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Role of the Fetoplacental Endothelium in Fetal Growth Restriction with Abnormal Umbilical Artery Doppler Velocimetry

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Abstract

Growth-restricted fetuses with absent or reversed end-diastolic velocities in the umbilical artery are at substantially increased risk for adverse perinatal and long-term outcome, even in comparison to growth-restricted fetuses with preserved end-diastolic velocities. Translational studies show that this Doppler velocimetry correlates with fetoplacental blood flow, with absent or reversed end-diastolic velocities signifying abnormally elevated resistance within the placental vasculature. The fetoplacental vasculature is unique in that it is not subject to autonomic regulation, unlike other vascular beds. Instead, humoral mediators, many of which are synthesized by local endothelial cells, regulate placental vascular resistance. Existing data demonstrate that in growth-restricted pregnancies complicated by absent or reversed umbilical artery end-diastolic velocities, an imbalance in production of these vasoactive substances occurs, favoring vasoconstriction. Morphologically, placentas from these pregnancies also demonstrate impaired angiogenesis, whereby vessels within the terminal villi are sparsely branched, abnormally thin, and elongated. This structural deviation from normal placental angiogenesis restricts blood flow and further contributes to elevated fetoplacental vascular resistance. Although considerable work has been done in the field of fetoplacental vascular development and function, much remains unknown about the mechanisms underlying impaired development and function of the human fetoplacental vasculature, especially in the context of severe FGR with absent or reversed umbilical artery end-diastolic velocities. Fetoplacental endothelial cells are key regulators of angiogenesis and vasomotor tone. A thorough understanding of their role in placental vascular biology carries the significant potential of discovering clinically relevant and innovative approaches to prevention and treatment of fetal growth restriction with compromised umbilical artery end-diastolic velocities.

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Introduction

Fetal growth restriction (FGR) confers substantial risk for adverse perinatal outcomes, including stillbirth, neonatal death, and complications related to prematurity. Beyond the perinatal period, children who were growth-restricted *in utero* remain at higher risk for neurocognitive delay, and they are more likely to develop obesity, metabolic syndrome, and cardiovascular disease later in life.[1–6] While current obstetric management paradigms may be able to time delivery in order to avert stillbirth in this population, long-term outcomes remain unchanged.[7–9]

Although abnormalities in the maternal circulation can certainly contribute to the pathophysiology of FGR, the fetoplacental vasculature also plays a critical role in normal development, as studies clearly indicate that growth-restricted fetuses with absent or reversed end-diastolic umbilical artery velocities (**AEDV/REDV**) suffer even worse outcomes than fetuses with FGR and ***preserved*** end-diastolic velocities.[5,10–16] As current clinical interventions have not been shown to improve outcome in FGR fetuses with AEDV/REDV, a thorough understanding of the fetoplacental vasculature, including its unique development and functional regulation, has the potential to open up new avenues of prevention and/or treatment.

Umbilical artery Doppler assessment in FGR

Both the Society for Maternal-Fetal Medicine and the American Congress of Obstetricians and Gynecologists endorse umbilical artery Doppler assessment in high-risk pregnancies with suspected FGR.[17,18] This recommendation is based upon a body of fundamental translational and clinical studies.

In an early, key ovine study, embolizing the fetoplacental cotyledons along the umbilical arteries resulted in higher placental vascular resistance as measured by radioactive microsphere count.[19] This, in turn, led directly to decreased umbilical artery end-diastolic velocities and higher peak systolic/diastolic (S/D) ratios.[19] Both these findings confirmed that velocity waveforms within the umbilical artery reflect placental vascular resistance.

Fetoplacental vascular resistance, as assessed by the umbilical S/D ratio as one example, normally decreases as gestation progresses.[20–22] In growth-restricted fetuses, however, umbilical artery end-diastolic velocities were frequently lower than expected for gestational age.[21,23,24] The elevated resistance represented by these low velocities correlated with placental structural and histopathologic abnormalities, as well as with adverse pregnancy outcomes.[25–29]

Subsequently, umbilical artery Doppler velocimetry underwent rigorous clinical testing. In general, the majority of these trials demonstrated a lack of benefit in the low-risk obstetric

population.[31–35] In contrast, when limited to women at risk for a potentially compromised fetus (i.e. “high-risk”), most trials found that umbilical artery Doppler testing offered some degree of value, with outcomes ranging from fewer emergency deliveries to less death and serious neonatal morbidities.[36–40] A key meta-analysis, as well as a recent Cochrane review, concluded that using umbilical artery Doppler in high-risk pregnancies reduced the risk of perinatal death by 29 to 38 percent, without increasing interventions like iatrogenic preterm delivery.[30,41] These findings solidified the role of umbilical artery Doppler ultrasonography in high-risk pregnancies. Despite the reduction in risk of perinatal death with use of umbilical artery Doppler velocimetry, however, existing studies demonstrate that overall survival and long-term outcomes are unchanged.[7–9] Thus, an in-depth understanding of the fetoplacental vasculature is needed if preventions and treatments mitigating this end-stage process are to be found.

