Familial Hypercholesterolemia & Pregnancy

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Disclosures

- Consultant: Aegerion Pharmaceuticals, Amarin, Amgen, AstraZeneca, Eli Lilly & Co., Genzyme, Sanofi, Alexion, Synageva, Recombine
- Contracted research: Aegerion, Genzyme, Pfizer
- Advisory board: Amgen, Aegerion, Sanofi, Regeneron, Genzyme, Akcea, Kowa Pharmaceuticals,
- Speakers bureau: Amgen, Genzyme, Aegerion, Regeneron, AstraZeneca, Merck & Co., Inc., Alexion/Synageva

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.”


Main changes in lipoprotein metabolism that occur in advancing gestation.

Familial Hypercholesterolemia (FH)

- Autosomal Dominant genetic disorder characterized by mutations in genes involved in the expression, functionality or metabolism of the LDL receptor
- Resulting in lifetime elevation of total and LDL cholesterol (and less common TG’s)
- Premature ASCVD
- HeFH 1:200 HoFH 1:250,000
The Agenda for Familial Hypercholesterolemia

(Circulation. 2015;132:00-00. DOI: 10.1161/CIR.0000000000000297.)

LDL cholesterol Levels in 5 pregnant women with FH

Netherlands Journal of Medicine July/August 2010, Vol. 68, No 7/8

Figure 1. LDL-C levels during pregnancy in women with and without FH

Netherlands Journal of Medicine July/August 2010, Vol. 68, No 7/8
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

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.

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.
NLA Recommendations 2011

• **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.

NLA Recommendations 2011

• **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

Note: The contents of the image are not visible due to the formatting issues.
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.


Patients with FH Are at Very High CVD Risk Before Age 40, Relative to the General Population

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Relative risk of CHD in FH patients vs general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>48.4</td>
</tr>
<tr>
<td>40-59</td>
<td>9.5</td>
</tr>
<tr>
<td>60-79</td>
<td>1.1</td>
</tr>
<tr>
<td>Overall</td>
<td>2.6</td>
</tr>
</tbody>
</table>

* Men (n = 605) * P < 0.01 vs general population.

* Women (n = 580) * Risk of CHD in FH Patients/Risk of CHD in General Population * P < 0.01 vs general population.

Statin Use

- High-intensity statin
- Low/moderate-intensity statin
- No statin

Intolerance: 60%
Patient preference: 11%
Physician preference: 11%
Pregnancy: 3%
Cost: 1%
Trial participation: 1%

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
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.


FELIC Study

Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study

Claudio Nepola, Christopher A Glass, Joseph J Mitsiades, Barrie Dobchuk, Francesco PO Veronesi, Wolf Feldman

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.

Lancet1999;354:1234-41

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."

Lancet1999;354:1234-41
Microphotographs of oil red 0 stained aortic sections from children

Presence of native and oxidised LDL, monocytes, and macrophages in aortic intima of children

Lesion sizes in aortic arch and abdominal aorta of children
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

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 Woman with FH in order to prevent unfavourable (epigenetic) consequences leading to atherosclerosis in their children.

Standardized Mortality Ratio (SMR) according to maternally and paternally inherited FH.

- Overall
- Maternal Inheritance
- Paternal Inheritance
- Females
- Males

Adapted from: J. Versmissen et al. / Atherosclerosis 219 (2011) 690-693

Inheritance pattern of familial hypercholesterolemia and markers of cardiovascular risk

- FH Father
- FH Mother
- Mean difference
- Log Cholesterol

- 1363 Children with FH aged between 0 and 19 years were studied
- 500 had inherited FH maternally, 563 paternally and 97.6% had a verified FH mutation
- Information about inheritance, mutation type and pretreatment levels of blood lipids and CRP was retrieved from the medical records.

Maternal inheritance of FH was not associated with detectable long-term effects in the offspring’s phenotype measured by adverse lipid profiles and increased CRP levels

Findings do not support the fetal origin of adulthood disease hypothesis

Endogenous Estrogens Lower Plasma PCSK9 & LDL-Cholesterol
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.


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
Source: Expert Review of Cardiovascular Therapy. 4.3 (May 2006): p345

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.

Kynamro Package insert accessed online
http://www.kynamro.com/~nws/impdirFiles/KN04AM00_PI.pdf
### Lipid Lowering Agents and Pregnancy Class

<table>
<thead>
<tr>
<th>Lipid Lowering Agent</th>
<th>Pregnancy Class</th>
</tr>
</thead>
<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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</tbody>
</table>

PCSK9 inhibition

- IgG antibodies, cross the placental barrier. The FDA’s experience with monoclonal antibodies in humans indicates that they are unlikely to cross the placenta in the first trimester; however, they are likely to cross the placenta in increasing amounts in the second and third trimester.

PSCK9 inhibition

- Pregnancy—there are no available data on use of alirocumab or evolocumab in pregnant women to inform a drug-associated risk; consider the benefits and risks of these medications and possible risks to the fetus when prescribing to pregnant women.

FH, Pregnancy & Apheresis

Low-Density Lipoprotein Apheresis Therapy During Pregnancy
Linda Cashin-Hempill, MD, Margaret Noone, RN, Jodi F. Abbott, MD, Carol A. Waksmonski, MD, and Robert S. Less, MD

“In conclusion, apheresis therapy with HELP was safe and efficacious during pregnancy in this patient with stable coronary artery disease and severe hypercholesterolemia.”

The American Journal of Cardiology Vol. 86 November 15, 2000
FH, Pregnancy and Apheresis

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.

Transfusion and Apheresis Science 44 (2011) 23–24

Use of Pregnancy Category D/X Meds

Statin Rx for Women of Child Bearing age
Dilemmas in treatment of women with familial hypercholesterolaemia during pregnancy

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 colesvelam and apheresis. Mipomersen is pregnancy category B.

PCSK9i may be an option in 2nd and 3rd trimester.

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

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- www.thefhfoundation.org
- www.learnyourlipids.com

Preggo Booth (available on the app store)