

# Maternal supraphysiological hypercholesterolemia leads to endothelial dysfunction of the human fetoplacental macro and microvasculature

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### Resumen

Maternal physiological hypercholesterolemia (MPH) occurs in pregnancy assuring fetal growth and development. However, maternal supraphysiological hypercholesterolemia (MSPH) leads to increased atherosclerosis in the fetal vasculature. In this study the maternal and neonatal total cholesterol (TCh) and lipoprotein levels were determined in a group of pregnant women and her newborns. A cut-off value for MSPH was established as maternal TCh levels at term of pregnancy  $>280$  mg/dl. Pregnancies with values over this cut-off point were associated with fetoplacental endothelial dysfunction evaluated as reduced endothelial-dependent vascular dilation in the macro- (umbilical vein;  $41 \pm 7\%$  and  $10 \pm 2\%$  for MPH and MSPH, respectively) and microvasculature (veins in placental stem villi;  $52 \pm 6\%$  and  $1 \pm 0.2\%$  for MPH and MSPH, respectively). The mechanisms involved in this phenomenon include reduced nitric oxide synthase (NOS) activity and therefore reduced nitric oxide (NO) availability in human umbilical vein endothelial cells (HUVEC; reduction of  $51 \pm 2\%$  compared with MPH) and human placental microvascular endothelial cells (HPMEC; reduction of  $83 \pm 4\%$  compared with MPH). MSPH was also associated with reduced synthesis of the eNOS cofactor tetrahydrobiopterin ( $BH_4$ ; reduction of  $87.5 \pm 5\%$  compared with MPH) as well as increased activity of arginases, a group of enzymes that compete with NOS for the substrate L-arginine (1.5 times compared with MPH). Interestingly, the restoration of the  $BH_4$  levels and the inhibition of arginases improved the endothelial function impaired by the MSPH condition. Therefore MSPH is a maternal condition likely involved in the endothelial dysfunction and the later development of atherosclerosis described for MSPH offspring. However, the mechanism(s) leading to the development MSPH as well as whether this maternal condition modifies the placental transport of cholesterol and therefore the fetal lipid function are actually unknown.

### Palabras clave

Pregnancy, Cholesterol