered. The risk benefit ratio of therapy needs to be heavily weighed before intervention of medical therapy. Clinical trials have historically not included women, and in particular pregnant ones. The 1977 guidance from the FDA "General Considerations for the Clinical Evaluation of Drugs" prohibited the participation of women of childbearing potential in phase 1 and early phase 2 studies.[10] The FDA issued a new guidance in 1993 that replaced the restriction on women in early phase trials and stated their new position as " (1) exclusion of women from early trials is not medically necessary because the risk of fetal exposure can be minimized by patient behavior and laboratory

testing and (2) initial determinations about whether that risk is adequately addressed are properly left to patients, physicians, local IRBs and sponsors, with appropriate review and guidance by the FDA."[11] Women are increasingly participating in early phase clinical trials, and the results of clinical trials submitted to FDA for new molecular entities between 2006 and 2007 showed that 65.9% of Phase 1 trials included female participants.[12]

In 1987, lovastatin was the first statin introduced and marketed in the United States by the pharmaceutical industry as an effective therapy to treat hypercholesterolemia in patients at risk for cardiovascular disease. It was designated pregnancy "category X" by the FDA. By definition, category X is assigned to drugs for which "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."[13] For lovastatin, the classification was in large part based on the assessment that there were no clear indications to warrant statin use during pregnancy (no benefit to outweigh any risk) rather than proven harm to pregnant mothers or their fetuses. It was argued that atherosclerosis is a long standing disease and thus discontinuation of the drug during pregnancy is not thought to influence the long term risk for cardiovascular disease in these patients. The "X" categorization was also based on theoretical concern for teratogenicity related to statin inhibition of cholesterol synthesis due to the known importance of this substrate during embryological development. Small studies demonstrated skeletal malformations in rodent models exposed to lipophilic statins.[14]

Traditionally, early information regarding the use of a drug during pregnancy has come from post-marketing studies. Pregnancy exposure registries, which are prospective observational studies that actively collect information of exposure during pregnancy and associated pregnancy outcomes, are a form of post-marketing studies. An additional form of post-marketing information is spontaneous reporting of pregnancy or pregnancy related adverse events or outcomes. Post-marketing surveillance of lovastatin and simvastatin (two lipophilic statins) published by Merck showed no relationship between early pregnancy statin exposure and adverse pregnancy outcomes.[15] Among 134 reports of exposure during pregnancy in which the pregnancy outcome could be ascertained, the rates of congenital anomalies and spontaneous abortion were 4% and 8%, respectively. The authors concluded that while the number of prospective reports available for evaluation was only sufficient to rule out a 3–4 fold increase in the frequency of congenital anomalies, the rates found in the study did not exceed those expected for the general population. Their conclusion was that no relationship existed between exposure to therapeutic doses of these agents and the occurrence of adverse pregnancy outcomes.[15] Follow up reports of the Merck pharmacological vigilance database found the rate of congenital anomalies in the exposed group (3.8%) was similar to the 3% background population rate and no specific patterns of anomalies were identified.[16] However, lovastatin maintained X categorization, mainly because of the lack of indication to use it in pregnancy. Subsequent statin drugs have been given the same designation, despite significant differences in biochemical properties and absence of appropriately controlled studies to assess teratogenicity in humans. Therefore, this class of medication has generally been avoided in pregnancy.

