Chronic hypertension and superimposed preeclampsia: screening and diagnosis

Nikos A. Kametas, MD, FRCOG; Diane Nzelu, MD, MRCOG; Kypros H. Nicolaides, MD, FRCOG

Superimposed preeclampsia complicates about 20% of pregnancies in women with chronic hypertension and is associated with increased maternal and perinatal morbidity compared with preeclampsia alone. Distinguishing superimposed preeclampsia from chronic hypertension can be challenging because, in chronic hypertension, the traditional criteria for the diagnosis of preeclampsia, hypertension, and significant proteinuria can often predate the pregnancy. Furthermore, the prevalence of superimposed preeclampsia is unlikely to be uniformly distributed across this high-risk group but is related to the severity of preexisting endothelial dysfunction. This has led to interest in identifying biomarkers that could help in screening and diagnosis of superimposed preeclampsia and in the stratification of risk in women with chronic hypertension.

Elevated levels of uric acid and suppression of other renal biomarkers, such as the renin-angiotensin aldosterone system, have been demonstrated in women with superimposed preeclampsia but perform only modestly in its prediction. In addition, central to the pathogenesis of preeclampsia is a tendency toward an antiangiogenic state thought to be triggered by an impaired placenta and, ultimately, contributing to the endothelial dysfunction pathognomonic of the disease. In the general obstetrical population, angiogenic factors, such as soluble fms-like tyrosine kinase-1 and placental growth factor, have shown promise in the prediction of preeclampsia. However, soluble fms-like tyrosine kinase-1 and placental growth factor are impaired in women with chronic hypertension irrespective of whether they develop superimposed preeclampsia. Therefore, the differences in levels are less discriminatory in the prediction of superimposed preeclampsia compared with the general obstetrical population.

Alternative biomarkers to the angiogenic and renal factors include those of endothelial dysfunction. A characteristic of both preeclampsia and chronic hypertension is an exaggerated systemic inflammatory response causing or augmenting endothelial dysfunction. Thus, proinflammatory mediators, such as tumor necrosis factor-α, interleukin-6, cell adhesion molecules, and endothelin, have been investigated for their role in the screening and diagnosis of superimposed preeclampsia in women with chronic hypertension. To date, the existing limited evidence suggests that the differences between those who develop superimposed preeclampsia and those who do not are, as with angiogenic factors, also modest and not clinically useful for the stratification of women with chronic hypertension.

Finally, pro—B-type natriuretic peptide is regarded as a sensitive marker of early cardiac dysfunction that, in women with chronic hypertension, may predate the pregnancy. Thus, it has been proposed that pro—B-type natriuretic peptide could give insight as to the ability of women with chronic hypertension to adapt to the hemodynamic requirements of pregnancy and, subsequently, their risk of developing superimposed preeclampsia. Although higher levels of pro—B-type natriuretic peptide have been demonstrated in women with superimposed preeclampsia compared with those without, current evidence suggests that pro—B-type natriuretic peptide is not a predictor for the disease.

The objectives of this review are to, first, discuss the current criteria for the diagnosis of superimposed preeclampsia and, second, to summarize the evidence for these potential biomarkers that may assist in the diagnosis of superimposed preeclampsia.

Key words: angiogenic factors, biomarkers, cell adhesion molecules, chronic hypertension, cytokines, diagnosis, endothelial dysfunction, endothelin, fetal growth restriction, interleukin-6, placental growth factor, pregnancy, proteinuria, pro—B-type natriuretic peptide, renin-angiotensin-aldosterone system, screening, soluble fms-like tyrosine kinase-1, superimposed preeclampsia, tumor necrosis factor-α, uric acid, uterine artery Doppler velocimetry, uteroplacental dysfunction, vascular cell adhesion molecule

Introduction

Chronic hypertension complicates 1% to 2% of pregnancies and constitutes the highest risk factor, among maternal characteristics and medical history, for the development of preeclampsia (PE).[1] Superimposed PE occurs in about 20% of women with chronic hypertension, and after adjustment for confounding factors, the risk of preterm superimposed PE is 5 to 6 times higher in women with chronic hypertension than in those without.[1] In superimposed PE, compared with PE alone, there is a higher incidence of adverse maternal and perinatal

From the Antenatal Hypertension Clinic, Division of Women's Health, Fetal Medicine Research Institute, King's College Hospital, London, United Kingdom (Drs Kametas, Nzelu, and Nicolaides); and Harris Birthright Research Centre for Fetal Medicine, Fetal Medicine Research Institute, King's College Hospital, London, United Kingdom (Drs Kametas and Nicolaides).

Received July 16, 2020; revised Nov. 16, 2020; accepted Nov. 16, 2020.

The authors report no conflict of interest.

