Familial Hypercholesterolemia & Pregnancy

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Disclosure of Financial Relationships

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Has disclosed relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

<table>
<thead>
<tr>
<th>Consultantship</th>
<th>Research Grants/Contracts</th>
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<tr>
<td>Liposcience, Aegerion, Novartis, AstraZeneca</td>
<td>Kowa, Aegerion</td>
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<td>Honoraria</td>
<td><strong>Speaker’s Bureau</strong></td>
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<td>GlaxoSmithKline, Merck, Amarin, Sanofi, Genzyme, AstraZeneca, Kowa</td>
<td>GlaxoSmithKline, Merck, Amarin, Sanofi, Genzyme, AstraZeneca, Kowa</td>
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Objectives

• Review Strategies for managing CVD risk in pregnant women or women who plan to become pregnant
• Review Counseling for women with FH of childbearing age
• Review impact of FH on offspring of FH mothers
• Review Drug safety in pregnancy
Outline

• Lipids and Pregnancy
• Recommendations regarding treating FH and pregnancy
• Risk to offspring and mother
• Treatment options for FH and pregnancy
50 Things Every Guy Should Know About Pregnancy

1. From the very moment she announces her pregnancy, she’ll be the center of attention — not you. Get used to it.

2. Your house is too small, it was always too small, and to suggest otherwise simply proves that your brain is too small.

15. Be careful about the word we. For instance, never say, “We don’t mind LDL apheresis at all.”

Pregnancy Rates for U.S. Women Continue to Drop

Sally C. Curtin, M.A., Joyce C. Abma, Ph.D., and Stephanie J. Ventura, M.A., National Center for Health Statistics; and Stanley K. Henshaw, Ph.D., Guttmacher Institute

The pregnancy rate in the US in 2009 was 102.1 per 1,000 for those aged 15–44, the lowest level in 12 years; only the 1997 rate of 101.6 has been lower in the last 30 years.

100% of these are in women!

1/200-500 are FH pregnancies 1/2000

Pregnancy rates were highest for women in their 20s

NCHS Data Brief No. 136 December 2013
Main changes in lipoprotein metabolism that occur in advancing gestation.
Levels of TC, TGs, HDL, and LDL 1 year before, during, and 1 year after gestation

LDL cholesterol Levels in 5 pregnant women with FH

Eapen et al Familial hypercholesterolemia and pregnancy Journal Clinical Lipidology 2012 6, 88-91
Figure 1. LDL-C levels during pregnancy in women with and without FH

LDL-C = low-density lipoprotein cholesterol; FH = familial hypercholesterolaemia.
Potential Issues/Concerns of FH during Pregnancy

- Maternal hyperlipidemia leads to atherosclerosis in the uteroplacental spiral arteries, hypercoagulation, local thrombosis, placental infarctions, and placental insufficiency leading to possible fetal compromise.
- FH in pregnancy may lead to more hypertensive disease. Links between preeclampsia & increased maternal lipid levels have been described.
- Multiple pregnancies, untreated lipids, may lead to increased risk of CVD (not substantiated by literature)
- Fetal exposure to elevated cholesterol level may have impact on outcomes

Eapen et al Familial hypercholesterolemia and pregnancy Journal Clinical Lipidology 2012
FH Pregnancy Recommendations NICE Guidelines 2009

- Limited treatment options make management of FH during pregnancy unclear
- NICE guidelines recommend that all women stop taking statins 3 months prior to attempting to conceive.
- Women who become pregnant while taking a statin or other systemically absorbed lipid-modifying agent, should be instructed to stop treatment immediately and be referred to an obstetrician for urgent fetal assessment.


Eapen et al Familial hypercholesterolemia and pregnancy Journal Clinical Lipidology 2012 6, 88-91
FH Pregnancy Recommendations NICE Guidelines 2009

• Women should not be started back on lipid lowering agents until they have completed lactation

• Currently the only medication that can be given during pregnancy is bile acid sequestrants. Side effects, however include constipation and elevated TG, especially in the 2nd and 3rd trimester

• Potentially new agents such as PCSK9 inhibitors and mipomersen may offer options in the future.

4.6 Women of childbearing age

4.6.1 Women with FH should receive pre-pregnancy counseling and instructions to stop statins, ezetimibe, and niacin at least four weeks before discontinuing contraception and should not use these medications during pregnancy and lactation.

4.6.2 Consultation with her healthcare practitioner regarding continuation of any other lipid medications is recommended.

