Placenta Messages to the Mother
Not Just Debris

Ralf Dechend, Anne Cathrine Staff

See related article, pp XX–XX

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 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. 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 al. 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.

The interface between the fetally derived placenta and maternal blood is formed by syncytium of multinucleated 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. 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. 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 al. 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 \( \mu \)m 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 deported trophoblast fragments to derive from so-called syncyial sprouts. Also, these syncyial 50- to 150-\( \mu \)m 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.\(^6\) The important and novel finding in this article is the demonstration of these syncyial fragments being biologically active, because they are able to initiate transcription and translation. The authors find that \( \approx \)25% of the maternal plasma sFlt1 can be ultracentrifuged from plasma taken during the last trimester of pregnancy. This indicates vesicle-borne sFlt, and not syncytial fragment-borne sFlt1, because syncyial 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 the maternal circulation may be carried by true microvesicles (of 100-1000 nm size). Rajakumar et al\(^2\) also confirmed that shedding of syncyial fragments and appearance of circulating placental microvesicles are increased in preeclampsia compared with normotensive pregnancy.

This deportation of living placental fragments and vesicles, followed by de novo translation of preexisting mRNA, represents a new mechanistic pathway for how the sFlt1 protein may appear in the maternal circulation during pregnancy. These data are the first that physically connect circulating trophoblast-derived fragments and microvesicles to antiangiogenesis. However, different mechanisms for sFlt1 export from the placenta have been suggested, including the release of matrix-bound sFlt1 by matrix-dissolving enzymes, such as heparinase.\(^7\)

Circulating microvesicles have been described in vascular diseases also outside pregnancy. The role of circulating cell microvesicles (derived from platelets and endothelial and other intravascular cells) as biological messengers in the pathophysiology of different cardiovascular disorders, including atherogenesis and atherothrombosis, has been studied recently.\(^8\) These microvesicles carry surface proteins and include cytoplasmic material of the parental cells, which are responsible for microvesicle-mediated biological effects. Approximately 25% of the procoagulant activity of stimulated platelet suspensions is associated with microvesicles. It has been shown that microvesicle shedding from the parental cells is not just a passive process induced by cellular dysfunction and apoptosis but a tightly regulated mechanism implicated in the interactions between various cell types.\(^8\) The role of microvesicles in cardiovascular disease, however far from being trophoblast derived, seems to have striking similarities to the role of microvesicles that Rajakumar et al\(^2\) present for preeclampsia. Hypertension causes increased shear stress, and microvesicles appear to be very sensitive to hemodynamic changes in hypertension. Furthermore, microvesicles represent a “link” between endothelial dysfunction and arterial thrombosis. Microvesicles released from endothelial cells in vivo have been shown to carry tissue factor on their surface. Likewise, Gardiner et al\(^9\) showed recently that syncyiotrophoblast fragments released from preeclampsia placenta showed increased tissue factor activity.

There are still many pieces of the puzzle that are missing to explain the role of placentally derived fragments and vesicles in preeclampsia development, as well as their role in normal pregnancy. How these fragments are formed is uncertain. Whether preeclampsia is merely an acceleration of processes that occur in uncomplicated pregnancies is unknown. The exact molecular pathways before the placental fragments are found in the maternal circulation are still to be discovered. The relationship between the generation of placenta structures of sprouts and knots and the circulating bioactive messages to the mother in forms of vesicles is not fully understood. We also need to learn more about any beneficial effects of the various types of trophoblast-derived circulating factors. For example, they could be important in modifying maternal immune processes during pregnancy. Recently it has been proposed that the clearance of deported trophoblast debris may be a mechanism by which the maternal immune system is maintained in a state of tolerance toward paternal antigens.\(^10\)

Rajukumar et al\(^2\) have made an important step forward in unraveling some of the complex interactions between the placenta and the mother that may contribute to development of preeclampsia and have shown us that placenta messages to the mother are certainly not just dead debris. These biological messages may have vital consequences, both for the mother and the offspring.

**Disclosures**

None.
References
Placenta Messages to the Mother: Not Just Debris
Ralf Dechend and Anne Cathrine Staff

Hypertension. published online January 3, 2012;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2012/01/03/HYPERTENSIONAHA.111.184861.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/