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Progression of gestational hypertension to pre-eclampsia: A cohort study of 20,103 pregnancies

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ABSTRACT

Objective: To investigate previously un-identified risk factors for the progression of gestational hypertension (GH) to pre-eclampsia (PE) by considering Grade III preterm placental calcification (PPC) and excessive weight gain (≧10 kgw) at 28 weeks gestation.

Methods: At a tertiary teaching hospital, obstetric ultrasonography was performed at 28 weeks gestation to establish a diagnosis of grade III PPC. Weight gain during pregnancy was recorded at the same time. Pregnancies complicated with chronic hypertension, major fetal congenital anomalies, termination before 24 weeks gestation, and abortion before 20 weeks gestation were excluded.

Results: In the current cohort study, 20,103 pregnancies were enrolled and categorized as normal blood pressure (NBP; n = 18,223) and GH-PE (n = 1880) groups. According to severity of the diseases, the GH-PE group was further divided into GH (n = 1088), PE (n = 792), and severe PE (n = 209) groups. There were significant differences between the NBP and GH-PE groups in known factors, including maternal age, BMI, parity, multifetal pregnancy, and co-morbidities (all $p < 0.001$), all of which increased the risk for GH-PE. Regarding the progression of GH to PE and severe PE, there was a much greater frequency of excessive weight gain (51.2% and 49.0% vs. 9.3%) or PPC (63.2% and 61.6% vs. 12.1%) in the severe PE and PE groups than the GH group. Logistic regression analysis revealed that PPC was a significant and independent risk factor for progression of GH to PE (OR, 13.71; 95% CI, 10.25–18.33) and severe PE (OR, 12.42; 95% CI, 8.89–17.35), as well as excessive weight gain during pregnancy (OR, 8.92; 95% CI, 6.67–11.92 and OR, 10.25; 95% CI, 7.30–12.40).

Conclusion: Being a pathologic implication, the presence of PPC or excessive weight gain during pregnancy may precede progression of GH, and can serve as a warning or marker that requires closer surveillance for maternal and fetal well-being. Based on the findings of PPC and excessive weight gain, at-risk pregnant woman should be counseled to facilitate early intervention or referral. In addition, avoiding excessive weight gain during pregnancy may reduce the risk of GH progression to PE.

1. Introduction

Hypertension is the most common medical complication during pregnancy. Approximately 70% of women diagnosed with a hypertensive disorder during pregnancy will have gestational hypertension/pre-eclampsia (GH-PE), with an overall prevalence of 6%–8% [1]. GH or pregnancy-induced hypertension is defined as a systolic blood pressure (BP) ≧ 140 mmHg or a diastolic BP ≧ 90 mmHg after 20 weeks gestation without the presence of proteinuria [1,2]. Some women with GH will subsequently progress to PE, which affects 2%–5% of pregnancies and is traditionally diagnosed by the combined presentation of high BP, proteinuria, and maternal organ dysfunction [1–5]. PE is one of the main causes of maternal and perinatal morbidity and mortality, especially in low- and middle-income countries [2,3,5], and predisposes mothers and fetuses to cardiovascular disease later in life [3,4,6–8]. Common risk factors for GH-PE include older age, first pregnancy, pre-pregnancy obesity (elevated body mass index [BMI]), multiple pregnancy, polycystic ovarian syndrome, chronic kidney disease, overt

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diabetes, and autoimmune disease [1–4,9–15]. However, in clinical practice these risk factors only predict 30% of women who will develop PE [3,4]. Although the two-stage model of abnormal trophoblastic invasion during placental implantation, placenta ischemia and subsequent endothelial injury have been established as the possible etiology and pathophysiology underlying GH-PE [1,2,4,9,16,17], the progression from GH to PE remains unexplained. Elevated BP may be related to decreased production of nitrogen oxide [2] or kynurenine [18], both of which may have an effect on vascular endothelium and serve as vasodilators, or be related to decreased production of carbon monoxide (CO) [19], which can promote angiogenesis, inhibit inflammation, relax vessels, and has been reported to protect against PE [20]. Nevertheless, much remains unknown regarding the mechanism and the marker of progression from hypertension alone to maternal renal and other organ dysfunction. Multiple biophysical and biochemical methods of detection or screening, including maternal uterine artery Doppler (UAD) in the first or second trimester [4,6,10,16,21–25], fetal aorta intima media thickness (aIMT) [6], placental volume on 3D ultrasound [16], and biochemical markers [9–11,15], have been developed for predicting PE among low-risk populations. Combinations of these methods appear promising [9–11,15,22–25], but need validation before use in clinical practice [3,10]. In women with GH alone, pregnancy outcomes are similar or superior to that seen in women with normotensive pregnancies [1]. In contrast, maternal and perinatal morbidities are substantially increased in women with PE [1]. If clinicians are able to identify biomarkers or a prodrome in gravidas with GH before progression to PE, perhaps counseling can be provided and enhanced monitoring or earlier intervention can be offered to reduce the occurrence of PE and associated complications.

