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Commentary

Uteroplacental Blood Flow

The Story of Decidualization, Menstruation, and Trophoblast Invasion

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Sexual reproduction in the ocean necessitates only the combination of gametes, followed by absorption of nutrients and oxygen from the surrounding watery medium. As life moved from the sea to the land, reproductive strategies required compensation for the loss of this aquatic environment. For mammals and a few other animals, the solution to this problem was the development of the placenta, the means by which the fetus extracts nutrients from its environment. As the animals that used the placenta evolved from small rodent-like creatures with short gestations to larger animals with prolonged gestations, the demands of the developing fetus grew. Whereas the placenta of the fetal pig, with a gestational period of a little less than 4 months, can extract sufficient nutrients from the mother by simple diffusion across the uterus to the placenta, the human fetus needs a far more complex uteroplacental relationship.

Several evolutionary solutions to the increased demands of fetuses can be observed.[1] One approach was a larger placenta. For example, the chinchilla has a neonatal:placental weight ratio of 30:1, whereas the human has a 6:1 ratio. Another means to greater nutritional support for the fetus was to increase the surface area of contact between fetal circulation in the placenta and maternal circulation. The pig fetus has a diffuse placenta that makes contact with the mother's uterus by a simple folded contact. The human placenta, on the other hand, has a complex villous structure, similar to the sea anemone's tentacles waving in the sea, that greatly increases the contact surface area between the mother's blood space and the fetal circulation. Despite this increased fetal-maternal contact, the system is still rather inefficient. We can quantify this by considering the amount of oxygen in the maternal blood that enters the human placenta and the amount of oxygen in the fetal blood that leaves the placenta. Maternal blood has a pO_2 of around 100, whereas the pO_2 of umbilical vein blood is around 35 to 40. This represents an efficiency of only 35 to 40%. Therefore, it also became necessary to greatly increase the flow of maternal blood into the intervillous space during pregnancy.[2,3] Without this increased maternal blood flow, preterm birth and fetal loss occur.[4] One of two mechanisms can increase maternal flow: increased total body blood flow or increased blood flow to the placental bed through the uterine spiral arteries. For the human, evolution has selected the latter mechanism, limiting the overall systemic effects that increased total body blood flow would produce.

The Nonpregnant State

In the nonpregnant state the uterine vessels carry <1% of the maternal cardiac output.[5] This is not surprising in light of the fact that a nonpregnant women needs to maintain a uterus that weighs only 50 g. At term, these same vessels must support a uterus, placenta, and fetus that can weigh up to 5000 g. How can these vessels meet such a hemodynamic challenge? Doubling the number of vessels in the uterus, for example, would have only doubled the total amount of flow into the placenta. An understanding of fluid mechanics gives us insight into how such a significant increase in total blood flow can be achieved without increasing the total number of vessels in the uterus.

Poiseuille's law of fluid flow in a cylinder states that flow is proportional to the radius to the fourth power.[6] Applying this law to the situation in the uterus, doubling the radius of a uterine vessel will increase the flow through that vessel 16 times. Comparison of vessels in the nonpregnant uterus to those at term reveals that these vessels can increase their radii by as much as tenfold. According to Poiseuille's law, this results in an increase in

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blood flow by a factor of 10,000! Clearly, the ability of uterine vessels to vary in diameter is a great advantage. The evolutionary problem then became how to convert small-caliber vessels in the nonpregnant state to large-caliber vessels during pregnancy, and then return them to their nonpregnant state and size when the pregnancy is completed. The answer lies in the relationship between the endometrium, uterine vessels, and invasive trophoblasts.

Invasive Trophoblasts, Decidualization, and Menstruation

Invasive trophoblasts are the key to the modulation of the state of the uterine vessels.[7] These unique cells leave the placenta, penetrate the endometrium and upper layers of the myometrium, selectively permeate the uterine spiral arteries, and modify these vessels to yield widened, low-resistance vascular channels that carry the markedly increased maternal blood flow to the placenta. Enacting this scenario takes a very delicate balancing of conflicting biological needs between the mother and fetus. The fetus, on the one hand, requires its invasive trophoblasts to penetrate the mother's uterus aggressively in search of vessels to modify. The mother, on the other hand, must protect herself from the invasive trophoblasts, lest they completely penetrate her uterus, causing her to hemorrhage and bleed to death.

