MATERNAL–FETAL FEATURES

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MAIN STEPS

1. Cholesterol and fatty acids relevance to the fetus
2. Supply ways
3. Maternal metabolic changes
4. Lipoprotein transport
5. Fetal lipoproteins
6. Lipoprotein imbalance impact
7. The fetal outcome
Cholesterol and fatty acids main functions

**CHO**

- cellular membrane constituent
- precursor of:
  - a. steroid hormone
  - b. bile acids
  - c. oxysterol
- pathway activator signal

**FAs**

cellular membrane constituent
+ Fuel provider

**Pregnancy related period determinant**

**Before implantation**

- precursor of progesterone synthesis
- It maintains the early pregnancy

**After implantation**

- embryogenesis
- morphogenesis
- central nervous system pattern
Fetal-maternal CHO intake and steroid hormonal synthesis regulation
Embryo, Yolk sac and trophoblast
In the human, the yolk sac and the allantois develop into the *umbilical cord*. This rope-like structure connects the developing fetus to the placenta. This structure contains blood vessels that transport waste materials out of the embryo's body. Veins inside the umbilical cord carry oxygen and nutrients to the embryo.

⭐ (*Umbilical cord* = *vitellus sac* + *allantois*)
Fetal Cholesterol and Fatty Acids supply

Mother and placental circulation

Mother to fetus
CHO and FAs
delivery

De novo synthesis

Embryo-fetus

The supply

The exogenous way

The endogenous way
CHO and TG INCREASE IN PREGNANT WOMEN

Maternal plasma CHO may increase through the 12th week of gestation while TGs reach the 150-300% of increase in the third trimester of pregnancy.
Hyperlipidemia and pregnancy

maternal physiological hyperlipidemia is manifest in pregnancy; CHO, TGs and FAs concentrations increase in both maternal plasma and erythrocytes thus allowing the fetus to rapidly receive and store fat, which exceeds by far that of any other nutrient.

Gil-Sánchez A, Curr Opin Clin Nutr Metab Care 2012
Lipoprotein metabolism in unpregnant women

Diagram showing the metabolism of lipoproteins including CHO synthesis, TG, CE, LP, VLDL, LDL, HDL, and Peripheral cells.
Intermediate Metabolism in Pregnancy

Metabolic maternal changes through gestation: shift from carbohydrates to lipids for maternal energy production in order to make nutrients available for the fetus

Di Cianni CG et al., Diabetes Metab Res Rev 2003
Maternal lipoprotein metabolism in late pregnancy

Barrett, Diabetes care 2014
Mother to fetus CHO and lipid exchange

Guardamagna O, Lipids metab in fetus, Springer 2016, in press
Nutrient transfer is regulated by the placenta itself through SPECIFIC enzymes, receptors and transport proteins; others nutrients are directly metabolized by the placenta.

Woollett LA, Am J Clin Nutr 2005
Placental uptake and efflux of maternal LPs

Guardamagna O, Lipids metab in fetus, Springer 2016, in press
The relationship of adipose tissue lipolytic activity with lipoprotein metabolism during late pregnancy and its role as a source of essential fatty acids (EFA) and long-chain polyunsaturated fatty acids (LC-PUFA) for the fetus.

E.Herrera, Horm Res 2006
Total plasma cholesterol levels in human umbilical cord plasma throughout gestation

<table>
<thead>
<tr>
<th>Week of gestation</th>
<th>CHO (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-16 (n=68)</td>
<td>85.4 ± 30.7</td>
</tr>
<tr>
<td>16.5-20 (n=19)</td>
<td>39.9 ± 21.0</td>
</tr>
<tr>
<td>26.5-32 (n=17)</td>
<td>67.8 ± 5.8</td>
</tr>
<tr>
<td>32.5-36 (n=16)</td>
<td>58.8 ± 13.6</td>
</tr>
<tr>
<td>36.5-40 (n=44)</td>
<td>51.4 ± 11.5</td>
</tr>
</tbody>
</table>

