

Pregnancy Induced Hypertension (PIH): Beyond Pregnancy

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Contrary to the belief that pregnancy-induced hypertension (PIH, or hypertensive disorders of pregnancy, HDP) and preeclampsia are benign conditions that do not extend harm past pregnancy, the evidence is growing that preeclampsia is a risk factor for future cardiovascular disease. Although most published data indicate that proteinuria during pregnancy does no long-term harm to the mother, more recent reports indicate that preeclampsia increases the risk of cardiovascular disease [1-7]. Recent research published on November 11, 2019 in the Journal of the American College of Cardiology confirms that women who have gestational hypertension or preeclampsia in at least one pregnancy have a higher cardiovascular risk than women without this history [7]. The authors conclude that a history of HDP can be a useful tool to refine atherosclerotic cardiovascular disease risk assessments. They added "However, future risk of diverse cardiovascular conditions in asymptomatic middle-aged women with prior HDP remains unknown". They also argued that "hypertensive disorders of pregnancy are associated with accelerated cardiovascular aging and more diverse cardiovascular conditions than previously appreciated", and commented that the cardiovascular risk after HDP is largely but not solely mediated by the development of chronic hypertension. Many authorities now regard pregnancy as a "cardiovascular stress test" [8].

There are also reports that preeclampsia increases the risk of end-stage kidney disease later in life [9,10]. Thus, in addition to being a "cardiovascular stress test", pregnancy can also be regarded as a "renal stress test". Urinary protein excretion increases in normal pregnancy from <150 mg/day in non-pregnant individuals to up to 300 mg/day in pregnancy. Thus, the threshold of abnormal protein excretion for the diagnosis of preeclampsia is >300 mg/24 hours or more than 2+ by dipstick testing according to the American College of Obstetrics and Gynecology Guidelines [11].

A recent study published by Kristensen et al in April 2019 reached the same conclusion. They investigated associations between pre-eclampsia and later risk of kidney disease using a nationwide register-based cohort in Denmark [12]. All women with at least one pregnancy lasting at least 20 weeks between 1978 and 2015 were included. Their main outcome measure was the hazard ratios comparing rates of kidney disease between women with and without a history of pre-eclampsia, stratified by gestational age at delivery and estimated the hazard ratio using Cox regression. They concluded

that "Pre-eclampsia, particularly early preterm pre-eclampsia, was strongly associated with several chronic renal disorders later in life." They commented that "More research is needed to determine which women are most likely to develop kidney disease after pre-eclampsia, what mechanisms underlie the association, and what clinical follow-up and interventions (and in what timeframe post-pregnancy) would be most appropriate and effective" [12].

Current ACOG criteria for the diagnosis of preeclampsia include increased blood pressure ($\geq 140/90$ mm Hg) on at least 2 occasions 4 hours apart, after 20 weeks of gestation, and either proteinuria (≥ 300 mg on a 24-hour urine collection, UPCR ≥ 0.3 mg/mg, or urine protein dipstick reading $> 2+$ if quantitative testing is not available) or, in the absence of proteinuria, high blood pressure plus another severe feature such as renal impairment, low platelets, impaired liver function, pulmonary edema, or cerebral or visual symptoms [11,13]. As we previously reported, blood pressure tends to dip in the first trimester of pregnancy [14]. Because current guidelines define preeclampsia as blood pressure $> 140/90$ mmHg, increases from its nadir to this value may represent an unrecognized prodrome. Further work is needed to define the normal blood pressure for the pregnant women.

Because the definition of hypertension in pregnancy ($> 140/90$ mmHg) is not evidence-based, and because blood pressure normally falls by up to 10-15 mmHg early in pregnancy, the threshold for the definition of hypertension in pregnancy should probably be lower than the threshold in non-pregnant individuals [14]. Defining hypertension as $> 140/90$ mmHg does not facilitate the early detection of HDP, and the current ACOG criteria for the diagnosis of preeclampsia impede early detection of the condition [11,13]. Early diagnosis of preeclampsia is critical since occurrence early in pregnancy is associated with a worse prognosis. Currently, the only recommended screening tool is blood pressure measurement throughout pregnancy, which does not detect early preeclampsia; more screening tools are needed. Also, current management of preeclampsia remains supportive targeting the prevention of complications by lowering blood pressure and preventing seizures by using antihypertensive medications and/or magnesium sulfate. Delivery remains the only definitive treatment for pre-eclampsia, and low dose aspirin remains the recommended approach for the prevention of pre-eclampsia in women at high risk.

From the work published by Maynard et al. we learned that placental ischemia is an early event, leading to placental production of a soluble factor(s) that cause maternal endothelial dysfunction resulting in the hypertension, proteinuria, and edema [15]. The authors confirmed that placental soluble FMS-like tyrosine kinase 1 (sFlt1), an antagonist of VEGF and placental growth factor (PlGF), is up regulated in preeclampsia, leading to increased systemic levels of sFlt1 that decrease after delivery. They also demonstrated that increased circulating sFlt1 in patients with preeclampsia is associated with decreased circulating levels of free VEGF and PlGF, resulting in endothelial dysfunction in vitro that can be rescued by exogenous VEGF and PlGF. They further reported that the administration of sFlt1 to pregnant rats induces hypertension, proteinuria, and glomerular endotheliosis, the classic lesion of preeclampsia. They concluded that excess circulating sFlt1 contributes to the pathogenesis of preeclampsia. Today, 16 years after their report, we are still seeking novel treatment(s) and diagnostic tools like sFlt1 biomarker that can be used in clinical practice. This goal is difficult to achieve due to multiple factors including medicolegal issues hindering clinical trials recruitment and the nature of the therapies. However, their work paved the road for the development of more novel therapies for the early diagnosis and management of preeclampsia. More research work is needed in genomic, proteomic, clinical and epidemiological domains.

In May, 2019 Phipps, et al. published their work regarding the pathogenesis, novel diagnostics, and therapies for pre-eclampsia [16]. They reported that “In the past decade, the discovery and characterization of novel antiangiogenic pathways have been particularly impactful both in increasing understanding of the disease pathophysiology and in directing predictive and therapeutic efforts”. Their review included the pathogenic role of antiangiogenic proteins released by the placenta in the development of pre-eclampsia, and novel therapeutic strategies directed at restoring the angiogenic imbalance observed during pre-eclampsia.

Finally, nephrologists usually do not obtain in-depth into obstetrical histories on their patients. Since emerging reports indicate that preeclampsia is a risk factor for future chronic kidney disease, it is imperative and prudent that they obtain a comprehensive obstetrical history, and screen those with a history of preeclampsia [17].

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