Formation of the Invasive Trophoblasts

Traditionally, two types of trophoblasts have been described: the cytotrophoblast and the syncytiotrophoblast. With the development of reproducible methods of trophoblast culture,[8] improved markers of trophoblast synthetic activity,[9] and a deeper understanding of the functions that trophoblasts play in the uteroplacental unit,[10–14] we now can identify more specific subsets of trophoblasts. These include the undifferentiated mononuclear precursor of all trophoblast forms, the cytotrophoblast; the endocrinologically active villous syncytiotrophoblast; the junctional trophoblast that attaches the anchoring villi to the maternal decidua at Nitabuch's layer; and the invasive intermediate trophoblast that migrates into the decidua, the myometrium, and finally the spiral arteries of the uterus (Figure 1).[15]

The presence of invasive trophoblasts within the decidua and myometrium has been appreciated for some time,[16–19] but it is only relatively recently that researchers have attributed specific markers, and hence specific functional characteristics, to these cells. The first clear marker of the invasive trophoblast was described by Kurman and colleagues,[20] who demonstrated that first-trimester invasive trophoblasts react with anti-human placental lactogen antibodies. They coined the term "intermediate" invasive trophoblasts partly because of their intermediate size between cyto- and syncytiotrophoblasts. Feinberg et al[11] demonstrated that these same cells express plasminogen activator inhibitor type 1, suggesting that intermediate invasive trophoblasts may use, in addition to the collagenases, the plasminogen activator system to perform their invasive function. More recently, Zhou et al[14,21,22] have shown that as trophoblasts leave the cell columns and enter the maternal space, they lose integrins for basement membrane interactions (possibly laminin) and gain integrins for fibronectin and type I collagen interactions.

Decidualization

To protect the mother from the onslaught of invasive trophoblasts migrating toward the uterine spiral arteries, the endometrial stroma transforms itself into a dense cellular matrix known as the decidua.[23] The decidua impedes the movement of invasive trophoblasts both by forming a physical barrier to cell penetration and by generating a local cytokine milieu that promotes trophoblast attachment rather than invasion.[7,24–28] The fate of the invasive trophoblasts is, in part, likely the result of the balancing of the invasive promoting proteases made by the trophoblasts and the inhibitors of invasion made by the decidua.[7,11,29,30] Fisher and colleagues have recently proposed that local oxygen tension in the decidua and upper myometrium also plays a role in regulating trophoblast invasion by forming a cytotactic gradient within the placental bed.[31–33] Thus, the ultimate disposition of any particular invasive trophoblast appears to be determined by the sum of the proinvasive factors (intrinsic invasive proteases made by the trophoblasts and the activators and attractants within the decidua) and the inhibitors of invasion (the physical barrier and the inhibitors of invasion made by decidua).[7,27,30,34–39] Imbalances on either side of this equation can lead to abnormally limited or abnormally excessive invasion.[23,26,33,40–43]

The first signs of the decidualization reaction can be seen as early as day 23 (10 days after the peak of the luteinizing hormone surge) of the normal menstrual cycle, when the spiral arteries of the endometrium first become prominent.[44] Over the next few days, the stromal cells surrounding the spiral arteries become increasingly eosinophilic and enlarged as the differentiating effect of progesterone transforms these cells into predecidual cells.[45] The progressive decidualization of the endometrial stroma in the later part of the menstrual cycle prepares the uterine lining for the presence of the invasive trophoblasts, but simultaneously closes the door to implantation.[46,47] Though the state of the endometrium in the later part of the cycle is ideal to protect the mother from the invasive trophoblasts in the event of a pregnancy, it is entirely unsuited for implantation. But how can a nonreceptive decidualized endometrium be returned to a receptive nondecidualized endometrium if no pregnancy occurs? The solution is menstruation.[48–50]

