Management of FH in Pregnancy: An art or an oxymoron?

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Disclosures

- Scientific advisory board:
  - Amgen, AstraZeneca, Sanofi Regeneron
Objectives

- Understand that preventing ASCVD requires practice of universal principles common to both genders.
- Recognition that diagnosis and treatment of lipid disorders in women poses unique challenges.
- Management of lipid disorders in women requires perspective of ASCVD prevention throughout a woman’s lifespan.
- Pregnancy + FH = ??????????????
  - Unique challenges
Patient Presentation: SJ

- 32 yo WF relocated to Charleston, SC in November 2010
- Seen in consultation for known FH
- CV history
  - SVT diagnosed age 14
  - Radiofrequency ablation at U Mass at age 20
  - Rare palpitations, frequent PVCs, intolerable fatigue on BB
Case: SJ

- FH diagnosed at age 12 yrs
- Initially treated with simvastatin
- Inadequate lowering of LDL-C, changed to rosvastatin
  - Intolerable myalgias
- Followed by Dr. Ross Simpson at UNC on atorvastatin 40 mg and ezetimibe 10 mg daily
- Atorvastatin 80 mg recommended, patient declined
SJ: Family history

- **Father**
  - Severe hypercholesterolemia
  - Suffered first MI at age 30 yrs
  - Died at age 44 yrs of recurrent MI

- **Mother**
  - Alive and well at age 55 yrs

- **Sister**
  - Severe hypercholesterolemia

- **Brother**
  - Severe hypercholesterolemia
  - First male relative to survive age 50 yrs

- **Paternal uncles**
  - 4 with hyperlipidemia and deceased before age 50 of ASCVD

- **Paternal grandfather**
  - Died in late 40s with MI
Case: SJ

- At time of presentation patient off of all lipid-lowering medication for 2 years
  - Pre-conception, pregnancy, birth of identical twin boys, lactation
Case: SJ

- Physical exam
  - WNL
  - No tendon xanthomas, arcus

- April 2010 restarted atorvastatin 40 mg

- May 2010 added ezetimibe 10 mg

- At age 33 yrs calcium scoring demonstrated evidence of subclinical atherosclerosis of LAD.
Case: SJ

- Labs
  - Untreated
    - TC 462 mg/dl, HDL-C 59 mg/dl, LDL-C 390 mg/dl, TG 56 mg/dl
  - On atorvastatin 40 mg, ezetimibe 10 mg
    - TC 189 mg/dl, HDL-C 52 mg/dl, LDL-C 129 mg/dl, TG 37 mg/dl
    - Patient declined further increase in statin dose
  - Intolerant rosuvastatin due to myalgias/cramps
Case: SJ

- April 2013
  - Discontinued LLT during IVF with frozen embryos
  - Unable to tolerate colesevelam
  - Diet, exercise, phytosterols

- Presented April 2014
  - 26 weeks pregnant
  - Symptomatic tachycardia
  - Low-dose BB prescribed
Case: SJ

- **February 2015**
  - Healthy 6 month old, 6 yo twins
  - TC 358 mg/dl, LDL-C 294 mg/dl, HDL-C 52 mg/dl, TG 38 mg/dl

- **Re-started atorvastatin 40 mg**
  - Declined ezetimibe

- **RTC**
  - TC 258 mg/dl, LDL-C 197 mg/dl

- **December 2015**
  - Recommended increase atorvastatin to 80 mg and add ezetimibe 10 mg

- **March 2016**
  - Did not add ezetimibe due to expense
  - TC 194 mg/dl, LDL-C 120 mg/dl

- Agreed to add ezetimibe when off-patent
FH and Pregnancy: Considerations

- How do lipid levels change during pregnancy in women with FH compared to women without FH?
- What are the consequences of FH for mother and child?
- What treatment options are safe for mother and child during pregnancy and breastfeeding?
Lipid levels through the ages in women

Women in menopausal transition in the Study of Women’s Health Across the Nation (SWAN)

- Increases in TC/LDL-C were substantial within a year of FMP
- Rate of change did not vary by ethnicity, suggesting that menopause has uniform influence on lipids
- Increase in TG was consistent with effects of chronological aging rather than ovarian aging.

