It has been ≈2 decades since the seminal report by Asahara et al., characterizing the isolation of endothelial progenitor cells (EPCs) from peripheral blood. Despite considerable debate on the most appropriate antigens for true identification of EPCs, several lines of evidence have emerged to show that they are recruited to sites of vascular lesions and may play a critical role in the repair of blood vessel damage, restoration of endothelial function, or neoangiogenesis after the fetal period. Although endothelial cell dysfunction is a hallmark of many cardiovascular diseases (including preeclampsia) and a growing body of literature suggests that reductions in the number and functionality of circulating EPCs play a role in adult cardiovascular diseases, whether alterations in EPCs contribute to fetal programming of disease is unclear.

Evidence suggests that circulating EPCs are reduced in preeclampsia and may contribute to endothelial dysfunction in these patients, but it remains unclear whether this represents a causal relationship in the pathophysiology of preeclampsia or is a biomarker for individuals susceptible to developing the condition. Moreover, the exact role of EPCs in developmental abnormalities and fetal programming remains unknown. Thus, the study by Muñoz-Hernandez et al. in the current issue of Hypertension seems to be the first to show that endothelial colony–forming cells (ECFCs), a subset of EPCs, are reduced in cord blood of preeclamptic pregnancies. This represents an intriguing finding and may be an important step toward identifying a putative mechanism for developmental programming in pregnancies affected by preeclampsia.

Preeclampsia is a common hypertensive disorder of pregnancy characterized by widespread endothelial dysfunction and vasoconstriction resulting from abnormalities in a variety of humoral factors, such as increased plasma soluble fms-like tyrosine kinase-1, decreased free circulating vascular endothelial growth factor (VEGF)/placental growth factor, and angiotensin type 1 receptor autoantibodies. Furthermore, preeclampsia often results in low birth weight and preterm birth, the attendant consequences of which (eg, antenatal glucocorticoid administration, neonatal oxygen therapy) contribute to long-term health risks for affected neonates. With this in mind, the absence of data on neonatal outcomes measurements is a limitation of this study by Muñoz-Hernandez et al. and further studies will be needed to determine how strong the associations are between low levels of cord blood ECFC in preeclampsia and deleterious neonatal consequences. Furthermore, the earliest gestational age in the present study (31 weeks) is on the cusp of very preterm delivery, thus the conclusions drawn are limited with respect to preeclampsia cases in which delivery is indicated very or extremely preterm (<28 weeks).

Low levels of circulating EPCs are reported from venous and cord blood in women with pregnancies complicated by preeclampsia and demonstrate increased senescence and decreased differentiation potential. Several of the prominent humoral factors known to play important roles in endothelial dysfunction and hypertension during preeclampsia may also directly contribute to the decreased EPCs and ECFCs observed in preeclamptic women and cord blood from their fetuses. The angiogenic molecule VEGF has been the subject of numerous recent studies investigating its role in blood pressure regulation during preeclampsia that has long been recognized as a critical regulator of EPC stimulation, recruitment, and differentiation. Thus, the low VEGF/placental growth factor state commonly observed in preeclampsia and idiopathic fetal growth restriction could provide a critical mechanistic link between angiogenic imbalance during pregnancy and developmental programming of diseases such as hypertension and bronchopulmonary dysplasia (BPD). Alternatively, angiotensin II signaling (via angiotensin type 1 receptor autoantibodies) and oxidative stress are recognized to contribute to cardiovascular and renal abnormalities in preeclampsia and are also reported to decrease EPC number and function in vitro and in vivo. The accompanying Figure illustrates several pathways known to contribute to hypertension in preeclampsia that may also facilitate programming effects on the fetus via reduced EPCs. Unfortunately, a limitation of the present study by Muñoz-Hernandez et al. is the lack of data on associations among the concentrations of soluble fms-like tyrosine kinase-1, VEGF, etc., in the maternal or fetal compartment and the levels of ECFCs in the cord blood. Further studies to identify how robust these putative links are will certainly be useful.

Preeclampsia is an independent risk factor for the development of BPD in survivors of preterm birth. Decreased concentrations of proangiogenic factors necessary for pulmonary vascular development are thought to play a causal role in the impaired alveologenesis associated with the development of BPD in humans and in animal models.
Cord blood levels of EPCs are reportedly reduced and have limited functional capacity in pregnancies with high risk for developing BPD. The present report suggests that circulating levels of EPCs in third trimester fetal blood may play a role in the development and health of the fetal vasculature. Furthermore, these observations suggest that adequate VEGF and angiogenic balance may be critical to recruit EPCs and promote adequate pulmonary vasculogenesis and angiogenesis and thus alveolar development. It is important to recognize an implicit assumption in this current line of thinking that cord blood ECFC levels reflect neonatal levels of ECFCs either circulating or in situ and that this is detrimental to organogenesis. This will be a challenging question to answer, but establishing relationships between other factors (soluble fms-like tyrosine kinase-1, VEGF, etc) in cord blood and amniotic fluid in relation to ECFCs may be an important step in the right direction.

The effect of gestational age on levels of EPCs in cord blood remains a point of debate. Preeclamptic pregnancies often result in preterm birth, so it is necessary to consider the normal progression of EPC levels during gestation to determine whether reduced levels in cord blood observed at delivery are because of a disease state or merely reflect gestational age. Borghesi et al10 recently reported that delivery at <28 weeks of gestation was associated with reduced cord blood ECFC levels compared with delivery after 28 weeks. Importantly, delivery at <28 weeks of gestation is considered extremely preterm and is associated with increased incidence of BPD. In contrast, Muñoz-Hernandez et al reported ECFC levels are reduced in preeclampsia when controlling for gestational age. Maternal body mass index is associated with increased levels of EPCs and preeclampsia and may also be another confounding variable. Muñoz-Hernandez et al addressed this also, reporting lower levels of ECFCs in preeclampsia independent of maternal body mass index. Nevertheless, the effect of gestational age and maternal body mass index requires further investigation in a larger patient population.

Although the pathogenesis of reduced EPCs in preeclampsia remains unknown, recent studies suggest that there may be several options (summarized in the Figure) to rescue endogenous VEGF signaling and EPC production in an effort to mitigate maternal hypertension, preterm delivery, and possibly fetal programming events. Previous studies report exercise training reduces incidence of preeclampsia and restores angiogenic balance and lowers blood pressure in the reduced uterine perfusion pressure model of preeclampsia in the rat. In addition to the many beneficial effects attributed to exercise, recent work suggests that wheel running activity increases EPC levels in the mouse. Viewed in concert with recent evidence that human alveolarization continues throughout childhood into adolescence, the possibility that an early life intervention like exercise could promote pulmonary endothelial angiogenic capacity, enhance postnatal alveolarization, and mitigate programming effects in offspring exposed to preeclampsia, neonatal hypoxia, or other pregnancy complications is truly intriguing and provides a new avenue of hope for improving outcomes of high-risk pregnancies.

Sources of Funding
This work was funded in part by grants from National Institutes of Health HL114096 and American Heart Association (AHA) SDG2600040 to J.S. Gilbert, and AHA SDG2280238 and Defense Medical Research and Development Program Grant No. W81XWH-10-2-0114/No. DM1027581 JTCG5 TATRC to A.T. Lovering.

Disclosures
None.

References


Decreased Endothelial Progenitor Cells in Preeclampsia and Consequences for Developmental Programming
Kara M. Beasley, Andrew T. Lovering and Jeffrey S. Gilbert

Hypertension. 2014;64:23-25; originally published online April 21, 2014;
doi: 10.1161/HYPERTENSIONAHA.114.03200
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 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/64/1/23

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/