The fetoplacental vasculature in FGR

Maternal hypoperfusion of the placenta is a common cause of FGR.[42,43] However, the fetoplacental vasculature is also an important component of placental perfusion and hence vital to fetal growth. This is demonstrated by a cohort of 34 growth-restricted fetuses; while all demonstrated abnormally low umbilical artery diastolic flow velocities, 21 of these pregnancies were found to have normal uterine artery Dopplers.[44] Thus, fetal growth abnormalities and abnormal umbilical artery Doppler velocimetry can occur even in the presence of normal maternal uteroplacental blood flow..[44]

Common placental pathologic findings in FGR include a small placenta, avascular terminal villi, fibrinoid necrosis, and multiple villous infarcts.[45–47] However, additional pathologic features often then diverge, depending upon whether umbilical artery end-diastolic velocity is absent/reversed or preserved. Placentas from pregnancies complicated by FGR with AEDV/REDV are significantly more likely to have marginal cord insertions when compared to those from growth-restricted pregnancies with preserved diastolic velocities, even those with elevated S/D ratios.[48] The stem villous vessels from placentas complicated by FGR with AEDV/REDV demonstrate luminal obliteration and concentric intimal and medial wall thickening, and the percentage of abnormal vessels directly correlate with fetoplacental vascular resistance.[27,49]

FGR placentas also differ at the microvascular level depending on whether end-diastolic velocities are present or absent. For example, those with preserved end-diastolic velocities have normal or more highly branched capillary beds.[26,50] In contrast, branches of mature intermediate villi are largely absent in FGR placentas with AEDV/REDV, and terminal capillaries appear thin and elongated.[27,51–53] This decrease in peripheral villous vasculature contributes to elevated fetoplacental vascular resistance.[27,52]

Fetoplacental endothelium

Understanding the mechanisms that underlie these placental pathologic findings lies, at least in part, in the fetoplacental endothelium. Throughout the body, the endothelium plays a key role in vascular physiology by regulating vasomotor tone, balancing pro- and anticoagulant activity, tempering inflammatory mediators, modulating cellular and nutrient trafficking,

and driving angiogenesis.[54] Endothelial cells are also subject to their local environment, leading to tissue-specific phenotypes. This heterogeneity is a key feature of the endothelium.[55–59]

The endothelium in the human placenta reaches approximately 550 km in length and occupies 15 square meters at term gestation.[60] Despite being found in continuity and within the same organ, the endothelium in the umbilical cord and in the placental vasculature can exhibit significant phenotypic diversity. Within the umbilical cord alone, endothelium from the human umbilical artery differs from that within the umbilical vein. For example, after culturing separately isolated endothelial cells from the umbilical vein and umbilical artery and further subjecting them to shear stress, the expression of endothelin-1, a vasoconstrictor, is significantly lower in human umbilical vein endothelial cells than in umbilical artery endothelial cells.[61] This may be one contributing mechanism that allows the umbilical vein to maintain proper patency in its setting of high flow.[61]

Estrogen receptors are expressed in a wide variety of tissue including endothelial cells and vascular smooth muscle cells.[62,63] With respect to vascular physiology, estrogen receptors regulate expression of multiple vasodilator and vasoconstrictor proteins, and whether a vessel constricts or dilates in response to estrogen appears to be dependent on estrogen receptor profile and tissue specificity.[62–68] Expression of genes related to estrogen biology can also vary within the fetoplacental endothelium. For example, estrogen receptor-β is expressed in higher quantities in human umbilical artery endothelial cells than human umbilical vein endothelial cells, as is 17 beta-hydroxysteroid dehydrogenase type 2, a gene that encodes an enzyme that converts estradiol into its less biologically active form estrone.[69,70] Although the physiologic implications of these specific findings on ***normal*** placental vascular biology remain incompletely understood, estrogen receptor-β expression is higher within fetoplacental endothelium from FGR placentas with AEDV/REDV compared to gestational age-matched, appropriately grown control subjects.[71] This higher estrogen receptor-β expression results in up-regulation of cyclooxygenase-2 (COX-2) expression and activity and down-regulation of vasodilator gene expression. These changes in gene expression of key enzymes shift the vascular prostanoid profile derived from endothelial cells toward production of vasoconstrictive mediators.[71,72]