4.6.3 In case of unintended pregnancy, a woman with FH should discontinue statins, ezetimibe, and niacin immediately and should consult with her healthcare practitioner promptly.
4.7 Treatment options during pregnancy

4.7.1 Statins, ezetimibe, and niacin should not be used during pregnancy. Use of other lipid lowering medications (e.g., colesevelam) may be considered under the guidance of the healthcare practitioner.

4.7.2 Consider LDL apheresis during pregnancy if there is significant atherosclerotic disease or if the patient has homozygous FH.
Integrated FH Guidelines

Review Articles

Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation

Gerald F. Watts, DSc, MD, PhD*, Samuel Gidding, MD, Anthony S. Wierzbicki, MD, Peter P. Toth, MD, PhD, Rodrigo Alonso, MD, W. Virgil Brown, MD, Eric Bruckert, MD, Joep Defesche, PhD, Khoo Kah Lin, MBBS, PhD, Michael Livingston, Pedro Mata, MD, Klaus G. Parhofer, MD, PhD, Frederick J. Raal, MD, PhD, Raul D. Santos, MSc, MD, PhD, Eric J. G. Sijbrands, MSc, MD, PhD, William G. Simpson, MD, David R. Sullivan, MBBS, Andrey V. Susekov, MD, PhD, Brian Tomlinson, MBBS, MD, Albert Wiegman, MD, PhD, Shizuya Yamashita, MD, PhD, John J. P. Kastelein, MD, PhD
Recommendations from International FH Foundation

- All women of child-bearing age should receive prepregnancy counseling, with appropriate advice given by the clinician on contraception, before starting a statin and this should be reinforced at annual review.
- Statins and other systemically absorbed lipid-regulating drugs should be discontinued 3 months before planned conception, as well as during pregnancy and breastfeeding.
- All adolescent girls should receive prepregnancy counseling, with appropriate advice on contraception given, before starting a statin and this should be reinforced at annual review.

Contraception

- Low estrogen–containing oral agents, intra-uterine devices, and barrier techniques are the preferred methods of contraception for women with FH.
- Intra-uterine devices, and barrier techniques are preferable for those older than 35 years of age.
- Women who become pregnant accidentally while on a statin could be reassured that the likelihood of fetal complications is low.

## Maternal Lipid Profile During Early Pregnancy and Pregnancy Complications and Outcomes: The ABCD Study

### Associations between first-trimester maternal TG and TC levels and maternal and perinatal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>%</th>
<th>Crude model</th>
<th>Model 1</th>
<th>Crude model</th>
<th>Model 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIH (n = 1962)</td>
<td>4.9</td>
<td>1.72 (1.21–2.43)</td>
<td>1.60 (1.10–2.33)</td>
<td>1.21 (0.96–1.53)</td>
<td>1.09 (0.85–1.40)</td>
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<tr>
<td>Preeclampsia (n = 1938)</td>
<td>3.7</td>
<td>1.85 (1.24–2.77)</td>
<td>1.69 (1.10–2.60)</td>
<td>1.25 (0.95–1.64)</td>
<td>1.12 (0.84–1.51)</td>
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<td>Preterm delivery (n = 3912)</td>
<td>5.3</td>
<td>0.83 (0.65–1.06)</td>
<td>0.90 (0.70–1.17)</td>
<td>0.93 (0.79–1.09)</td>
<td>0.99 (0.83–1.17)</td>
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<tr>
<td>SGA (n = 3912)</td>
<td>9.3</td>
<td>1.06 (0.87–1.29)</td>
<td>0.97 (0.79–1.19)</td>
<td>0.97 (0.85–1.10)</td>
<td>0.98 (0.86–1.12)</td>
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<tr>
<td>LGA (n = 3912)</td>
<td>9.3</td>
<td>1.44 (1.20–1.71)</td>
<td>1.48 (1.23–1.78)</td>
<td>1.10 (0.97–1.25)</td>
<td>1.08 (0.95–1.22)</td>
</tr>
<tr>
<td>Child loss (n = 3944)</td>
<td>1.4</td>
<td>0.85 (0.50–1.45)</td>
<td>0.77 (0.44–1.32)</td>
<td>0.89 (0.64–1.23)</td>
<td>0.88 (0.64–1.22)</td>
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J Clin Endocrin Metab.
Pregnancy Outcomes in Familial Hypercholesterolemia
A Registry-Based Study

Ieva Toleikyte, MSc; Kjetil Retterstøl, MD; Trond Paul Leren, MD; Per Ole Iversen, MD

**Background**- Women with familial hypercholesterolemia (FH) are prone to early cardiovascular disease and death. It is unknown whether FH adversely affects pregnant women and birth outcomes.