Menstruation

Menstruation, the breakdown and sloughing of the endometrial lining at the end of a hormonally driven cycle, is seen only in higher primates and humans.[48] Interestingly, these same species are the only animals that exhibit

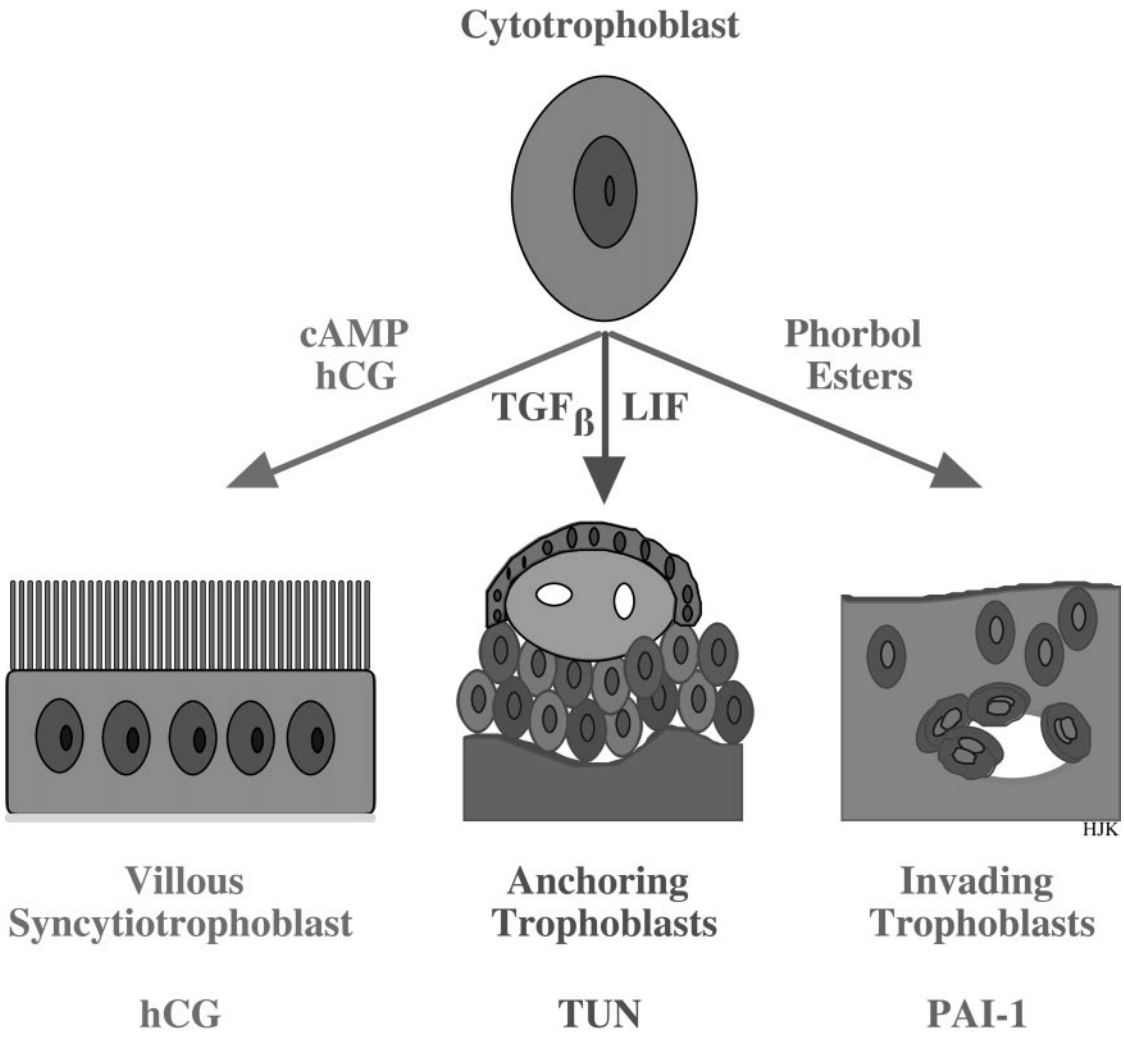

Figure 1. Pathways of trophoblast differentiation. Just as the undifferentiated basal layer of the skin gives rise to differentiated keratinocytes, the cytotrophoblast (the stem cell of the placenta) gives rise to the differentiated forms of trophoblasts. **Left:** Within the chorionic villi, cytotrophoblasts fuse to form the overlying syncytiotrophoblast. The villous syncytiotrophoblast makes the majority of the placental hormones, the most studied of which is human chorionic gonadotropin (hCG). Cyclic adenosine monophosphate (cAMP) and its analogues, and more recently hCG itself, have been shown to direct cytotrophoblast differentiation toward a hormonally active syncytiotrophoblast phenotype. **Center:** At the point where chorionic villi make contact with external extracellular matrix (decidual stromal ECM in the case of intrauterine pregnancies), a population of trophoblasts proliferates from the cytotrophoblast layer to form the second type of trophoblast, the junctional trophoblast. The junctional trophoblasts make a unique fibronectin, trophouteronectin (TUN), that appears to mediate the attachment of the placenta to the uterus. Transforming growth factor-β (TGF_β) and, more recently, leukemia inhibitory factor (LIF) have been shown to down-regulate hCG synthesis and up-regulate TUN secretion. **Right:** Finally, a third type of trophoblast, the invasive intermediate trophoblast, differentiates toward an invasive phenotype and leaves the placenta entirely. In addition to making human placental lactogen, these cells also make urokinase-type plasminogen activator and type 1 plasminogen activator inhibitor (PAI-1). Phorbol esters have been shown to increase trophoblast invasiveness in *in vitro* model systems and to up-regulate PAI-1 in cultured trophoblasts.

evidence of trophoblast invasion of uterine vessels, supporting the contention that menstruation is a biological necessity in species that exhibit trophoblast invasion. Thus, it appears that menstruation is the mechanism by which the endometrium reestablishes a receptive phase following a cycle without conception. This would help to explain the complex nature of the menstrual cycle with an estrogen-driven proliferative phase (to rebuild the lost endometrial tissue) followed by a progesterone-driven differentiation phase (that first opens the window of receptivity and later closes this window with the onset of decidualization).[51,52]