Grade III placental calcification, characterized by significant formation of indentations or ring-like structures within the placenta (Fig. 1) [26], is often found in term pregnancies and regarded as a physiologic aging process without clinical significance [26–28]. However, the presence of calcifications before 36 weeks gestation (preterm placental calcification [PPC]) may represent an unusual change. McKenna et al. [29] reported that grade III placental calcification at 36 weeks gestation is associated with pregnancy-induced hypertension and fetal growth restriction. Furthermore, we have found that PPC is a major risk factor for adverse maternal and neonatal outcomes [30,31]. Our studies revealed that in both low-risk and high-risk pregnancy populations, the antenatal finding of PPC is significantly associated with preterm delivery, low birth weight, low Apgar scores, and neonatal death [30,31]. In another study, we showed that PPC is an independent risk factor for stillbirth [32], and may be an early pathologic placental change during pregnancy. If PE represents a late and more serious consequence following placental insufficiency [2,4,16], we postulate that PPC may represent incipient changes in PE via a similar mechanism. In addition, pre-pregnancy obesity is a well-known risk factor for GH-PE [2–4,10,12–15] as a result of increased chronic inflammation, oxidative stress, and evoked endothelial cell activation within the placenta [33–35]. Based on similar reasoning, can excessive weight gain during pregnancy result in an increased rate of progression to PE? Thus, the purpose of this study was to investigate the previously un-identified risk factors for the progression of GH to PE in consideration of the aforementioned risk factors for hypertensive disorders in pregnancy.

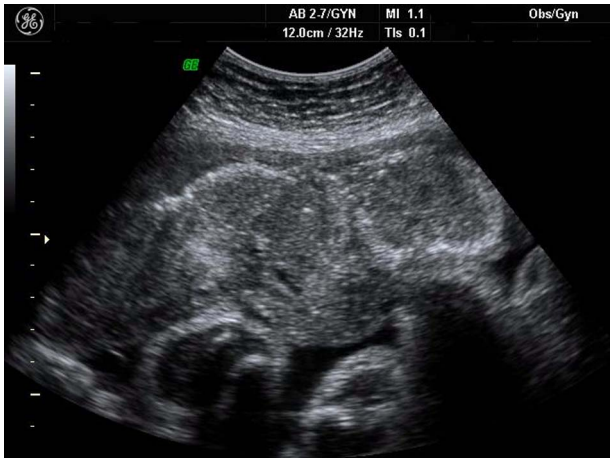

Fig. 1. Grade III placental calcification according to the Grannum classification. Diffuse echogenic lines (indentations) extending from the chorionic plate to the basal layer are noted.

2. Materials and methods

2.1. Study design and sample

This cohort study was conducted in a tertiary teaching hospital with an average of ≥200 deliveries per month. The hospital provides both routine obstetric clinics (available to all women) for general low-risk pregnancies and special obstetric clinics (requiring referral) for high-risk pregnancies. All pregnant women can receive prenatal care in the routine obstetric clinics without referral. All women with antenatal complications noted in the routine clinics or at other hospitals are transferred to our special obstetric clinics for evaluation and management. The study was approved by the local Institutional Review Board of the hospital, followed the principle of the declaration of Helsinki, and met the guidelines of the responsible governmental agency.

All of the pregnant women were screened by obstetric ultrasonography at 28 weeks gestation to establish the diagnosis of PPC. Grade III placental calcification is defined by the presence of echogenic indentations extending from the chorionic plate to the basal layer, thus dividing the placenta into discrete components resembling cotyledons. All ultrasound examinations were performed using a Voluson 730 (GE Medical Systems, Zipf, Austria) equipped with a 2.8–10-MHz transabdominal transducer by one qualified obstetrician to avoid inter-observer bias. All images were further reviewed by another experienced obstetrician to ensure the accuracy of the diagnosis.

All pregnancies of women in the obstetric clinics were considered for the study. Initial screening was performed to exclude pregnancies in women who did not deliver at our hospital, or had missing data in the medical record. Because the current study focused on progression of GH to PE, women who had chronic hypertension before 20 weeks gestation were not included and evaluated in the study. In addition, pregnancies with major fetal congenital anomalies, termination before 24 weeks gestation, and abortion before 20 weeks gestation, all of which can affect the mother and fetus and confound the analysis, were excluded from this study. Except for the women who met the aforementioned exclusion criteria, all pregnancies were enrolled by means of an ordinary survey rather than obstetrician's preference (highly-selected samples) to decrease selection bias.

Basic information, including age, BMI, and parity, all of which are known to be potential risk factors for GH and PE, as well as general medical history and co-morbidities, were retrieved at the first antenatal visit. Ascertainment of smoking during pregnancy, identification of multi-fetal pregnancy or major congenital fetal anomalies based on ultrasonography, and diagnoses of chronic or gestational hypertension and gestational diabetes were made on subsequent visits between 8 and 28 weeks gestation. The diagnosis of chronic hypertension is made by a history of pre-existing hypertension prior to pregnancy or ≧2 measurements of hypertension noted at 8, 12, and 16 weeks gestation. The diagnosis of GH is made by ≧2 measurements of hypertension (systolic BP ≧ 140 mmHg or diastolic BP ≧ 90 mmHg) noted at 20, 24, and 28 weeks gestation without proteinuria and not treated using anti-hypertensive medications, including hydralazine, methdopa, and nifedipine. According to *Williams Obstetrics*, PE is defined as hypertension during pregnancy (BP ≧ 140/90 mmHg) accompanied by proteinuria