Hypertriglyceridemia, Inflammation, & Pregnancy

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Disclosure of Financial Relationships

- None
Objectives

- Review mechanisms of hypertriglyceridemia (HTG) and inflammation (INF) in CVD
- Review strategies for managing hypertriglyceridemia (HTG) and inflammation (INF) in pregnant women or women who plan to become pregnant
- Review Counseling for women with HTG/INF of childbearing age
- Review impact of HTG/INF on offspring
- Review Drug safety in pregnancy
Hypertriglyceridemia, Inflammation and the Atherogenic Lipoprotein Phenotype

- High non-HDL-C
- Delayed clearance of TG enriched remnants
- High inflammatory markers i.e. hs-CRP, Lp-PLA2, IL-6, ICAM, VCAM
- High Triglycerides
- Low HDL-C
- Oxidized “sticky” lipoproteins
- High VLDL-C
- Small dense LDL particles
Cholesterol-Carrying Lipoproteins

Different isolates of chylomicron remnants of predetermined size were labeled with Cy5 fluorescence (in yellow). Lipoprotein preparations of different size were perfused in situ through rabbit carotid arteries for an equal length of time under physiological conditions.

Proctor et al., *Arterioscler Thromb Vasc Biol.*, 2004;24: 2162-7
Main changes in lipoprotein metabolism that occur in advancing gestation.
Levels of TC, TG, HDL, and LDL 1 year before, during, and 1 year after gestation.
Postprandial Hepatic Lipid Load

Poor Clearance 6-10 hours postprandial
Patient Profile:
- Hypertriglyceridemia
- Chronic inflammation
- CHD/risk equivalent
- Diabetes and/or Metabolic Syndrome
- Non-HDL >130 mg/dL

Normal Clearance 2-4 hours postprandial
Patient Profile:
- <2 risk factors

Turley S. et al., Am J Physiol Gastrointest Liver Physiol, 2008; 295: G813–G822
Increased TGs Correlated to Increased hs-CRP in Women

Figure 2: Cross-sectional associations between geometric mean C-reactive protein (CRP) concentration and some conventional risk factors and other characteristics

Mean CRP concentration was adjusted to age 50 years. Error bars represent the 95% CIs. BP = blood pressure.

$r$ = Pearson’s correlation coefficient (95% CI) for association between the risk marker and log, CRP concentration in men and women combined.
Inflammation Predicts CVD Risk in Women

Figure 1. Relative Risk of Cardiovascular Events among Apparently Healthy Postmenopausal Women According to Base-Line Levels of Total Cholesterol and Markers of Inflammation.
Each marker of inflammation improved risk-prediction models based on lipid testing alone, an effect that was strongest for hs-CRP and serum amyloid A.

Ridker P., NEJM, 2000; 342:836 - 843
PROVE-IT: Risk of Cardiovascular Event Equal in Patients with Elevated Inflammation or LDL-C and Increased by Elevated Triglycerides > 150 mg/dL

Figure 3. Cumulative Incidence of Recurrent Myocardial Infarction or Death from Coronary Causes, According to the Achieved Levels of Both LDL Cholesterol and CRP.

The median value of each marker is included for the sake of completeness, since no patient had the exact median value of either marker.

Ridker P., NEJM, 2005; 352: 20 - 28

JACC, Miller M. et al., 2008; 51(7): 724-730
Potential Issues/Concerns of HTG/INF during Pregnancy

- Maternal hyperlipidemia leads to atherosclerosis in the uteroplacental spiral arteries, hypercoagulation, local thrombosis, placental infarctions, and placental insufficiency leading to maternal risk and possible fetal compromise.
- HTG/INF in pregnancy may lead to more hypertensive disease. Links between preeclampsia & increased maternal lipid levels have been described.
- Fetal exposure to elevated cholesterol, TG, and inflammatory levels may have impact on outcomes.

Sparse and Incomplete Data for Treatment of HTG/INF in Pregnancy

• 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.
• Omega 3s and new agents such as PCSK9 inhibitors and mipomersen may offer potential options in the future.
• Limited treatment options make management of lipids 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.