**Conclusion**- Women with FH do not appear to have a higher risk of preterm delivery or of having infants with low birth weight or congenital malformations than women in general, but, although this is unlikely, some undetected bias may obscure the real differences.

*Circulation. 2011;124:1606-1614.*
Our results suggest that maternal hypercholesterolaemia during pregnancy induces changes in the fetal aorta that determine the long-term susceptibility of children to fatty-streak formation and subsequent atherosclerosis.

If so, cholesterol-lowering interventions in hypercholesterolaemic mothers during pregnancy may decrease atherogenesis in children.
FELIC Study

“Serial cross-sections through the entire aortic arch and abdominal aorta of 156 normocholesterolaemic children aged 1–13 years, who died of trauma and other causes. Children were classified by whether their mother had been normocholesterolaemic (n=97) or hypercholesterolaemic (n=59) during pregnancy. Atherosclerosis was correlated with 13 established or potential risk factors.”

Lancet 1999; 354: 1234–41
Microphotographs of oil red 0 stained aortic sections from children

A: early fatty streak
B: shoulder area of transitional lesion
C: advanced lesion

Lancet 1999; 354:1234–41
Presence of native and oxidised LDL, monocytes, and macrophages in aortic intima of children

Lancet 1999; 354:1234–41
Lesion sizes in aortic arch and abdominal aorta of children

Lancet 1999; 354: 1234–41
Maternal Hypercholesterolemia and Treatment During Pregnancy Influence the Long-Term Progression of Atherosclerosis in Offspring of Rabbits

Wulf Palinski, Francesco P. D’Armiento, Joseph L. Witztum, Filomena de Nigris, Florencia Casanada, Mario Condorelli, Mercedes Silvestre, Claudio Napoli

Abstract—Maternal hypercholesterolemia during pregnancy is associated with enhanced fatty streak formation in human fetuses and faster progression of atherosclerosis during childhood even under normocholesterolemic conditions. A causal role of maternal hypercholesterolemia in lesion formation during fetal development has previously been established in rabbits. The same experimental model is now used to establish that maternal hypercholesterolemia or ensuing pathogenic events in fetal arteries enhance atherogenesis later in life. Five groups of rabbit mothers were fed chow, cholesterol-enriched chow, or cholesterol-enriched chow plus 1000 IU vitamin E, 3% cholestyramine, or both during pregnancy. Offspring of all groups (n=136) were fed a mildly hypercholesterolemic diet for up to a year and had similar cholesterol levels. Aortic lesion sizes and lipid peroxidation products in plasma and lesions in offspring were determined at birth, 6 months, or 12 months. Lesion progression in offspring of hypercholesterolemic mothers was greater than in all other groups. At each time point, offspring of hypercholesterolemic mothers had 1.5- to 3-fold larger lesions than offspring of normocholesterolemic mothers (P<0.01), with the greatest absolute differences at 12 months. Maternal treatment reduced lesions by 19% to 53%, compared with offspring of untreated hypercholesterolemic mothers (P<0.01), with the greatest effect in the vitamin E groups. At 12 months, lesions in offspring of all vitamin E and cholestyramine-treated mothers were similar to those of normocholesterolemic mothers. Lipid peroxidation end-products in lesions and plasma showed analogous differences between groups as lesions (P<0.01). Thus, pathogenic programming in utero increases the susceptibility to atherogenic risk factors later in life and maternal intervention with cholesterol-lowering drugs or antioxidants reduce postnatal lipid peroxidation and atherosclerosis in their offspring. (Circ Res. 2001;89:991-996.)
Maternal V. Paternal FH Inheritance

Arterioscler Thromb Vasc Biol. 2010;30:2673-2677
Accelerated subclinical coronary atherosclerosis in patients with familial hypercholesterolemia

- Development of CAD is accelerated in intensively treated male and female FH patients. The extent of CAD is related to gender and cholesterol levels and ranges from absence of plaque in one out of 6 patients to extensive CAD with plaque causing >50% lumen obstruction in almost a quarter of patients with FH.

L.A. Neefjes et al. / Atherosclerosis 219 (2011) 721-727
Maternal inheritance of familial hypercholesterolemia caused by the V408M low-density lipoprotein receptor mutation increases mortality

Jorie Versmissen\textsuperscript{a}, Ilse P.G. Botden\textsuperscript{a}, Roeland Huijgen\textsuperscript{b}, Daniëlla M. Oosterveer\textsuperscript{a}, Joep C. Defesche\textsuperscript{b}, Thea C. Heil\textsuperscript{a}, Anouk Muntz\textsuperscript{a}, Janneke G. Langendonk\textsuperscript{a}, Arend F.L. Schinkel\textsuperscript{a}, John J.P. Kastelein\textsuperscript{b}, Eric J.G. Sijbrands\textsuperscript{a,*}

\textsuperscript{a} Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands
\textsuperscript{b} Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
Maternal inheritance of familial hypercholesterolemia caused by the V408M low-density lipoprotein receptor mutation increases mortality

Mortality rates are more increased when FH is inherited through the mother, supporting the fetal origin of adulthood disease hypothesis with all cause death, the most indisputable outcome measure. Future research should explore safe options for cholesterol-lowering therapy of pregnant Women with FH in order to prevent unfavourable (epigenetic) consequences leading to atherosclerosis in their children.