Within chorionic plate and stem villous vessels, microarray data also demonstrate differences in gene expression between arterial and venous endothelial cells. Compared to placental arterial endothelial cells, placental venous endothelial cells more strongly express genes associated with transport activity and lipid metabolism, suggesting that venous endothelial cells may have a phenotype that allows for enhanced nutrient transport to the fetus.[74] In contrast, most of the genes in placental arterial endothelial cells are associated with signal transduction and other molecular pathways including vascular endothelial growth factor A (VEGF) signaling.[74] VEGF stimulates angiogenesis and stabilizes newly formed vessels.[75–78] Thus, the fact that placental arterial endothelial cells express more genes related to VEGF signaling than placental venous ones do suggests that placental arterial endothelial cells play a more important role in forming the fetoplacental vasculature.

Epigenetic regulation also plays a role in placental endothelial cell diversity. For example, genome-wide methylation studies have found that venous endothelial cells in the chorionic plate demonstrated higher degrees of hypomethylation than arterial endothelial cells in the same location..[79] For example, increased promoter methylation was found within the proximal promoter region of the endothelial nitric oxide synthase gene in placental arterial endothelial cells compared to venous endothelial cells, resulting in higher nitric oxide synthase expression by placental venous endothelial cells.[79,80] While the implications of these findings are not yet clear, it is possible that higher nitric oxide within the placental venous circulation contributes to maintenance of proper blood flow to the fetus. Interestingly, umbilical arterial endothelial cells from FGR pregnancies demonstrate decreased methylation at these same promoter sites compared to umbilical arterial endothelial cells from normal pregnancies, suggesting that stable alterations in gene expression potential that arise during development may affect fetoplacental vascular function.[80]

Further demonstrating the heterogeneity of endothelial cells within the placenta, placental microvascular endothelial cells differ from macrovascular umbilical vein endothelial cells. Functionally, placental microvascular endothelial cells secrete more prostanoids including 6-keto prostaglandin F1α (stable metabolite of the vasodilator prostacyclin) and thromboxane B2 (stable metabolite of the vasoconstrictor thromboxane A2) than do umbilical vein endothelial cells.[59] Placental microvascular endothelial cells also proliferate in greater quantities than umbilical vein endothelial cells in response to VEGF.[59] Thus, some investigators have suggested that human umbilical vein endothelial cells, the most commonly used endothelial cell type for experiments, may not always be the best model to study the biology of placental endothelial cells.[59,81] Instead, endothelial cells isolated from a particular part of the placenta (e.g. arterial vs. venous and macrovascular vs. microvascular) that is most applicable to the specific area of study might serve as a better model of investigation.

Fetoplacental endothelial cells and mediation of vascular function

In most vascular beds, small arterioles contribute to most of the vascular resistance via autonomic and humoral influences.[54,82] However, placental chorionic plate and stem villous vessels, which are similar in size to these arterioles, uniquely lack innervation.[83] Instead, their vasomotor tone is solely controlled by locally produced vasoactive mediators, most of which are endothelially-derived.[84,85] These placental vessels also respond differently to humoral factors than vessels in other vascular beds. For example, the placental vasculature is the only vascular bed that has been reported to constrict rather than dilate in response to prostaglandin E2.[86] It also demonstrates blunted responses to other vascular mediators including acetylcholine, bradykinin, and angiotensin II.[87–89]

Fetoplacental endothelial cells are essential for vasoactive mediator responses such as nitric oxide-dependent vasodilatation and endothelin-1-mediated vasoconstriction within stem villous vessels, substantiating an endothelial role in control of fetoplacental vascular function.[83,90] In a study comparing concentrations of vasoactive mediators in cordocentesis specimens between gestational age-matched, appropriately grown fetuses and FGR fetuses

(with 60 percent of these fetuses with AEDV/REDV and the other 40 percent with an umbilical artery S/D ratio of > 95th percentile for gestational age), investigators found that endothelin-1 concentrations were significantly higher, while 6-keto prostaglandin F1α levels were lower in the FGR population in comparison to the controls.[91] This suggests that circulating levels of vasoconstrictors are increased and vasodilators are decreased in FGR fetuses. Similarly, others have also confirmed that 6-keto prostaglandin F1α is synthesized in lower quantities within the umbilical artery in the setting of FGR.[86,92,93] The exact mechanisms that underlie these changes in endothelial cell-derived vasoactive mediators have not been fully elucidated. Existing literature, however, has demonstrated that in addition to changes in endothelial estrogen receptor-β leading to alterations in vascular prostanoid production as previously described, fetal COX-2 gene polymorphisms that correlate to decreased COX-2 gene expression were associated with more placental malperfusion and FGR.[94]