Johnston HJ Jr, Ped Res, 1982
# Umbilical cord plasma lipoprotein levels

<table>
<thead>
<tr>
<th>Week of gestation</th>
<th>CHO (mg/dl)</th>
<th>LDL CHO (mg/dl)</th>
<th>HDL CHO (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-32</td>
<td>68.0 ± 7.0</td>
<td>44.0 ± 5.0</td>
<td>24.0 ± 2.0</td>
</tr>
<tr>
<td>33-34</td>
<td>73.0 ± 7.0</td>
<td>49.0 ± 6.0</td>
<td>24.0 ± 2.0</td>
</tr>
<tr>
<td>35-36</td>
<td>65.0 ± 7.0</td>
<td>35.0 ± 3.0</td>
<td>22.0 ± 4.0</td>
</tr>
<tr>
<td>37-38</td>
<td>64.0 ± 4.0</td>
<td>37.0 ± 3.0</td>
<td>23.0 ± 2.0</td>
</tr>
<tr>
<td>39-40</td>
<td>56.0 ± 2.0</td>
<td>30.0 ± 2.0</td>
<td>22.0 ± 1.0</td>
</tr>
<tr>
<td>41-42</td>
<td>53.0 ± 3.0</td>
<td>28.0 ± 2.0</td>
<td>22.0 ± 1.0</td>
</tr>
</tbody>
</table>
LPs, apoprotein and enzyme activity variation in fetal plasma compared to maternal plasma

Guardamagna O, Lipids metab in fetus, Springer 2016, in press
FETAL LIPOPROTROTEINS CHARACTERISTICS

1. HDL
   main lipoprotein class in the cord blood

2. LDL

1. Fetal HDL differs from adult ones:
   a. $\text{HDL}_2 > \text{HDL}_3$ sub-fraction
   b. high apoE contents
   c. apoA-4 enrichment

   ➢ Atheroprotective effect of fetal HDL apoproteins
     a. by LCAT activation
     b. by CETP lowering

2. Steroid hormones production
   a. i.e: dehydroepiandrosterone sulfate
FETAL CHO AND FAs supply

MOTHER AND PLACENTAL CIRCULATION

Mother to fetus
CHO and FAs delivery

The exogenous way

EMBRIIO/FETUS

De novo synthesis

Jurevics HA, J Lipid Res 1997

CHO: higher than in adults

Avis HJ, Current Opinion in Lipidology 2009

Sterols levels

The endogenous way

Satured FAs and PUFA

Herrera E, Eur J Clin Nutr 2004

ME Baardman, Am J Obstet Gynecol 2012

Vuorio, J Lab Clin Med 2002
Role of apo E in maternal-embryonal cholesterol transport

Witsch-Baumgartner, J med genet 2004
Maternal apo E as a modifier in Smith-Lemli-Opitz syndrome.

Witsch-Baumgartner, J med genet 2004
CHOLESTANOL CHANGE IN CORD BLOOD AND AT 1 YRS OF AGE

Vuorio, j lab clin med 2002
The origin of fetal sterols in second-trimester amniotic fluid: endogenous synthesis or maternal-fetal transport?

Correlation between sterols and gestational age

ME Baardman, Am J Obstet Gynecol 2012
Fetal-maternal lipids imbalance and outcome

- Microsomaia
- Macrosomia
- Fetal malformations

- IUGR
- ECLAMPSIA
- DIABETES
- DIABETES
- SLOS

Adult CVD increased risk?

MATERNAL FH
<table>
<thead>
<tr>
<th>MATERNAL DISORDERS</th>
<th>FETAL CONSEQUENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>High LDL CHO Preterm birth</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>Altered placental transfer of lipids High TGs</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Malformation and macrosomia High VLDL and LDL</td>
</tr>
<tr>
<td>Intrauterine Growth Restriction</td>
<td>Low CHO, LDL CHO, HDL CHO High TGs</td>
</tr>
<tr>
<td><strong>FETAL DISORDER</strong></td>
<td></td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>Central nervous system anomalies Deficient CHO</td>
</tr>
</tbody>
</table>
Defects in the cholesterol biosynthetic pathway

- Smith–Lemli–Opitz syndrome (SLOS): congenital multiple anomaly/intellectual disability syndrome
- Inherited deficiency of 7-dehydrocholesterol (7DHC)-reductase (DHCR7 gene).
- Deficient CHO levels
- Altered function of cellular membranes
- IUGR: 67–100% of affected fetuses
- multiple congenital anomalies, mentally retardation
Maternal diabetes
Gestational diabetes mellitus (GDM) and maternal diabetes mellitus type 1 or 2