J. Versmissen et al. / Atherosclerosis 219 (2011) 690–693
Standardized Mortality Ratio (SMR) according to maternally and paternally inherited FH.

Adapted from: J. Versmissen et al. / Atherosclerosis 219 (2011) 690–693
Inheritance pattern of familial hypercholesterolemia and markers of cardiovascular risk LDL-C, TG’s and CIMT
Endogenous Estrogens Lower Plasma PCSK9 & LDL-Cholesterol

**P<0.01, ***P<0.001.
The study evaluated how increased levels of endogenous estrogens modulate cholesterol and lipoprotein metabolism in women.

Conclusion — In women, apolipoprotein B-containing particles and circulating PCSK9 are reduced when endogenous estrogens are high, indicating that endogenous estrogens induce hepatic LDL receptors partly through a posttranscriptional mechanism.

Estrogens do not stimulate bile acid or cholesterol synthesis.

Estrogen & PCSK9 levels in pregnancy
Serum PCSK9 was significantly higher in Maternal versus Control cohorts (493.1 versus 289.7 ng/mL; \( P < 0.001 \), resp.), while the Newborn cohort was significantly lower than Maternal (278.2 versus 493.1 ng/mL; \( P < 0.0001 \), resp.).

PCSK9 was significantly correlated with TC and HDL-C in Maternal and with TC, LDL-C, and HDL-C in Newborn cohorts.
Treatment interventions and Premature cardiovascular disease in young women with heterozygous familial hypercholesterolemia

- Familial hypercholesterolemia (FH) leads to premature atherosclerosis, a process that starts in childhood.
- Incidence of cardiovascular disease in young FH women is lower than in FH men, but compared with the general population they are at an highly increased risk.
- After identification of FH in a female, lifestyle adjustments should be made and lipid lowering drugs should be started around puberty.
- Statins are the first drugs of choice and a target low-density lipoprotein-cholesterol level of 1.8-2.6 mmol/l should be reached.

Barbara A Hutten, John JP Kastelein, Anouk van der Graaf and Maud N Vissers
Treatment

- Controlling hypercholesterolemia during pregnancy is particularly important in women with established CHD
- ? Impact on the severity of FH in offspring who inherit the condition
- Bile acid sequestrants are the only safe agents to control hypercholesterolemia in pregnancy (category B)
- Mipomersen also pregnancy category B
- **Pregnancy Category B:** There are no adequate and well-controlled studies in pregnant women. Mipomersen and Colesevelam should be used during pregnancy only if clearly needed.

*Journal of Clinical Lipidology* (2014) 8, 148–172

Kynamro Package insert accessed online

http://www.kynamro.com/~media/Kynamro/Files/KYNAMRO-PI.pdf
# Lipid Lowering Agents and Pregnancy Class

<table>
<thead>
<tr>
<th>Lipid Lowering Agent</th>
<th>Pregnancy Class</th>
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<tbody>
<tr>
<td>Statins</td>
<td>X</td>
</tr>
<tr>
<td>Fibrates</td>
<td>C</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>C</td>
</tr>
<tr>
<td>Niacin</td>
<td>C</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>C</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>B</td>
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Eapen et al Familial hypercholesterolemia and pregnancy Journal Clinical Lipidology 2012 6, 88-91
“In conclusion, apheresis therapy with HELP was safe and efficacious during pregnancy in this patient with stable coronary artery disease and severe hypercholesterolemia.”
Two women reported. One affected by autosomal recessive hypercholesterolemia premature atherosclerosis and the other with HeFH.

LDL Apheresis is a therapeutic option should be utilized with less hesitation in high-risk hyperlipidemic pregnant women.
Use of Pregnancy Category D/X Meds

**Article**

**Annals of Internal Medicine**

**Documentation of Contraception and Pregnancy When Prescribing Potentially Teratogenic Medications for Reproductive-Age Women**

Eleanor Bimla Schwarz, MD, MS; Debbie A. Postlethwaite, RNP, MPH; Yun-Yi Hung, PhD; and Mary Anne Armstrong, MA

**Background:** Certain medications are identified by the U.S. Food and Drug Administration (FDA) as class D or X because they increase the risk for birth defects if used during pregnancy.

