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Why is placentation abnormal in preeclampsia?

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Abstract

The causes of preeclampsia remain one of the great medical mysteries of our time. This syndrome is thought to occur in two stages with abnormal placentation leading to a maternal inflammatory response. Specific regions of the placenta have distinct pathological 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 hemi-allogeneic, co-expressing 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 amongst the smooth muscle cells that form the tunica media. As a result, the spiral arteries attain the physiological properties that are required to adequately perfuse the placenta. 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 while 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 downregulation of epithelial-like molecules that are indicative of their ectodermal origin and upregulation of numerous receptors and ligands that are typically 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

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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 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 downregulates 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, as these pathways could be valuable therapeutic targets for reversing abnormal placental function in patients.

Keywords

cytotrophoblast; dysgenesis; placenta; preeclampsia; neoplasm; pregnancy; natural killer cells; HLA-G; angiogenic factor; anti-angiogenic factors; placental growth factor; PlGF; soluble VEGFR-1; endoglin; spiral arteries; endothelial cells; inflammation

Given that many central aspects of normal pregnancy remain enigmatic (*e.g.*, immune tolerance of the hemi-allogeneic fetus, initiation of labor), it is not surprising that explaining what goes wrong in preeclampsia is a challenging undertaking. The fact that this pregnancy complication has a placental component has been known for decades¹. The defects involve some of the most interesting and unusual cell-cell interactions in all of human biology. That these cells are from two individuals—a mother and her offspring—and three genomes—maternal, paternal and fetal—adds even greater fascination.

Formation of the affected area, the maternal-fetal interface, is a complex process (reviewed in^{2,3}; diagrammed in Figure 1). In normal pregnancy, mononuclear cytotrophoblast (CTB) 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 one end to the placenta and at the other end to the uterus. These so-called CTB 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 CTB aggregates, nascent columns that fail to make contact with the uterine wall. Termed cell islands, it is unclear why they are numerous in some pregnancies and not others⁴. They may be a sign of compensatory mechanisms in response to oxidative stress as we found that the appearance of these structures correlated with maternal smoking⁵ and cigarette use is protective against PE⁶. Islands have also been reported as increased in PE⁷. 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 PE. If this is the case, they could be signs of failed compensation. At present it is technically impossible to visualize islands *in vivo* due to the low resolution of the available imaging techniques. With improved methods, it may eventually be possible to make this type of correlation, which would also lend insights into the origin of this syndrome.

Once CTBs enter the uterus they begin the process of radically altering its structure. In many areas, the uterine luminal epithelium is lost as CTBs track along its surface, in part, guided and fueled by the histiotrophe secretions of the glands⁸. Using cancer-like mechanisms, such as matrix metalloproteinases, CTBs invade the epithelial basement membrane that underlies these cells⁹. In response, stromal cells of the interstitium decidualize, a differentiation process that is driven by progesterone and cAMP¹⁰. Morphological and molecular changes ensue¹¹. 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 location¹². Their protein repertoire also changes. The products include hormones such as prolactin and many immune-type molecules. In culture, medium from isolated CTBs influences decidual stromal cell gene expression, including the induction of angiogenic factors, evidence of crosstalk¹³. CTBs also work cooperatively with decidual cells, for example, in production of a chemokine repertoire (*e.g.*, CCL3) that retains the unusual population of immune cells (primarily NK cells with fewer numbers of macrophages and T-cells)¹⁴ that are recruited to the uterus during a nonpregnant cycle¹⁵.

CTB transformation of the uterine vasculature is a singular process, without direct parallels in biology or pathology. Some tumors coopt parts of this program, a haphazard process as compared to the precisely patterned structural changes that placental cells bring about during the first and second trimesters of pregnancy¹⁶. In the columns, they begin the process of vascular mimicry in which they downregulate the production of many epithelial-like molecules that are indicative of their ectodermal origin and upregulate numerous receptors and ligands that are typically expressed by endothelial or vascular smooth muscle cells (reviewed in¹⁷). 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 CTBs also modulate vascular endothelial growth factor ligands and receptors, at some point in the differentiation process expressing every (mammalian) family member. The end result of this dramatic transformation is a placental cell with the molecular code of arterial endothelium. Likely, it is this switch that enables their extensive interactions with spiral arteries. CTBs migrate up these vessels and replace, in a retrograde fashion, the maternal endothelial lining. They also insert themselves amongst the smooth muscle cells that form the tunica media. This process, which encompasses the decidual portions of the arteries, extends into the inner myometrial segments. As a result, the spiral arteries attain the physiological and mechanical properties that are required to adequately perfuse the placenta. In comparison, invasion of the venous side of the uterine circulation is minimal, limited to the extent required to enable blood return. Somewhat paradoxically, immune cells are also

involved in this transformation with NK cells cooperating in the process by secreting factors such as VEGF family members that play a role in the physiological transformation of the spiral arteries¹⁸.