Lipid levels during pregnancy

- Women may have significant undiscovered dyslipidemia before pregnancy.
- May be associated with conditions that increase risk of pregnancy-related complications: diabetes, PCOS, genetic lipid disorders.
- FH is more common than genetic disorders routinely screened for in pregnancy.
- No recommendations for routine FH screening.

Gestational changes in lipoprotein metabolism
Lipid levels in normal pregnancies

- Following conception, there is a decrease in TG, TC, and LDL to a nadir at 2nd gestational month.
- Levels then increased with peak at the delivery month.
- Note that TC and TG do not exceed 250 mg/dl at any time.

Lipids/lipoproteins in pregnancy

- Maternal hyperlipidemia is one of the most consistent metabolic changes during pregnancy.
  - Total cholesterol: increases 25-50%
  - LDL-C: can increase by as much as 66%
  - TGs: can increase 1.5- to 3-fold
  - Total cholesterol and TG levels in women with normal pregnancies should not exceed 250 mg/dL.

- May have a biological role in the need for increased sex hormone synthesis and maintenance of adequate nutrient supply for pregnant mother and fetus.

Circulation. 2011;124:1606-1614
Am J Obstet Gynecol. 2007;197:610 e611-e617
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- Women with FH show relative changes in lipids that are similar to those in healthy women.
  - However, absolute increase is greater in women with FH.

Circulation. 2011;124:1606-1614
Am J Obstet Gynecol. 2007;197:610 e611-e617
LDL-C levels during pregnancy in FH

- 22 FH vs. 149 non-FH patients
- Both non-FH and FH women had similar significant relative increases in TC, LDL-C, and TG.
- Absolute increase was more pronounced in FH women.

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

LDL-C = low-density lipoprotein cholesterol; FH = familial hypercholesterolaemia.
LDL-C levels in FH women

- Five patients 28-37 years of age
- Pre-pregnancy LDL-C 259 to 495 mg/dl (“probable FH”)
- None with ASCVD
- All with planned pregnancies, off statin
- All prescribed colesevelam
  - Compliant: LDL-C increase 68 mg/dl
  - Non-compliant: LDL-C increase 185 mg/dl

LDL-C levels (mg/dl) in the five women at time of probable FH diagnosis (Baseline LDL), while on statin treatment (Pre-pregnancy statin-treated LDL) and during pregnancy (Pregnancy LDL).

Management of FH

European Heart Journal. doi:10.1093/eurheartj/eht273
Management of FH

Cumulative event-free survival (%) in FH

Follow-up (years)

European Heart Journal. doi:10.1093/eurheartj/eht273
Cholesterol-lowering treatment has been associated with improved outcomes.
What are consequences for the FH mother?

- **Case: SJ**
  - Initiated statin therapy age 12 yrs.
  - By age 37 yrs. she had been **off of all LLT** for approximate total of 4 years for conception, pregnancy, and lactation.
  - Inadequate lowering of **LDL-C** due to intolerance of rosuvastatin, non-compliance with recommendations to increase atorvastatin to 80 mg, and inability to afford ezetimibe.
What are consequences for the FH mother?

- Normal pregnancy: general vasodilatation and reduced systemic vascular resistance, mainly mediated by endothelium derived nitric oxide (NO).
  - Endothelial-dependent vasodilator function: brachial artery flow mediated dilatation (FMD).

- In a normal pregnancy, FMD is enhanced throughout the pregnancy because of increased NO bioactivity.
  - Endothelial dysfunction precedes clinically apparent atherosclerosis and key event in pre-eclampsia.
  - Attenuated FMD associated with other ASCVD risk factors, including advancing age, elevated SBP, smoking, obesity, and hyperlipidemia, and low HDL-C concentrations.