Positive relation between mother-fetus lipids
  a. Maternal hypertriglyceridaemia and hyperglycaemia
  b. Cord blood level lipoproteins increase

Outcome:
  a. Early pregnancy: poor metabolic control and fetal malformations
  b. Late pregnancy: fetal macrosomia and neonates large for gestational age (LGA)
MATERNAL HYPERCHOLESTEROLEMI:

**FETUS/NEWBORN**
1. FETUS have a good nutritional status
2. Preterm birth risk
3. Shows increased LDLc levels
4. HeFH fetus has higher LDLc if mother inherited

**MOTHER**
- PROCOAGULANT PROFILE
- fetal-uteroplacental circulation CHANGES
CHOLESTEROL CHANGE IN CORD BLOOD AND AT 1 YRS OF AGE in FH and non-FH subjects

Vuorio, j lab clin med 2002
Mother Pre-eclampsia
placental dysfunction
cause of maternal and fetal morbidity

- Marked dyslipidaemia
  a. increased TGs levels
  b. HDL-C reduction
  c. increased small dense LDL particles

- Hypertension

- Oxidative stress and endothelial cell activation
  a. systemic inflammatory condition

Outcome:

- Acute atherosis and atherosclerotic placental lesions
  a. reduced placental perfusion, placental/fetal hypoxia

  Fetal lipids changes (TGs increase, TC and HDL)
### Lipids, lipoproteins and apolipoproteins in maternal and fetal blood in normal and pre-eclamptic cases

<table>
<thead>
<tr>
<th></th>
<th>Maternal</th>
<th></th>
<th>Fetal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n = 42)</td>
<td>PEC (n = 46)</td>
<td>(p) Value</td>
<td>Normal (n = 39)</td>
</tr>
<tr>
<td>TChol (mg/dl)</td>
<td>245.0 (208.5; 296.3)</td>
<td>293.5 (263.3; 355.3)</td>
<td>0.001</td>
<td>86.0 (72.0; 109.0)</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>52.0 (46.8; 54.0)</td>
<td>54.0 (50.5; 63.0)</td>
<td>0.016</td>
<td>53.0 (48.0; 57.0)</td>
</tr>
<tr>
<td>LDLc (mg/dl)</td>
<td>160.5 (117.8; 199.3)</td>
<td>179.5 (151.5; 221.3)</td>
<td>0.034</td>
<td>32.0 (25.0; 50.0)</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>212.0 (160.8; 269.3)</td>
<td>350.5 (273.8; 424.0)</td>
<td>&lt;0.001</td>
<td>39.0 (29.0; 52.0)</td>
</tr>
<tr>
<td>ApoA-I (mg/dl)</td>
<td>181.0 (147.0; 210.3)</td>
<td>204.0 (174.8; 230.3)</td>
<td>0.032</td>
<td>79.0 (64.0; 86.0)</td>
</tr>
<tr>
<td>ApoB (mg/dl)</td>
<td>135.5 (120.5; 175.8)</td>
<td>164.0 (127.8; 187.8)</td>
<td>0.028</td>
<td>34.0 (25.0; 39.0)</td>
</tr>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>33.5 (9.7; 65.6)</td>
<td>24.9 (14.5; 42.0)</td>
<td>0.39</td>
<td>5.0 (3.0; 7.0)</td>
</tr>
<tr>
<td>LDLc/HDLc</td>
<td>3.15 (2.46; 4.23)</td>
<td>3.32 (2.62; 3.95)</td>
<td>0.55</td>
<td>0.63 (0.52; 1.07)</td>
</tr>
</tbody>
</table>

Intrauterine growth restriction (IUGR)
Small for gestational age newborn

**MOTHER**
- insufficient trophoblast development
- atheroclerotic placental lesions
- low maternal LDLc-C and TC

**FETUS**
- HDL-C and LDL-C decrease in the cord blood
- oxLDL/LDL ratio increase
- TG significantly increased

**OUTCOME**
pathogenic links between low birth weight for gestational age and adulthood cardiovascular events is suggested.
The fetal hypothesis

The lower fetal/newborn weigh

The higher the CVD risk
Fetal oxLDL concentration and oxLDL/LDL-C ratio in IUGR

Antioxidant enzymes, antioxidant potential, and lipid peroxidation parameters in maternal and umbilical cord plasma and in placental tissue of gestationally hypercholesterolaemic (H, n = 35) and normocholesterolaemic (N, n = 34) groups

