Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity

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While preeclampsia is complex, it masquerades as a simple syndrome defined traditionally by only 2 of its components: new hypertension and new proteinuria. It basically develops in 2 stages: an earlier placental problem (including deficient placentation) and a later maternal syndrome (systemic vascular inflammation).

First stage of preeclampsia

After implantation, the spiral arteries are invaded and plugged by cytotrophoblast until about 8 weeks of gestation. Unplugging starts where placentation is shallowest and the plugs are smallest, at the pole opposite the cord insertion; it then progresses circumferentially around the chorionic sac. At 8−9 weeks the chorionic villi are not mature enough to sustain the oxidative stress that comes with their first contact with oxygenated blood and atrophy to form the chorion laeve. In the later phases (10−12 weeks), the more mature villi withstand the oxidative stress and survive to form the definitive placenta.[1] Deep endovascular invasion of the spiral arteries by trophoblast is associated with full artery remodeling, including their deep myometrial segments. When remodeling fails, the quality of uteroplacental perfusion is altered from a constant low pressure flow to one that is more pulsatile, at higher pressure. In time this injures the chorionic villi, both hydrodynamically and biochemically (ischemia-reperfusion injury).[2]

The damaged chorionic villi then secrete various factors that together induce the end-stage maternal syndrome, which appears many months later. In this model, early unplugging, restricted spiral artery invasion, and impaired remodeling are all parts of deficient placentation, a process that begins shortly after implantation and is likely to be affected by decidual prepregnancy factors. The details, however, remain to be proven.

Second stage of preeclampsia

The clinical syndrome is caused by maternal systemic endothelial activation.[3] Endothelial activation is intrinsic to the inflammatory response and inevitably involves the maternal systemic inflammatory network including leukocyte and complement activation, the acute phase response, perturbed coagulation function, insulin resistance, and hyperlipidemia.[3] These broader responses are important in nonpregnancy in relation to the vascular inflammation of arterial disease, often exacerbated by type 2 diabetes mellitus and obesity. They also explain the extent of the changes stimulated by preeclampsia, which is much more complex than its traditional definition suggests. However, the 2-stage model, as formulated, cannot explain why fetal growth restriction is much less of a problem at term compared to early-onset disease.[4]

What links the 2 stages of preeclampsia?

The key part of the placenta is its microvillous epithelial contact with maternal blood: the multinucleated syncytiotrophoblast (STB) lining the villi. Oxidative and other stresses cause STB dysfunction, which stimulates release of multiple factors, which are not yet fully defined. Many are proinflammatory, including STB microvesicles, and some contribute to what is called angiogenic balance, as well as stimulating vascular inflammation. Angiogenesis is the formation of new vessels by sprouting from existing vessels. Many factors are involved that are both proangiogenic and antiangiogenic.[3] Two major proangiogenic players are vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).[5] Both have several isoforms. VEGF, in addition, has splice variants. This is not a simple system.[6] STB secretes PlGF and a soluble decoy receptor for VEGF and PlGF (named soluble VEGFreceptor-1 or sFlt1), which inhibits their activity. Hence sFlt1 is a major antiangiogenic factor. But these factors do not simply control angiogenesis. More important is that they maintain normal endothelial structure and function, which is probably more relevant to the pathogenesis of the preeclampsia syndrome.

Preeclampsia is characterized by excessive release from STB of sFlt1 and soluble endoglin, which is indirectly antiangiogenic. Circulating PlGF is reduced. Excessive antiangiogenic activity causes a preeclampsia-like syndrome in nonpregnant experimental animals and nonpregnant humans being treated with VEGF antagonists for cancer. Placentally induced angiogenic imbalance adds a unique twist to vascular inflammation not usually encountered in nonpregnant individuals. But the underlying processes are essentially inflammatory.

The discovery of these trophoblast-derived markers closely associated with preeclampsia[7] sparked intensive research of their use as biomarkers for diagnosis and prediction since 2003. The results have been both useful and disappointing. In general the angiogenic biomarkers work for early-onset