Trophoblast Invasion

Anatomy of Trophoblast Invasion

The morphological aspects of human trophoblast invasion have been examined in great detail over the last 20 years.[11,17,31,39,43,53–58] Since it is difficult to reliably obtain human material before 4 weeks of gestation, much of our morphological understanding of the earliest phases of trophoblast invasion has been extrapolated from monkey material.[59–62] Examination of monkey implantation sites has revealed that trophoblasts begin to migrate down into the maternal spiral arteries as early as 10 days

after fertilization, and at 14 days, many of the spiral arteries beneath the conceptus are totally occluded.[62] The specificity of this vascular interaction is revealed by the fact that no such invasion takes place in the veins. Do human trophoblasts behave in the same fashion? This question has been more difficult to answer, and addressing it has demanded varied approaches.

Hustin and Schaaps, using anatomical and ultrasonographic approaches, suggested that there is in fact trophoblast plugging of the maternal spiral arteries and a coincident decrease in maternal perfusion of intervillous space until 12 weeks of gestation.[63] Rodesch et al[64] then hypothesized that it is critical that maternal blood flow to the embryo be limited very early in gestation to protect the conceptus from excessively high oxygen levels during critical early stages of differentiation. This concept was supported by Coppens et al,[65] whose study of serial ultrasounds on normal pregnant women between 8 and 14 weeks showed no uteroplacental blood flow in the first trimester but a significant increase at approximately 12 weeks, which reached maximal levels at 14 weeks. More recently, Burton et al critically examined the Boyd Collection, 12 early-pregnancy hysterectomy specimens ranging from 43 to 130 days of gestation housed in the Department of Anatomy at the University of Cambridge, and showed that there was significant blockage of the maternal spiral arterioles by trophoblasts at points of contact with the intervillous space between 6 and 8 weeks, but that this blockage was gradually eliminated between 8 and 12 weeks of gestation.[66]