In 1970, Brosens and colleagues described the defects in CTB patterning of the uterus that are frequently associated with PE¹. CTB invasion of the interstitial uterine compartment is frequently shallow, although not consistently so. In many locations, spiral artery invasion is incomplete. Rather than the robust process that occurs in normal pregnancy, there are many fewer endovascular CTBs. Some vessels retain portions of their endothelial lining with relatively intact muscular coats, while others are not modified. As a result, they fail to enlarge to the extent that is required to deliver an adequate supply of maternal blood to the placenta. Several vessel abnormalities are evident—acute atherosclerosis, fibrin deposits and the accumulation of lipid-laden macrophages¹⁹. In other settings, such as atherosclerosis, these so-called foam cell infiltrates are associated with inflammation²⁰, a process with interesting relevance to formation of the maternal-fetal interface and aberrations thereof.

Pathological changes are also evident in the rest of the placenta, which is comprised of the floating chorionic villi. They include fibrin deposition, formation of syncytial knots and syncytiotrophoblast sloughing, either as cells or debris²¹. The intrinsic vasculature of the placenta may also be aberrant, and signs of vascular damage apparent. These changes are thought to be secondary to reduced perfusion of the maternal-fetal interface, which can be detected long before the signs of PE appear²². However, PE is also associated with reduction in the surface area of the villi²³. The close ties between abnormalities in CTB patterning of maternal vessels, hypoperfusion of the placenta and reductions in surface area, presumed to occur in that order, are likely to set up a viscous cycle that culminates in PE. However, it is conceivable that any component of this circuit could be the driver rather than poor perfusion being the sole instigator.

None of these pathologies are unique features of PE^{24–26}. The constellation is most frequently associated with the severe early onset form of the condition rather than the appearance of this pregnancy complication at term. However, this conclusion is tempered by the fact that the precisely patterned interactions between CTBs and maternal cells that are observed earlier in gestation degrade toward term. Presumably placental connections to the uterus and its vasculature weaken in preparation for birth. For example, CTBs occupancy of the uterine arteries appears to regress²⁷. Thus, it is difficult to determine whether the defects that are the hallmark of severe PE were once present in the late onset form of this syndrome or never occurred. Regardless, it is clear that some features of PE placentas overlap other conditions. Deficient invasion of spiral arteries has long been understood to also occur in IUGR^{22, 28}. Likewise, more recent work has shown that some cases of preterm birth are also associated with deficient remodeling of the spiral arterioles²⁹. Additionally, PE-associated lesions of the spiral arteries are also not specific to PE, but rather shared among many pregnancy complications. The aberrations of the floating chorionic villi are also nonspecific. Why poor placentation leads to PE in some women and other similarly affected pregnancies end in seemingly very different complications (or with a normal birth) is a key unanswered question.

Ultimately, the answer probably lies in the different molecular pathways that are involved, which drive divergence of the phenotypes, with fetal placental and maternal factors being key players. Some of the placental defects that are associated with the severe forms of PE that occur in the late second trimester/early third trimester interval, necessitating delivery, are understood. The stereotypical process by which CTBs invade the uterine wall is an elaborate differentiation process. Every major transition is marked by dramatic changes in the molecules that the cells express. These stage-specific antigens have enabled researchers to ask whether faulty CTB invasion in PE mirrors failures in portions of the differentiation program that lead to uterine invasion. In fact, this is the case (reviewed in³⁰). In this syndrome, CTBs within the uterine wall retain portions of their original epithelial-like phenotype and fail to fully transform into vascular-like cells. We theorize that this mixed identity may hinder their interactions with uterine vessels.

Molecular defects involving other types of molecules are also apparent. Given the “two-stage” theory of PE, immune regulators are particularly relevant. Specifically, abnormal placentation, the first stage, is proposed to lead to immune activation, the second stage^{31, 32}. In this family of molecules, HLA-G is an interesting example. Among all the cells of the body, the expression of this non-classical major histocompatibility complex class I molecule is limited to invasive CTBs³³. As with the vasculogenic factors, HLA-G expression, which is normally upregulated to the full extent in the columns, is substantially diminished³⁴. Whether or how HLA-G functions in preventing maternal immune responses is not yet clear. NK cell KIR2DL4 has been implicated and refuted as the HLA-G receptor^{35–37} as well as LILRB1 and 2^{38, 39}. A detailed understanding of HLA-G functions in normal pregnancy would, in turn, enable analysis of the predicted shifts in PE, thereby providing important new insights into the immunological component of this syndrome. Of note, myriad other immune alterations have been documented in PE (reviewed in⁴⁰).

