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The correlation of morphological and thrombotic villous arterial lesions with fetal Doppler echocardiographic measurements in the placentas of low-risk term pregnancies

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ABSTRACT

Objective: Few studies have correlated the placental vasculature with fetal cardiac function other than umbilical artery Doppler assessment in low-risk pregnancies. We assessed the contribution of the placental vasculature to fetal echocardiographic parameters using histopathological and morphometric analyses of placental resistance arteries.

Study design: Thirty-four low-risk singleton term pregnancies were assessed, including 24 thrombosis-negative cases (no/minimal gross and histological placental abnormalities) and 10 thrombosis-positive cases (histologically identified chorionic plate/stem vessel thrombosis). Fetal ventricular Doppler inflow velocities (E and A waves) and myocardial systolic (S′), early (E′), and late diastolic (A′) tissue Doppler velocities were measured within three days before birth. The myocardial performance index (MPI′) was calculated. Morphometric variables of placental stem villi arterioles (external diameter 10–150 μm) were examined, including the mean arteriolar density, total cross-sectional lumen area, and wall area/total vessel area (WA/TVA) ratio.

Results: The thrombosis-positive group had a higher umbilical artery pulsatility index and a lower tricuspid E′/A′ ratio compared to the thrombosis-negative group. The WA/TVA ratio of stem villi arterioles was negatively correlated with tricuspid E, A, and S′ velocities as well as the E/E′ ratio (n = 34). The tricuspid MPI′ was positively correlated with the total cross-sectional lumen area of stem villi arterioles (n = 34).

Conclusion: We conclude that changes in several fetal echocardiographic parameters are associated with placental vascular histopathological and morphological characteristics in a low-risk population. Further studies are needed to assess whether fetal echocardiographic assessment is a promising prenatal predictor of placental vascular histopathological and morphological characteristics in the general population.

Introduction

The feto-placental unit constitutes a unique, independent cardiovascular system. The placenta is the largest fetal vascular bed, where approximately one-third of fetal cardiac output circulates; therefore, the placental vascular bed is closely related to the total peripheral resistance throughout the entire fetal systemic circulatory system [1,2]. Several studies have reported the association of placental vascular morphology with umbilical artery Doppler findings in complicated pregnancies and their perinatal outcomes [3–5]; placental villous vascular lesions, such as reduced arteriolar density and occlusive or constrictive placental small arteries, were found in abnormal umbilical artery Doppler studies of growth restricted fetuses. Wang et al. suggested that placental vascular endothelial dysfunction may underlie the correlation between villous vascular lesions and abnormal feto-placental blood flow [6,7].

It was hypothesized that changes in placental small arteries and arterioles affect fetal cardiovascular hemodynamics, since the arterial pressure gradient across the placental vascular bed occurs at the level of placental small arteries and arterioles, which bear

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the burden of large volumes of fetal blood through the entire placenta [8]. Animal studies showed that placental embolization significantly increased placental vascular resistance and afterload to the fetal heart [9], and impaired fetal myocardial contractility [10,11]. These findings suggest that altered placental vascular resistance affects not only umbilical hemodynamics, as demonstrated by the Doppler waveform analysis, but also fetal cardiac function.

Hemodynamic adaptation of the feto-placental unit to fetal and placental development is closely associated with appropriate development of the fetus in physiological and pathological conditions [12]. Our previous study suggested that the total size of the placental vascular bed affects fetal cardiac function, at least in low-risk term human pregnancies [13], and, moreover, it was reported that a large variation is observed in the architecture of third trimester placental vascularization, even in low-risk pregnancies [14]. Taken together, these findings indicate the possible presence of coordinated adaptation between fetal cardiac function and the placental vascular bed during fetal development, including late gestation. Nevertheless, to our knowledge, there have been no human studies correlating placental vessel morphometry with fetal cardiac function other than umbilical artery Doppler assessment.

Therefore, we assessed the contribution of the human placental vasculature to fetal cardiac function using histopathological and morphometric analyses of placental resistance arteries. This was then confirmed by evaluating the morphological characteristics of placental stem villi arterioles and fetal Doppler echocardiographic parameters in low-risk term human pregnancies with or without histological placental vascular thrombosis.

Methods

The Ethics Committee of the Hamamatsu University of Medicine approved this study (No. 22-4). All participants provided written informed consent before enrollment. Participants were recruited from a population that delivered at Hamamatsu University Hospital from July 2010 to June 2011. Gestational age was confirmed by the fetal crown-rump length at the first-trimester. Normal fetal anatomy was examined by ultrasound scans. In order to assess fetal heart function just before delivery without labor, the study population consisted of singleton pregnancies delivered at term ($\geq$37 weeks of gestation) through elective repeat cesarean section or cesarean section because of the baby's position, and was categorized into two groups: controls, defined as cases with no/minimal gross and histological placental abnormalities (thrombosis-negative group); and pathological cases, defined as cases with histological placental findings of chorionic plate/stem vessel thrombosis (thrombosis-positive group). Baseline maternal and neonatal characteristics were obtained from medical records. Exclusion criteria were described as follows: pregnancies with diabetes, autoimmune disease, preeclampsia, any clinical or serological signs of intrauterine infection. Low-risk pregnant women were selected using the criteria above by one of the authors (HI). Participants who had active labor and/or rupture of the membrane prior to fetal echocardiography were excluded from the study.

