Triglycerides & Pregnancy

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• Oklahoma University Health Sciences Center
• VA Medical Center, Oklahoma City
• Past President SWLA,
• Executive Committee NLA
• ABCL Board
Triglycerides & Pregnancy
OUTLINE

• Implications of dyslipidemia in pregnancy
• Pre-Pregnancy screening and CVD risk management
• Lipids in Pregnancy
  – Normal changes
  – Abnormal changes
  – Pathological disorders
• Post Pregnancy Considerations
PRE PREGNANCY

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2.4 (2.0-2.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.7 (6.9-8.5)</td>
</tr>
<tr>
<td>Obesity - BMI category (Kg/m²)</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>Only 42.4 (40.3-44.5)!!!!</td>
</tr>
<tr>
<td>25-&lt;30</td>
<td>25.9 (24.3-27.7)</td>
</tr>
<tr>
<td>30-&lt;35</td>
<td>16.2 (15.0-17.6)</td>
</tr>
<tr>
<td>≥35</td>
<td>25.4 (23.6-27.2)</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>25.4 (23.6-27.2)</td>
</tr>
<tr>
<td>C K Disease</td>
<td>2.9 (2.4-3.5)</td>
</tr>
</tbody>
</table>

NHANES 1999-2012
Pre-pregnancy cardiometabolic and inflammatory risk factors and subsequent odds of a hypertensive disorder in pregnancy

How well do we screen?
N=3,015 National repr sample

- 61% of women reported Gyn or Ob visit in past year
  - regardless of income - lack of time is why they can’t go to the doctor
- More women than men forgo health care because of cost
- Largest burden is with the uninsured
  - Work place feasibility, sick leave, child care, no transportation
- Rates of screening Lipids
  - 58% 18-44yo, 78% 45-64 yo
- Lower than for bp screening
Missed opportunities for preventive health care

• Women’s Health care “Patchwork quilt with gaps”

• National Health Interview Survey
  – Of Women ages 18-64
    • 15% seen by general medical physicians
    • 62% Gynecologists alone
    • 23% both

Those seen by GYN receive more counseling and preventive services

Ehrenthal, DB  Curr Opin Cardiol 2013
<table>
<thead>
<tr>
<th>Missed opportunities for preventive health care</th>
</tr>
</thead>
<tbody>
<tr>
<td>• (2 health care plans - 3.6 million members)</td>
</tr>
<tr>
<td>- New DX hypertension</td>
</tr>
<tr>
<td>• <strong>Hypertension recognized &lt; 1/3 in course of care!</strong></td>
</tr>
<tr>
<td>• Dx ½ as likely by Ob/Gyn</td>
</tr>
<tr>
<td>• Rural setting obese women more likely to have counseling for CVD risk reduction</td>
</tr>
<tr>
<td>• <strong>&lt; 70% had lipid screening</strong>, nutrition counsel, weight management - <strong>regardless of specialty!</strong></td>
</tr>
</tbody>
</table>

Ehrenthal, DB Curr Opin Cardiol 2013
Missed opportunities for preventive health care

• Recent Title X clinic screening for CVD risk
  – Protocol driven
  – Majority of women in need of referral for hypertension, diabetes, dyslipidemia, smoking and dyslipidemia received them

• However **few women were able to complete the referrals or participated in risk reduction strategies**

• A better understanding of barriers to referral care among low-income women is needed!

Ehrenthal, DB Curr Opin Cardiol 2013
Missed opportunities for preventive health care

- Majority of Ob/Gyns go beyond reproductive care
  - knowledge, skill deficits, liability concerns, barriers of practice structure - difficulty getting 1st care referrals!
- More Ob/Gyns likely to recommend follow up testing for diabetes than primary care physicians (Internists, Fam Med, DO)
- Nearly all primary care providers screen for CVD risk
- 70% of Ob/Gyns screen consistently
- **Limited knowledge about Preeclampsia and future CVD risk - all specialties!**

Ehrenthal, DB Curr Opin Cardiol 2013
Pg. rates for women 25-29 have not changed!
Rates for women in their 30s to 40s have increased!
Childbearing and Obesity in Women: Weight Before, During, and After Pregnancy

