Hypertension in pregnancy: The endocrine and metabolic aspect

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ABSTRACT

Hypertension is the most common medical disorder complicating pregnancy. However, how pregnancy incites or aggravates hypertension remains unsolved despite decades of intensive research. Various endocrine and metabolic mechanisms have been postulated to contribute to the pathogenesis of hypertension in pregnancy. Understanding the endocrine aspect of the possible pathophysiological mechanism might open new vistas in prediction, prevention and management of this condition.

Key words: Gestational hypertension, hypertension, pregnancy

INTRODUCTION

Pregnancy hypertension complicates around 5–10% of all pregnancies. 10–15% of the half million maternal deaths that occur every year are associated with hypertensive disorders of pregnancy. However, how pregnancy incites or aggravates hypertension remains unsolved despite decades of intensive research. Indeed, hypertensive disorders of pregnancy remain among the most significant and intriguing unsolved medical problems complicating pregnancy.

ETIOLOGY AND PATHOPHYSIOLOGY

During the past centuries, a number of etiologies of hypertension in pregnancy have been suggested, but most have not stood the test of time. Preeclampsia appears to be a culmination of a number of maternal, placental, and fetal factors. This communication highlights the various endocrine and metabolic aspects of hypertension in pregnancy.

Endocrine and metabolic risk factors
Apart from obstetric risk factors such as nulliparity, extremes of maternal age, multiple gestation, and hydatidiform mole, various metabolic and endocrine conditions predispose to preeclampsia. Diabetes, chronic hypertension, and chronic renal disorders are associated with preeclampsia. Diabetes is associated with an increased risk for preeclampsia (around 20%), and diabetic microvascular disease further increases this risk. However, this estimate is far modest than the 50% incidence reported in historical cohorts. Of women with chronic hypertension antedating pregnancy, 25% develop preeclampsia. Renal insufficiency with and without diabetes also is an important risk factor.

Obesity is a risk factor for preeclampsia. Even in women of normal weight, there is a linear relationship between pre-pregnancy body mass index and the frequency of preeclampsia. The mechanism may be related to increased insulin resistance because preeclampsia is more common in another setting of increased insulin resistance: gestational diabetes.

ENDOTHELIAL DYSFUNCTION

There is a growing body of support for endothelial
dysfunction as a pathophysiologic component of preeclampsia. Endothelium profoundly influences the response of vascular smooth muscle to vasoactive agents. Nitric oxide (NO), a bioactive material produced by normal endothelium, acts synergistically with prostacyclin as a local vasodilator and inhibitor of platelet aggregation.[9] Production of NO is reduced with endothelial cell injury. It is posited that the placenta directly or indirectly produces factors that alter endothelial function. Candidate molecules include cytokines, placental fragments, free radicals and reactive oxygen species.[9]

**Metabolic Abnormalities**

Abnormalities of uric acid clearance have long been recognized as a consistent phenomenon in preeclampsia, and are regarded as a function of decreased glomerular filtration.[10] It has been recently found out that uric acid clearance changes earlier in preeclamptic pregnancy than does the glomerular filtration rate (GFR), suggesting a tubular rather than a glomerular dysfunction. Although the exact mechanism for the urate clearance change is not established, the common feature in the suggested mechanisms is decreased renal perfusion.[11]

Preeclampsia is characterized by an increase in insulin resistance. Levels of circulating lipids, which are physiologically elevated in normal pregnancy, are accentuated even further in women with preeclampsia.[12] Triglycerides and fatty acid levels are elevated, changes that antedate clinically evident disease by weeks to months.[13] Levels of the high-density lipoprotein (HDL) cholesterol are reduced in preeclamptic women,[14] whereas levels of low-density lipoprotein (LDL) are increased.[15]

**Renin–Angiotensin–Aldosterone System**

The renin-angiotensin-aldosterone system (RAAS) is important in pressure and volume regulation in normal pregnancy. Abnormalities of the RAAS have been proposed as causal factors in preeclampsia. Most investigators agree that the angiotensinogen level remains elevated in preeclampsia.[16] Despite the reduced content of the vascular compartment in preeclampsia, the intense vasoconstriction characteristic of preeclampsia results in a physiologic perception of overfill, suppressing renin release. The reduced renin activity in preeclampsia results in reduced angiotensin II and aldosterone concentrations compared with concentrations in normal pregnancy.

