Placental problems in early pregnancy associated with five-fold increased risk of OB and fetal disorders

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First-trimester ultrasound scanning to pinpoint placental vascular disorders may be used to identify women at risk of developing serious obstetric complications. A new study in The *American Journal of Pathology* finds that patients with the highest degree of uterine artery blood flow resistance have an almost five-fold increased chance of developing preeclampsia, fetal growth restriction, or stillbirth than other pregnant women. Increased cell death and reduced insulin-like growth factor-2 (IGF2) expression were found to be possible causal factors of abnormal placental development.

"Study of the placenta after delivery has limited value since by that time the disease process has progressed to the point that delivery is indicated. If we are to institute treatments to ameliorate, or ideally prevent, the consequences of poor placentation, then an understanding of the pathophysiology in the first trimester is necessary," explained Dr. Karin Leslie of the Fetal Medicine Unit of St George's Hospital in London (UK).

A successful pregnancy requires the establishment of vascular connections between mother and embryo via the placenta, and failure to do so is associated with serious obstetric and fetal disorders. Placentation, which refers to the development of the placenta and attachment of the fetus to the uterus during pregnancy, partly requires remodeling of the maternal uterine spiral arteries. Uterine artery Doppler

(UtAD) ultrasound can measure uterine artery blood flow, and high-resistance UtAD in the first trimester is associated with increased risk of placental complications.

Using UtAD ultrasound in ongoing pregnancies, participants were divided according to resistance index (RI) scores, with high-resistance defined as a mean RI > 95th percentile and normal RI as

The researchers next analyzed placental tissue from women with high RI undergoing termination of pregnancy for nonmedical reasons and compared the findings to women with normal RI. Enrolled women were pregnant with one fetus with gestational age of 9 to 14 weeks and were attending the clinic for termination of pregnancy in the first trimester. Cases with fetal structural abnormalities or maternal conditions such as renal disease, connective tissue disease, cardiac disease, or diabetes were excluded from the study.

"We found evidence that first trimester pregnancies with high RI have differentially regulated placental gene expression, higher placental levels of cell death, and lower levels of IGF2 compared with normal RI pregnancies. These changes are apparent several months before the clinical consequences of placental insufficiency become evident," noted Dr. Leslie. The investigators also measured antioxidant enzyme activity and found that glutathione peroxidase activity decreased and superoxide dismutase activity increased in placental tissue from high RI pregnancies.

Interestingly, the researchers had initially hypothesized that placental hypoxia and oxidative stress might be important contributors to poor placentation. However, no differences between the groups were observed, with both high and normal RI placentae showing evidence of hypoxia and oxidative stress as measured by expression of hypoxia inducible factor (HIF)-1α and -2α or heat shock protein (HSP)70,

presence of nitrotyrosine residues, and lipid peroxidation. "Our data support the concept that in the first trimester low oxygen levels and mild oxidative stress are a normal physiological state," stated lead investigator Dr. Judith Cartwright, of the Fetal Medicine Unit of Saint George's Hospital in London (UK).

"Investigating the pathogenesis of the clinical consequences of poor placentation such as fetal growth restriction, preeclampsia, and stillbirth has traditionally been hampered by our inability to study these pregnancies in the first trimester, when the critical events for successful placental development occur," added Dr. Cartwright. Although the research is still in its early stages, these results suggest that problems detected early in pregnancy could direct future studies toward specific therapeutic targets.

More information: "Increased Apoptosis, Altered Oxygen Signaling, and Antioxidant Defenses in First-Trimester Pregnancies with High-Resistance Uterine Artery Blood Flow," by Karin Leslie, Guy StJ Whitley, Florian Herse, Ralf Dechend, Sandra Ashton, Ken Laing, Baskaran Thilaganathan, Judith E Cartwright (DOI: dx.doi.org/10.1016/j.ajpath.2015.06.020). This article appears online ahead of The *American Journal of Pathology*, Volume 185, Issue 10 (October 2015)

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