# Why is placentation abnormal in preeclampsia?

Susan J. Fisher, PhD

The causes of preeclampsia remain one of the great medical mysteries of our time. This syndrome is thought to occur in 2 stages with abnormal placentation leading to a maternal inflammatory response. Specific regions of the placenta have distinct pathologic features. During normal pregnancy, cytotrophoblasts emigrate from the chorionic villi and invade the uterus, reaching the inner third of the myometrium. This unusual process is made even more exceptional by the fact that the placental cells are hemiallogeneic, coexpressing maternal and paternal genomes. Within the uterine wall, cytotrophoblasts deeply invade the spiral arteries. Cytotrophoblasts migrate up these vessels and replace, in a retrograde fashion, the maternal endothelial lining. They also insert themselves among the smooth muscle cells that form the tunica media. As a result, the spiral arteries attain the physiologic properties that are required to perfuse the placenta adequately. In comparison, invasion of the venous side of the uterine circulation is minimal, sufficient to enable venous return. In preeclampsia, cytotrophoblast invasion of the interstitial uterine compartment is frequently shallow, although not consistently so. In many locations, spiral artery invasion is incomplete. There are many fewer endovascular cytotrophoblasts, and some vessels retain portions of their endothelial lining with relatively intact muscular coats, although others are not modified. Work from our group showed that these defects mirror deficits in the differentiation program that enables cytotrophoblast invasion of the uterine wall. During normal pregnancy, invasion is accompanied by the down-regulation of epithelial-like molecules that are indicative of their ectodermal origin and up-regulation of numerous receptors and ligands that typically are expressed by endothelial or vascular smooth muscle cells. For example, the expression of epithelial-cadherin (the cell-cell adhesion molecule that many ectodermal derivatives use to adhere to one another) becomes nearly undetectable, replaced by vascular-endothelial cadherin, which serves the same purpose in blood vessels. Invading cytotrophoblasts also modulate vascular endothelial growth factor ligands and receptors, at some point in the differentiation process expressing every (mammalian) family member. Molecules in this family play crucial roles in vascular and trophoblast biology, including the prevention of apoptosis. In preeclampsia, this process of vascular mimicry is incomplete, which we theorize hinders the cells interactions with spiral arterioles. What causes these aberrations? Given what is known from animal models and human risk factors, reduced placental perfusion and/or certain disease states (metabolic, immune and cardiovascular) lie upstream. Recent evidence suggests the surprising conclusion that isolation and culture of cytotrophoblasts from the placentas of pregnancies complicated by preeclampsia enables normalization of their gene expression. The affected molecules include SEMA3B, which down-regulates vascular endothelial growth factor signaling through the PI3K/AKT and GSK3 pathways. Thus, some aspects of the aberrant differentiation of cytotrophoblasts within the uterine wall that is observed in situ may be reversible. The next challenge is asking what the instigating causes are. There is added urgency to finding the answers, because these pathways could be valuable therapeutic targets for reversing abnormal placental function in patients.

**Key words:** angiogenic factor, cytotrophoblast, endoglin, endothelial cell, HLA-G, inflammation, placenta, PLGF, pregnancy, spiral artery

Given that many central aspects of normal pregnancy remain enigmatic (eg, immune tolerance of the hemiallogeneic fetus, initiation of labor), it is not surprising that an explanation of what goes wrong in preeclampsia is a challenging undertaking. The fact that this pregnancy complication has a placental component has been known for decades.[1] The defects involve some of the most interesting and unusual cell-cell interactions in all of human biology. That these cells are from 2 individuals (a mother and her offspring) and 3 genomes (maternal, paternal, and fetal) adds even greater fascination.

Formation of the affected area, the maternal-fetal interface, is a complex process[2,3] (Figure 1). In normal pregnancy, mononuclear cytotrophoblast cells at the tips of placental anchoring villi depolarize, leaving the basement membrane to which they are attached in the rest of the placenta. The emigrating cells become strongly adherent to one another, forming aggregates that are attached at 1 end to the placenta and at the other end to the uterus. These so-called cytotrophoblast columns must have sufficient structural integrity to bridge the gap between the placenta and the uterus. Additionally, these "highways" conduct the invasive cells that breach the uterine wall, migrating as far as the inner third of the myometrium where they stop for as yet unexplained reasons.

Interestingly, some early gestation placentas have large numbers of cytotrophoblast aggregates, which are nascent columns that fail to make

From the Division of Maternal-Fetal Medicine, Center for Reproductive Sciences, Department of Obstetrics, Gynecology and Reproductive Sciences; The Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research; Department of Anatomy, University of California, San Francisco, San Francisco, CA.

Received Aug. 13, 2015; accepted Aug. 16, 2015.

Supported in part by grants from the National Institutes of Child Health and Human Development (P50 HD055764 and R37 HD076253).

The authors report no conflict of interest.