Dysregulated expression of vasculogenic and/or angiogenic factors has also been implicated in the maternal signs of PE. Several lines of evidence led investigators in this direction. For example, it has been known for some time that factors in the blood of PE patients damage cultured endothelial cells⁴¹. Given that many of the maternal signs of PE—hypertension, proteinuria and edema—can be explained by vascular damage, there has been intensive interest in identifying the factors that are involved. During the last ten years, the concept of an angiogenic imbalance has emerged (reviewed in^{26,42}). For example, in PE, a soluble VEGF receptor (sFLT1), which sequesters this ligand, and endoglin, a TGF β family member, circulate at higher levels. Conversely, PLGF levels dramatically decrease. Recreating this milieu in pregnant rodents leads to a PE-like syndrome, including hypertension, proteinuria and the kidney lesions that are typically observed in this syndrome as well as cerebral vascular changes, which may be related to the seizure component. What causes this imbalance? In some cases, the placenta appears to be the source. For example, in severe PE, isolated CTBs from the affected placentas produce higher levels of sFLT1 than control cells⁴³. Microarray analyses also show that sFLT1 and endoglin production are upregulated at the mRNA level in this syndrome⁴⁴ together with the dysregulation of other angiogenic factors⁴⁵. However, it is likely that the maternal vasculature also contributes to observed shifts in the circulating levels of these molecules.

This body of work is an interesting example of how basic research into the causes of PE can lead to changes in clinical care. With regard to prediction and diagnosis of PE, sFLT1, endoglin and PLGF levels in maternal blood have been proposed as biomarkers⁴⁶. More recently, PLGF measurements in combination with certain clinical risk factors were shown to have the highest positive predictive value at 14–16 wks of gestation. Adding measurements of sFLT, endoglin or other proposed biomarkers did not increase performance⁴⁷. However, the authors cautioned that improvements, such as the addition of other molecular measurements to the test, were needed to achieve clinical utility. With regard to treatment, there is interest in whether reducing sFLT1 levels in women with the severe early onset form of PE could safely prolong their pregnancies, leading to better outcomes.

Although less well studied in comparison to the placental defects, the uterine lining may also be abnormal in PE. The vasculature and/or any of the cells that reside in this location could be involved. For instance, PE is associated with increased maternal risk of cardiovascular disease later in life⁴⁸. Whether CTB failure to properly remodel uterine arteries is due to a damaged substrate is an interesting question. Are these faulty interactions a proxy for more widespread vessel disease that is not yet evident? The more frequent occurrence of PE in women with hypertension prior to pregnancy could be indicative of such a relationship⁴⁹. In this regard, a recent study found evidence of impaired decidual angiogenesis (and lymphangiogenesis) in these patients⁵⁰. With regard to specific cell types, molecular defects in the decidua have been described early in pregnancy before for the signs of PE appear⁵¹. Additionally, overexpression of VEGF in the decidua leads to a PE-like syndrome in mice⁵². With regard to the immune cells that occupy the uterus during pregnancy, PE-associated failure of Treg induction has been reported⁵³. Given the important role of decidual NK cells in remodeling of the spiral arteries, it is not surprising that their aberrant activation has been proposed in PE^{54, 55}.

The burning question remains as to the causes of the morphological and molecular defects summarized above. Animal models are one source of answers (reviewed in^{56,57}). There are downsides to studying PE, which is specific to human pregnancy, in animals that do not naturally develop this syndrome. Also, the placental component of PE, deficient endovascular invasion, is rarely observed in these models, probably due to the many unique aspects of the human placenta—from its cellular composition to formation of the maternal-fetal interface. However, there are also significant upsides to employing animal models in terms of drawing causal relationships.