No funding was received for this article.

This paper is part of a supplement.

Corresponding author: Nikos A. Kametas, MD, FRCOG. nick.kametas@kcl.ac.uk

0002-9378/$36.00 • https://doi.org/10.1016/j.ajog.2020.11.029

outcomes, including preterm delivery, birth of small-for-gestational-age neonates, operative delivery, admission to the neonatal intensive care unit (NICU), and pulmonary edema.[2,3]

The objectives of this review are, first, to discuss current criteria for the diagnosis of superimposed PE in women with chronic hypertension and, second, to summarize evidence for potential biomarkers that may assist in the diagnosis of superimposed PE.

Diagnostic Criteria for Chronic Hypertension

Outside of pregnancy, recommendations for the diagnosis of stage 1 and 2 hypertension were recently updated with new blood pressure (BP) thresholds (Table 1).[4] In pregnancy, hypertension is defined using the traditional cutoff of ≥140/90 mm Hg measured on ≥2 consecutive occasions at least 4 hours apart.[5] Thus, chronic hypertension in pregnancy refers to hypertension either predating pregnancy or occurring in the first 20 gestational weeks.[5] In 90% of those with chronic hypertension, the cause is primary and accompanied by a family history or lifestyle factors, such as obesity.[4] Less commonly, chronic hypertension is secondary to underlying renal, vascular, or endocrine disorders.[4]

TABLE 1
A comparison of the 2014 and 2017 classifications of BP in adults according to the Joint National Committee on the prevention, detection, evaluation, and treatment of high blood pressure

BP category	Systolic BP (mm Hg)		"and" or "or"	Diastolic BP (mm Hg)	
	2014	2017		2014	2017
Normal BP	<120	<120	and	<80	<80
Elevated BP	120–139	120–129	and[a]	80–89	<80
Stage 1 hypertension	140–159	130–138	or	90–99	80–89
Stage 2 hypertension	≥160	≥140	or	≥100	≥90

BP, blood pressure.

[a] The 2014 guidelines are "and/or" for the diagnosis of elevated BP.

Kametas. Screening and diagnosis of superimposed preeclampsia. Am J Obstet Gynecol 2022.

Diagnostic Criteria for Superimposed Preeclampsia

The diagnosis of PE has traditionally relied on the combination of proteinuria and hypertension.[6] There are 3 main limitations to this definition in the case of superimposed PE in women with chronic hypertension. First, in women with chronic hypertension, the high BP predates the pregnancy. Second, proteinuria can coexist in about 10% of women with chronic hypertension. This is most commonly because of nephrosclerosis caused by long-standing hypertension and, less commonly, because of the presence of secondary causes, such as diabetes or renal disease.[7,8] Third, this definition does not take into account that PE is a multiorgan disease such that even in the absence of proteinuria, hypertensive women with evidence of renal, hepatic, hematological, or neurologic involvement are at a substantial risk of morbidity.[9] In acknowledgment of this, the American College of Obstetricians and Gynecologists (ACOG) and the International Society for the Study of Hypertension in Pregnancy (ISSHP) broadened their definition of PE to encompass any evidence of end-organ dysfunction as summarized in Table 2.[10,11] Thus, the diagnosis of superimposed PE is based on the new development of thrombocytopenia, liver dysfunction, renal insufficiency, or symptoms suggestive of PE in women with chronic hypertension (Table 2).

Inclusion of blood pressure and proteinuria

The fact that women with chronic hypertension have hypertension predating pregnancy and proteinuria can be present in the first trimester of pregnancy[7] potentially renders BP redundant and proteinuria less sensitive for the diagnosis of superimposed PE. However, there are studies indicating a relationship between BP control and increase in proteinuria and the development of superimposed PE.[12–14] These studies raise the question of whether BP parameters along with serial quantification of proteinuria should be included in screening for or in the definition of superimposed PE.

There is good evidence that the incidence of preterm superimposed PE is related to first-trimester BP control in women with chronic hypertension. A study of 586 women with chronic hypertension reported that the incidence of preterm superimposed PE as defined using the ISSHP criteria (2014) was 7% in those who presented in the first trimester of pregnancy with a BP of <140/90 mm Hg without antihypertensive medications and 20% in those with a BP of ≥140/90 mm Hg despite antihypertensive medications.[15] In addition, 2 further studies reported a 2- and 4-fold increase in the risk of superimposed PE in women with chronic hypertension and a mean arterial BP of ≥95 mm Hg in the first trimester of pregnancy[13] and a diastolic BP of ≥100 mm Hg in the second trimester of pregnancy, respectively.[14] Although models incorporating BP parameters along with maternal characteristics perform modestly in the prediction of superimposed PE,[13,16] the performance is equivalent, if not better, to those incorporating biomarkers discussed later in the review (Table 3).

