Preeclampsia is a major pregnancy complication, affecting 5% of all pregnancies, that is responsible for >50,000 maternal deaths annually. The only cure for preeclampsia is delivery, which, in early onset cases, will be a premature one. The adverse acute and chronic clinical impact on the mother and the child may be severe; the cost to society is immense. Preeclamptic women are at increased risk of cardiovascular disease later in life. The in utero environment also has significant influence on lifelong health of the offspring, and children of preeclamptic pregnancies run increased risk for disease later in life. The in utero environment also has significant influence on lifelong health of the offspring, and children of preeclamptic pregnancies run increased risk for adolescent hypertension and adult cardiovascular disease.

Preeclampsia is characterized by new hypertension and proteinuria developing in the second half of the pregnancy. The exact pathogenesis of the disease is far from understood, but it is accepted today that the placenta itself plays an essential role. Oxidative stress, circulating placental-derived factors, immunologic factors, nutrition, physical activity, and genetic variance are all important. A 3-stage preeclampsia model has been proposed where the last stage represents the clinical illness.1 Dysregulated immunologic factors (stage 1) underlying defective placentation with reduced invasion of fetal extravillous trophoblast cells and reduced remodeling of maternal uteroplacental spiral arteries (stage 2) are initial pathophysiological events. An unfavorable uteroplacental circulation ensues, with enhanced oxidative and endoplasmic reticulum stress and increased release of trophoblast-derived factors to the maternal circulation, which are thought to contribute to an excessive maternal inflammatory response and endothelial dysfunction. This induces the maternal clinical signs of preeclampsia with hypertension and proteinuria (stage 3).

Older clinicians will recall that preeclampsia used to be called “toxemia of pregnancy,” because clinicians believed that a circulating toxin was poisoning the mother. Because the condition went away after delivery, the conclusion that the poison comes from the placenta would appear most reasonable. There is no evidence today for such a “toxic substance” being sent from preeclamptic placentas, but Rajakumar et al2 present a new function for the placental “debris.” There is increasing support for the placenta’s essential role in sending important messages to the mother, messages that will increase her blood pressure. The last decade has brought a plethora of new and interesting results from preeclampsia research, particularly regarding the role of placenta-derived circulating antiangiogenic proteins in pregnancy, with a shift toward a more “antiangiogenic” state.3

The interface between the fetally derived placenta and maternal blood is formed by syncytiotrophoblasts, which is a result from the fusion of an underlying mononucleate cytotrophoblast. The syncytiotrophoblasts come into direct contact with maternal blood in the placental intervillous space (Figure). It has been known for >100 years that multinucleate fragments of trophoblast break away from the surface of the placenta and enter the maternal circulation in preeclampsia. It has more recently been shown that this also occurs in normal pregnancy but to a significantly lesser extent. Today we know that these deported trophoblast-derived structures are one part of a spectrum of traffic of material derived from the syncytiotrophoblast. This material includes trophoblast-derived, anucleate microvesicles and the much smaller trophoblast-derived nanovesicles, which together have been called placental debris.4 Apoptosis may be a mechanism regulating the shedding of subcellular debris. The words “debris” and “garbage” are, however, misleading, because all subcellular vesicles may not be waste from a tired placenta but instead be important bioactive messengers from the fetally derived placenta to the mother.

The placentally derived debris or cellular fragments in the maternal circulation have been variously named, and their names may indicate their vesicle size, such as microvesicles (ectosomes), nanovesicles (exosomes), syncytial aggregates, syncytiotrophoblast microvesicles, and so on.5 In the maternal circulation, they are believed to contribute to a generalized systemic inflammation, endothelial dysfunction, followed by hypertension and proteinuria in the pregnant woman. Although the precise mechanisms are unknown, there is evidence that the vesicles can modify the sequence of several cellular responses that contribute to the proinflammatory phenotype and impair maternal vascular dilatation.

In the present issue of Hypertension, an exciting article from Rajakumar et al2 reports novel mechanistic data on one route by which the “antiangiogenic” protein soluble fms-like tyrosine kinase 1 (sFlt1), which is generated in the placenta, enters the systemic maternal circulation. The authors show
that some placenta structures easily detach from the placenta and result in free, multinucleated fragments of 50 to 150 μm diameter that are loaded with sFlt1 protein and mRNA. The terminology of the trophoblast derived structures is not consistent in the literature, as the authors themselves highlight. The authors call these placenta structures for syncyial knots, whereas other authors argue for the exported trophoblast fragments to derive from so-called syncyial sprouts. Also, these syncytial 50- to 150-μm fragments may not be described as microparticles by other authors, because this is not consistent with the common understanding of the term, which refers to much smaller anucleate vesicles of 100 to 1000 nm in diameter. The important and novel finding in this article is the demonstration of these syncytial fragments being biologically active, because they are able to initiate transcription and translation. The authors find that ≥25% of the maternal plasma sFlt1 can be ultracentrifuged from plasma taken during the last trimester of pregnancy. This indicates vesicle-borne sFlt1, and not syncyial fragment-borne sFlt1, because syncytial fragments are filtered away in the pulmonary circulation and are vanishingly rare in peripheral blood. Further research is needed to establish whether the sFlt1 in maternal circulation may be carried by true microvesicles. Rajakumar et al also confirmed that maternal circulation and are vanishingly rare in peripheral blood. Further research is needed to establish whether the sFlt1 in maternal circulation may be carried by true microvesicles.

Figure. The intervillous space of the placenta. Maternal blood bathes the villous trees, which are covered by syncyiotrophoblasts (SYN), that are underlaid by a population of progenitor cells called cytotrophoblasts (cSTB). The syncyial knots are formed on these villi, and trophoblast-derived material is transferred into the maternal circulation. EVT indicates extravillous trophoblasts (figure from Open Access source: Zeldovich VB et al. Invasive extravillous trophoblasts restrict intracelullar growth and spread of Listeria monocytogenes. PLoS Pathog. 2011;7:e1002005. doi:10.1371/journal.ppat.1002005).
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Placenta Messages to the Mother: Not Just Debris
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