- US women 35-44 yo - greatest increase in prevalence of obesity in past 45 yrs!
  - Associated Hypertriglyceridermia!
- 45% of women begin Pg. overweight or obese
  - Up from 24% in 1983!
- 43% of PG women gain more weight than is recommended
- Maternal overweight and obesity most common hi-risk OB condition
  - Gestational diabetes, hypertensive disorders, newborn macrosomia, perinatal complications

36(2) : 317-28
Fertility and Dyslipidemia
Window of Opportunity

• Maximum fertility both genders is 23 yrs.
• By Age 32 it begins to decline
• This is a wonderful opportunity (9 years) for Preventing CVD risk in Pg or for their offspring by lifestyle and/or meds – in motivated people!
• It takes time to affect change and CVD Risk Factors
  – Obesity (low HDL, Hi TG, high nonHDL Cholesterol)
  – Dyslipidemia
  – Smoking
  – BP
Fetal Considerations
When does metabolic syndrome begin?
Lipid Changes in Pg. and CVD

- Controlling diabetes pre-pregnancy reduces fetal cardiac anomalies
- Dyslipidemia – Historically considered physiologic with little clinical relevance and not routinely measured!
  - Increased fatty streaks in aortas of 6 mos. old fetuses of mothers with hypercholesterolemia
  - FELIC study - maternal dyslipidemia associated with increase aortic atherosclerosis in normo-cholesterolemic children
- New Zealand While Rabbits - diet induced maternal dyslipidemia - dose dependent fetal and postnatal atherogenesis, maternal cholestyramine reduced it
- Murine Model supportive
  - multiple animal models similar story
- Double blind studies have not been performed
  - Ethics, feasibility, horizon

Palinski W Circulation. 2014;129:2066-2077
Chronic Non Communicable Disease

Hanson, M. Progress in Biophysics and Molecular Biology 106 (2011) 272e280
Fetal Developmental Programming

• Pre-Pregnancy
  – Genetic, metabolic, smoking, maternal, paternal

• Pregnancy
  – Malnutrition, stress, chemicals, steroids, cardiomyopathy, preeclampsia, gestational diabetes, smoking, Met Syndrome, gestational hyperlipidemia, obesity, IUGR, LGA, placental function, hypoxia
  – **Fetal epigenetic changes - DNA methylation**

• Post Pregnancy
  – Genetics, lifestyle risk
    • Immune response, inflammation, endothelial dysfunction,
    • atherogenesis

• Adult Phenotype at different genetic set points – cardio-metabolic disease with Obesity and Metabolic Syndrome

Palinski W Circulation. 2014;129:2066-2077
Lipids & Atherogenesis Dynamic

- Pg increased permeability of vascular endothelium by small molecules
  - Increased by diabetes
  - Active transport mechanisms of lipids to fetus
- Different in different stages of Pg.
- Fetus shunts fat early in gestation depending upon liver maturity
- Pericardial fat in fetus early
  - later liver shunts it to protect the brain

Gunitilake, R Abstract 2014
OUHSC Annual Research Day

Palinski W Circulation. 2014;129:2066-2077
BMI & Fetal Outcomes

- Even modest increases in maternal BMI were associated with increased risk of fetal death, stillbirth, neonatal death, perinatal death, and infant death.
- Weight management guidelines for women who plan pregnancies should take these findings into consideration to reduce the burden of fetal deaths, stillbirths, and infant deaths.

Kaplan-Meier curves for death rates in offspring according to maternal BMI category showing increased adjusted all cause premature **mortality in offspring of obese mothers** (BMI >30).

Reynolds R M et al. BMJ 2013;347:bmj.f4539

Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1,323,275 person years
Non-linear relation of maternal BMI with mortality in offspring, showing that odds of offspring death was more among mothers with low or high BMI before pregnancy compared with mothers with BMI of 23. Offspring aged 34-61.
Cardiometabolic outcomes of Offspring at age 32 by quartile of maternal pre Pg weight and weight gain both during Pg

- BMI\Waist
- TG
- Blood Pressure
- Insulin resistance

Hochner, H. et al 2012
Circulation 125(11):1381
2012
Mother
TC, TG, HDL, LDL 1 yr. before, during and 1 year after Pg. n=8,700

