



The History of Statins and Pregnancy

Leyla Sahin, MD, Acting Deputy Director for Safety

Division of Pediatrics and Maternal Health

Office of New Drugs, Center for Drug Evaluation and Research

OTIS-MotherToBaby Annual Meeting June 26th, 2022

Disclaimer

- I do not have any financial disclosures to report
- This presentation represents the views of the speaker, and not the official position of the FDA



Cholesterol

The infographic features a white silhouette of a human figure on a black background. The internal organs, including the heart, lungs, liver, and intestines, are highlighted in purple and green. Three callout boxes provide additional information: one about cholesterol's importance, one about liver and cell production, and one about genetics. The text is in white and yellow, with some key phrases in bold.

CHOLESTEROL IS IMPORTANT
Cholesterol has a bad rap. In reality, your body needs cholesterol to make hormones, vitamin D, and bile acids that help you digest food in your intestines. Cholesterol keeps you healthy.

However, too much of one type (LDL or Low-Density Lipoproteins) or not enough of another (HDL or High-Density Lipoproteins) can put you at risk for heart disease, heart attack, or stroke.

The cells in your body as well as your liver produce cholesterol, which is needed to ensure the body functions properly.

YOUR LIVER & other cells PRODUCE ABOUT 75% of your BLOOD CHOLESTEROL

GENETICS plays a big role in how much cholesterol your body produces

Some people inherit genes that cause their bodies to produce too much cholesterol, or keep their body from absorbing enough cholesterol. They could still have high cholesterol even if they're not eating food that's high in cholesterol.

<https://www.fda.gov/drugs/drug-safety-and-availability/cholesterol-and-statins-infographic>

Cholesterol and Pregnancy*



- Physiologic increases occur in pregnancy (LDL and HDL up to 50%, triglycerides increase 2-4 x)
- Cholesterol is an essential component for cell proliferation and development, including in the fetus, through placental transfer of maternal cholesterol and fetal synthesis

*Maternal lipid metabolism during normal pregnancy and its implications to fetal development. Herrera E, Ortega-Senovilla H. *Clin Lipid* (2010) 5 (6), 899-911;

Estimating fetal cholesterol synthesis rates by cord blood analysis in intrauterine growth restriction and normally grown fetuses
Pecks, Ulrich ; Bornemann, V; Klein, A; et al. *Lipids in Health and Disease*, 2019-10-25, Vol.18 (1), p.185-185

History of Statins



- First statin approved in the U.S. in 1987 (lovastatin)
- Currently available statins: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin (available as brand names and generics)
- Lowers low density lipoprotein (LDL) by inhibiting the liver enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA), involved in the synthesis of cholesterol and helps the liver remove cholesterol already in the systemic circulation

how **STATINS** work

THE MAIN GOAL OF CHOLESTEROL TREATMENT

is to lower LDL (bad cholesterol) levels. When diet and exercise are not enough to reduce cholesterol to goal levels, doctors often prescribe medication—the most prominent being statins. By interfering with the production of cholesterol, statin medications can slow the formation of plaques in the arteries.

Cholesterol plaques build up slowly, eventually resulting in blocked arteries (atherosclerosis), and reducing the flow of oxygen-rich blood to your heart. This can lead to heart disease.

BAD CHOLESTEROL (LDL) sticks to the arteries and FORMS PLAQUE

statins help BLOCK PRODUCTION of LDL in the liver

The body needs cholesterol to function, but sometimes, based on genetics, food intake, and activity, the body produces too much cholesterol. Statins block an enzyme that's key to the liver's production of cholesterol. This inhibits the liver's ability to produce cholesterol. The goal is less cholesterol in the bloodstream and a reduction in risk for high-cholesterol-related diseases.

<https://www.fda.gov/drugs/drug-safety-and-availability/cholesterol-and-statins-infographic>

Statins: Approved Indications Include: (varies, based on drug)



- To reduce the risk of mortality and stroke in adults with established coronary heart disease, cerebrovascular disease, peripheral vascular disease, and/or diabetes, who are at high risk of coronary heart disease events.
- To reduce the risk of mortality in adults with elevated LDL, without clinically evident coronary heart disease.
- As an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia.
- In adults and pediatric patients aged 8 years (or 10 years) and older with heterozygous familial hypercholesterolemia.
- As an adjunct to other LDL-C-lowering therapies to reduce LDL-C in adults with homozygous familial hypercholesterolemia.
- As an adjunct to diet for the treatment of adults with:
 - Primary dysbetalipoproteinemia or hypertriglyceridemia.