**Angiogenic and Antiangiogenic Proteins**

Angiogenic imbalance is used to describe excessive amounts of antiangiogenic factors that are hypothesized to be stimulated by worsening hypoxia at the uteroplacental interface. Trophoblastic tissue of women destined to develop preeclampsia overproduces at least two antiangiogenic peptides that enter the maternal circulation much before the clinical manifestations of preeclampsia.[17,18] Soluble Fms-like tyrosine kinase 1 (sFlt-1) is a variant of the Flt-1 receptor for placental growth factor (PIGF) and vascular endothelial growth factor (VEGF). Increased maternal sFlt-1 levels inactivate and decrease circulating free PIGF and VEGF concentrations, leading to endothelial dysfunction. Soluble endoglin (sEng) is a placenta-derived 65-kDa molecule that blocks endoglin, which is a co-receptor for the transforming growth factor (TGF)-β family. This soluble form of endoglin inhibits various TGF-β isotopes from binding to endothelial receptors and results in decreased endothelial NO-dependent vasodilatation. Levels of these peptides begin to increase in maternal serum, months before clinical preeclampsia develops, and they are being investigated as markers for prediction of preeclampsia.

**Conclusion**

The etiology and pathogenesis of gestational hypertension and preeclampsia remain unknown. Despite all efforts, there are no reliable tests to predict the development of preeclampsia and there are no effective therapeutic methods to prevent preeclampsia. As a result, gestational hypertension and preeclampsia remain a major obstetric problem, accounting for a large percentage of maternal and perinatal morbidities. Until more multicenter trials are performed in this area and evidence is strong enough to guide management; management of women with pregnancy hypertension will continue to be based on consensus and expert opinion. Understanding the endocrine aspect of the possible pathophysiological mechanisms might open new vistas in understanding and managing this important medical disorder complicating pregnancies.

**References**

1. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: A systematic review. Lancet 2006;367:1066-74.
2. Sibai BM, Caritis S, Hauth J, Lindheimer M, VanDorsten JP, MacPherson C, et al. Risks of preeclampsia and adverse neonatal outcomes among women with pregestational diabetes mellitus. National Institute of Child Health and Human Development
3. Chesley L. Hypertensive Disorders in Pregnancy. New York: Appleton-Century-Crofts; 1978.

4. Sibai BM, Lindheimer M, Hauth J, Caritis S, VanDorsten P, Klebanoff M, et al. Risk factors for preeclampsia, abruptio placenta, and adverse neonatal outcomes among women with chronic hypertension. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 1998;339:667-71.

5. Purdy LP, Hantsch CE, Molitch ME, Metzger BE, Phelps RL, Dooley SL, et al. Effect of pregnancy on renal function in patients with moderate-to-severe diabetic renal insufficiency. Diabetes Care 1996;19:1067-74.

6. Bodnar LM, Ness RB, Markovic N, Roberts JM. The risk of preeclampsia rises with increasing prepregnancy body mass index. Ann Epidemiol 2005;15:475-82.

7. Roach VJ, Hin LY, Tam WH, Ng KB, Rogers MS. The incidence of pregnancy-induced hypertension among patients with carbohydrate intolerance. Hypertension Pregnancy 2000;19:183-9.

8. Moncada S, Palmer RM, Higgs EA. Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacol Rev 1991;43:109-42.

9. Greer IA, Lyall F, Perera T, Boswell F, Macara LM. Increased concentrations of cytokines interleukin-6 and interleukin-1 receptor antagonist in plasma of women with preeclampsia: A mechanism for endothelial dysfunction? Obstet Gynecol 1994;84:937-40.

10. Schaffer N, Dill L, Cadden J. Uric acid clearance in normal pregnancy and preeclampsia. J Clin Invest 1943;22:201.

11. Mayn A, Hubel CA, Roberts JM. Hyperuricemia and xanthine oxidase in preeclampsia, revisited. Am J Obstet Gynecol 1996;174:288-91.

12. Hubel C, Roberts J. Lipid metabolism and oxidative stress. In: Lindheimer M, Roberts J, Cunningham F, editors. Chesley’s Hypertensive Disorders in Pregnancy. Stamford, CT: Appleton and Lange; 1999. p. 453-86

13. Lorentzen B, Endresen M, Clausen T, Henriksen T. Fasting serum free fatty acids and triglycerides are increased before 20 weeks of gestation in women who later develop preeclampsia. Hypertens Pregnancy 1994;13:103.

14. Hubel CA, Shakir Y, Gallaher MJ, McLaughlin MK, Roberts JM. Low-density lipoprotein particle size decreases during normal pregnancy in association with triglyceride increases. J Soc Gynecol Investig 1998;5:244-50.

15. Rosing U, Samsioe G, Olund A, Johansson B, Kallner A. Serum levels of apolipoprotein A-I, A-II and HDL-cholesterol in second half of normal pregnancy and in pregnancy complicated by pre-eclampsia. Horm Metab Res 1989;21:376-82.

16. Hansens M, Keirse MJ, Spitz B, van Assche FA. Angiotensin II levels in hypertensive and normotensive pregnancies. BJOG 1991;98:155-61.

17. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111:649-58.

18. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med 2006;355:992-1005.