Lipids in Pregnancy

- Pharmacological amounts Estrogens increase TGs by stimulating hepatic production of VLDL and inhibiting hepatic and adipose lipoprotein lipase
- Progesterone apposes these actions
- E/P and VEGF, TNF alpha (and other cytokines and inflammatory factors) are important contributors of Insulin Resistance
- Pregnancy is a STRESS TEST

Wiznitzer, A Amer J Obstet Gynecol 2009
Lipids in Pregnancy

- Lipids vary during Pg. initial decrease then a nadir during first trimester followed by gradual increase and peak before delivery
- **Hi Levels of TGs are associated with an increased risk for preeclampsia and gestational diabetes (n=1,209)**
- Hyperlipidemia is common in 2nd ½ of PG as physiologically required mechanism to maintain stable fuel for fetus
  - Likely pathologic indicating a metabolic syndrome
Triglycerides in Pregnancy

Under non-pregnant conditions the TG content in HDL and LDL are low compared to VLDL. In nl Pg women there is a significant increase in TG in all lipoprotein fractions.

Plasma lipoprotein TG in women at then 3rd trimester of pregnancy (red) and at post-lactation.

Herrera E. Eur J Clin Nutr 2000;54:Suppl 1 S47-S51
Small low-density lipoproteins and vascular cell adhesion molecule-1 are increased in association with hyperlipidemia in preeclampsia

- Preeclampsia is characterized by endothelial dysfunction prompted by increase in TG and FFAs.
- Smaller LDL can induce endothelial dysfunction
- TG, Apo B, small LDL increased in preeclampsia
- VCAM1 (indicator of endothelial dysfunction) increased - not associated with particles
- Are changes from ApoB or LDL?

Dyslipidemia and Preeclampsia & Gestational Diabetes

- Endothelial dysfunction – some indication secondary to oxidative stress and decreased release of prostacyclin
- Altered lipoprotein lipase, enhanced endothelial uptake of FAs, esterified to TG
  - Metabolic syndrome
  - Gestational diabetics - higher TG

Wiznitzer, A Amer J Obstet Gynecol 2009
Lipid profile in non-obese pregnant women with polycystic ovary syndrome: A prospective controlled clinical study

Palumbo, S et al 2014 Steroids

Adverse Pg. Outcomes
PCOS=32% Control 11.3%
Lipid Changes in P{g

- Trig and Cholesterol usually not > 332 and 337 mg/dL
- Extreme values can occur (Trig>1000 mg/dL)
  - Pre-existing, coexistent medical disorders
  - Co-existent Pg. disorders, limited to gestational period (DM,PET), supra-physiologic, dysbetalipoproteinemia, partial LPL deficiency and Apo E3/3 phenotype

Basaran,A 2009 Reproductive Science 16 (5):531
Lipid levels with medical conditions

- Hypothyroidism, OH consumption, LMW Heparin, glucocorticoids, psychotropic meds, kidney disease, lipodystrophy
- Effects not well characterized
- Observed hyperlipidemia is independent of Diabetic status ....

Gestational Diabetes...Any degree of glucose intolerance with onset of first recognition during pregnancy – Triglyceride Connection

- Most with GDM have glucose intolerance that begins in pregnancy
- Some have Type 2 DM unrecognized prior
- 10% with GDM have circulating islet-cell antibodies &/or HLADR3 or DR4....increase risk for Type 1 post delivery (exact risk unknown)

Gestational Diabetes
Oral Hypoglycemic Agents

• Primary effect is to enhance insulin secretion
• As of 2014, ACOG has not supported use of oral agents over insulin in pregnancy- Widely used however!
• In US major objection is/was the theoretical risk of:
  – Congenital fetal anomalies
  – Fetal macrosomia
  – Neonatal hypoglycemia
• Emergence of a new generation of agents has lead to a re-examination of this issue: Glyburide & Metformin
• No evidence of harm - both cross the placenta
Gestational Diabetes

**Glyburide**

- A second generation sulfonylurea
- MOA: Increases insulin secretion & decreases insulin resistance by lowering glucose toxicity
- Onset of action 4 hrs, duration of action 10 hrs.
- Cross the placenta (minimal?)
- Category B drug
- Effects on fetus unknown
Metformin & GDM2

- Safety profile of metformin (class B) in the first trimester and apparent lack of teratogenicity has been well documented.