History of Statin Pregnancy Labeling



- Contraindicated in pregnancy
 - Concerning nonclinical data
 - Increased mortality in offspring and increased skeletal malformations in rats (10 x human exposure)
 - Increase mortality and developmental delays in rats (pre and postnatal studies) (12 x human exposure)
 - No benefit to use in pregnancy
 - Concern that cholesterol is needed for fetal development
- Contraception recommended for females of reproductive potential

A photograph of a pregnant woman in a grey business suit sitting at a desk with a laptop. She is looking at the screen, and her left hand is resting on her pregnant belly. The image is semi-transparent, serving as a background for the text.

FDA Update of Statins' Pregnancy Labeling

Data



- Published observational studies of first trimester exposures have not indicated risk for birth defects
- Data on miscarriage are limited



FDA Drug Safety Communication 7-20-2021

FDA



FDA requests removal of strongest warning against using cholesterol-lowering statins during pregnancy; still advises most pregnant patients should stop taking statins

Breastfeeding not recommended in patients who require statins

7-20-2021 FDA Drug Safety Communication

What safety information is FDA announcing?

The U.S. Food and Drug Administration (FDA) is requesting removal of its strongest warning against using cholesterol-lowering statin medicines in pregnant patients. Despite the change, most patients should stop statins once they learn they are pregnant. We have conducted a comprehensive review of all available data and are requesting that statin manufacturers make this change to the prescribing information as part of FDA's ongoing effort to update the [pregnancy and breastfeeding information](#) for all prescription medicines.

Patients should not breastfeed when taking a statin because the medicine may pass into breast milk and pose a risk to the baby. Many can stop statins temporarily until breastfeeding ends. However, patients requiring ongoing statin treatment should not breastfeed and instead use infant formula or other alternatives.

What is FDA doing?

We are requesting revisions to the information about use in pregnancy in the prescribing information of the entire class of statin medicines. These changes include removing the contraindication against using these medicines in all pregnant patients. A contraindication is FDA's strongest warning and is only added when a medicine should not be used because the risk clearly outweighs any possible benefit. Because the benefits of statins may include prevention of serious or potentially fatal events in a small group of very high-risk pregnant patients, contraindicating these drugs in all pregnant women is not appropriate.

FDA expects removing the contraindication will enable health care professionals and patients to make individual decisions about benefit and risk, especially for those at very high risk of heart attack or stroke. This includes patients with homozygous familial hypercholesterolemia and those who have previously had a heart attack or stroke. Statins are safe to use in patients who are

- Available data have not indicated a risk for major birth defects
- Females of reproductive potential no longer need contraception
- Statins still not recommended for majority of patients
 - hyperlipidemia treatment can be interrupted during pregnancy
- Individualized benefit-risk for high-risk patients
 - homozygous familial hypercholesterolemia
 - established atherosclerotic cardiovascular disease

Updated Statin Class Labeling (2022) (excerpts)



8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Discontinue statin when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient.

Drug name decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol; therefore, drug name may cause fetal harm when administered to pregnant patients based on the mechanism of action. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

(Continued) Updated Statin Class Labeling (2022)



Data

Human Data

A Medicaid cohort linkage study of 1152 statin-exposed pregnant women compared to 886,996 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders – including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use – using propensity score-based methods. The relative risk of congenital malformations between the group with statin use and the group with no statin use in the first trimester was 1.07 (95% confidence interval 0.85 to 1.37) after controlling for confounders, particularly pre-existing diabetes mellitus. There were also no statistically significant increases in any of the organ-specific malformations assessed after accounting for confounders. In the majority of pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence of a malformation, lack of control for certain confounders such as body mass index, use of prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

Summary



- Statin class labeling recently revised to remove contraindication in pregnancy and reflect available data
- History of statins shows that it takes a long time to get pregnancy safety data...uncertainty still remains...how can we do better?

Thank You



References



- FDA Drug Safety Communication on statins and pregnancy
[Statins: Drug Safety Communication - FDA Requests Removal of Strongest Warning Against Using Cholesterol-lowering Statins During Pregnancy | FDA](#)
- Statin Use in Pregnancy Is it Time for a Paradigm Shift? Mauricio R, Khera A. Circulation 2022 Feb 15; 145(7): 496-498.