Pre-pregnancy maternal obesity associates with endoplasmic reticulum stress in human umbilical vein endothelium


**Abstract**

Obesity associates with the endoplasmic reticulum (ER) stress-induced endothelial dysfunction. Pregnant women with pre-pregnancy maternal obesity (PGMO) may transfer this potential risk to their offspring; however, whether ER stress occurs and associates with foetoplacental endothelial dysfunction in PGMO is unknown. We studied the l-arginine transport and nitric oxide (NO) synthesis in human umbilical vein endothelial cells (HUVECs) from women with PGMO or with a normal pre-pregnancy weight. We analysed the expression and activation of the ER stress sensors protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1α (IRE1α), and activating transcription factor 6 (ATF6). PGMO associated with lower endothelial NO synthase activity due to increased Thr495-inhibitor and decreased Ser1177-stimulator phosphorylation. However, higher expression and activity of the human cationic amino acid transporter 1 was found. PGMO caused activation of PERK and its downstream targets eukaryotic initiation factor 2 (eIF2α), C/EBP homologous protein 10 (CHOP), and tribbles-like protein 3 (TRB3). Increased IRE1α protein abundance (but not its phosphorylation or X-box binding protein 1-mRNA splicing) and increased c-Jun N-terminal kinase 1 phosphorylation was seen in PGMO. A preferential nuclear location of the activating transcription factor 6 (ATF6) was found in HUVECs from PGMO. All the changes seen in PGMO were blocked by TUDCA but unaltered by tunicamycin. Thus, PGMO may determine a state of ER stress via upregulation of the PERK–eIF2α–CHOP–TRB3 axis signalling in HUVECs. This phenomenon results in foetoplacental vascular endothelial dysfunction at birth.

**Keywords**

Obesity; Pre-pregnancy; Endoplasmic reticulum stress; Endothelium; Arginine; Nitric oxide