- Prematurity?

- A follow-up study is currently underway to assess the offspring of the women enrolled in the MIG trial at 2 years of age.
Glyburide or Metformin vs. Insulin for GDMA2

• Advantages for oral treatment of GDMA2
• Lower cost and Improved Compliance
• 1 vial of 10cc of Regular insulin=$37.99
• 1 vial of 10cc of NPH insulin=$37.99
• A box of 100 syringes=$19.00
• 30 day supply of glyburide or metformin (max dose)=$4.00 at Walmart
• or $43.99 at Walgreen’s
Hypertensive Disorders in Pregnancy
Triglyceride Connection

<table>
<thead>
<tr>
<th>Categories</th>
<th>Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Those with HTN who become pregnant</td>
<td>• Chronic hypertension</td>
</tr>
<tr>
<td>• Those who develop HTN disorders during pregnancy</td>
<td>• CHTN with superimposed preeclampsia</td>
</tr>
<tr>
<td></td>
<td>• Gestational hypertension</td>
</tr>
<tr>
<td></td>
<td>• <strong>Preeclampsia</strong></td>
</tr>
<tr>
<td></td>
<td>• <strong>Eclampsia</strong></td>
</tr>
<tr>
<td></td>
<td>• Transient hypertension</td>
</tr>
</tbody>
</table>
## Effects of Selected Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>INCREASED</td>
</tr>
<tr>
<td>ESTROGEN</td>
<td></td>
</tr>
<tr>
<td>GLUCOCORTICOIDS</td>
<td></td>
</tr>
<tr>
<td>BBLOCKERS</td>
<td></td>
</tr>
<tr>
<td>VALPROATE</td>
<td></td>
</tr>
<tr>
<td>SERTALINE</td>
<td></td>
</tr>
<tr>
<td>ISORETENOID</td>
<td></td>
</tr>
<tr>
<td>CYCLOSPORIN,TACROLIMUS,ETC</td>
<td></td>
</tr>
</tbody>
</table>
Chylomicronemia

- Hi VLDL & Chylomicrons (V)
- TG > 1000 (usually > 2000 mg/dL)
- Risk for pancreatitis
- Clinical features
  - Eruptive xanthoma    peripheral neuropathy
  - Hepatosplenomegaly    Dyspnea
  - Lipemia retinalis    Memory loss/dementia
  - Abdominal pain without pancreatitis
Severe Hypertriglyceridermia

- Reduce fat calories (15%)
- Insulin therapy (acute insulin infusion)
- TPN
- Omega 3 – fatty acids (4-10g/d) - 20-45% reduction
  - Fish Oil (840 mg/1 gram capsule) TG > 500 mg/dL
  - Gemfibrozil 600mg bid or Fenofibrate 145-200
    - Class C
- Goal:
  - Trigs < 400 mg/dL to prevent pancreatitis
Hypertriglyceridemia

Case series

MCTG 10-30g/day
Topical sunflower oil 1tblsp subcut
Niacin
Gene therapy
Plasma-pheresis

Goldberg, A.S. 2012 JCEM 97(8):2589
Post Partum
## Preeclampsia vs. no – 1 yr. P. Partum!

<table>
<thead>
<tr>
<th></th>
<th>Preeclampsia (n = 70)</th>
<th>Normo tensive (n = 70)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>77.3 (20.2)</td>
<td>71.8 (14.7)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.0 (7.0)</td>
<td>26.0 (5.0)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>BMI (kg/m²), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25 (healthy)</td>
<td>23 (32.9)</td>
<td>34 (48.6)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>25-30 (overweight)</td>
<td>20 (28.6)</td>
<td>23 (32.9)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30 (obese)</td>
<td>27 (38.6)</td>
<td>13 (18.6)</td>
<td></td>
</tr>
<tr>
<td>Wt gain – pre to Post</td>
<td>1.83 (3.58)</td>
<td>0.59 (2.18)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Systolic</td>
<td>120.0 (11.9)</td>
<td>111.3 (9.3)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81.5 (10.3)</td>
<td>72.7 (8.1)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>63.6 (55.2)</td>
<td>44.7 (27.9)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.18 (1.02)</td>
<td>0.83 (0.52)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.69 (0.85)</td>
<td>4.30 (0.76)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>97</td>
<td>85</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>56.7</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>105</td>
<td>92</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>NonHDL cholesterol</td>
<td>124</td>
<td>108</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Microalbumin/creatinine (mg/mmol)</td>
<td>0.80 (0.40, 2.68)</td>
<td>0.51 (0.40, 0.90)</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