It has been argued that women with chronic hypertension and uncontrolled BP should be managed in the same way as those with superimposed PE.[17] One cohort study that included 142 women with chronic hypertension defined uncontrolled BP as ≥ 140/90 mm Hg despite antihypertensive use demonstrated an increase in preterm delivery before 34 weeks from 1.3–50% when compared with those reaching the target threshold of <140/90 mm Hg.[18] Similarly, a cohort study of 120 women with chronic hypertension but defining uncontrolled BP as ≥160/110 mm Hg irrespective of antihypertensive medications demonstrated higher rates of preterm birth, low birthweight, extremely

TABLE 2
Comparison of the previous and updated diagnostic criteria for preeclampsia: NHBPEP, ACOG, and ISSHP

Condition	NHBPEP (1990–2000)	ACOG (2002)	ISSHP (2001)	ACOG (2013)	ACOG (2018)	ISSHP (2014)	ISSHP (2018)
Hypertension	De novo hypertension occurring beyond 20 weeks gestation plus at least one of the following:						
Proteinuria	• ≥300 mg/d • ≥1+ dipstick	• ≥300 mg/d • On 2 occasions ≥1+ dipstick	• ≥300 mg/d • ≥1+ dipstick	• ≥300 mg/d • ≥1+ dipstick • PCR ≥0.3 mg/dL	• ≥300 mg/d • ≥2+ dipstick • PCR ≥0.3 mg/dL	• ≥300 mg/d • ≥2+ dipstick	• ≥300 mg/d • ≥1+ dipstick • PCR ≥0.3 mg/dL
Renal insufficiency				• 1.10 mg/dL • Doubling in serum creatinine	• 1.10 mg/dL • Doubling in serum creatinine	• 1.02 mg/dL	• 1.02 mg/dL
Abnormal liver function				• >2×normal	• >2×normal	• >2×normal	• ALT and AST>40 IU/L
Thrombocytopenia				• PLT <100×10^9/L	• PLT <100×10^9/L	• PLT <150×10^9/L	• PLT <150×10^9/L
Uteroplacental insufficiency						• Fetal growth restriction	• Fetal growth restriction[a] • Abnormal umbilical artery Doppler analysis • Stillbirth
Symptoms of PE				• Neurologic complications • Pulmonary edema	• Neurologic complications • Pulmonary edema	• Neurologic complications	• Neurologic complications

ACOG, American College of Obstetricians and Gynecologists; *ALT*, alanine transaminase; *AST*, aspartate aminotransferase; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *NHBPEP*, National High Blood Pressure Education Program; *PCR*, protein creatinine ratio; *PE*, preeclampsia; *PLT*, platelet.

[a] The ISSHP guidelines (2018) have recommended that signs of uteroplacental insufficiency should not be included in the diagnosis of superimposed PE.

Kametas. Screening and diagnosis of superimposed preeclampsia. Am J Obstet Gynecol 2022.

low birthweight, and admission to the NICU than those with a BP of <160/110 mm Hg.[19] Despite this apparent relationship between BP and adverse pregnancy outcomes, studies have failed to identify BP thresholds that are clinically relevant in differentiating chronic hypertension from superimposed PE. For this reason, although uncontrolled BP may warrant further investigation for underlying superimposed PE, current guidelines advise against incorporating this as a defining feature.[10]

Renal insufficiency and proteinuria are still considered the hallmark features of PE, complicating 75% of those diagnosed with the disease.[20] Women with chronic hypertension and significant proteinuria in the first trimester of pregnancy have a 4-fold increase in the risk of superimposed PE as defined using the National High Blood Pressure Education Program criteria.[7] Furthermore, the rate of superimposed PE increased with increasing baseline levels of 24-hour protein excretion.[7] Further research is needed in women with chronic hypertension to ascertain whether quantification of baseline proteinuria and serial assessment thereafter would facilitate a more comprehensive stratification and identify those at particularly high risk of developing adverse outcomes.

Previously, in women with chronic hypertension and first-trimester proteinuria, superimposed PE was defined arbitrarily as a "sudden increase," or a clear change, in the level of baseline proteinuria.[5] This has now been removed from the criteria as studies have indicated that in previously normotensive women who develop PE, changes in the degree of proteinuria has little correlation with adverse maternal or perinatal outcomes.[21,22] However, little is known as to the importance of an escalation in urinary protein excretion during pregnancy in women with baseline proteinuria and chronic hypertension. In small cohorts of women with chronic kidney disease, a more than 2-fold increase in baseline proteinuria is associated with a higher likelihood of developing superimposed PE as defined using the ISSHP criteria (2014) than those who have stable levels of urinary protein excretion throughout