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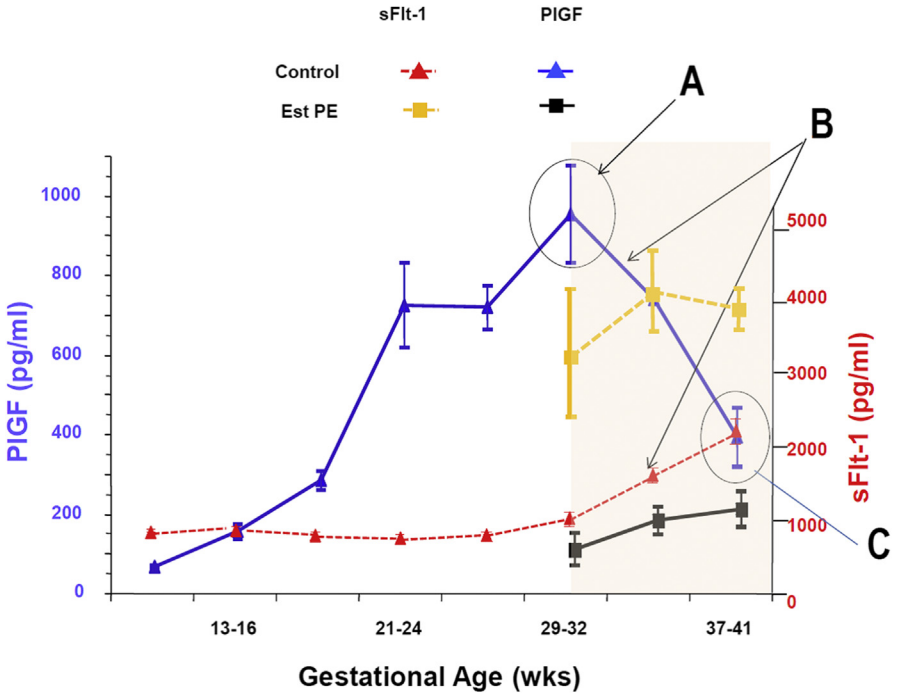
FIGURE
Markers of syncytiotrophoblast stress—positive and negative—in normal pregnancy



In normal pregnancy placental growth factor (PlGF [*blue triangles*]) rises steadily to 29—32 weeks (A) and falls thereafter until delivery (B). On the same time course, soluble vascular endothelial growth factor receptor 1 (sFlt1 [*red triangles*]) increases (B). By term, normal values of both biomarkers are close to those of established (preeclampsia (PE [*yellow and black squares*]) (C).

Adapted from Levine et al.[9]

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(delivery <34 weeks) but not late-onset preeclampsia. Attempts to find alternative factors have hitherto not been very successful. Why is this? Here we suggest that it is because, in terms of cellular mechanisms, such circulating factors are not biomarkers of preeclampsia but of STB cellular stress. Viewed from the latter perspective they increase our understanding of both preeclampsia (independently of their biomarker functions) and of problems of placental postmaturity.

Cellular stress responses, homeostasis, inflammation, and the integrated stress response

Why should maternal and fetal medicine specialists be interested in cellular stress responses? The answer is because they are key to understanding preeclampsia and a range of related placentally mediated diseases.

Cellular stress and stress responses are central to biology. All cells have homeostatic programs to survive stress. Numerous stressors elicit multiple, but highly coordinated responses (integrated stress response[4]). One stressor may stimulate multiple overlapping responses. As an example, oxidative stress response is also elicited by endoplasmic reticulum, inflammatory, and other stresses. In response to stress, cells increase the production of rescue or protective factors such as heat-shock proteins or antioxidants (a positive response), while reducing the production of others that are temporarily redundant (a negative response) to conserve energy. When it is stressed, the endoplasmic reticulum becomes overloaded with partially synthesized proteins and has to slow production (the unfolded protein response).

The Figure shows the well-known trends with gestational age of circulating sFlt1 and PlGF, in normal pregnancy or preeclampsia. We know that both these factors are mainly derived from trophoblast including STB and that in preeclampsia this villous tissue is biologically stressed. The evidence is wide-ranging. At one extreme this includes STB necrosis, apoptosis, autophagy, and excessive release of extracellular vesicles, which are all features of severely affected preeclampsia placentas. It also includes lesions of malperfusion that are better defined now histopathologically than they were previously. STB oxidative and endoplasmic reticulum stress have been documented.[4] Endoplasmic reticulum stress selectively inhibits protein synthesis, and not surprisingly, in STB, it is present in relation to fetal growth restriction and early-onset preeclampsia. sFlt1 behaves as a typical positive stress response protein in that various stressors, for example hypoxia, oxidative stress, thrombin, tumor necrosis factor-alfa, or angiotensin II, all increase sFlt1 release from trophoblast.[4]

Circulating PlGF declines in preeclampsia. There are 2 possible reasons, not necessarily mutually exclusive. The first is that the PlGF is bound to the increased amounts of