Smith 2009
Childbearing and Obesity in Women: Weight Before, During, and After Pregnancy

• Weight tends to be retained or increases after Pg. on in to the next one
• Overweight and obese women 6xs more likely to exceed weight gain recommendations in Pg.
  — these women are predisposed to higher post partum weight gain and retention after Pg.
• 13% to 20% of women are 5 kg or more above their preconception weight by 1 year postpartum!

Gunderson, E.P. Ostet Clin NA 2009
Preterm delivery
Later maternal CVD risk

• Health and Aging and Body Composition Study
• CVD more prevalent in those with preterm infant
• ODDS for CVD among mothers who delivered a pre-term low birth weight infant were 3.31 xs higher

Catov, J.M. 2007 Epidemiology 18(6):733
Childbearing and Obesity in Women: Weight Before, During, and After Pregnancy

- Weight gain and overweight during midlife are strong independent predictors of CVD particularly among women.
- Weight gain and overweight during midlife are strong independent predictors of Met Syndrome, Type II DM and early mortality.

Hubert, H.B. 1983 Circulation 67:968
Willet, W.C. 1995 JAMA (273):461
Cardiovascular consequences of having preeclampsia/eclampsia: Systematic reviews and Meta-analyses Case/Control & Cohort Studies

• ODDS for CVD 2.48 Case/Control
• ODSS for CVD 2.3 Cohort

• ODDS for CVD 2.28 Case/Control
• ODDS for CVD 1.76 Cohort

Sarak, D. Amer Heart Journal 2008
Brown, MC Er J Epidemiol 2013
When does metabolic syndrome begin?

***Gestational Diabetes - 10 yr. Risk
Type 2 DM = 39%
Hypertension = 10.3%
Dyslipidemia = 27%

Hi Risk in Pg. vs. Low Risk (Odds=7x higher!)
BMI > 30 Kg/m²
Glucose > 90 mg/dL
Insulin > 7.8 mUI⁻¹
Triglycerides >212 mg/dL
HDL<62 mg/dL
Systolic BP > 105 mmHg

Bardin A Nutrition and Diabetes 2013 e72
Take Home Message(s)
Excursions into Metabolic Syndrome During Pregnancy

Sattar & Greer, 2002; Adapted from Deborah Ehrenthal, MD, FACP

Population with complicated pregnancies
Healthy population
Threshold for vascular or metabolic disease
Take Home Message(s)

• Screen, Dx & Treat
  – before
  – during
  – and after Pg.
  – Break the viscous generational cycle
Cardiovascular Risk Factors During Women’s Reproductive Years

• Traditional
  – Smoking, Diabetes, hi BP, Dyslipidemia, Inactivity

• Reproductive Risks
  – PCOS, Infertility, Adverse PG Outcomes (preterm delivery, low birth weight, hypertensive disorders, gestational diabetes)

• Behavioral Risks
  – Physical Inactivity, poor diet, obesity, lactation

• Be Pro-Active! —
  – DO WHAT YOU CAN DO to reduce the Epigenetic Burden for generations to come!
# CVD and Programming Research Agenda