TABLE 3
Summary of the studies evaluating the performance of biomarkers in the prediction of superimposed preeclampsia in women with chronic hypertension

Author, y	Biomarker	n[a]	TM	Definition	AUC (95% CI)	Sensitivity	Specificity	LR+	LR−	PPV	NPV
BP											
Rovida et al, 2012[120]	MAP	100	First	ISSHP (2002)	0.47 (0.34–0.59)	—	—	—	—	—	—
Rovida et al, 2012[120]	MAP	100	Second	ISSHP (2002)	0.66 (0.55–0.76)	—	—	—	—	—	—
Lecarpentier et al, 2010[13]	MAP	211	Second	ACOG (2002)	0.72	82.00	55.00	1.81 (0.83–3.98)	—	—	—
Lecarpentier et al, 2010[13]	SBP	211	Second	ACOG (2002)	0.68	—	—	—	—	—	—
Lecarpentier et al, 2010[13]	DBP	211	Second	ACOG (2002)	0.69	—	—	—	—	—	—
Giannubilo et al, 2006[16]	24 h DBP	223	Second	NHBPEP (1990)	—	95.00	89.00	—	—	—	—
Giannubilo et al, 2006[16]	24 h SBP	223	Second	NHBPEP (1990)	—	88.00	92.00	—	—	—	—
Renal markers											
Bramham et al, 2020[66]	ACR	90	First	ISSHP (2014)	0.87 (0.73–1.00)	—	—	—	—	—	—
Bramham et al, 2020[66]	ACR	90	Second	ISSHP (2014)	0.79 (0.57–1.00)	—	—	—	—	—	—
Parrish, 2010[32]	Uric acid	73	Third	NHBPEP (1990)	—	—	—	1.61 (0.19–14.00)	0.97 (0.88–1.10)	—	—
Salahuddin et al, 2007[27]	Uric acid	19	Third	ACOG (2002)	0.70	68.00	78.00	3.1	0.40	—	—
August et al, 2004[31]	Uric acid	110	Second	—	—	—	—	—	—	—	—
Lim et al, 1997[30]	Uric acid	23	Third	NHBPEP (1990)	—	54.00	78.00	—	—	—	—
Angiogenic factors											
Bramham et al, 2020[66]	PIGF	90	Second	ISSHP (2014)	0.78 (0.55–1.00)	—	—	—	—	—	—

Kametas. Screening and diagnosis of superimposed preeclampsia. Am J Obstet Gynecol 2022.

(continued)

TABLE 3
Summary of the studies evaluating the performance of biomarkers in the prediction of superimposed preeclampsia in women with chronic hypertension
(continued)

Author, y	Biomarker	n[a]	TM	Definition	AUC (95% CI)	Sensitivity	Specificity	LR+	LR−	PPV	NPV
Nzelu et al, 2020[12]	PlGF	650	First	ISSHP (2014)	0.58 (0.54–0.61)	—	—	—	—	—	—
Nzelu et al, 2020[12]	sFlt-1	650	First	ISSHP (2014)	0.55 (0.51–0.58)						
Sunderji et al, 2010[83,b]	sFlt-1	457	Second and third	ACOG (2002)	0.98 (0.95–1.00)	96.00	4.00	—	—	—	—
Sunderji et al, 2010[83,b]	PlGF	457	Second and third	ACOG (2002)	0.98 (0.96–1.00)	96.00	5.00	—	—	—	—
Salahuddin et al, 2007[27]	sFlt-1	19	Third	ACOG (2002)	0.94	84.00	95.00	16.00	0.20	—	—
Salahuddin et al, 2007[27]	sEng	19	Third	ACOG (2002)	0.87	84.00	79.00	4.00	0.20	—	—
Zeeman et al, 2003[123]	Inhibin A	61	Second and third	NHBPEP (2000)	—	38.00	95.00	7.60	0.65	—	—
Inflammatory markers											
Nzelu et al, 2020[107]	VCAM	650	First	ISSHP (2014)	0.54 (0.49–0.59)	—	—	—	—	—	—
Uterine artery Doppler											
Rovida et al, 2012[120]	PI	100	Second	ISSHP (2002)	0.75 (0.65–0.83)	—	—	—	—	—	—
Roncaglia et al, 2008[121]	RI	182	Second and third	ISSHP (2002)	—	75.00	70.00	0.36	2.50	28.00	95.00
Giannubilo et al, 2006[16]	RI	223	Second	NHBPEP (1990)	—	69.00	87.00	—	—	—	—
Zeeman et al, 2003[123]	PI	56	Second	NHBPEP (1990)	—	33.30 (0.80–90.60)	77.10 (62.70–88.00)	—	—	8.30 (0.20–38.50)	94.90 (82.70–99.40)
Frusca et al, 199[122]	RI	78		ACOG (2002)	—	76	84.00	—	—	64.00	91.00