Despite its teleological attractiveness, the first trimester low-flow concept has not been universally accepted.[67–69] The controversy over this issue, however, seems to have been settled recently with the use of an advanced oxygen sensing probe. In this issue of *The American Journal of Pathology*, Jauniaux et al[70] report the direct documentation of a significant increase in placental intervillous oxygen tension, and hence maternal perfusion of the placenta, between 8 and 12 weeks of gestation. This article also reports that, coincident with this increased perfusion and oxygen tension within the placenta between 8 and 12 weeks, there is a corresponding increase in anti-oxidant systems, including catalase, glutathione peroxidase, and superoxide dismutase, presumably to counteract the oxidative stress of the increased intervillous perfusion and oxygen tension. If we accept trophoblast plugging and the first trimester low-flow concept, one question remains: how are the first-trimester embryo's nutritional needs met? Hustin and Schaaps suggested that the intervillous space is bathed by an acellular fluid that could be plasma filtered by the trophoblastic shell.[63] Burton and colleagues have offered another possibility (Burton GJ, Watson AL, Hempstock J, Skepper JN, Jauniaux E, submitted). By examining multiple human implantation sites preserved in the Boyd Collection,[66] these investigators noted the presence of dilated endometrial glands below openings to the intervillous spaces. It is well known that the endometrial glands of early pregnancy are characterized by hypersecretion.[71] Combining these observations, Burton and colleagues have suggested that secretions from the hypersecretory endometrial glands contribute nutrients to the embryo in the first trimester. In confirmation of this hypothesis, these workers noted in several specimens glandular secretions within the intervillous spaces near the openings of the gland mouths. Their hypothesis is not unreasonable in light of the fact that other animals, most notably the rabbit and pig, bathe their early conceptuses in endometrium-derived fluids, such as uteroglobin,[72–74] which has also been recently identified in the human.[75]

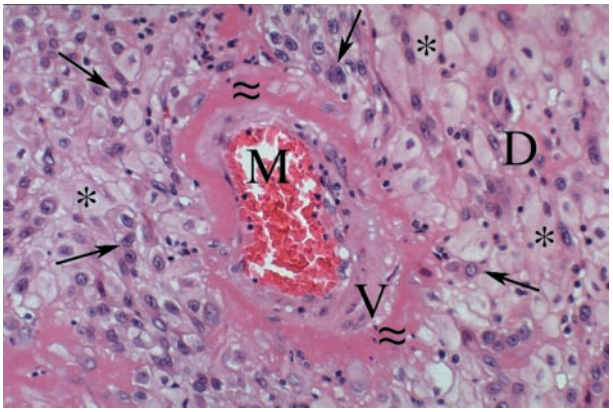

Figure 2. Invasive trophoblasts. Uterine spiral artery (V) containing maternal blood (M) from a 4-week pregnancy. The maternal endometrium (D) has become decidualized, meaning that the stromal cells have been transformed into large, pale cells (*). Infiltrating between these decidual cells are the invasive trophoblasts (some examples are highlighted by **arrows**) which have begun to modify the vessel wall (≈).