More recent epidemiologic data also do not support teratogenicity concerns of statins in general and for pravastatin in particular. Exploration of the National Birth Defects Prevention Study and the Slone Epidemiology Center Birth Defects Study as well as other population-based registries failed to show an association between pravastatin exposure and birth defects.[17–20] The Medical Genetics branch of the National Institutes of Health reviewed 214 pregnancy exposures to statins that were reported to the FDA from 1987 to 2001.[20] Of the 70 evaluable cases reviewed in the final report, 20 cases of pravastatin exposure were included. No congenital malformations or adverse pregnancy outcomes occurred in the pravastatin exposed group. Moreover, a Canadian population based pregnancy registry that collected data on women exposed to statins and other cholesterol-lowering agents prior to pregnancy and in the first trimester showed no pattern, or increased rate, of congenital abnormalities in 288 women with live births.[18] No congenital anomalies were found in women exposed to pravastatin. In addition, a prospective observational cohort study by the Motherisk program in Toronto did not find any malformation patterns or increased malformations in infants of 64 women with first trimester exposure to statins compared with women without exposure to known teratogens.[19] In summary, these data do not support pravastatin being teratogenic. However, the major drawbacks from these cohorts are their limited sample size and the fact that most of them assessed statin exposure during the first trimester of pregnancy. For women who conceive while taking statins, the current recommendation is to discontinue treatment as soon as possible. Therefore, most of the statin-exposed patients in the previously mentioned cohorts discontinued statin use as soon as they discovered the pregnancy. The effects of long-term (throughout the pregnancy) pravastatin use on fetal and neonatal health are unknown, as is the long-term cardiovascular and endocrine outcomes in these neonates.

Maternal safety concerns

Information from clinical trials of non-pregnant women cannot always be used in determining efficacy and safety of a drug in pregnant women. Physiologic changes in body weight and fat composition, increased plasma volume and glomerular filtration rate, alterations in activity of various cytochrome P450 enzymes, and changes in gastrointestinal motility, among many other physiologic changes during pregnancy, may alter the pharmacokinetics of a drug in pregnant women. The FDA established a draft framework in 2004 for conduction of pharmacokinetic and pharmacodynamic studies in pregnant women.[21] This guideline suggests that pregnant women may be included in pharmacokinetic studies if the following conditions, summarized in Table 1[21], are met from the code of regulations 45 CFR 46, Protection of Human Subjects. Additionally, pharmacokinetic studies should be conducted if any of the following conditions summarized in Table 2[21], are met. Study design should include dosing considerations during different trimesters, collecting pharmacokinetic information postpartum so that a woman can be her own control, evaluating study participants that are representative of a typical patient population, and enrolling enough subjects to detect pharmacokinetic differences large enough to warrant dose adjustments for use during pregnancy.[21]

Thorough evaluation of the safety profile for a therapeutic intervention (pravastatin) for preeclampsia prevention must also focus on potential maternal risks. Large scale placebo

controlled randomized clinical trials have established conclusive evidence that long term use of statins reduces cardiovascular risk in non pregnant individuals.[22–24] Pooled data from these trials also yielded critical information about the risk of adverse events from pravastatin use. A prospective analysis of three large randomized clinical trials, the West of Scotland Coronary Prevention Study, the Cholesterol and Recurrent Events, and the Long-term Intervention with Pravastatin in Ischemic Disease, collectively accumulated more than 112,000 person-years of exposure in double blind randomized trials.[22–25] These trials compared pravastatin (40 mg daily) to placebo. During five years of exposure, there were no differences in rates of abnormal hepatic profile (1.4% in both groups), and there were no cases of myopathy in either group. In a prospective trial of heart transplant patients, a group at increased risk for side effects related to statin therapy, onset of side effects including abnormal hepatic profile and abnormal creatine kinase was identified through routine screening to allow modification of statin dose.[26] In this study, only 3% of patients required discontinuation of therapy.[26] This is partly explained by the fact that CYP3A-dependent metabolism represents only a minor pathway in pravastatin elimination and there is no clinically important pharmacokinetic interaction of pravastatin with CYP3A inhibitors. These data suggest that pravastatin is generally considered to be safe and tolerable. While we have little data to assess maternal safety of statin therapy in pregnancy, however it seems unlikely that risks for hepatic injury or rhabdomyolysis would be increased compared to a non-pregnant population.