In this context, transgenic mice are often the model system of choice, enabling functional confirmation of a molecule's role in the human disease or the discovery of new pathways. For example, when transgenic female mice expressing angiotensinogen were mated with transgenic males expressing renin, the mothers developed hypertension and proteinuria that resolved after delivery. There was histological evidence of placental damage, glomerular nephritis and myocardial hypertrophy⁵⁸. Pregnant mice that lack the expression of catechol-O-methyltransferase develop a PE-like syndrome attributable to the absence of 2-methoxyoestradiol, which inhibits angiogenesis⁵⁹. Transgenic mice were used to show the importance of balancing fetal and maternal adrenomedullin levels to correct formation of the

maternal-fetal interface^{60, 61}. Atrial natriuretic peptide-converting enzyme (*e.g.*, corin), which activates this peptide, promotes trophoblast invasion and spiral artery remodeling. In mice, lack of corin results in PE-like signs during pregnancy⁶². Pregnant MMP-9 null mice develop features of PE, including growth restriction, possibly due to deficient trophoblast invasion⁶³. Beside transgenic approaches, rodent models have been exploited in other ways. Davisson *et al.* (2002)⁶⁴ showed that mice with borderline high blood pressure, the BPH/5 strain, develop hypertension, proteinuria and glomerular nephritis during pregnancy, ultimately delivering smaller litters. Overexpression, via viral vectors, of angiogenic factors (*e.g.*, sFlt1, endoglin) in pregnant rats produces features of PE⁶⁵.

Reductions in uterine perfusion are used to model one of the causes of PE. In the 1940s, Ogden and Page sought to demonstrate direct ties between placental hypoxia and the signs of PE. Using pregnant dogs as the model, they showed that constricting the abdominal aorta between the origins of the renal and uterine arteries increased blood pressure (1940). Since then many investigators have followed in their footsteps, reproducing these results in several animal models. Some of the most convincing evidence has come from work with non-human primates. Aortic banding via the same strategy that was used in dogs results in many features of PE: hypertension, proteinuria, glomerular nephritis and increased levels of circulating sFLT1, which were attributable to increased mRNA expression by the placenta and peripheral blood mononuclear cells⁶⁶. However, The placental effects are diametrically opposite to those observed in PE. CTB invasion of the uterus is dramatically increased, reaching the periphery of the myometrium⁶⁷. Currently, the reduced uterine perfusion pressure model, developed by Granger and colleagues, is most widely used due to its high degree of reproducibility and low cost as compared to nonhuman primates^{68, 69}. Uterine perfusion is reduced ~40% by restricting blood flow at several points—the aorta above the iliac bifurcation and the right/left uterine arcades⁶¹. The sequelae include many PE features such as hypertension, proteinuria and aspects of the immunological dysregulation observed in this syndrome (*e.g.*, increases in TNF- α , IL-6, CD4+ T cells). Additionally, the production of agonistic autoantibodies to the angiotensin AT1 receptor is observed, with subsequent activation contributing to the hypertension that is a hallmark of PE⁷⁰. However, this model also fails to reproduce the placental component of PE. Why? The answer may lie in the fact that the ability of human CTBs to proliferate in response to hypoxia is largely lost after the uteroplacental circulation is established around the end of the first trimester⁷¹. This appears not to be the case in the aforementioned animal models.

Important insights into the causes of PE can also be gained from the risk factors that predispose a pregnant woman to develop this syndrome. They include a family history of this disorder, nulliparity, multiple pregnancy, previous PE, African American race, egg donation and overweight/obesity^{72, 73}. The contribution of a positive family history and PE in a prior pregnancy is taken as evidence of a genetic component as does the influence of African American race. In the latter instance, it is interesting to note the unique features of PE in this population, which may include more severe signs⁷⁴. In this context, different KIR B regions appear to protect sub-Saharan Africans and Europeans from PE⁷⁵. The risk conferred by nulliparity may reflect the beneficial effects of uterine remodeling during an initial pregnancy on subsequent placentation. Egg donation entails maternal exposure to

third party antigens with unknown consequences. Being overweight or obese, which is associated with low-grade inflammation, could also play a role at the level of metabolic dysregulation, likely an important factor in placental health⁷⁶. Of note, BMI is the most rapidly growing modifiable risk factor, having a dose-response relationship with PE and the severe forms of this syndrome. Individual disease states are also informative. Diabetes is an important risk factor reinforcing the contributions of vascular and immune alterations as well as a metabolic component to the etiology of PE. Anti-phospholipid syndromes are associated with the increased risk of PE and in its most severe forms⁷⁷. In some pregnant patients with systemic lupus erythematosus, IFN α induces an anti-angiogenic milieu, increasing the sensitivity of endothelial cells to soluble FLT-1, and contributing to the pathogenesis⁷⁸.

Where should future efforts to understand the role of placental dysgenesis in PE be directed? Work from our group revealed the surprising conclusion that CTBs isolated from the placentas of affected pregnancies normalized their gene expression over 48 h *in vitro*⁷⁹. Although caveats abound, this unexpected finding suggests that some aspects of the aberrant differentiation of CTBs within the uterine wall that is observed *in situ* may be reversible. This unexpected result points to the importance of environment factors in driving the phenotype. The next challenge is identifying what they are. It is clear that this will be no easy task as the mechanisms are doubtlessly complicated and intertwined. Given what is known from animal models and human risk factors, reduced perfusion and/or certain disease states (metabolic, immune and cardiovascular) lie upstream of the eventual derangement of the maternal-fetal interface. There are new clues to the longstanding mystery of why placentation is abnormal in PE and added urgency to finding the answers, as these pathways could be valuable therapeutic targets for reversing abnormal placental function in patients.

