Gestational Hypertension and Preeclampsia: Are They the Same Disease?

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INTRODUCTION

Preeclampsia, complicating 5% to 8% of pregnancies, has been traditionally defined by an elevated blood pressure (over 140/90 mmHg on at least 2 occasions at least 6 hours apart) and proteinuria, at or beyond 20 weeks' gestation.[1,2] In 2013, the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy recommended that the definition of PE should be extended to include cases without evidence of proteinuria, provided that the hypertension is accompanied by evidence of end-organ involvement.[2] PE is associated with an increased risk of adverse pregnancy outcome, including prematurity, placental abruption, and intrauterine growth restriction.[3] In contrast, gestational hypertension is defined by an elevated BP at or beyond 20 weeks' gestation in the absence of proteinuria[1,2] and is considered to be a transient condition (Figure 1).[1] The development of proteinuria later in pregnancy changes the final diagnosis to preeclampsia. Otherwise, the final diagnosis is determined according to a re-evaluation of BP recordings at approximately three months postpartum. For women who are then normotensive (the most common scenario[4]), the final diagnosis is transient HTN of pregnancy (Figure 1). Persistence of GHTN for more than three months postpartum is consistent with a diagnosis of chronic hypertension.

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For clinicians who provide management for women with hypertension in pregnancy, several issues are of interest with respect to the importance of distinguishing between GHTN and PE. The first is the long-standing controversy of whether GHTN is an independent clinical entity or merely a mild or pre-onset form of PE. A second and more practical issue is determining the risk of progression of GHTN to PE. A third issue is quantifying the degree to which GHTN is associated with adverse pregnancy outcomes. Although GHTN is the most common form of hypertension in pregnancy,[5] most researchers have focused their efforts on PE because of its implications for maternal–fetal health, whereas information about the implications of a diagnosis of GHTN is much more limited. Herein, we attempt to summarize the most up to date information available to address these important clinical questions.

1. Is gestational hypertension an independent clinical entity or a "pre-preeclampsia" state?

We will approach this question by comparing the epidemiologic, pathologic, pathogenetic, and hemodynamic characteristics of GHTN and PE.[6] Several observations indicate that GHTN and PE have distinct epidemiologic features, including some differences in their underlying risk factors. In a large Swedish population-based study, several factors were common to the two conditions, whereas multiple pregnancy and diabetes mellitus were exclusively associated with PE.[7] A secondary analysis of the WHO Antenatal Care Trial, involving almost 40 000 women, had similar findings.[8] While primiparity and maternal respiratory disease were associated only with PE, antepartum hemorrhage (OR 1.4; 95% CI 1.1 to 1.7) and

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a history of large for gestational age newborn (OR 1.7; 95% CI 1.3 to 2.2) were limited to women with GHTN.

Several studies have addressed the risk of recurrence of GHTN and PE in a subsequent pregnancy. Overall, the risk of recurrence is higher in women with prior GHTN (20% to 47%) than in women with prior PE (5% to 10%).[9,10] Furthermore, in a large retrospective study, women with prior GHTN were more likely to experience GHTN (26%) than PE (6%) in a subsequent pregnancy, whereas women with previous PE had a similar 6% risk of recurrence of either PE or GHTN.[11]

Only two studies comparing placental pathology in pregnancies complicated by GHTN versus PE have been published, and both identified differences in placental pathology between the two conditions. Correa et al.[12] found that GHTN and PE had some placental pathologic features in common, but women with PE had placentas characterized by a higher number of syncytial knots and by differences in the size and distribution of fibrin deposits. In a more recent retrospective study of 150 women, placentas from women with PE were characterized by a trend towards higher rates of decidual vasculopathy (47% vs. 33%; $P = 0.08$) and villous infarction (50% vs. 38%; $P = 0.1$),[13] suggesting that placental ischemia is confined to PE.

Vascular biology studies have suggested that there is a contrasting pathophysiology between PE and GHTN. Noori et al. compared endothelial dysfunction and angiogenic markers in women with GHTN and PE.[14] They followed 159 women from 10 weeks' gestation to three months postpartum. Flow-mediated dilatation (a sonographic measure of vascular endothelial function) was abnormal only in those with PE; women with GHTN had flow-mediated dilatation that was similar to non-hypertensive control subjects. Similarly, maternal blood levels of the anti-angiogenic markers sFlt1 and sEng were elevated only in women with PE.[14] In concordance with these findings, Verlohren et al. reported that the ratio of the anti-angiogenic marker sFlt1 to the pro-angiogenic marker PlGF (sFlt1/PlGF) was significantly elevated in women with PE, but not in those with GHTN, again suggesting that only PE is characterized by an anti-angiogenic milieu.[15] Furthermore, in a prospective study of 110 pregnant women, levels of endothelial microparticles (associated with endothelial cell damage) were found to be significantly higher in women with PE but not GHTN.[16] Khalil et al. compared the effect of treatment with α-methyldopa on the levels of angiogenic markers in women with GHTN and PE.[17] They found that α-methyldopa treatment was associated with a significant reduction (50%) in sFlt1 and sEng levels in women with PE, but not in women with GHTN (whose levels were much lower). In a recent study, Sandrim et al. found differences in the polymorphism of vascular endothelial growth factor between women with GHTN and women with PE, raising the possibility of differences in the genetic predisposition for each.[18] Another group found that the sensitivity of platelets to prostaglandin E_1 was decreased only in women with PE, suggesting that platelet activation is a characteristic specific to PE and not GHTN.[19] In a recent meta-analysis of the use of antiplatelet agents for the prevention of PE, it was found that these agents decreased the risk of PE in either moderate- or high-risk women, while such a beneficial effect in the prevention of GHTN was observed only among high-risk women.[20] Collectively, these findings suggest that endothelial dysfunction and an imbalance between pro- and anti-angiogenic factors are characteristics specific for PE but not for GHTN.

Pathophysiologic changes are different in women with PE and those with GHTN, including decreased maternal blood volume among the former.[21] In addition, there is recent evidence that non-invasive hemodynamic measures, such as changes in cardiac output and peripheral vascular resistance, precede the onset of severe PE by several weeks in high-risk women.[22,23] Such a tool may also be useful for predicting PE in the specific group of women with new onset of isolated hypertension in pregnancy, since the detection of increased total peripheral resistance and increased cardiac output in these cases may reflect the presence of early stage PE rather than GTHN.

Another aspect to be considered is the long-term outcome following pregnancies complicated by GTHN or PE. Most of the studies conducted to date have been focused on the long-term risks of cardiovascular morbidity and mortality. Most of these studies have found that women with either GHTN or PE are at increased risk of chronic hypertension, ischemic heart disease, cerebrovascular disease, and venous thromboembolism, although the risk was higher for women with severe PE than for women with GHTN.[24–27] One important limitation of many of these studies, most of which are based on coding diagnoses, is that a considerable proportion of women with GTHN may in fact have had undetected chronic hypertension.

ABBREVIATIONS

BP	blood pressure
GHTN	gestational hypertension
HTN	hypertension
PE	preeclampsia
PlGF	placental growth factor
sEng	soluble endoglin
sFlt	soluble fms-like tyrosine kinase-1