ACOG, American College of Obstetricians and Gynecologists; *AUC*, area under the curve; *CI*, confidence interval; *DBP*, diastolic blood pressure; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *LR−*, negative likelihood ratio; *LR+*, positive likelihood ratio; *MAP*, mean arterial pressure; *NHBPEP*, National High Blood Pressure Education Program; *NPV*, negative predictive value; *PI*, pulsatility index; *PlGF*, placental growth factor; *PPV*, positive predictive value; *RI*, resistance index; *SBP*, systolic blood pressure; *sEng*, soluble endoglin; *sFlt-1*, soluble fms-like tyrosine kinase-1; *VCAM*, vascular cell adhesion molecule.

[a] Only studies analyzing women with chronic hypertension separately from other high-risk cohorts included; [b] Preeclampsia before 37 weeks of gestation.

Kametas. Screening and diagnosis of superimposed preeclampsia. Am J Obstet Gynecol 2022.

pregnancy (3% vs 70%).[23] Therefore, as with uncontrolled BP, larger studies are needed to determine whether changes in proteinuria in women with chronic hypertension may be used as a diagnostic criterion of superimposed PE.

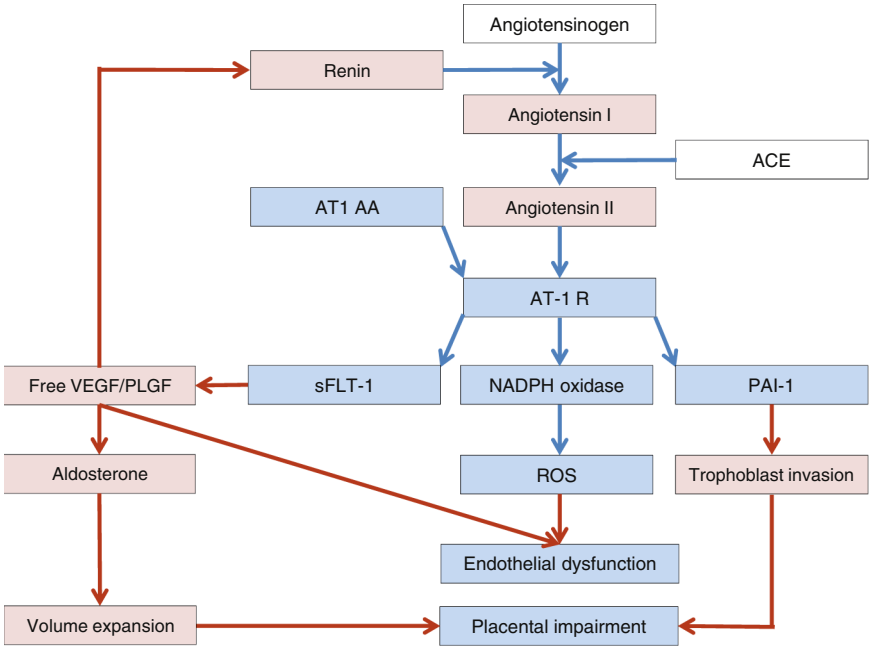
Inclusion of uteroplacental dysfunction

The ISSHP criteria for the diagnosis of PE, both in the 2014[10] and 2018[24] guidelines, are similar to those of the ACOG but include uteroplacental insufficiency (Table 2).[10] Such inclusion could be problematic in pregnancies complicated by chronic hypertension in which the distribution of birthweight adjusted for gestational age at delivery is skewed to the left of the distribution for uncomplicated pregnancies.[1] This suggests that chronic hypertension per se is associated with uteroplacental insufficiency. Consequently, in the updated ISSHP guidelines (2018), uteroplacental dysfunction has been removed as a criterion for superimposed PE in women with chronic hypertension.[24]

Screening and Diagnosis of Superimposed Preeclampsia: Biomarkers

The objective of first-trimester screening is to identify women with chronic hypertension at particularly high risk of superimposed PE and reduce the impact of the disease through therapeutic strategies, such as BP optimization. The objective of screening for superimposed PE in the late second and third trimesters of pregnancy is to predict the onset of the disease within the subsequent few weeks; earlier diagnosis of the clinical signs of the disease could potentially improve perinatal and maternal outcomes through interventions, such as timely delivery. The alterations in renal, angiogenic, inflammatory, and cardiac biomarkers observed before and at the time of the clinical onset of the disease have led to interest in their potential to differentiate between those with chronic hypertension who are at risk of developing superimposed PE and those who are likely to remain uncomplicated. Table 3 provides a summary of the studies evaluating the performance of these biomarkers in the prediction of superimposed PE in women with chronic hypertension.