Concomitant with endovascular plugging of the maternal spiral arteries, the process of trophoblast penetration of the maternal spiral arteries and their conversion to low-resistance channels begins (Figure 2). Pijnenborg and colleagues, after examination of many placental bed biopsies from the first and second trimesters, proposed a two-wave hypothesis for trophoblast invasion: an initial interstitial invasion in the first trimester followed by endovascular invasion in the second trimester.[17,18,76,77] Matijevic et al,[78] using transabdominal color flow and pulsed Doppler imaging, showed that these changes were complete at around 17 weeks of gestation and that impedance to blood flow is lowest in the uterine arteries in the central area of the placental bed, consistent with the invasive trophoblast physiological changes seen in placental bed biopsies in that region.[18] Pijnenborg also made the observation in his studies that the interstitial trophoblasts were able to modify the maternal arteries indirectly, presumably via paracrine action, simply by surrounding these vessels.[18] One possible mediator of this action is nitric oxide (NO), which is capable of markedly vasodilating arteries and arterioles. In support of this concept, Nanaev et al,[79] from examination of the guinea pig placental bed, have suggested that NO production by invasive trophoblasts may augment maternal vascular dilation before trophoblast penetration. However, Lyall et al[57] have recently demonstrated in the human that invasive trophoblasts do not express NO synthase, raising doubts about the role of NO in maternal vascular dilation in the human. Further research will be necessary to iden-

tify what other paracrine factors, if any, may assist in the modification of the maternal spiral arteries.

Not all investigators concur on the role of invasive trophoblasts in maternal vascular remodeling. Craven et al have proposed that the maternal decidua, not the invasive trophoblasts, mediates this transformation.[80] However, given the voluminous literature supporting the role of invasive trophoblasts as the mediators of maternal vascular transformation in pregnancy, validation of the Craven hypothesis must await further observation. Despite the unresolved issues surrounding our understanding of the anatomy of trophoblast invasion, it is still far better than our understanding of the mechanisms that regulate trophoblast invasion.[17,18,76,77]

Regulation of Trophoblast Invasion

The precise mechanisms by which trophoblasts migrate from the placenta into the uterus, direct their movement toward the maternal spiral arteries, modify these vessels to form the low resistance channels needed to carry the increased maternal blood flow to the placenta, limit their invasion to the upper third of the uterus, and finally are eliminated after delivery are not known. However, some pieces of this story are understood, and, with increased investigation, we continue to make progress in this area.[7,30,81] Because trophoblast invasion appears to involve many steps, it is not surprising that trophoblasts use a variety of tools to perform these many functions.

The first challenge for the trophoblasts is to alter their differentiation pathway from that of a villous trophoblast to an anchoring trophoblast.[7,15] This process occurs, in part, due to contact of trophoblasts with the decidua, via either paracrine stimulation or direct contact with the decidual extracellular matrix (ECM). Vicovac et al have recently shown that villi incubated in direct contact with decidua form cell columns, suggesting that signals in the decidual ECM play a role in this differentiation switching,[82] although these studies do not rule out a diffusible paracrine. In fact, there is clear evidence for the presence of decidual cytokines that have a profound effect on trophoblast differentiation.[7,9] For example, transforming growth factor-β is not only made by the decidua,[25,83] it has also been shown to alter trophoblast differentiation toward an anchoring phenotype.[9,15,84] Leukemia inhibitory factor, an endometrial cytokine that has been shown to be essential for mouse implantation,[85,86] has also been identified in human endometrium[87,88] and has also been shown to alter trophoblast differentiation from a villous to an anchoring phenotype (Figure 1).[89]

Although markers of invasive trophoblasts have been described,[11,20,37,90] the factors that direct trophoblast differentiation toward an invasive phenotype have not been established. Suggested regulators of trophoblast invasion include epidermal growth factor,[36] colony stimulating factor-1,[91,92] protein kinase C activators,[93] hepatocyte growth factor,[94] and even oxygen.[31–33]