Circ J. 2006;70(6):768-72
What are consequences for the FH mother?

- In healthy pregnant women, increased gestational age is associated with improved endothelium-dependent vasodilation responses regardless of concurrently appearing lipid changes.

- FMD% correlated directly with gestational age, vessel size, TC, and TG, but not with LDL-C or HDL-C.

Circ J. 2006;70(6):768-72
What are consequences for the FH mother?

- Previous reports of hyperlipidemia in pregnancy
  - Atherosis in uteroplacental spiral arteries
    - Along with hypercoagulation may result in thrombosis and placental infarctions, placental insufficiency, and fetal compromise.
  - Epidemiological data suggests HL associated with preterm delivery
  - Low birth weight
  - Small prospective study suggested increase in premature delivery in FH women vs. healthy reference group.

Circulation. 2011;124:1606-1614
What are consequences for the FH mother?

- Medical Birth Registry of Norway and Medical Genetics Laboratory
  - 2319 births of 1093 women with HeFH (no HoFH identified)
  - Mean age for first pregnancy 28 yrs
  - Mean pre-pregnancy TC 380 mg/dl
  - Predominantly white women

- 106 different LDL-R mutations identified

Circulation. 2011;124:1606-1614
What are consequences for the FH mother?

- Similar fertility rates among FH vs. non-FH women
- 4.8% used statin/BAS during early pregnancy—no increase in premature termination
- Frequency of prematurity did not differ by LDL-R mutation type.
- Introduction of statins had no apparent effect on prematurity or low birth weight.
- Congenital malformations increased over f/u in both FH and non-FH women.

Circulation. 2011;124:1606-1614
What are consequences for the FH mother?

- No significant differences in prematurity, low birth weight, or congenital malformations among FH compared to non-FH women.

- Frequency of prematurity, low birth weight, congenital malformations did not differ among FH mutation types.

- No significant differences in frequencies of eclampsia, preeclampsia, pregnancy-induced hypertension.

- No increase in risk for mother or infant during pregnancy or delivery.

Circulation. 2011;124:1606-1614
Guidelines for management of FH in pregnancy
Executive Summary

Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients

Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia

Anne C. Goldberg, MD, FNLA, Chair*, Paul N. Hopkins, MD, MSPH, Peter P. Toth, MD, PhD, FNLA, Christie M. Ballantyne, MD, FNLA, Daniel J. Rader, MD, FNLA, Jennifer G. Robinson, MD, MPH, FNLA, Stephen R. Daniels, MD, PhD, Samuel S. Gidding, MD, Sarah D. de Ferranti, MD, MPH, Matthew K. Ito, PharmD, FNLA, Mary P. McGowan, MD, FNLA, Patrick M. Moriarty, MD, William C. Cromwell, MD, FNLA, Joyce L. Ross, MSN, CRNP, FNLA, Paul E. Ziajka, MD, PhD, FNLA

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National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2

Terry A. Jacobson, MD*, Kevin C. Maki, PhD, Carl E. Orringer, MD, Peter H. Jones, MD, Penny Kris-Etherton, PhD, Geeta Sikand, MA, Ralph LaForge, MSc, Stephen R. Daniels, MD, PhD, Don P. Wilson, MD, Pamela B. Morris, MD, Robert A. Wild, MD, PhD, MPH, Scott M. Grundy, MD, PhD, Martha Daviglus, MD, PhD, Keith C. Ferdinand, MD, Krishnaswami Vijayaraghavan, MD, Prakash C. Deedwania, MD, Judith A. Aberg, MD, Katherine P. Liao, MD, MPH, James M. McKenney, PharmD, Joyce L. Ross, MSN, CRNP, Lynne T. Braun, PhD, CNP, Matthew K. Ito, PharmD, Harold E. Bays, MD, W. Virgil Brown, MD

On behalf of the NLA Expert Panel

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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 Wiegen, MD, PhD, Shizuya Yamashita, MD, PhD, John J. P. Kastelein, MD, PhD

