

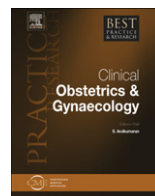


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## Decidualisation and angiogenesis

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The timing of decidualisation and vascular processes during the implantation period is of paramount importance for the development of a receptive endometrium suitable for implantation. The endometrium transforms during the secretory phase into a well-vascularised receptive tissue characterised by increased vascular permeability, oedema, proliferation and differentiation of stromal cells into decidual cells, invasion of leucocytes, vascular remodelling and angiogenesis. Decidualisation continues in the presence of conception and an influx of immune cells, trophoblasts and vascular adaptation will occur. Vascular changes include spiral artery remodelling, angiogenesis and the induction of angiogenic factors. Disturbances in uterine blood supply are associated with first-trimester miscarriages and third-trimester perinatal morbidity and mortality caused by pre-eclampsia and foetal growth restriction. This article assesses decidual vascular changes during human implantation, and evaluates the involvement of angiogenesis in the pathogenesis of miscarriages, pre-eclampsia and intrauterine growth restriction.

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Pregnancy is a unique condition, which has intrigued scientists for decades. Much progress has been made in understanding the events at the implantation site. The growing foetus requires maternal blood for its nutrition, but direct interaction of maternal leucocytes with allogeneic foetal cells would be unfavourable. Instead, the foetus surrounds itself with a specialised tissue, the trophoblast, with which it can tap into the maternal blood without provoking a detrimental immune response. The mother prepares for and responds to pregnancy with both systemic and local adaptations. Locally, significant physiologic adaptations of the uterine environment take place to facilitate implantation, including decidualisation and vascular remodelling. In addition, the highly invasive nature of trophoblasts is kept in control by the decidua. The timing of decidual and vascular processes during the implantation period is of paramount importance for the development of a receptive endometrium suitable for implantation.

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Disturbances in uterine blood supply are associated with first-trimester miscarriages and third-trimester perinatal morbidity and mortality caused by pre-eclampsia and intrauterine growth restriction (IUGR).<sup>1–3</sup> This article assesses the role of decidual angiogenesis during human implantation and evaluates the involvement of angiogenesis in the pathogenesis of miscarriages, pre-eclampsia and IUGR.

## Angiogenesis

### *Angiogenesis and vasculogenesis*

Blood-vessel formation develops through two different processes: vasculogenesis and angiogenesis. Both processes are critical during a developing pregnancy. Vasculogenesis is the formation of blood vessels from precursor cells, which differentiate into endothelial cells and form new vascular networks. This form of vessel development is important during foetal organogenesis and early placental development. Angiogenesis is the formation of new vessels from existing vessels by elongation, intussusception or sprouting of endothelial cells. These multi-step processes involve activation and proliferation of endothelial cells, degradation of their basal membrane, migration through the surrounding extracellular matrix (ECM), attracting pericellular smooth muscle cells and maturation of vessels.<sup>4,5</sup> Several factors have been identified as important regulators of angiogenesis, including vascular endothelial growth factor-A (VEGF-A), placental growth factor (PlGF), the angiopoietin family and proteases. In turn, these regulators are modulated by various factors such as steroidal hormones, decidual stromal cells, immune cells and extravillous trophoblasts (EVTs).<sup>5,6</sup>

### Angiogenic factors

The best-known regulators of angiogenesis are VEGF, PlGF, the angiopoietin family and proteases. VEGF-A interacts with the two receptors, VEGFR-1 (Fms-related tyrosine kinase 1, Flt-1) and VEGFR-2 (kinase insert domain receptor, KDR), to promote endothelial cell proliferation, cell migration, apoptosis and vascular permeability.<sup>7</sup> The full-length VEGFR-1 receptor is not the predominant one in women, but a truncated soluble version named soluble Flt-1 (sFlt1) is. This molecule binds VEGF-A and PlGF and prevents their binding to the full-length receptor and inhibits their functions.<sup>5</sup> The regulators of VEGF-A expression are hypoxia, oestrogen, progesterone and the receptors Flt-1 and KDR.<sup>7–9</sup>

PlGF shares biochemical and functional features with VEGF and interacts with VEGFR-1 (Flt-1). PlGF and VEGF have synergistic effects in the induction of angiogenesis, but PlGF-induced vessels are more mature and stable than VEGF-induced vessels.<sup>10,11</sup>

The angiopoietins, and their receptor tyrosine kinase with immunoglobulin-like and EGF-like domains-2 (TIE-2), play a regulating role in angiogenesis. Angiopoietin-1 (Ang-1) maintains vessel integrity and plays a role in the later stages of vascular remodelling, which results in the development of more complex vascular networks.<sup>12,13</sup> Angiopoietin-2 (Ang-2) is a functional antagonist of Ang-1, is induced by hypoxia and leads to loosening of cell–cell interactions and allows access to angiogenic inducers such as VEGF-A.<sup>14</sup> Ang-1, together with VEGF-A, increases vessel diameter, the presence of pericytes and vascular network maturation. Ang-2 and VEGF promote longer vessels, more complex network of vessels and increased number of sprouting cells.<sup>15</sup>

Proteolysis is essential for decidual remodelling, vascularisation and migration of various cells during implantation, such as trophoblasts, uterine natural killer cells (uNKs) and endothelial cells.<sup>16–18</sup> Key regulators of proteolysis belong to the family of matrix metalloproteinases (MMPs) and to the plasmin–plasminogen system.<sup>17,18</sup>

The MMPs are a still-expanding family of 26 zinc-requiring enzymes that play a role in matrix remodelling and cell–matrix interactions. The membrane-associated localisation of membrane-type-MMPs (MT-MMPs) makes them suited for pericellular proteolysis.<sup>19</sup> MMP activity is modulated by growth factors, cytokines, plasmin, steroid hormones and several activated MMPs. Specific inhibitors are four tissue inhibitors of metalloproteinases (TIMPs).<sup>20</sup> MT1-MMP is the best-known MT-MMP, which degrades ECM and promotes cell migration, angiogenesis and tumour metastasis.<sup>19,20</sup> MT2- and MT3-MMP are less well studied and are known to be involved in cell migration and invasion. MT1-, MT2- and MT3-MMP induce angiogenesis.<sup>21</sup>

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