FIGURE 1
Interaction between renin-angiotensin-aldosterone system and angiogenic factors in preeclampsia.



Renin cleaves angiotensinogen to produce Ang I, which is further converted to Ang II by ACE. In pregnancies complicated by PE, levels of renin, Ang I and II are reduced. Despite lower levels, women with PE demonstrate increased sensitivity to the vasoconstricting effects of Ang II, partly due to increased peripheral expression of its AT-1 R. Autoantibodies that stimulate the AT-1 receptor (AT 1-AA) have also been reported in women with PE. AT-1 AA activation of AT-1 R up-regulates the production of sFLT-1, PAI-1 and NADPH oxidase. sFLT-1 inhibits VEGF, which further suppresses renin and leads to a reduction in VEGF-mediated production of aldosterone. NADPH oxidase enhances the production of ROS and PAI-1 decreases trophoblastic invasion causing endothelial dysfunction and placental impairment, respectively. In comparison to normal pregnancy, white squares indicate no differences, blue squares indicate increased levels and pink indicate suppressed levels in pregnancies complicated by PE. Adapted from Verdonk et al.[34]

ACE, angiotensin converting enzyme; *Ang*, angiotensin; *AT-1 R*, AT-1 receptor; *PAI-1*, plasminogen activator inhibitor 1; *PE*, preeclampsia; *ROS*, reactive oxygen species; *VEGF*, vascular endothelial growth factor.

Kametas. Screening and diagnosis of superimposed preeclampsia. Am J Obstet Gynecol 2022.

Renal biomarkers

The correlation between elevated levels of serum uric acid and PE has been known for decades. The proposed reasons for hyperuricemia in women with PE include decreased renal tubular excretion because of a reduction in glomerular filtration rate, observed in many cases of PE, and increased oxidative stress triggered by an impaired placenta.[25] Hyperuricemia has been implicated in the pathophysiology of PE through its inhibition of nitric oxide–dependent trophoblastic invasion causing placental impairment and up-regulation of proinflammatory mediators and reactive oxygen species causing endothelial dysfunction.[25] However, as a predictor of adverse maternal and fetal outcomes in the general obstetrical population, serum uric acid performs poorly.[26] Nonetheless, several investigators have examined the clinical utility of uric acid in differentiating chronic hypertension from superimposed PE.[27–32] One study found no difference in the levels of uric acid between normotensive controls and women with chronic hypertension irrespective of whether they developed

superimposed PE or not.[28] This is contrary to 3 other studies that have reported elevated levels of uric acid from the first trimester of pregnancy to the postpartum period in women with chronic hypertension who developed superimposed PE compared with those who did not.[29−31] August et al[28] were able to develop a prediction model using a cutoff of 3.6 mg/dL for serum uric acid along with 2 other parameters measured at 20 weeks of gestation; a systolic BP of >140 mm Hg and a plasma renin activity of >4 ng/mL/hr. The probability of developing superimposed PE was 86% if all 3 factors were present but the overall performance as a predictor was modest with an area under the curve (AUC) of 0.69.[31]

As with uric acid, although alterations in the renin-angiotensin-aldosterone system (RAAS) have been documented in women with PE, their significance remains controversial. In the aforementioned study that incorporated plasma renin into their prediction model, there was no difference reported between those with superimposed PE and those without at 12 or 20 weeks of gestation.[31] The same group later demonstrated suppression of RAAS as indicated by lower plasma renin and urinary aldosterone at 28 and 36 weeks of gestation in women with superimposed PE.[29] A mechanistic link between the angiogenic imbalance and the decreased RAAS profile observed in PE has been proposed, including impaired vascular endothelial growth factor (VEGF)-mediated stimulation of aldosterone synthase because of increases in soluble fms-like tyrosine kinase-1 (sFlt-1) (Figure 1).[33−36]

Angiogenic biomarkers

The pathophysiological processes by which chronic hypertension confers an increased risk of PE remain poorly understood. In women with PE, particularly preterm PE, impaired placentation results in a cascade of placental hypoperfusion, oxidative stress, and systemic release of trophoblast-derived factors.[37] This then triggers an exaggerated inflammatory response leading to generalized endothelial dysfunction that underlines many of the clinical manifestations of the disease.[38] A central pathogenetic mechanism in this cascade leading to PE is a tendency toward an antiangiogenic and proinflammatory state.[39]