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Familial hypercholesterolaemia: identification and management

Clinical guideline
Published: 27 August 2008
nice.org.uk/guidance/cg71
Clinical update

Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society


Institute for Translational Medicine and Therapeutics, University of Pennsylvania, 8039 Maloney Building, 3600 Spruce Street, Philadelphia, PA 19104, USA

Received 13 March 2014; revised 19 May 2014; accepted 13 June 2014
AHA Scientific Statement

The Agenda for Familial Hypercholesterolemia
A Scientific Statement From the American Heart Association

Samuel S. Gidding, MD, FAHA, Chair; Mary Ann Champagne, RN, MSN, FAHA;
Sarah D. de Ferranti, MD, MPH; Joep Defesche, PhD; Matthew K. Ito, PharmD;
Joshua W. Knowles, MD, PhD, FAHA; Brian McCrindle, MD, MPH, FAHA;
Frederick Raal, MD, PhD; Daniel Rader, MD, FAHA; Raul D. Santos, MD, PhD;
Maria Lopes-Virella, MD, PhD, FAHA; Gerald F. Watts, DSc, MD, PhD;
Anthony S. Wierzbicki, MD, PhD, FAHA; on behalf of the American Heart Association
Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular
Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics
and Translational Biology, and Council on Lifestyle and Cardiometabolic Health

Circulation. 2015; 132: 2167-2192
Groups with Special Considerations: From Pregnancy to Menopause

- Women should be screened for dyslipidemia before pregnancy or as part of the routine obstetrical laboratory examination.
  - Strength E, Quality Low

- For women taking lipid-lowering medications prior to pregnancy, all except bile acid sequestrants, should be stopped when the woman becomes pregnant, or is trying to become pregnant.
  - Strength B, Quality Moderate
Groups with Special Considerations: From Pregnancy to Menopause

- Women should be educated on the importance of pregnancy avoidance when lipid-altering therapies other than bile acid sequestrants are used.
  - Strength A, Quality Moderate

- Total cholesterol and TG levels in women with normal pregnancies should not exceed 250 mg/dL. If they do, the clinician should consider and evaluate preexisting or acquired medical or obstetrical conditions, including hypothyroidism, chronic kidney disease, liver disease, uncontrolled diabetes mellitus, or preeclampsia.
  - Strength A, Quality Moderate
Groups with Special Considerations: From Pregnancy to Menopause

- Hypercholesterolemia during pregnancy and breast feeding, especially in women with FH, may be treated with bile acid sequestrants.
  - Strength B, Quality Low

- Women with FH may be treated with LDL apheresis during pregnancy and breast feeding.
  - Strength A, Quality Low
Background – Groups with Special Considerations: From Pregnancy to Menopause

Lipid lowering agents and pregnancy categories*

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<th>Lipid-lowering class or agent</th>
<th>Pregnancy category†</th>
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<td>Statins</td>
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<td>Fibrates</td>
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<td>Mipomersen</td>
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*Categories previously established by the FDA to indicate the potential of a drug to cause birth defects if used during pregnancy: B (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women), C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks), and X (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).

U.S. FDA. Pregnancy and lactation labeling final rule. 2015.
Background – Groups with Special Considerations: From Pregnancy to Menopause

Pregnancy categories were removed from drug labeling per the new FDA labeling guidance effective June 30, 2015, and instead drug labeling will include a summary of the risks of using a drug during pregnancy and lactation, discussion of data supporting that summary, and relevant information to assist health care providers in treatment decisions for pregnancy (8.1), lactation (8.2), and females and males of reproductive potential (U.S. FDA 2015).