The role that nitric oxide regulation plays in FGR remains uncertain. Suggesting decreased nitric-oxide-mediated vasodilation, the umbilical artery of FGR pregnancies has been found to exhibit less nitric oxide synthase protein expression than controls in an ovine model; [95] similarly, transport of L-arginine, the precursor to nitric oxide, is down-regulated in human umbilical vein endothelial cells of pregnancies complicated by FGR.[96] In contrast, other studies have found that nitric oxide synthesis in FGR pregnancies is unaffected or actually upregulated, perhaps representing compensation for the vascular derangements of FGR.[97–100] T

In addition to humoral mediators, potassium (K^+) channel expression is a major component of endothelial interaction with smooth muscle.[101] Although the specifics of all the various K^+ channels are beyond the scope of this review, K^+ channels generally have the ability to form pores and to influence cell membrane potential, thereby helping regulate vascular smooth muscle tone. Fetoplacental endothelial cells express functional K^+ channels, which play a role in controlling placental vascular resistance.[102] For example, blocking K^+ channels within chorionic plate arteries and veins of FGR pregnancies increases basal tone.[103]

Angiogenesis of the fetoplacental vasculature

In addition to endothelial cell-mediated regulation of vasomotor tone, the anatomic configuration of the villous vasculature is also critical to fetoplacental blood flow. Vasculogenesis, the *de novo* formation of blood vessels, normally occurs within the human placenta by approximately 6 weeks gestation, resulting in formation of tertiary villi (Figure 1; I).[104] As pregnancy progresses, these tertiary villi continue to differentiate and expand into immature intermediate villi and stem villi (Figure 1; II–IV). Concomitantly, there is a gradual increase in angiogenesis, whereby new blood vessels form from pre-existing vessels.[105–107] However, the rate of angiogenesis significantly accelerates starting at around 25 weeks gestation, leading to exponential increases in the total length of the villous vascular tree, continuing until 40 weeks gestation (Figure 1; V).[60,108] This sustained angiogenesis of the fetoplacental vasculature is a key reason for the normal, progressive increase in umbilical artery end-diastolic velocities that occurs as gestation advances.

As mentioned previously, villous capillary density is either normal or even increased in FGR placentas with preserved end-diastolic velocities, even if the S/D ratio is greater than the 95th percentile for gestational age.[51–53] In contrast, pregnancies complicated by FGR with AEDV/REDV have sparsely branched and abnormally thin capillaries, leading to fewer capillary loops.[51–53,109,110] This decreased branching results in lower volume density, which in turn provides a structural basis for elevated fetoplacental vascular resistance.[111]

The mechanisms underlying this impaired angiogenesis in human fetoplacental vasculature remain incompletely elucidated, but endothelial cells are essential in the process of angiogenesis. They initiate the process by increasing vascular permeability and degradation of the endothelial cell basement membrane.[112] Endothelial cells then proliferate and migrate, contact each other, form lumen, and finally, recruit pericytes and other cell types to stabilize the newly formed vessel.[112,113]

Various endothelial cell-derived angiogenic and anti-angiogenic factors are important for this process to occur. These include VEGF, soluble fms-like tyrosine kinase-1 (sFLT1), placental growth factor (PlGF), and fibroblast growth factor 2 (FGF2). While derangements in maternal serum levels of these factors have been implicated in disorders of placentation such as FGR, there is growing evidence that they also play a role in development of the fetoplacental vasculature.[114–122] Compared to controls, endothelial cells isolated from placentas of pregnancies complicated by FGR with AEDV/REDV show evidence of impaired angiogenesis, as manifested by deficient tube formation (i.e. formation of capillary-like structures *in vitro*).[123] One mechanism that contributes to this deficient angiogenic potential in endothelial cells derived from FGR with AEDV/REDV is abnormal regulation of VEGF expression.[123] Imbalances between these angiogenic and antioangiogenic factors have also been found within fetal blood. For example, umbilical vein sFLT1 and FGF2 levels are increased in FGR pregnancies, while PlGF concentrations are decreased.[124] Additionally, there was a positive correlation between umbilical vein sFLT1 and umbilical artery pulsatility index in FGR fetuses, while PlGF was negatively correlated.[118] In contrast, these factors within the umbilical vein had no correlation to uterine artery pulsatility index, suggesting that the balance between angiogenic and antiangiogenic factors within the fetal circulation may play a direct role in fetoplacental angiogenesis.[118]

Conclusion

Normal intrauterine growth is dependent upon not just the maternal environment, but also the fetal component of placental perfusion. Impaired fetoplacental blood flow clinically manifests as absent or reversed end-diastolic velocities in the umbilical artery; in the setting of FGR, this Doppler finding portends a significantly elevated risk for adverse pregnancy outcome.