<table>
<thead>
<tr>
<th></th>
<th>Maternal plasma</th>
<th>Placental tissue</th>
<th>Cord plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>TBARS (mmol MDA)**</td>
<td>83 ± 8</td>
<td>118 ± 12*</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>8-isoPGF2α Isoprostane (pmol per mmol⁻¹ creatinine)</td>
<td>54 ± 11</td>
<td>82 ± 15**</td>
<td>ND</td>
</tr>
<tr>
<td>XO (miu)**</td>
<td>0.28 ± 0.05</td>
<td>0.84 ± 0.23**</td>
<td>0.012 ± 0.008</td>
</tr>
<tr>
<td>CAT (iu)**</td>
<td>17 830 ± 2350</td>
<td>9852 ± 1136*</td>
<td>80 ± 9.6</td>
</tr>
<tr>
<td>SOD (U)**</td>
<td>90 ± 21</td>
<td>82 ± 18</td>
<td>2.0 ± 0.8</td>
</tr>
<tr>
<td>GSH-Px (iu)**</td>
<td>1.3 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>6.2 ± 1.6</td>
</tr>
<tr>
<td>AOP (U)**</td>
<td>205 ± 27</td>
<td>189 ± 24</td>
<td>1.64 ± 0.32</td>
</tr>
</tbody>
</table>

in blood and placental tissue:
- thiobarbituric acid reactive substance (TBARS)
- xanthine oxidase (XO)
- superoxide dismutase (SOD)
- glutathione peroxidase (GSHPx)
- catalase (CAT)
- antioxidant potential (AOP)

Liguori, BJOG 2007
Immunohistochemistry of placental microvessels from normocholesterolaemic mothers (A, C) and hypercholesterolaemic mothers (B, D)
Birth Weight and Subsequent Cholesterol Levels
Exploration of the “Fetal Origins” Hypothesis

Huxley, JAMA 2004
Prevalence of preterm birth within percentiles of maternal cholesterol level

Edison, Pediatrics 2007
The fetal genome impact on maternal LPs: TG related genes polymorphism

<table>
<thead>
<tr>
<th>FETAL GENES</th>
<th>MATERNAL LPs, outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH PLACENTAL EXPRESSION</strong></td>
<td></td>
</tr>
<tr>
<td>• LPL N291S allele</td>
<td>Preeclampsia, Pancreatitis risk?</td>
</tr>
<tr>
<td>• APOE2/E2</td>
<td>Higher LDL-C, CVD risk?</td>
</tr>
<tr>
<td><strong>LOW PLACENTAL EXPRESSION</strong></td>
<td></td>
</tr>
<tr>
<td>• ApoCIII S2 allele</td>
<td>No LPs change</td>
</tr>
</tbody>
</table>
LPL maternal and fetal genetic polymorphism affecting maternal LPS

Descamps O., J Lipid Res 2005
ApoE maternal and fetal genetic polymorphism affecting maternal LPS

![Graph showing LDL-C and ApoB levels with groups A to D and presence or absence of APOE*E2 in mothers and newborns.](image)

Descamps O., Lipid Res 2005
Genetic factors numbers and LDL-C, HDL-C change

maternal APOE*E2, newborn APOE*E2, maternal APOC3*S2 or LPL*S447X in mothers and newborns

maternal APOE*E2, no maternal APOC3*S2 or newborn APOC3*S2.

Descamps O, Atherosclerosis 2004
CONCLUSION

- Strict interrelationship between mother and fetus LP phenotypes
  a. Maternal lipids modified by newborn polymorphisms
  b. Genetic polymorphisms affect the steroid production
  c. Environmental conditions

- Fetus: higher CHO and Tgs synthesis rates

- LPs transport from maternal blood through the placenta, by transporters or by aqueous diffusion
  a. CHO transport mainly supported by HDL subclass
  b. Among FAs LC-PUFA uptake by the placenta is preferential.

- In utero fetal metabolic programming
  a. Barker “in utero programming of chronic disease”
  b. Fetal lipid profile may determine the early development of preatherosclerotic lesions in fetus questionable
  c. Could the CHD risk of individuals may be determined in part by the genotypes of their mother, beyond the risk conferred by their own genotypes?