U.S. FDA. Pregnancy and lactation labeling final rule. 2015.
LDL apheresis during pregnancy

- No published clinical trials

- Case reports or case series demonstrated safety for both mother and fetus, normal fetal maturation.
  - Reduced volumes of plasma treated
  - Supplemented iron due to depletion of apoferritin

- No therapeutic guidelines for apheresis in pregnancy for women with FH

Transfusion and Apheresis Science. 2015;53:283-7
Lifestyle Therapies: Nutrition

- **<7% of energy from saturated fat, with minimal intake of trans fatty acids** to lower levels of atherogenic cholesterol (low-density lipoprotein cholesterol [LDL-C] and non-high-density lipoprotein cholesterol [non-HDL-C]).

- **Limit cholesterol intake to <200 mg/day** to lower levels of atherogenic cholesterol (LDL-C and non-HDL-C).

- There are individuals who are hyper-responders to dietary cholesterol because of genetic or other reasons. For known or suspected hyper-responders, further reduction in dietary cholesterol beyond the <200 mg/day that is recommended as part of the cardioprotective eating pattern for the management of dyslipidemia may be considered. Consumption of very low intakes of dietary cholesterol (near 0 mg/day) may be helpful for such individuals.
Lifestyle Therapies: Nutrition

- Dietary saturated fat may be partially replaced with unsaturated fats (mono- and polyunsaturated fats), as well as proteins, to reach a goal of <7% of energy from saturated fats.

- Weight loss of 5-10% body weight is generally recommended for overweight or obese individuals to lower atherogenic lipoprotein lipids and improve other atherosclerotic cardiovascular disease (ASCVD) risk factors.
Lifestyle Therapies: Nutrition

- Eating patterns that contain a moderate quantity of carbohydrate, lower glycemic index and load, and higher protein, have been associated with modest benefits for weight loss and maintenance.

- Plant sterols and stanols (~2 g/day) are recommended for cholesterol lowering, as well as viscous fibers (5 to 10 g/day or even greater, if acceptable to the patient), as adjuncts to other lifestyle changes. However, individuals with phytosterolemia (sitosterolemia) should avoid foods that are fortified with stanols and sterols.
Lifestyle Therapies: Nutrition

- Consumption of at least three 1-oz. equivalent servings per day of fiber-rich whole grains is recommended.

- Consumption of ≥4 servings/week (1 oz. per serving) of nuts (including the legume, peanuts) is recommended, because nut consumption has been consistently associated with reduced ASCVD risk. Nuts may be included in the diet as a protein food and as a source of healthy fat (predominantly unsaturated fatty acids).

- Soy protein foods are one source of plant protein, among others (e.g., nuts, legumes), that may be used as a substitute for protein foods high in saturated fat as part of a cardioprotective eating pattern.
Lifestyle Therapies: Nutrition

- Nutrition education/medical nutrition therapy (MNT) by a registered dietitian nutritionist with follow-up and monitoring are recommended to promote long-term dietary adherence. Clinicians should, when feasible, refer patients to a registered dietitian nutritionist for MNT to individualize a cardioprotective dietary pattern and promote successful lifestyle modifications.
Summary and Take-Home Points

- Management of FH presents unique challenges for clinicians caring for women contemplating pregnancy, and during pregnancy and lactation.
- Lifestyle therapies including heart-healthy, low-saturated fat, low-cholesterol diet, phytosterols and viscous fibers, exercise, and avoidance of tobacco are the foundation of management for the FH patient.
- Prescription medications other than BAS (and possibly mipomersen in HoFH) should be discontinued a minimum of 1 month and possibly as long as 3 months in FH women prior to trying to conceive, and in women who are pregnant or breastfeeding.
  - Discontinue statins, ezetimibe, niacin
- In the case of unintended pregnancy, discontinue statins, ezetimibe, niacin and consult with clinician, though risk of complications appears to be low.
Summary and Take-Home Points

- LDL apheresis may be considered during pregnancy for women with HeFH and significant clinical ASCVD or HoFH.

- Mipomersen (Pregnancy Category B) may be considered during pregnancy for women with HoFH and unacceptably high levels of LDL-C if the benefits are considered to outweigh potential risks.

- There is currently no available data on safety or efficacy of PCSK9 inhibitors in pregnancy or during breastfeeding.

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