In normal pregnancy, placentation occurs in an environment of relative hypoxia, which up-regulates production of proangiogenic VEGF and down-regulates the production of another proangiogenic factor, placental growth factor (PlGF).[40−42] The source of the increase in VEGF remains largely unknown, but possible sites include the decidua, placenta, or maternal vascular smooth muscle cells.[43,44] Trophoblastic production of the antiangiogenic sFlt-1 in the first trimester of pregnancy is a physiological response to counteract the overspill of VEGF into the maternal circulation.[45,46] With advancing gestational age and improved placental oxygenation, production of VEGF and consequently sFlt-1 remains low, but production of PlGF increases.[47] In pregnancies that develop PE, an imbalance between these pro- and antiangiogenic factors is thought to precede the clinical onset of the disease.[39]

Studies in the general obstetrical population have shown that the proangiogenic PlGF is decreased as early as the first trimester of pregnancies later complicated by PE[48−56] and that the antiangiogenic factors, sFlt-1 and soluble endoglin (sEng), are increased in the last few weeks before and during the clinical presentation of PE.[47−58] The evidence suggests that sFlt-1 and sEng act together to cause endothelial dysfunction. sFlt-1 blocks VEGF-mediated regeneration of endothelial cells, and sEng impairs transforming growth factor-β1 binding to its cell surface receptors decreasing endothelial nitric oxide signaling.[59,60] Therefore, algorithms incorporating these angiogenic factors have been extensively studied in the general obstetrical population for the screening and diagnosis of PE.[51,61,62]

There is limited evidence characterizing the performance of sFlt-1, sEng, and PlGF in women with chronic hypertension as screening and diagnostic biomarkers for superimposed PE.[63−66] It has been proposed that the preexistence of endothelial dysfunction in women with chronic hypertension may impact on the circulating levels of these biomarkers.[67] This is supported by 4 studies outside of pregnancy that have demonstrated elevated VEGF in patients with chronic hypertension compared with normotensive controls.[68−71] The authors of these studies suggested that elevated VEGF represents underlying endothelial dysfunction as the production of VEGF is up-regulated by vascular shear stress and endothelial cell injury.[68] On the contrary, the evidence is conflicting regarding sFlt-1 levels between those with chronic hypertension and normotensive controls, with both decreased[68] and increased levels[71] demonstrated in hypertensive subjects.

Angiogenic factors in addition to sFlt-1, sEng, and PlGF, such as inhibin A, have also been investigated and found to be elevated before the onset of superimposed PE but have not been proven to be clinically useful in the diagnosis or prediction (Tables 3 and 4).[72,73]

First trimester of pregnancy. First-trimester screening studies in general obstetrical populations have reported that, in those that subsequently develop PE, serum PlGF is reduced. Therefore, PlGF has been incorporated into screening models for the first-trimester prediction of PE.[48,51−53] The evidence supporting PlGF as a first-trimester predictor for superimposed PE in women with chronic hypertension is less promising. A total of 3 studies in women with chronic hypertension reported no significant differences in serum PlGF at 12 to 14,[65] 12 to 15,[66] or 11 to 27[64] weeks of gestation between those who subsequently developed superimposed PE and those that did not. We have previously demonstrated that first-trimester serum PlGF in our cohort of women with chronic hypertension is lower than normotensive controls, but this difference is more marked in those who later developed superimposed PE.[12] However, despite this, first-trimester levels of PlGF performed poorly in the prediction of superimposed PE.[12] Our findings were in agreement with an earlier study that demonstrated reduced first-trimester levels of PlGF in women with chronic

hypertension who later developed PE, but this decrease was less than in healthy women who later developed PE.[74] These findings support the logic that, first, a lesser degree of placental impairment is required in women with chronic hypertension to trigger the development of superimposed PE, and second, that chronic hypertension, independent of the development of superimposed PE, is associated with placental impairment. Therefore, first-trimester levels of PlGF are unlikely to discriminate between those with chronic hypertension who will later develop superimposed PE and those who will not.

Given the emerging role of sFlt-1 in the pathophysiology of PE, studies have examined the relationship of serum sFlt-1 in the first trimester of pregnancy with the later development of PE in the general obstetrical population. The evidence is contradictory with some studies reporting increased[61,75] or decreased[76,77] concentrations of sFlt-1 in the first trimester of pregnancy and others reporting no significant difference from normotensive pregnancies.[47,78–80] The performance of first-trimester sFlt-1 in the prediction of PE occurring before and after 34 weeks of gestation is modest with AUCs of 0.717[6] and between 0.602[75] and 0.743,[61] respectively, reported in the general obstetrical population. In women with chronic hypertension, the findings from the existing studies would suggest that first trimester serum sFlt-1 does not have a major contributory role to the later development of superimposed PE. Two studies examining sFlt-1 at 12 to 15[65] or 11 to 27[64] weeks of gestation in women with chronic hypertension were not significantly different between those that developed superimposed PE and those who did not. We found that in women with chronic hypertension, compared with normotensive controls, first-trimester sFlt-1 was reduced, and the reduction was greater in those that developed superimposed PE; we postulated that in the presence of impaired placentation, early placental hypoxia is not accompanied by an increase in sFlt-1 because of the inability of the impaired placenta to produce this receptor.[12]