Fetal echocardiography was performed within three days before birth using a Philips HD11 XE instrument equipped with a S8-3 transducer. All conventional pulsed Doppler and pulsed-tissue Doppler recordings were obtained during fetal quiescence at a fetal heart rate of between 120 and 160 bpm. The fetal heart rate was calculated from the consecutive myocardial tissue Doppler velocity waveforms, as previously described [13]. Echocardiographic measurements were carried out by an observer (KS) who was blinded to clinical information. The angle of insonation was kept $<30^{\circ}$ with no angle correction. The umbilical artery pulsatility index (PI) was defined as placental

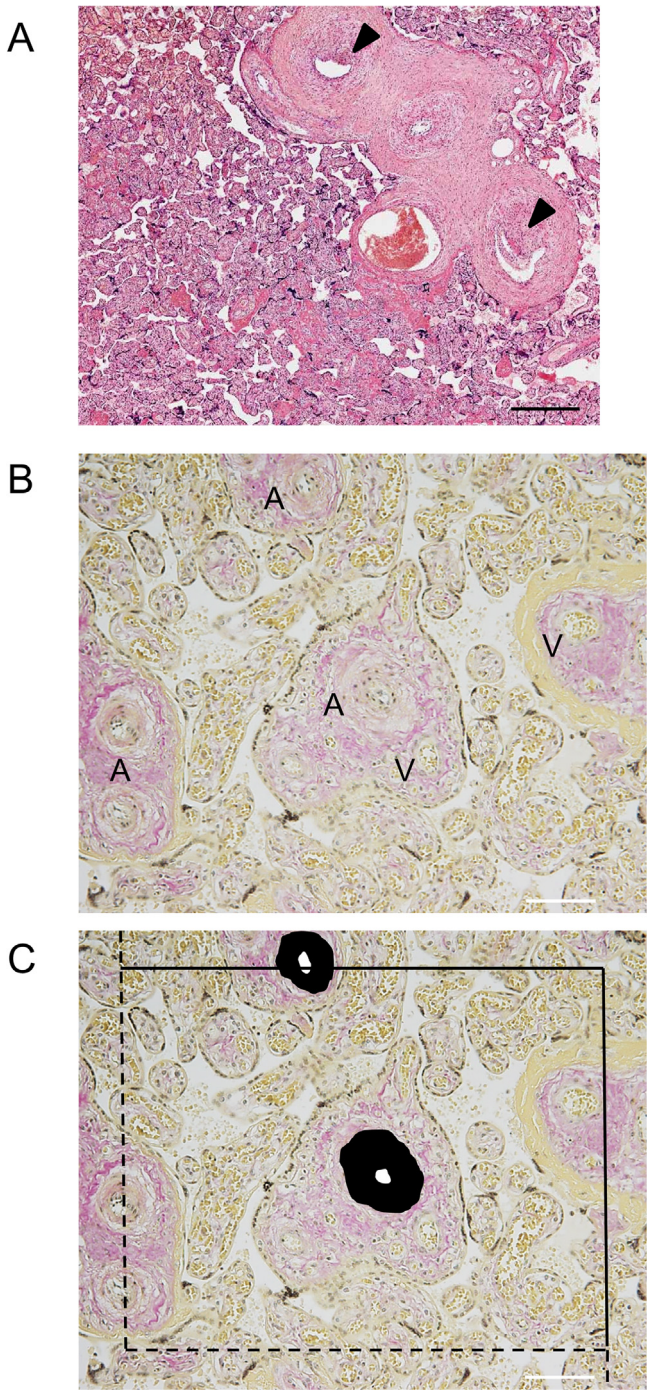

Fig. 1. Representative pathological findings from H & E staining in a placenta with villous vessel thrombosis are shown in A ($\times$40 objective); Arrowheads indicate the endothelial cushion in the walls of the placental stem villi arteries. B, Photomicrograph showing placental stem villi from a sampled placental section (elastin van Gieson stain, $\times$200 objective). Letters A and V indicate a stem villi arteriole or venules, respectively. C, Pairs of perpendicular lines were superimposed on a digital image for systemic-random sampling of stem villi arterioles. The solid and dashed lines show the acceptance or forbidden lines, respectively. Any stem villi arteriole that touched or crossed the solid line or was entirely within the grid was included in the count. Conversely, any stem villi arteriole that touched or crossed the dashed line was excluded from the count. The arteriolar wall area between the outer border of the smooth muscle layers and intima layer is highlighted with Image-Pro plus software version 4.5 (Media Cybernetics). Black bar, 500 μm; white bars, 100 μm.