Uteroplacental Blood Flow in Pregnancy

Measurement of Blood Flow in Pregnancy

The action of the invasive trophoblasts on the maternal spiral arteries leads to a very low resistance uteroplacental circulation, which facilitates the marked increase in blood flow seen in these vessels at term. Using a variety of techniques, many groups have estimated the amount of blood flow into the gravid uterus.[95–99] This work has demonstrated that at term a woman's total blood volume increases by about 40% compared to her nonpregnant state.[100] Concomitantly, her cardiac output rises 30 to 35% and the total uteroplacental blood flow increases to about 25% of her total cardiac output.[101,102] Direct measurements of uterine blood flow in the nonpregnant state have shown a combined uterine artery flow in the follicular phase to be approximately 45 ml/minute,[103] whereas the total uterine flow at term has been estimated to be as high as 750 ml/minute,[96] representing an almost 17-fold increase in flow to the uterus. Improvements in techniques to estimate blood flow in the gravid uterus have suggested that this last calculation may be too high. Thaler et al[99] used a transvaginal duplex Doppler ultrasonography system to compare the blood flow characteristics in the ascending uterine artery before and during pregnancy in the same patient and determined that there was a 3.5-fold increase in blood flow, still a significant increase in total blood flow to the gravid uterus.

Regulation of Maternal Blood Flow to the Placenta

As Jauniaux et al[70] have shown in this issue of *The American Journal of Pathology*, maternal blood flow to the placenta appears to be restricted in the first trimester, but begins to increase in earnest at approximately 12 weeks of gestation. Beyond this jump in uteroplacental blood flow, is there evidence of additional modulation of maternal perfusion of the placenta? Studies have shown that a number of exogenous factors can modulate maternal perfusion to the placenta, but little is known about how, if at all, the uteroplacental circulation is regulated in normal pregnancy.

A significant amount of our understanding of what factors are able to alter uteroplacental blood flow comes from *in vitro* studies of isolated maternal uterine arteries and arterioles. Hansen et al[104] showed that vasoactive intestinal polypeptide and substance P are capable of dilating isolated uterine arteries. Skajaa et al[105] demonstrated the ability of Mg^{2+} ions to relax uterine arteries, confirming experimentally what has been known for many years about magnesium sulfate's efficacy in the treatment of preeclampsia.[106] Endothelin 1 and endothelin 3 were shown to be potent vasoconstrictors of uterine arteries.[107] Fried and Liu[108] confirmed endothelin's action on isolated uterine arteries and demonstrated an inhibition of ~60% of this effect with the addition of nifedipine and diltiazem, both calcium channel blockers. Kublickiene et al[109] showed a similar *in vitro* effect of isradipine on endothelin-induced uterine vessel vasoconstriction. Re-

laxin, another vasodilator, however, was shown not to be effective in dilating isolated uterine vessels *in vitro*.[110]

Other investigators have looked directly at the uteroplacental circulation to assess the role of pharmacological agents. For example, Neri et al[111] infused L-arginine, the substrate for NO, intravenously into pregnant women, assessed uteroplacental vessel pulsatile index by ultrasound, and showed a 14% decrease in vascular resistance in women with pre-existing intrauterine growth retardation. Using an oral route, Amit et al[112] showed that isosorbide dinitrate, a NO donor, had a significant effect on the resistance index in the uterine artery, independent of maternal heart rate. Low-dose aspirin, though it does not appear to alter uteroplacental blood flow,[113] may nevertheless have some benefit for patients with preeclampsia.[114]

Not all pharmacological agents are prescribed. Nicotine exposure through smoking has a significant vasoconstrictive effect on uterine vessels,[115,116] causing decreased perfusion while the mother is smoking and for 15 minutes after the completion of a cigarette.[117] Cocaine, a well known vasoconstrictor in other organ systems,[118,119] has profound effects on the uteroplacental circulation,[120] possibly through increased production of thromboxane.[121] The vasoconstrictive effect of cocaine can be so potent that it can cause severe intrauterine fetal damage and death due to a profound decrease in uteroplacental blood flow.[122–126]

In a holistic approach, Longo has looked at uteroplacental blood flow in the context of the whole pregnant patient.[127] He has proposed that there exists a feedback loop between the developing fetus, placenta, and mother, mediated by fetal steroids, that regulates the maternal cardiovascular adaptations seen in pregnancy to optimize fetal growth and development. Abnormalities in this complex network of hormonal regulation may contribute to poor fetal outcome.