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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, forming 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, remodeling 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. NK, natural killer; mφ, macrophage. Figure and legend reprinted with permission from *Development*⁸⁰.

In preeclampsia, integrin $\alpha 1$ expression is strongly downregulated

Figure 2.

VE-cadherin is not detected on cytotrophoblasts (CTBs) in pre-eclamptic placentas. Sections of age-matched 26-wk control (CON, A–D) and HELLP pre-eclamptic (PE, E–H) tissue double stained for cytokeratin (CK; A, C, E, and G) and VE-cadherin (B, D, F, and H). (A, B) Control anchoring villus and placental bed. VE-cadherin staining is not detected on villous CTBs but is present on CTBs within columns and the uterine wall. (C, D) Section of a maternal spiral artery in control placental bed tissue. VE-cadherin staining is especially strong on intravascular CTBs and CTBs that are associated with the vessel wall. (E, F) Section of preeclamptic anchoring villus and placental bed. VE-cadherin staining is not detected. (G, H) Section through a small blood vessel surrounded by CTBs. VE-cadherin is not detected on vessel-associated CTBs or CTBs within the surrounding tissue. However, the endothelial cells (EC) that line the vessel did stain (arrows). Figure and legend reprinted with permission from *Journal of Clinical Investigation*⁸¹.

Symbol	Title	sPE v. nPTL Fold Change			
		0°	12°	24°	48°
GH2	growth hormone 2	9	8	8	6
CRH	corticotropin releasing hormone	10	6	3	ns
PSG11	pregnancy specific beta-1-glycoprotein 11	6	6	4	ns
OLAH	oleoyl-ACP hydrolase	7	5	4	ns
PSG7	pregnancy specific beta-1-glycoprotein 7	6	5	4	ns
PSG1	pregnancy specific beta-1-glycoprotein 1	5	5	4	ns
KISS1	KiSS-1 metastasis-suppressor	6	4	4	ns
PSG4	pregnancy specific beta-1-glycoprotein 4	5	5	4	ns
HOPX	HOP homeobox	5	5	3	ns
PLAC1	placenta-specific 1	5	4	4	ns
PSG6	pregnancy specific beta-1-glycoprotein 6	4	4	4	ns
PSG9	pregnancy specific beta-1-glycoprotein 9	4	4	4	ns
ADAM12	ADAM metalloproteinase domain 12	4	4	4	ns
SEMA3B	semaphorin 3B	4	3	3	ns
ENDOU	endonuclease, polyU-specific	4	3	3	ns
PSG5	pregnancy specific beta-1-glycoprotein 5	3	3	3	ns
TPPP3	tubulin polymerization-promoting protein family member 3	3	3	3	ns
GPC3	glypican 3	2	3	3	ns
ALPP	alkaline phosphatase, placental (Regan isozyme)	7	4	ns	ns
CYP19A1	cytochrome P450,19A1	4	4	ns	ns
FRZB	frizzled-related protein	3	3	ns	ns
EFHA2	EF-hand domain family, member A2	2	2	ns	ns
LOC284561	hypothetical protein LOC284561	5	ns	ns	ns
INHBA	inhibin, beta A	5	ns	ns	ns
PLAC4	placenta-specific 4	5	ns	ns	ns
STEAP4	STEAP family member 4	4	ns	ns	ns
C9orf27	chromosome 9 open reading frame 27	3	ns	ns	ns
MUC1	mucin 1, cell surface associated	3	ns	ns	ns
MAN1C1	mannosidase, alpha 1C1	3	ns	ns	ns

Figure 3.

Severe PE-associated aberrations in cytotrophoblast (CTB) gene expression return to control values after 48 hours of culture. RNA was collected immediately after the cells were isolated (0 hour) and after 12, 24, and 48 hours in culture. The relative gene expression levels for CTBs isolated from gestational age matched placentas of patients who delivered due to severe PE (n = 5) relative to noninfected preterm labor (nPTL) are shown as a heat map. The average fold changes for each time point (severe PE vs. nPTL) are shown. ns, no significant difference (LIMMA). Figure and legend reprinted with permission from *Journal of Clinical Investigation*⁷⁹. The data are a truncated form of the original heatmap that was published.