American Journal of Obstetrics and Gynecology (2006) **195**, 40–9

ELSEVIER

American Journal of Obstetrics & Gynecology

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Shared and disparate components of the pathophysiologies of fetal growth restriction and preeclampsia

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Received for publication March 15, 2005; revised May 25, 2005; accepted July 13, 2005

KEY WORDS
Preeclampsia
Fetal growth retardation
Placenta
Metabolic syndrome x
Cytokines

Intrauterine growth restriction (IUGR) and preeclampsia differ in their association with maternal disease but share a similar placental pathology. Moreover, mothers who have had pregnancies complicated by preeclampsia or IUGR are at elevated later-life cardiovascular risk. Why, then, do some women develop IUGR and others develop preeclampsia? In this clinical opinion, based on a review of the literature, we hypothesize that both women experiencing preeclampsia and IUGR enter pregnancy with some degree of endothelial dysfunction, a lesion that predisposes to shallow placentation. In our opinion, preeclampsia develops when abnormal placentation, through the mediator of elevated circulating cytokines, interacts with maternal metabolic syndrome, comprised of adiposity, insulin resistance/hyperglycemia, hyperlipidemia, and coagulopathy. IUGR develops in the absence of antenatal metabolic syndrome. Among these women, the baby is affected by shallow placentation but the mother does not develop clinically apparent disease. This conceptualization provides a testable framework for future etiologic studies of preeclampsia and IUGR.
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Intrauterine growth restriction (IUGR) and preeclampsia are pregnancy-specific disorders that have in common abnormal placental implantation.[1,2] Yet the maternal manifestations of these 2 diseases are profoundly different. Early onset preeclampsia is manifest by maternal hypertension and proteinuria progressing to a systemic hypoperfusion of multiple maternal organs, and often accompanied by subnormal fetal growth[3-4]; IUGR, always involving impairment of fetal growth, has no appreciable clinical impact on the mother.[5] Fetal growth restriction appears to be accompanied by the syndrome of preeclampsia when abnormal placentation interacts with maternal constitutional factors.[6] Specifically, many mothers who develop early onset preeclampsia possess preexisting but subclinical risks for cardiovascular disease (see details below).[7] However, recent reports show that women who have had an IUGR baby also experience an elevated risk for later life ischemic heart disease that is independent of preeclampsia and also independent of many potentially confounding factors, including socioeconomic and behavioral factors.[8-11] Furthermore, before and after pregnancy, women with growth-restricted babies (without

Funding by AI44151 and AI48909 from the NIAID; HD30367 from NICHD; and HS10592 from AHRQ.

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0002-9378/$ - see front matter © 2006 Mosby, Inc. All rights reserved.
doi:10.1016/j.ajog.2005.07.049

preeclampsia) are more likely to experience elevated blood pressure.[12-14] These and other recent findings suggest that maternal susceptibility to cardiovascular risk is not unique to preeclamptic mothers with growth restricted babies. Why, then, do women with IUGR not develop preeclampsia?

In this review of existing literature, we hypothesize that both IUGR and preeclampsia arise from a maternal predisposition to endothelial dysfunction, which contributes to shallow placental implantation and results in later-life elevations in maternal cardiovascular disease. During the affected pregnancy, our review of the literature documents a chain of pathophysiologic changes arising from an endothelial-induced placental abnormality. We posit that this involves release of placental cytokines that interact with a maternal metabolic syndrome, elements of which include adiposity, insulin resistance/hyperglycemia, hyperlipidemia, coagulopathies, and maternal inflammatory mediators, to produce the accelerated disease state of preeclampsia. Possibly, infection may also accelerate cytokine release.[15,16] Absence of maternal metabolic syndrome or other exogenous inflammatory triggers, we hypothesize, precludes the mother from developing appreciable maternal pathology (Figure). This clinical opinion (the details of which are presented in the sections to follow) extends existing theories of the pathogenesis of preeclampsia[4] by suggesting a key role for maternal endothelial dysfunction, is coherent with emerging data on IUGR,[8-11] and provides a unifying pathophysiologic model for preeclampsia and IUGR.