Translational studies have demonstrated clear correlation between Doppler velocimetry and fetoplacental perfusion, with absent or reversed end-diastolic velocities denoting abnormally elevated resistance within the placental vascular tree. The physiology of this flow impediment is twofold, comprised of both functional and structural etiologies.

The fetoplacental vasculature is unique in its lack of innervation, singular in being independent from the autonomic regulation to which other vascular beds are subject. Instead, existing data suggest that resistance within this system is regulated largely by humoral mediators from local endothelial cells. In pregnancies complicated by FGR with AEDV/REDV, an imbalance in these mediators yields a humoral milieu favoring vasoconstriction. Inhibited and impaired angiogenesis further contribute to placental vascular resistance in this population, creating structural changes that restrict blood flow.

Significant work has been done in the field of fetoplacental vascular formation and function. However, in the current absence of effective clinical management strategies for cases of FGR with AEDV/REDV, continued investigation into the physiological, cellular, molecular, and epigenetic regulation of the fetoplacental vasculature and endothelium are needed. This knowledge is essential if either preventive or therapeutic approaches that will truly improve perinatal and long-term outcomes are to be discovered.

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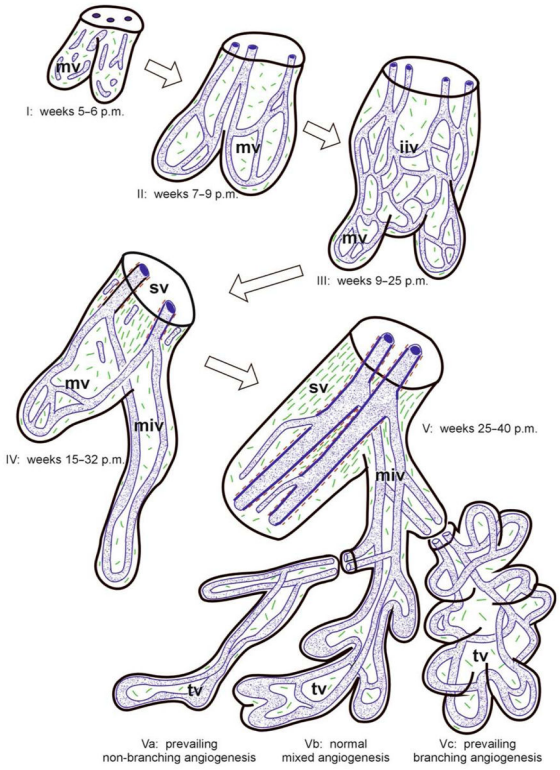

Figure 1. Fetoplacental villous development throughout pregnancy

(I) In post-menstrual (p.m.) weeks 5–6, fetal capillary segments are formed by vasculogenesis within mesenchymal villi (mv). **(II)** These fuse to form a simple capillary bed in weeks 7–8. **(III)** Between 9–25 weeks, this capillary bed expands by angiogenesis as mesenchymal villi develop into immature intermediate villi (iiv). **(IV)** Immature intermediate villi become transformed into stem villi (sv), while peripheral mesenchymal villi are transformed into mature intermediate villi (miv) between weeks 15–32. Concomitantly, centrally located capillaries develop into stem villous vessels, and the peripheral vasculature elongates. **(V)** In the last half of pregnancy, there is continued angiogenesis as terminal villi (tv) develop, resulting in the villous morphology demonstrated in **Vb**. In placentas from FGR pregnancies with preserved end-diastolic velocities, villi either resemble that illustrated in **Vb** or **Vc**, whereas FGR pregnancies complicated by AEDV/REDV have villi similar to that depicted in **Va**. (**Blue:** Endothelial tubes; **Brown:** Vascular smooth muscle cells; **Green:** Collagen fibers). From: Benirschke K, Burton GJ, Baergen RN. Architecture of normal villous trees. In: *Pathology of the human placenta*. New York, NY: Springer-Verlag Berlin Heidelberg; 2012: 122. With permission from Dr. Kurt Benirschke, Dr. Graham Burton, and Dr. Rebecca Baergen in addition to Springer Science + Business Media.