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.
Microphotographs of oil red 0 stained aortic sections from children

- **early fatty streak**
- **shoulder area of transitional lesion**
- **advanced lesion**

Lancet 1999; 354:1234 – 41
## Lipid Lowering Agents: Pregnancy Class and Reductions in Atherogenicity


<table>
<thead>
<tr>
<th>Lipid Lowering Agent</th>
<th>Pregnancy Class</th>
<th>Reduces Lipid Cholesterol, Particles, and Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>X</td>
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<tr>
<td>Fibrates</td>
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<tr>
<td>Niacin</td>
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<tr>
<td>Eicosapentaenoic Acid</td>
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</tr>
<tr>
<td>Colesevelam</td>
<td>B</td>
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</tr>
</tbody>
</table>
Biosynthesis and Metabolism of Polyunsaturated Fatty Acids Leading Towards (n-6) or Away from (EPA) Inflammation

1-series PG

18:3n-6

20:3n-6

3-series LT

18:4n-3

20:4n-3

3-series PG

20:5n-3

5-series LT

Arachidonic acid

Eicosapentaenoic acid

Docosahexaenoic acid

Inflammation and immunity

COX

LOX

Δ5-desaturase

REVERSAL: Plaque Regression Occurs when Inflammation is Reduced below Median CRP<2.0mg/L

Nissen et al., *NEJM*, 2005; 352: 29-38
Fig. 2. Representative examples of the OCT analysis.

In an example from the EPA group (A), the fibrous cap thickness increased (120 μm to 200 μm) and the lipid arc decreased (133 degrees to 119 degrees) over 7.9 months of follow-up. In an example from the control group (B), the fibrous cap thickness decreased (120 μm to 110 μm) and the lipid arc increased (127 degrees to 131 degrees) over 8.1 months of follow-up. The white arrows indicate the fibrous cap thickness. The yellow arrows indicate the lipid arc. OCT = optical coherence tomography. EPA = ethyl eicosapentaenoic acid.
JELIS: Rapid Benefit Shown with EPA Therapy Suggests Anti-Inflammatory, Anti-coagulant, and/or Normo-rhythmic Mechanisms


Omacor/Lovaza Carotid Endarterectomy Intervention (OCEAN) Trial: Surgical Carotid Plaque Analysis After 7-102 Days Omacor/Lovaza 2g/day Therapy

“The average differences in EPA and DHA in plaque phospholipids reported by Thies et al. were 85% and 9% respectively, compared with control. This compares with differences of 100% and 13% for EPA and DHA in the current study, although DHA was not significantly different in plaques phospholipids between the two groups. Thus it appears that substantial incorporation of EPA into advanced plaques occurs within a relatively short time frame.”

Fish Oil Supplements: Oxidation Reduces Content and Effectiveness

What’s in “fish oil” capsules? Each 1000 mg capsule contains a minimum of 25 and up to 45 different fatty acids.

Figure 1 | The actual n-3 PUFA content (EPA + DHA) contained in individual retail fish oil products in relation to the claimed content (dotted line).

Comparative Effects of EPA and DHA on Lipid Peroxidation in Membrane Vesicles

Values are mean ± SD (N=6). *P<0.001 versus control; †P<0.001 versus EPA (Student-Newman-Keuls multiple comparisons test; overall ANOVA: P<0.0001, F=39.884).

Take-home Points

- Women with HTG/INF can be treated with lipid lowering medications during child bearing years if not pregnant or trying to get pregnant.
- Safest treatment during pregnancy is colesevelam. Mipomersen is pregnancy category B. EPA is pregnancy category C.
- Children of mothers with HTG/INF are at greater risk of atherosclerotic disease than children of non-HTG/INF mothers.
- Risk to offspring with HTG/INF does not seem to be impacted by male vs. female inheritance but data is mixed.
- Counseling women with HTG/INF and CAD prior to and/or during pregnancy is recommended.
- Treating young women with HTG/INF early is important to reduce treatment needs later in life and to start treatment prior to possible interruption during pregnancy.