From the outset, we note that this discussion focuses on the specific subset of IUGR that derives from placental/maternal causes and the subset of preeclampsia that results in growth-restricted babies.[17] This represents about three quarters of pregnancies complicated by IUGR and many of the preeclamptic pregnancies occurring early in gestation (eg, before 35 weeks).[18]

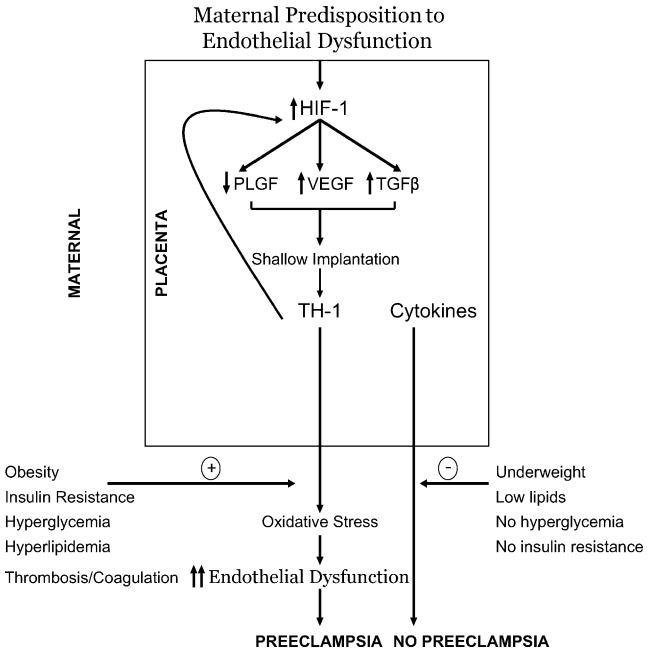

Figure Schematic of Proposed Pathogenesis of IUGR and Preeclampsia.

Evidence for endothelial dysfunction in IUGR and preeclampsia

Preexisting conditions that often involve endothelial dysfunction are common to IUGR and preeclampsia. These include hypertension,[19,20] renal disease, systemic lupus erythematosus,[21,22] and older age.[23] The relationships between these cardiovascular risk conditions and preeclampsia or IUGR are generally strong (associations often in the range of 2- to 8-fold); involve dose-response relationships between severity of preexisting disease and pregnancy-related risk; and demonstrate a temporality whereby the cardiovascular risk conditions precede pregnancy-specific disease.[19-24] All of this suggests that cardiovascular risk conditions that often involve endothelial dysfunction predispose to IUGR/preeclampsia.[25,26] Further support for this view lies in the observation that family history of hypertension, coronary heart disease, and stroke elevates preeclampsia risk.[27,28]

During pregnancy, accelerated endothelial dysfunction is a central feature of both preeclampsia and IUGR. Endothelial activators such as vascular cellular adhesion molecule-1 (VCAM), intercellular adhesion molecule-1 (ICAM), endothelin-1, cellular fibronectin, and E-selectin are elevated in the maternal serum and plasma of women with both conditions,[29-36] although activator levels in preeclampsia exceed those observed in IUGR. Markers of endothelial dysfunction are evident months before the clinical recognition of preeclampsia.[30] At 23 to 25 weeks of pregnancy, both women with IUGR and preeclampsia are more likely to demonstrate impaired uterine artery Doppler waveforms[37] and (compared with women with normal uterine artery Doppler results) to experience reduced flow mediated dilation of the brachial artery.[26] The reductions in brachial artery dilation were greater for women with preeclampsia than IUGR. This suggests that endothelial dysfunction may precede both preeclampsia and IUGR, albeit the degree of endothelial dysfunction may be greater in preeclampsia.

Women with preeclampsia have demonstrable endothelial dysfunction postpartum, as measured by noninvasive plethysmography and ultrasound.[38,39] Moreover, the high prevalence of later hypertension and cardiovascular disease among women with previous preeclampsia speaks to their tendency to ultimate endothelial disease.[8,40-44]

Mothers who have had an IUGR baby also appear to be at elevated risk for later ischemic heart disease. This

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