Angiogenic factors in placentas from pregnancies complicated by fetal growth restriction (Review)

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Abstract. The placenta is the organ that is responsible for providing the developing fetus with all the nutrients necessary for its growth and is also responsible for removing fetal waste. Placentation is a crucial process that includes angiogenesis. Angiogenesis involves not only the fetal circulation, but also placental and endometrial vascular changes. In this study, we review the literature regarding any impairment in the angiogenic process in placentas from pregnancies complicated by fetal growth restriction (FGR). Angiogenesis is regulated by a list of factors, also known as growth factors, such as the vascular endothelial growth factor (VEGF), the placental growth factor (PlGF) and the basic fibroblastic growth factor (bFGF), as well as the partial pressure of oxygen in the feto-placental vessels. Other factors, such as transcriptional factors, also play a pivotal role, controlling the above-mentioned growth factors. Alterations in these pathways have been described in cases of growth-restricted fetuses. In this review, we provide an insight into these processes and identify the most crucial factors involved.

Contents

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1. Vessel growth and angiogenesis

Two distinct types of vessel growth have been defined (1,2): a) Vasculogenesis, that is the formation of new blood vessels from hemangiogenic stem cells, derived from mesenchymal cells, that differentiate into hemangioblastic stem cells. This process occurs essentially during fetal development. Vasculogenesis can be divided in three main steps: i) the induction of hemangioblasts and angioblasts, mediated mainly through the fibroblast growth factor (FGF); ii) the assembly of primordial vessels, mediated mainly by the vascular endothelial growth factor/vascular endothelial growth factor receptor system (VEGF/VEGFR); and iii) the transition to angiogenesis (3-6). b) Angiogenesis, that is the formation of new branches from pre-existing vessels. This process occurs in the female reproductive tract during the formation of the *corpus luteum*, during endometrial development and during embryo implantation and placentation. Angiogenesis can be further divided in two forms: sprouting and non-sprouting angiogenesis (intussusception) (7-10). The process of angiogenesis has three phases: initiation, proliferation-invasion and maturation-differentiation. All of these processes are essential for the normal uteroplacental development.

Twenty one days post conception (dpc), the vascularisation of placental villi commences as the result of the *de novo* formation of capillaries inside the villi and not as the protrusion of embryonic vessels into the placenta (11,12). Firstly, mesenchymal-derived macrophages (Hofbauer cells) appear that express angiogenic growth factors initiating vasculogenesis (13). Angiogenic growth factors are also expressed by the maternal decidua and macrophages mediating trophoblast invasion (13). Subsequently, the formation of the first vessels occurs (approximately 28 dpc) and erythrocytes are detected by 32 dpc (2). The hemangiogenic precursor cells that migrate toward the periphery are transformed to mesenchymal cells from inside the villi (1,6). During this time, the vasculature of the uterus undergoes three important adaptive changes: vasodilation, increased permeability and growth and development of new vessels in order to increase its blood supply (14-16).

Branching or sprouting angiogenesis, meaning the lateral ramification of pre-existing tubes, leads to the formation of a

capillary network (17). During this process, various changes occur, including the increase of the vascular permeability, degradation of basement membrane, increase in endothelial cell proliferation and migration, formation of endothelial cell tubes and recruitment of pericytes to the outside of the capillary to form a stable vessel (3). After the sixth week of gestation and beneath the trophoblast that covers the villous surface, capillaries are arranged in a web-like pattern, as a basal lamina is forming around them. From week 15 onwards, the intermediate villi gradually become stem villi, as a fibrosal core is formed by the fusion of large vessels. In these newly formed larger villi the diameter of the vessels is up to 100 mm, and they are surrounded by cells expressing α and γ smooth muscle actins, vimentin and desmin, and finally exhibit the full spectrum of cytoskeleton antigens (18). After week 24 of gestation, branching angiogenesis is followed by non-branching angiogenesis: this involves the formation of mature intermediate villi, specialized in gas exchange between the maternal and fetal circulation. The maturation of intermediate villi leads to the formation of terminal villi that contain 1-2 long, poorly branched capillary loops, which coil and bulge through the trophoblastic surface (19). During this process there is a decreased trophoblast proliferation and increased endothelial proliferation.

The terminal villi that contain the long poorly branched capillaries continue to grow and form large sinusoids in order to overcome the total fetoplacental vascular impedance. Increasing fetal blood pressure aids this dilation and fetoplacental blood flow reaches 40% of the fetal cardiac output throughout gestation (20).

The process of maternal uterine vessels remodelling is described as pseudovasculogenesis (21). Until the sixth week of gestation, uterine arteries (spiral arteries) have high resistance and low capacity (6). The invasion of cytotrophoblasts into the decidua leads to the rearrangement of maternal endothelial cells that results in low resistance and high capacity vessels (22). Maternal veins undergo similar but less profound changes. Pseudovasculogenesis is completed at approximately the 20th week of gestation (23-25).