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which of the CVD risk factors during pregnancy or maternal dysmetabolic conditions are actually responsible for developmental programming?</td>
<td>Epidemiological associations between risk factors of developmental programming and offspring CVD Demonstration of causality in experimental models of specific risk factors</td>
</tr>
<tr>
<td>Can pathogenic programming by specific risk factors be prevented?</td>
<td>Dietary and drug interventions in experimental models</td>
</tr>
<tr>
<td>How effective is conventional prevention or treatment before pregnancy?</td>
<td>Prospective studies on offspring of mothers treated under existing guidelines before or during pregnancy</td>
</tr>
<tr>
<td>How effective are safe dietary interventions during pregnancy?</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>How safe are current cholesterol-lowering, anti-inflammatory, or antioxidant drugs during pregnancy?</td>
<td>Critical review of case reports Epidemiology Clinical trials</td>
</tr>
<tr>
<td>What is the relative contribution of developmental programming to offspring CVD compared with genetic susceptibility and postnatal risk factors?</td>
<td>Epidemiology focusing on specific maternal risk factors and postnatal lifestyle Animal studies</td>
</tr>
<tr>
<td>What fetal cells/tissues/organs are programmed?</td>
<td>Identification of epigenetic changes in tissues of humans and experimental animals</td>
</tr>
<tr>
<td>What epigenetic mechanisms affect CVD mechanisms or manifestations in offspring?</td>
<td>Association studies in humans Studies testing causality of specific mechanisms in experimental models</td>
</tr>
<tr>
<td>Does maternal immunomodulation influence developmental programming in humans?</td>
<td>Initially, retrospective studies only</td>
</tr>
</tbody>
</table>
**Brief overview of maternal triglycerides as a risk factor for pre-eclampsia**

<table>
<thead>
<tr>
<th>Author &lt;reference&gt;</th>
<th>TG division compared</th>
<th>Higher TG decreases risk</th>
<th>Odds ratio (95% CI)</th>
<th>Higher TG increases risk</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clausen 2001 &lt;17&gt;</td>
<td>2 vs 1</td>
<td></td>
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<td>Cohort</td>
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<td></td>
<td>3 vs 1</td>
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<tr>
<td>Enquobahrie 2004 &lt;22&gt;</td>
<td>2 vs 1</td>
<td></td>
<td></td>
<td></td>
<td>Cohort</td>
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<td></td>
<td>3 vs 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Williams 2003 &lt;18&gt;</td>
<td>2 vs 1</td>
<td></td>
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<td></td>
<td>Case-control</td>
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<tr>
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<td>3 vs 1</td>
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<td></td>
<td>4 vs 1</td>
<td></td>
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<tr>
<td>Ware-Jauregui 1999 &lt;26&gt;</td>
<td>2 vs 1</td>
<td></td>
<td></td>
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<td>Case-control</td>
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<tr>
<td></td>
<td>4 vs 1</td>
<td></td>
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</tbody>
</table>
PRE-ECLAMPSIA KILLS

US Pregnancy-Related Mortality

Hypertriglyceridemia late pregnancy associated with small dense low-density lipoproteins & large buoyant high-density lipoproteins n= 36 Hispanics 35-36 weeks and postpartum

• TG = 218, Cholesterol 234, ApoB 130 mg/dL
• 97% classified is pattern B or Intermediate
• Predominance of small dense LDL was associated with TGs
• HDL 2 mass was increased

Silliman, K. Metabolism 1994
Low-density lipoprotein particle size decreases during **normal pregnancy** in association with triglyceride increases

- Uncomplicated nonsmoking Pg. women without metabolic disorder
- LDL diameter decreased with advancing gestation 16-20 wks. evident vs. 5-12 weeks
- 70% pattern B
- LDL diameter was inversely correlated with TG, ApoB and cholesterol (r-.6)
- All changes were reversed post partum

Hubel, C.A. JSGI 1998
Association of lipid levels during gestation with preeclampsia and gestational diabetes mellitus: a population-based study

Wiznitzer, A. Amer J Obstet Gynecol 2009
Glyburide & Gestational Diabetes

• Langer 2000: only RCT of 404 patients, demonstrated similar efficacy of glyburide & insulin in glucose control & pregnancy outcome.

• Conway 2004: retrospective study of 75 patients, found glyburide was useful in achieving glycemic control.

• Jacobson 2005: retrospective study of 584 patients found similar efficacy between glyburide & insulin, but higher rates of preeclampsia and phototherapy in the glyburide group.
Parity and cardiovascular disease risk among older women: how do pregnancy complications mediate the association?