The Obstetric-Fetal Pharmacology Research Unit network trial

Given the potential for benefit of statin therapy for women at high risk for preeclampsia, as well as the reassuring safety profile, the Obstetric-Fetal Pharmacology Research Unit network funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development of the National Institutes of Health embarked on a pilot prospective randomized trial of pravastatin for preeclampsia prevention. The objectives of this study are to determine the pharmacokinetic parameters and collect preliminary safety data for pravastatin use during pregnancy. Additional secondary objectives are to evaluate its pharmacodynamics when used as a prophylactic daily treatment in reducing the pathological imbalances preceding the development of preeclampsia in high-risk women. This study was conducted under the FDA Investigational New Drug application regulation. The study design was an exploratory, dose finding, escalating, randomized, double blind, and placebo controlled trial of pregnant women at high risk for preeclampsia. Patients will be randomized to 2 cohorts of pravastatin (10 or 20 mg) or placebo, each containing 20 subjects, with evaluation of pharmacokinetic data following the completion of each cohort (Clinicaltrials.gov IdentifierNCT01717586). Findings from this study will shed the light on pravastatin biodisposition in pregnancy, optimal dosing, and rate and severity of side effects. These data are essential in designing future large clinical trials to evaluate pravastatin utility in preventing preeclampsia and its associated adverse outcomes.

Conclusion

With many women getting pregnant at advanced age, and/or with significant chronic illness, and thus being exposed to multiple medications during pregnancy, it is prudent to examine

the safety of drugs during pregnancy in a systematic way. As we come to understand the pathophysiologic similarities of many disease processes, as illustrated by the overlap between cardiovascular disease and preeclampsia, it is clear that many therapeutic interventions currently used outside of pregnancy may be candidates for treatment of pregnancy-specific diseases and warrant attention in obstetrical research. Pregnancy poses particular challenges in drug studies given both the issues of potential fetal risk as well as altered maternal physiology, and these studies require particular expertise on the part of pharmacologists and maternal and fetal medicine specialists. The Obstetric Pharmacology Research Unit network is uniquely poised to address these research questions and help provide the necessary pharmacologic and clinical tools to provide access to novel therapies and improve care for pregnant women in the 21st century.

Acknowledgement:

The project described was supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) [5U10HD057753 and U10HD047891] and does not necessarily represent the official views of the NICHD or the National Institutes of Health.

References

1. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. Circulation. 1 18 2000;101(2):207–213. [PubMed: 10637210]
2. Shaw SM, Fildes JE, Yonan N, Williams SG. Pleiotropic effects and cholesterol-lowering therapy. Cardiology. 2009;112(1):4–12. [PubMed: 18577880]
3. Rodie VA, Freeman DJ, Sattar N, Greer IA. Pre-eclampsia and cardiovascular disease: metabolic syndrome of pregnancy? Atherosclerosis. 8 2004;175(2):189–202. [PubMed: 15262174]
4. Berends AL, de Groot CJ, Sijbrands EJ, et al. Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease. Hypertension. 4 2008;51(4):1034–1041. [PubMed: 18259037]
5. Hatanaka T Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. Clinical pharmacokinetics. 12 2000;39(6):397–412. [PubMed: 11192473]
6. Nanovskaya TN, Patrikeeva SL, Paul J, Costantine MM, Hankins GD, Ahmed MS. Transplacental transfer and distribution of pravastatin. American journal of obstetrics and gynecology. 10 2013;209(4):373 e371–375. [PubMed: 24070396]
7. Zarek J, DeGorter MK, Lubetsky A, et al. The transfer of pravastatin in the dually perfused human placenta. Placenta. 8 2013;34(8):719–721. [PubMed: 23746925]
8. McTaggart F, Buckett L, Davidson R, et al. Preclinical and clinical pharmacology of Rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. The American journal of cardiology. 3 8 2001;87(5A):28B–32B. [PubMed: 11137829]
9. van Vliet AK, van Thiel GC, Huisman RH, Moshage H, Yap SH, Cohen LH. Different effects of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors on sterol synthesis in various human cell types. Biochimica et biophysica acta. 1 3 1995;1254(1):105–111. [PubMed: 7811739]
10. FDA. General Considerations for the Clinical Evaluation of Drugs. 1977; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071687.pdf.
11. FDA. Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. 1993; http://www.fda.gov/regulatoryinformation/guidances/ucm126552.htm.
12. Pinnow E, Sharma P, Parekh A, Gevorkian N, Uhl K. Increasing participation of women in early phase clinical trials approved by the FDA. Women's health issues : official publication of the Jacobs Institute of Women's Health. Mar-Apr 2009;19(2):89–93.
13. FDA. Federal Register. Vol 441980:37434–37467.
14. Dostal LA, Schardein JL, Anderson JA. Developmental toxicity of the HMG-CoA reductase inhibitor, atorvastatin, in rats and rabbits. Teratology. 12 1994;50(6):387–394. [PubMed: 7778043]