2. Fetal growth restriction and angiogenesis

Fetal growth restriction (FGR) is currently a complex condition in the field of obstetrics. The failure of the fetus to achieve its genetically determined growth potential is associated with significantly increased perinatal morbidity and mortality, and is also a major determinant of cardiovascular disease and glucose intolerance in adult life. FGR is not a disease entity with a unique pathophysiology (26). The term FGR is generally used for a fetus that presents reduced growth velocity (<10th percentile). A variety of factors have been involved in FGR, including infectious, congenital abnormalities, drug abuse or chemical substances, abnormalities of the placenta, as well as immunological and anatomical factors. In most cases, however, incomplete placentopoiesis (placental formation) is the cause for the insufficient supply of nutrients and oxygen to the fetus that subsequently causes the deceleration of its growth (27).

Angiogenesis is a placental factor which plays an important role in the development of FGR (28-32). FGR occurs as a result of inadequate vascular transformation and terminal villus formation (28). The terminal villi of FGR cases are less in number and size compared to cases of normal pregnancy (33,34) (Fig. 1). Cotyledonary arteries are thin and less-branched, whereas villous vessels exhibit fewer branches and most of their loops are uncoiled (33,35,36). Previous spectral Doppler imaging studies have demonstrated abnormal placental blood flow associated with vascular abnormalities in 60% of cases of FGR (37,38), strongly indicating a correlation between placental vascular pathology and FGR.

Based on the type of FGR (early or late onset) there are two models that may occur in the placental tissue (39). Uteroplacental insufficiency is the cause of the early onset of growth restriction and results in increased branching angiogenesis. More common is late onset FGR due to placental failure and is accompanied by straight and unbranched capillaries, along with reduced cytotrophoblast proliferation, increased syncytial nuclei and erythrocyte congestion. All these suggest an increased rate of trophoblast proliferation. This situation has been interpreted as placental hyperoxia (39,40). Thus, fetoplacental blood flow is severely impaired and transplacental gas exchange is poor, placing the fetus at risk of hypoxia and acidosis (40).

3. Angiogenic growth factors in fetal growth restriction

A successful pregnancy outcome depends on the proper development of the fetoplacental vasculature in the villous core, which begins with the infiltration of cytotrophoblasts in the endometrium and is completed in conjunction with the spiral arteries (41,42). It is widely accepted that shallow trophoblast invasion may lead to fetal hypoxia and impaired growth (43). The proper and timely proliferation and differentiation of the villous cytotrophoblast stem cells, which are controlled by hypoxia, are crucial for adequate placentation and initiation of angiogenic pathways (44,45). Numerous factors are thought to play a role in normal vascular adaptation to implantation (17).

The results from studies on animal models have shown that at the initial stages of pregnancy where the partial pressure of oxygen (PO_2) is decreased, an increased action of regulatory factors exists, mainly from hypoxia-inducible factor (HIF)-1, HIF-2 and HIF-3. HIF-1 comprises a basic response of a cell to the hypoxic conditions. It is constituted by two subunits, HIF-1α and HIF-1β (ARNT). HIF-1α forms a heterodimer with HIF-1β and HIF-1, acts on the cell nucleus and regulates the expression of many genes that play a role in angiogenesis (Fig. 2), the cell cycle and metabolism (46). HIF-2 has a similar function, while existing data for HIF-3 are insufficient. The regulation of these factors is crucial for the angiogenic processes and may be impaired in pathological conditions, such as preeclampsia or FGR. We have previously demonstrated the downregulation of prolyl hydroxylase 3 (PHD-3) in placentas from pregnancies complicated by FGR: PHD-3 hydroxylates HIF-α in order to bind with von Hipple-Lindau (vHL), leading to its proteasomal degradation. As PHD-3 regulates the HIF-mediated hypoxic response in FGR, we hypothesized that fetal adaptation to hypoxia ranges from impaired to adequate, as observed by the gradient of PHD-3 downregulation in relation to the severity of FGR (47).

Numerous other factors are thought to play a role in normal vascular adaptation to implantation (48). The VEGF-A and

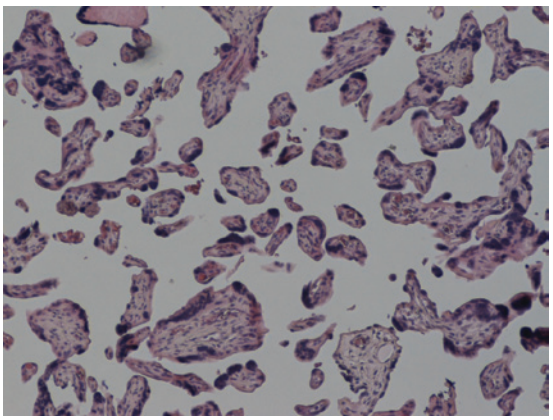

Figure 1. Hypoxic small placenta at the 28th week of gestation in a pregnancy complicated by FGR: there is marked distal villous hypoplasia with prominent syncytial knots and ample intervillous space (hematoxylin and eosin stain, x100).