• Health and Aging and Body Composition Study
• N=540  47% AA
• Nulliparous women less CVD than Parrous (185 vs. 30%)
• After adjustment for perinatal complications – toxemia, lbw, preterm, stillbirth
• ODDS for CVD among Parrous women 1.95 (1.03, 3.7)
• With complications CVD prevalence 2.67 times higher

Catov , J.M. Ann Epidemiol 2008
Common Diagnoses In Ob/Gyn That Increase Lifetime Cardiovascular Disease (CVD) Risk

- Pregnancy-induced Hypertension, Gestational Diabetes (GDM), Polycystic Ovary Syndrome (PCOS), premature delivery
- Hypertension (HTN), Diabetes, Hyperlipidemia
- Smoking, Overweight/Obesity, Unhealthy Diet, Lack of Exercise

Source: Mosca 2011, Wild 2010
Early pregnancy lipid concentrations and spontaneous preterm birth

Catow, JM AJOG 2007
Lipoprotein particles in preeclampsia: susceptibility to oxidative modification women with preeclampsia vs. normal PG women

- Pre-eclamptic women Higher TG and LDL
- Conjugated diene production & shorter lag time for LDL and HDL in pre-eclamptic women
- HDL and LDL particles more susceptible to oxidative modification and plasma concentration of LDL particles not HDL particles were increased in Pre-eclamptics

Wakatsuki, A. Obstet Gynecol 2000
Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses Case/Control Studies

Sarak, D. Amer Heart Journal 2008
Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses Cohort Studies

Sarak,D. Amer Heart Journal 2008

<table>
<thead>
<tr>
<th>Study</th>
<th>relative risk (random)</th>
<th>95% CI</th>
<th>Weight %</th>
<th>relative risk (random)</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Jonsdottir 1995</td>
<td>8.51</td>
<td>2.12 [1.29, 3.49]</td>
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<td>Hannaford 1997</td>
<td>16.10</td>
<td>1.65 [1.26, 2.16]</td>
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<td>Irgens 2001</td>
<td>11.11</td>
<td>2.12 [1.42, 3.16]</td>
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<td>Smith 2001</td>
<td>8.39</td>
<td>3.54 [2.14, 5.85]</td>
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<td>Kestenbaum 2003</td>
<td>11.19</td>
<td>2.53 [1.70, 3.77]</td>
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<td>Wilson 2003</td>
<td>4.43</td>
<td>1.24 [0.53, 2.65]</td>
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<td>Funai 2005</td>
<td>13.04</td>
<td>3.07 [2.18, 4.33]</td>
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<tr>
<td>Kaaja 2005</td>
<td>4.78</td>
<td>2.50 [1.20, 5.20]</td>
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<td>Ray 2005</td>
<td>10.62</td>
<td>2.85 [1.64, 4.32]</td>
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<tr>
<td>Wikstrom 2005</td>
<td>11.82</td>
<td>2.27 [1.56, 3.22]</td>
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<tr>
<td>Total (95% CI)</td>
<td>100.00</td>
<td>2.23 [1.95, 2.78]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 15.34, df = 9 (P = 0.08), I² = 41.3%
Test for overall effect: Z = 0.32 (P < 0.00001)
Maternal gestational weight gain and offspring risk for childhood overweight or obesity

N=4,145 women offspring 2-5 yrs. Sridhar, SB Am J Ob/Gyn 2014
Diabetes in Pregnancy Dietary Care

- Nutritional counseling ideal
- 30 kcal/kg/day
- Pre-pregnant weight
- Most appropriate diet not established...
- Carbohydrate 60%
- Protein 20%
- Fat 20%
- Saturated 10%
- Unsaturated 10%
ANTIHYPERTENSIVES CONSIDERED SAFE IN PREGNANCY

- Methyldopa (Aldomet) 250-1000 mg qid
- Labetolol (Nomodyne) 100-1200 mg bid
- Nifedipine (Procardia) 10-30 mg tid
- Nifedipine (Procardia XL) 30-60 mg qd
- Hydralazine (Apresoline) 10-75 mg qid
- Minoxidil (Loniten) 5-10 mg qd
- Clonidine (Catapres) 0.1-0.2 mg bid
MEDICATIONS THAT CAUSE HYPERTENSION in PG

- Corticosteroids
- Cyclosporine
- Contraceptives
- Amphetamines
- Sympathomimetics
- Ephedrine
- Cocaine!
Sex Steroids Levels in Pg.