15. Manson JM, Freyssinges C, Ducrocq MB, Stephenson WP. Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy. Reprod Toxicol. Nov-Dec 1996;10(6):439–446. [PubMed: 8946557]
16. Pollack PS, Shields KE, Burnett DM, Osborne MJ, Cunningham ML, Stepanavage ME. Pregnancy outcomes after maternal exposure to simvastatin and lovastatin. Birth defects research. Part A, Clinical and molecular teratology 11 2005;73(11):888–896. [PubMed: 16163683]
17. Petersen EE, Mitchell AA, Carey JC, Werler MM, Louik C, Rasmussen SA. Maternal exposure to statins and risk for birth defects: a case-series approach. American journal of medical genetics. Part A 10 15 2008;146A(20):2701–2705. [PubMed: 18792975]
18. Ofori B, Rey E, Berard A. Risk of congenital anomalies in pregnant users of statin drugs. British journal of clinical pharmacology. 10 2007;64(4):496–509. [PubMed: 17506782]
19. Taguchi N, Rubin ET, Hosokawa A, et al. Prenatal exposure to HMG-CoA reductase inhibitors: effects on fetal and neonatal outcomes. Reprod Toxicol. 10 2008;26(2):175–177. [PubMed: 18640262]
20. Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. American journal of medical genetics. Part A 12 15 2004;131(3):287–298. [PubMed: 15546153]
21. FDA. Guidance for Industry Pharmacokinetics in Pregnancy - Study Design, Data Analysis, and Impact on Dosing and Labeling. 2004; http://www.fda.gov/scienceresearch/specialtopics/womenshealthresearch/ucm133348.htm.
22. Sacks FM, Pfeffer MA, Moyé LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med. 1996;335:1001–1009. [PubMed: 8801446]
23. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349–1357. [PubMed: 9841303]
24. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med. 1995; 333:1301–1307 [PubMed: 7566020]
25. Pfeffer MA, Keech A, Sacks FM, et al. Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. Circulation 5 21 2002;105(20):2341–2346. [PubMed: 12021218]
26. Marzoa-Rivas R, Crespo-Leiro MG, Paniagua-Marin MJ, et al. Safety of statins when response is carefully monitored: a study of 336 heart recipients. Transplantation proceedings. 11 2005;37(9):4071–4073. [PubMed: 16386629]

Table 1:

Criteria for inclusion of pregnant women from the code of regulations 45 CFR 46, Protection of Human Subjects

Previous Supportive Studies	Preclinical studies, including pregnant animals, and clinical studies, including non-pregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses
Risk	The risk to the fetus is not greater than minimal, and the purpose of the research is the development of important biochemical knowledge, which cannot be obtained by any other means

Table 2:

Conditions in which to conduct pharmacokinetic studies during pregnancy

Known Use	The drug is known to be used by pregnant women, especially in the second and third trimesters.
Anticipated Use	For a new drug or indication, if there is anticipated or actual use of the drug in pregnancy.
Consequences of Use	Use is expected to be rare, but the consequences of uninformed dosages are great (e.g. narrow therapeutic range drugs, cancer chemotherapy).
Pregnancy Likely to Alter Pharmacokinetics	Pregnancy is likely to alter the pharmacokinetics of a drug (e.g. renally excreted drug) significantly and any of the above apply.