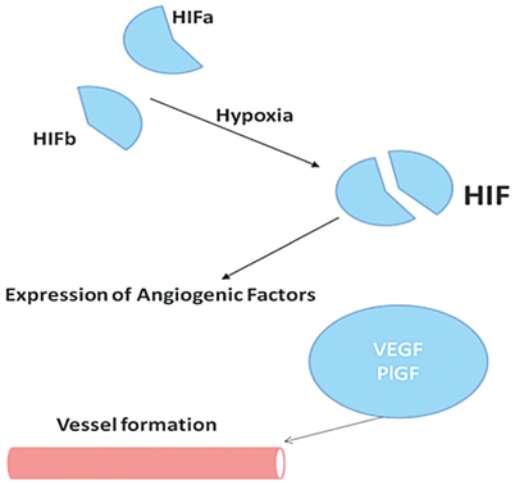

Figure 2. Activation of the hypoxia-inducible factor (HIF) angiogenic pathway. VEGF, vascular endothelial growth factor; PlGF, placental growth factor.

placental growth factor (PlGF) are possibly the factors that have been most studied (49-51). VEGF interacts with VEGFR-1 (Flt-1) and VEGFR-2 (KDR) to promote endothelial cell proliferation, cell migration and vascular permeability (15,52-54). PlGF shares biochemical and functional features with VEGF and interacts with VEGFR-1 (Flt-1). PlGF and VEGF-A have synergistic effects regarding angiogenesis, but vessels induced by PlGF are more mature and stable than vessels induced by VEGF-A (55,56). PlGF is abundantly expressed in the human placenta. Both VEGF-A and PlGF may be important paracrine regulators of decidual angiogenesis and autocrine mediators of trophoblast function (51,57). Of note, increased soluble VEGFR-1 (sVEGFR-1) has been identified in FGR placentas (58-61). sVEGFR-1 binds to VEGF-A and PlGF and decreases their free concentration in the blood, thereby inhibiting the growth factor interaction with their receptors, leading to endothelial cell dysfunction (62). sVEGFR-1 also serves as a direct inhibitor of cytotrophoblast invasion (61). PlGF expression is significantly increased in placentas from pregnancies complicated by severe FGR, whereas VEGF expression is decreased,

Table I. Various stimulatory and inhibitory factors involved in angiogenic processes during placental development.

Stimulators	Inhibitors
Angiogenin	Fibronectin
aFGF	Tsp-1
bFGF	Prolactin
IL-8	Endostatin
TGF-α	TNF-α
TGF-β	TXA2
Proliferin	
PDGF	
G-CSF	
Leptin	

aFGF, fibroblast growth factor, acidic; Tsp-1, bFGF, fibroblast growth factor, basic; IL-8, interleukin-8; TGF-α, transforming growth factor-α; TGF-β, transforming growth factor-β; PDGF, platelel-derived growth factor; G-CSF, granulocyte-colony stimulating factor; Tsp-1, thrombospondin 1; TNF-α, tumor necrosis factor-α; TXA2, thromboxane A2.

although the serum levels of these factors demonstrate conflicting results (63). Other studies have provided evidence linking the complement system to the above imbalance of angiogenic factors, associated with placental dysfunction, and have identified a new effector of immune-triggered pregnancy complications (64).

A second family of growth factors, the angiopoietins, is also known for their regulating capacity regarding angiogenesis (65). Angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) bind with equal affinity to their receptor, TIE-2, but have different functions. Ang-1 maintains vessel integrity and plays a role in the later stages of vascular remodeling (65). Ang-2, a functional antagonist of Ang-1, leads to the loosening of cell-cell interactions and allows access to angiogenic inducers, such as VEGF (66). The co-expression of VEGF and Ang-2 induces angiogenesis, but Ang-2 results in vascular regression in the absence of angiogenic signals (67). Ang-1 and Ang-2 have both been detected in decidual and placental tissues (51,66).

Various decidual cell types are capable of producing angiogenic factors. Decidual stromal cells, glandular epithelial and perivascular smooth muscle cells have been found to produce a variety of angiogenic factors (51). Uterine natural killer cells are also abundantly present in first-trimester decidua and are known to produce PlGF, VEGF, Ang-1 and Ang-2 (68).

Local oxygen concentration is another important element that influences the factors mentioned above. Low oxygen levels upregulate VEGF but downregulate PlGF, while the opposite occurs with high oxygen levels, whereby VEGF is downregulated and PlGF is upregulated (69,70). Also, under low oxygen, the Ang-1:Ang-2 ratio shifts in favor of Ang-2, leading to vessel instability, angiogenesis and vessel remodeling (20,71). Other stimulators and inhibitors presented in Table I participate in angiogenic pathways and are potentially crucial in FGR pathophysiology.

In conclusion, data obtained from numerous research studies suggest that abnormal levels of angiogenic and anti-angiogenic

growth factors may partly be responsible for the pathophysiology associated with pregnancies complicated by FGR. Further investigation is required in order to clarify whether the involvement of these factors is a primary mechanism leading to the abnormal development and function of the placenta and the clinical presence of FGR in pregnancy or whether the alterations in the placental expression of the angiogenic/antiangiogenic growth factors reflect other, still unidentified and underlying mechanisms.

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