Estrogen

Progesterone

Progesterone Levels During Pregnancy
Gestation and Lipids

- First 2/3 gestation mother anaerobic state, increasing her fat depots
  - hyper-phagia and enhanced lipogenesis

- Last 1/3 mother switches to catabolic state.
  - Glucose most abundant nutrient crossing the placenta
  - causes maternal hypoglycemia despite an increase in
    - gluconeogenesis

- Adipose tissue lipolytic activity increases – raised FFA and glycerol reach liver, increase in hepatic production of TG, more circulating VLDLs.

- Enhanced CETP enriched LDL and HDL with TG
Gestation and Lipids

• Glycerol also a gluconeogenic substrate saving amino acids for the fetus

• Fasting conditions, FA, via beta-oxidation are converted into ketone bodies - easily cross the placenta and metabolized by the fetus

• Enhanced liver production of VLDL-TG together with decreased adipocyte LPL, increased plasma CETP & hepatic lipase cause both an increment in LDL particles and particle TG

• Maternal TG do not cross the placenta, but are hydrolyzed by LPL releasing FA to the fetus.
Gestation and Lipids

• Changes in lipid metabolism during Pg promote accumulation of maternal fat stores in early and mid Pg and enhance mobilization in late Pg
• Cholesterol is used by placenta for steroid synthesis, and fatty acids for placental oxidation and membrane formation
• Anabolic phase in preparation for rapid fetal growth in late PG

Basaran 2009
Gestation and Lipids

• A third mechanism by which maternal hypertriglyceridemia benefits offspring is its contribution to milk synthesis in preparation for lactation.

• With decreased adipocyte LPL, TG more available to breasts. Around parturition rapid increases in LPL expression and activity in mammary glands.
  • Due to both increased prolactin and insulin levels and a specific enhancement in mammary gland insulin sensitivity.

• Mammary induction of LPL facilitates clearing of maternal TG for milk synthesis. Essential FA from the diet become available to the nursing infant.
Gestational Diabetes Prevalence

• US: 2-5% (1.4-14%)
• NA & Hispanic>AA>Caucasian
• Increasing in all groups*
• Increased maternal age
• Obesity
• Varies worldwide & among racial/ethnic groups

Lipoprotein Changes in T2DM

- **Triglyceride-rich lipoproteins**
  - Increased particle number
  - Increased postprandial concentrations
  - Triglyceride enriched and cholesterol enriched particles

- **LDL**
  - Increased particle number
  - Small dense particles

- **HDL**
  - Decreased particle number
  - Changes in particle composition

Mazzone 2008
OBJECTIVES

• Clinical Lipidologist will become familiar with the implications of Dyslipidemia/TG before, during and after Pregnancy
• Clinical lipidologist will become familiar with Obstetrical considerations of dyslipidemia/TG in PG and the consequences
• Clinical Lipidologist will be able to describe principles of Dyslipidemia management during gestation
• Clinical Lipidologist will be familiar with strategies for reducing long term CVD risk for women who plan who are or recently have been Pregnant (PG)
# Total and Rate of Weight Gain by Pre-Pg BMI

<table>
<thead>
<tr>
<th>Pre Pg. BMI</th>
<th>BMI (Kg/m²)WHO</th>
<th>Total Range(lbs)</th>
<th>Rates 2&lt;sup&gt;nd&lt;/sup&gt; LBS/week</th>
<th>Rates 3&lt;sup&gt;rd&lt;/sup&gt; LBS/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>28-40</td>
<td>0.51(0.44-0.58)</td>
<td>1(1-1.3)</td>
</tr>
<tr>
<td>NL weight</td>
<td>18.5-24.9</td>
<td>25-35</td>
<td>0.42(0.35-0.5)</td>
<td>1(0.8-1)</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>15-25</td>
<td>0.28(0.23-0.33)</td>
<td>0.6(0.5-0.7)</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30</td>
<td>11-20</td>
<td>0.22(0.17-0.27)</td>
<td>0.5(0.4-0.6)</td>
</tr>
</tbody>
</table>

Assumes 0.5-2Kg(1.1-4.4lbs) weight gain in first.

Provisional NL BMI twins 37-54lbs, overweight 31-50lbs, obese 25-42lbs.
Slide title
Presentation