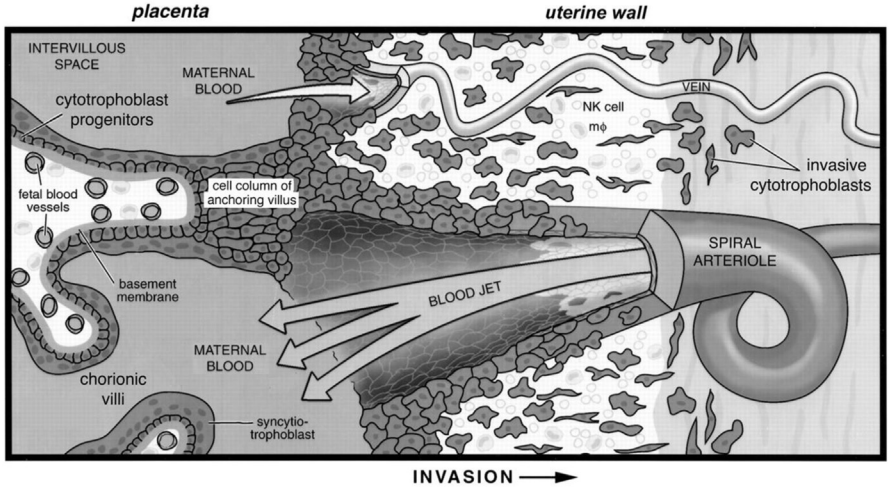
Corresponding author: Susan J. Fisher, PhD. sfisher@cgl.ucsf.edu

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2015.08.042

FIGURE 1

**Placental cytotrophoblasts invade the uterine wall where they breach veins and extensively remodel maternal spiral arterioles**




The bulk of the placenta is composed of numerous tree-like projections termed *chorionic villi* where maternal-fetal exchange occurs. These structures mediate the passage of nutrients, gases, and wastes between fetal blood, which circulates through the villous core, and maternal blood, which circulates through the intervillous space. The uteroplacental circulation is established by cytotrophoblasts that acquire an invasive/endothelial phenotype as they leave the placenta and enter the uterine wall. Differentiation begins when cytotrophoblast progenitors that reside in a single layer surrounding the stromal core of anchoring villi emigrate to form a cell column. These structures attach to the uterine wall and give rise to cells that invade the underlying decidual stroma. Invasive cytotrophoblasts breach uterine blood vessels, connecting both the arterial and the venous circulation to the intervillous space. However, once this connection is made, remodelling of the venous side is halted. By contrast, cytotrophoblasts migrate up the lumina of spiral arterioles, eventually replacing the endothelial lining of the vessels and part of the muscular wall. This process encompasses the decidual and inner third of the myometrial segments of these vessels.

*mø*, macrophage; *NK*, natural killer.

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*Fisher. Placentation in preeclampsia. Am J Obstet Gynecol 2015.*

contact with the uterine wall. Termed *cell islands*, it is unclear why they are numerous in some pregnancies and not others.[4] They may be a sign of compensatory mechanisms in response to oxidative stress because we found that the appearance of these structures correlated with maternal smoking,[5] and cigarette use is protective against preeclampsia.[6] Islands have also been reported to be increased in preeclampsia.[7] It would be interesting to know whether they are found more frequently during the early stages of placental development in pregnancies that are destined to be complicated by preeclampsia. If this is the case, they could be signs of failed compensation. At present, it is technically impossible to visualize islands in vivo because of the low resolution of the available imaging techniques. With improved methods, it may be possible eventually to make this type of correlation, which would also lend insights into the origin of this syndrome.

Once cytotrophoblasts enter the uterus, they begin the process of radically altering its structure. In many areas, the uterine luminal epithelium is lost as cytotrophoblasts track along its surface, in part, guided and fueled by the histiotrophe secretions of the glands.[8] Using cancer-like mechanisms, such as matrix metalloproteinases, cytotrophoblasts invade the epithelial basement membrane that underlies these cells.[9] In response, stromal cells of the interstitium decidualize, a differentiation process that is driven by progesterone and cyclic adenosine monophosphate.[10] Morphologic and molecular changes ensue.[11] The formerly fibroblast-like cells take on a rounded appearance as they deposit a collection of basement membrane molecules and extracellular matrix components (laminin, type IV collagen, heparan sulfate proteoglycan, and fibronectin) in a pericellular location.[12] Their protein repertoire also changes. The products include hormones such as prolactin and many immune-type molecules. In culture, medium from isolated cytotrophoblasts influences decidual stromal cell gene expression, which includes the induction of angiogenic factors, evidence of cross-talk.[13] Cytotrophoblasts also work cooperatively with decidual cells, for example, in production of a chemokine repertoire (eg, CCL3) that retains the unusual population of immune cells (primarily natural killer cells with fewer numbers of macrophages and T-cells)[14] that are recruited to the uterus during a nonpregnant cycle.[15]

Cytotrophoblast transformation of the uterine vasculature is a singular process, without direct parallels in biology or pathology. Some tumors coopt parts of this program, which is a haphazard process as compared with the precisely patterned structural changes that placental cells bring about during the first and second trimesters of pregnancy.[16] In the columns, they begin the process of vascular mimicry in which they down-regulate the production of many epithelial-like molecules that are indicative of their ectodermal origin and up-regulate numerous receptors and ligands that are typically expressed by endothelial or vascular smooth muscle cells.[17] For example, the expression of epithelial-cadherin, the cell-cell adhesion molecule that many ectodermal derivatives use to adhere to one another, becomes nearly undetectable, replaced by vascular-endothelial cadherin, which