The transport of cholesterol from mother to fetus across the placental barrier has long been neglected. Although cholesterol is of vital importance for fetal development as a key constituent of cell membranes, precursor of steroid hormones and metabolic regulators (oxysterols), and a modulator of hedgehog signaling, it was generally assumed that most of it is synthesized de novo by the fetus and, to a lesser extent, by cells on the fetal side of the placenta. A contribution of placental cholesterol to fetal growth was supported by the fact that LDL-cholesterol concentrations in the umbilical cord vein (which delivers placental blood to the fetus) are greater than those in umbilical arteries,\(^1\) and by the ability of maternal–fetal cholesterol transport mechanism but also in- and leads to increased susceptibility to atherosclerosis later in life.\(^5,6\) Investigations of developmental programming of cardiovascular disease also revealed that fetal cholesterol levels are much higher in midpregnancy than at term birth and correlate with maternal cholesterol before the sixth month of gestation, consistent with transplacental cholesterol passage.\(^4,7\)

In humans, maternal cholesterol must be transported across the endothelial cells of the fetal chorionic villi. As it enters the placenta, it is immediately transferred to the syncytiotrophoblast and be secreted on their basolateral side. Second, it must be transported across the endothelial cells of the fetal microvessels. To date, it has been established that cultured trophoblast cells express LDL receptors (LDLR), LDLR-related proteins (LRP), scavenger receptors A (SR-A), and HDL-binding scavenger receptors B1 (SR-B1) on their apical side.\(^8\) Cholesterol taken up by internalization of receptor-bound apoB- or apoE-carrying lipoproteins and oxidized LDL, and from SR-B1-bound HDL, is then released on the basolateral side.\(^8\) Uptake of cholesterol by endothelial cells is well understood, but the mechanisms by which placental endothelial cells transport cholesterol to the fetal microcirculation, the regulation of efflux, and their ability to deliver substantial quantities of cholesterol were unknown. In this issue of Circulation Research, an article by Stefulj et al fills this important gap and not only elucidates the final link in the maternal–fetal cholesterol transport mechanism but also indicates how it may be regulated (Figure).\(^9\)

By comparing cholesterol export mechanisms in human placental endothelial cells (HPECs) to those of human umbilical vein endothelial cells (HUVECs), the authors show that HPECs released significantly more cholesterol to lipid-free apoA-I, whereas both cell types delivered similar amounts of cholesterol to HDL. Furthermore, exposure of HPECs, but not HUVECs, to natural or synthetic ligands of liver-X-receptors (LXR) increased cholesterol efflux to both of these acceptors. LXR activation increased expression of ABCA1 and ABCG1 but did not alter that of ABCG4 and SR-BI. Conversely, inhibition of ABCA1 or silencing of ABCG1 markedly decreased cholesterol efflux to apoA-I and HDL. Cholesterol efflux from LXR-stimulated HPECs to HDL via ABCG1 was further increased when HDL was enriched with apoE. Immunohistochemistry confirmed that ABCA1 and ABCG1 were mainly, if not exclusively, expressed on the luminal (fetal) side of HPECs, consistent with its selective role in cholesterol efflux toward the fetal circulation. Together, these data establish that HPECs are unique among endothelial cells, in so far as they are capable of transporting substantial amounts of cholesterol to the fetal circulation, and that this mechanism is further increased by LXR-induced upregulation of ABCA1 and ABCG1.

An experiment mimicking the placenta in mothers developing extensive hypercholesterolemia during pregnancy (by preloading HPECs with LDL or cholesterol) confirmed that HPECs are not just capable of transferring markedly more cholesterol to the fetus but that they actually do so under conditions similar to those encountered in vivo, provided that enough acceptors are present. This, however, was not accom-
panied by an upregulation of ABCA1 and ABCG1 (except for a modest induction of the latter by cholesterol-loading only). As the authors explain, other regulatory factors must be involved. This prompts some thoughts about the role of maternal–fetal cholesterol transport and its in vivo regulation throughout pregnancy (Figure, right side).

We have to presume that the basic machinery of HPECs isolated at term birth is representative of placental endothelial cells throughout pregnancy and that gestational age does not affect function, but we do know that the placental conditions undergo dramatic temporal changes throughout pregnancy. For example, maternal cholesterol levels increase in the third trimester, even in normocholesterolemic mothers, whereas fetal cholesterol is exceedingly high at the end of the second trimester and then declines linearly toward term. Even in the absence of maternal hypercholesterolemia, oxidative stress is therefore bound to vary greatly, as are lipid peroxidation products, such as oxidized LDL, oxidized fatty acids, and reactive oxygen species (ROS), which interfere with several oxidation-sensitive nuclear signaling pathways, including nuclear factor κB, peroxisome proliferator-activated receptor, and, indirectly, LXR (at least in macrophages). Thus, both the regulation and the extent of maternal–fetal cholesterol transport are likely to undergo substantial physiological variation throughout pregnancy.

In fetuses with SLO, there is a vital dependence on maternal cholesterol that must be satisfied irrespective of the maternal cholesterol level. The greatest regulatory stimulus therefore probably comes from the fetal side, in the form of increased plasma levels of cholesterol acceptors and LXR activation. Both major natural LXR activators, 24S- and 27OH-cholesterol, are present in the fetal circulation and elevated in SLO, suggesting that LXR-mediated upregulation of ABCA1 and ABCG1 indeed contributes to increased cholesterol transfer in vivo. Maternal dietary cholesterol supplementation also appears to convey benefits to SLO fetuses. This is consistent with the present observation in cholesterol and LDL-enriched HPECs (Figure 5B and 5C in the article by Stefulj et al) and suggests that signaling by increased maternal cholesterol may be beneficial in the presence of synergistic fetal signals.

In contrast, extensive maternal hypercholesterolemia alone is clearly pathogenic and results in atherogenic programming. The present data indicate that increased cholesterol availability on the maternal side substantially increases transfer, consistent with results in humans and animal models, but that no significant upregulation of LXR occurs in the absence of fetal costimuli. This is a relief, because it indicates that maternal hypercholesterolemia does not automatically trigger maximum upregulation of cholesterol transport. Signaling in HPECs of hypercholesterolemic mothers appears to
be influenced by additional factors, some of which may be compensatory/defensive. In fact, studies in humans have shown that the placenta is both the target of maternal oxidative stress and a modulator of fetal oxidative stress.\textsuperscript{15} Furthermore, extensive data exist on atherogenic programming of arterial endothelial cells by maternal hypercholesterolemia, obesity, the metabolic syndrome, and diabetes.\textsuperscript{16,17} It is therefore likely that changes in HPEC signaling are similarly early and extensive.

Fortunately, atherogenic programming in offspring of hypercholesterolemic mothers can be prevented by interventions reducing fetal exposure to maternal hypercholesterolemia and oxidative stress,\textsuperscript{6,14} including by targeted maternal immunostimulation.\textsuperscript{18} It would be interesting to see whether such interventions also influence signaling in HPECs and, conversely, whether targeting of HPEC signaling protects offspring against atherogenic programming.

**Sources of Funding**

Supported by National Heart, Lung, and Blood Institute grant R01-HL-089559 and Ellison Medical Foundation Senior Scholar Award AG-SS 1851-07.

**Disclosures**

None.

**References**


**Key Words:** placenta • endothelial cells • cholesterol transport • developmental programming • arteriosclerosis