**Objective:** To assess pregnancy rates and the frequency of contraceptive counseling documented with prescriptions for class D or X drugs filled by women of reproductive age.

**Design:** Description of prescriptions filled in 2001.

**Setting:** A large health maintenance organization in northern California in 2001.

**Patients:** 488,175 women age 15 to 44 years who filled a total of 1,011,658 class A, B, D, or X prescriptions.

**Measurements:** Medications dispensed, contraceptive counseling, and pregnancy testing.

**Results:** A class D or X prescription was filled by 1 of every 6 women studied. Women who filled a prescription for class D or X medications were no more likely than women who filled prescriptions for safer, class A or B medications to have received contraceptive counseling, filled a contraceptive prescription, or been sterilized (48% vs. 51% of prescriptions). There was little variation by clinical indication in rates of contraceptive counseling with class D or X prescriptions, except for isotretinoin. Women who filled a class D or X prescription were only slightly less likely to have a pregnancy documented within 3 months than women filling a class A or B prescription (1.0% vs. 1.4% of prescriptions).

**Limitations:** International Classification of Diseases, Ninth Revision, codes underestimate contraceptive counseling. Documentation of a positive pregnancy test after filling a prescription may overestimate medication use in early pregnancy. Women who filled several prescriptions are overrepresented in prescription analyses.

**Conclusion:** Prescriptions for potentially teratogenic medications are frequently filled by women of childbearing age without documentation of contraceptive counseling.


For author affiliations, see end of text.
Statin Rx for Women of Child Bearing age

HMG-CoA Reductase Inhibitor—Informed Consent Form for Women of Childbearing Age

I have reviewed the information on HMG-CoA Reductase Inhibitors and listened to my healthcare practitioner and understand all of the following:

- HMG-CoA Reductase Inhibitors can cause severe birth defects to the developing fetus of pregnant females if taken during pregnancy.
- I must NOT take HMG-CoA Reductase Inhibitors if I am pregnant and/or think of becoming pregnant.
- I am not pregnant now and do not plan to become pregnant during treatment with HMG-CoA Reductase Inhibitors.
- I must use two forms of effective birth control one month prior and during my treatment with HMG-CoA Reductase Inhibitors.
- Birth control methods may fail. No birth control is absolutely safe.
- I must stop taking my HMG-CoA Reductase Inhibitors and contact my physician if:
  - My menstrual period is delayed while on HMG-CoA Reductase Inhibitor treatment
  - I become pregnant while on HMG-CoA Reductase Inhibitor treatment

I acknowledge that all the above points have been fully explained to me by my healthcare practitioner and that I understand these points fully.

Patient Signature _______________________________ Date 01/16/2007

Block Scheduling

Clinician Signature _______________________________ Date 01/16/2007

James A. Underberg, MD
Dilemmas in treatment of women with familial hypercholesterolaemia during pregnancy

D.M. Kusters\textsuperscript{1,2*}, S.J.M. Homsma\textsuperscript{1}, B.A. Hutten\textsuperscript{1}, M.T.B. Twickler\textsuperscript{1}, H.J. Avis\textsuperscript{1,2}, J.A. van der Post\textsuperscript{4}, E.S.G. Stroes\textsuperscript{1}

Departments of \textsuperscript{1}Vascular Medicine, \textsuperscript{2}Paediatrics, \textsuperscript{3}Clinical Epidemiology, Biostatistics and Bioinformatics, \textsuperscript{4}Obstetrics & Gynaecology, Academic Medical Centre, Amsterdam, the Netherlands, \*corresponding author: tel.: +31 (0)20-566 60 23, fax: +31 (0)20-566 93 43, e-mail: d.m.kusters@amc.uva.nl
Take home points

- Women with FH can be treated with lipid lowering medications during child bearing years if not pregnant or trying to get pregnant.
- Safe treatments during pregnancy include colesevelam and apheresis. Mipomersen is pregnancy category B.
- LDL-Apheresis represents a treatment option.
- Risk to offspring with FH does not seem to be impacted by male vs. female inheritance but data is mixed.
- Counseling women with FH and CAD to avoid pregnancy is recommended.
- Treating young women with FH early is important to reduce treatment needs later in life and to start treatment prior to possible interruption during pregnancy.
Thank You

- Email: james.underberg@nyumc.org
- Twitter: @LipidDoc
- Don’t forget the NLA Selfie Contest!