Preeclampsia: Pathology of Trophoblast Invasion

Preeclampsia, the clinical state before full-blown eclampsia (seizures), is one of the toxemias of pregnancy. Its basic clinical definition is a "pregnancy-specific condition of increased blood pressure accompanied by proteinuria, edema, or both."[106] Despite the simplicity of this description of clinical signs and symptoms, the etiology of the disease has remained elusive.[22,56,128–145] Many phenomena have been investigated, but the recurring theme appears to be an abnormally low blood flow into the placenta.[19,141] One of the difficulties has been to distinguish between primary cause and secondary effects.[130–135,138,146] Part of this difficulty may be attributable to the fact that the common end result, low uteroplacental blood flow, may be caused by many primary defects.[14,22,42,147–149] Therefore, preeclampsia/eclampsia may not be a disease, but a syndrome with many causes. Significantly, one of the most frequent findings in preeclampsia is decreased or absent trophoblast invasion of the maternal spiral arteries.[19,56,150–153]

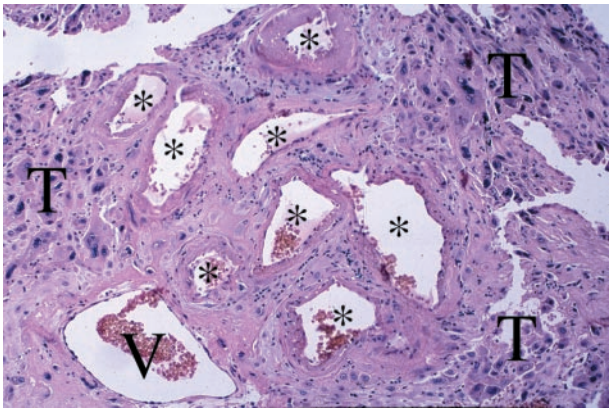

Figure 3. Failure of invasive trophoblasts to penetrate the maternal spiral arteries. Normally the invasive trophoblasts (T) infiltrate through the endo- and myometrium, reach the spiral arteries (*), and convert their muscular walls into pliant channels. In cases of preeclampsia, the trophoblasts often do not complete the final arterial penetration, possibly due to the maternal lymphocytes that commonly surround the spiral arteries. Compensatory maternal hypertension can lead to additional spiral artery damage or even occlusion. V, maternal uterine vein.

Decreased or absent trophoblast invasion may be a consequence of primary defects in the invasive trophoblasts or in the environment that the trophoblasts are attempting to invade. Studies have shown that in some cases of preeclampsia there are abnormalities in trophoblast function, including but not limited to integrin expression,[22,58] thrombomodulin gene expression,[154] glycogen metabolism,[155] decreased galactose-α-1–3 galactose expression,[156] and expression of plasminogen activator inhibitor-1.[157] In an unusual clinical presentation, preeclampsia has been associated with trisomy 13, the chromosome that carries the gene for type IV collagen.[147] Placental bed biopsy in this multiparous woman carrying a trisomy 13 fetus showed lack of trophoblast invasion of maternal spiral arteries.[147] These trophoblasts may have had difficulty invading through the maternal ECM because of increased type IV collagen production. In addition to primary trophoblast defects, many cases of preeclampsia appear to be related to maternal immunological reaction against the invading trophoblasts.[128,134] Some authors have suggested that the invasive trophoblasts exhibit "shallow invasion" in cases of preeclampsia.[42,135] However, this finding is not confirmed by clinical observation. The most common clinical finding in cases of preeclampsia is that the invasive trophoblasts have reached the vicinity of the spiral arteries, but have not penetrated them,[7,15,19] as can be seen from a placental bed biopsy in a typical case of preeclampsia (Figure 3). Failure to convert the maternal spiral arteries into low-resistance channels can induce the placenta to secrete vasoactive substances that result in maternal hypertension.[146,158] If the maternal blood pressure rises significantly, the spiral arteries can be damaged and may even become occluded, leading to placental infarction.[4,141,159]

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