Second and third trimesters. Similarly, the relationship between the alterations in angiogenic factors in women with chronic hypertension and the development of superimposed PE in the latter half of pregnancy remains less clearly defined than in the general obstetrical population.[63–66]

Perni et al[65] performed a longitudinal study in 109 women with chronic hypertension, measuring PlGF, sFlt-1, and sEng from the first trimester of pregnancy to the postpartum period. At the time of delivery, all women with superimposed PE demonstrated lower PlGF and elevated sFlt-1 and sEng than those without superimposed PE.[65] Before delivery, sFlt-1 and sEng were elevated at 20 and 28 weeks of gestation, respectively, in those who developed preterm superimposed PE only, and PlGF was significantly lower in all women with superimposed PE at 28 weeks of gestation.[65] Similar findings were reported in 4 smaller studies of angiogenic factors in women with chronic hypertension and superimposed PE.[66,81–83] One study reported higher levels of second-trimester sFlt-1 and lower levels of PlGF before the clinical onset of superimposed PE with no difference in sEng.[81] When women with superimposed PE were excluded, the differences in sFlt-1 and PlGF observed were diminished between women with chronic hypertension and the controls suggesting that it was the PE itself rather than the underlying condition that is associated with the alterations in the angiogenic factors.[81] These findings are in agreement with Bramham et al[66] who found that PlGF was significantly lower in women with superimposed PE than those without and normotensive controls at 26 weeks of gestation. The third study demonstrated increased levels of predelivery sFlt-1 in women with superimposed PE compared with those with uncontrolled hypertension, defined as a BP of <140/90 mm Hg, alone and also normotensive controls with no difference in PlGF.[82] Women with uncontrolled hypertension but without superimposed PE had increased levels of sFlt-1 compared with the normotensive controls.[82] Although the authors of this study did not suggest an underlying mechanism for this, it may be that elevated sFlt-1 in women with uncontrolled hypertension is a response to elevated levels of VEGF. Outside of pregnancy, a direct correlation between mean arterial BP and VEGF has been reported.[69]

One further study included a group of normotensive controls that subsequently developed PE.[83] This study found that PlGF was significantly lower and sFlt-1 significantly elevated in women with chronic hypertension and normotensive controls who developed preterm PE at 20 weeks of gestation compared with those who did not.[83] The alterations in the levels of angiogenic factors were more pronounced in normotensive women with new-onset PE. Unfortunately, only 1 of these studies was adequately powered to assess the predictive performance of the angiogenic factors for the diagnosis of superimposed PE in women with chronic hypertension. PlGF screening is performed moderately as a predictor for superimposed PE at 26 weeks of gestation in women with chronic hypertension with an AUC of 0.78.[66]

In contrast to these studies, others have reported no difference in the levels of second-trimester sFlt-1 in women with chronic hypertension who developed superimposed PE and those who did not.[63,84,85] One of these studies included a normotensive control group who later developed PE and found that levels of sFlt-1 and sEng were higher in the controls than in women with chronic hypertension and superimposed PE with no difference in PlGF between the 2 groups.[63] Again, these studies did not perform any prediction modeling.

Other studies have evaluated these angiogenic factors in a mixed cohort of women considered at high risk of developing PE, including women with chronic hypertension, chronic kidney disease, multiple gestation, pregestational diabetes, obesity, and previous PE without subanalyses as separate groups.[64,67,73,87–88] There are 2 main limitations to this approach. First, women within each subgroup vary in their a posteriori risk of PE. For example,

TABLE 4
Summary of the studies evaluating levels of sFlt-1, PlGF, and sEng in women with chronic hypertension (with and without superimposed PE) and previously normotensive women (with and without PE)

		Chronic hypertension				Normotensive women			
		Superimposed PE		No superimposed PE		PE		No PE	
Author, y	Gestation (wk)	n	Level	N	Level	N	Level	n	Level
sFlt-1 (pg/mL)									
Nzelu et al, 2020[12]	11–13	202		448		—	—	142	
Costa et al, 2016[63]	32	13	2438	46	1459	4	4323[a]	27	2242
Metz et al, 2014[84]	20	103	N/A	284	N/A	—	—	—	—
Maynard et al, 2013[81]	28–32	6	N/A	16	N/A	—	—	59	N/A
Perni et al, 2012[66,b]	20–36	8	9476[c]	73	2892	—	—	—	—
Sunderji et al, 2010[84,b]	20–36	9	59,533[c]	18	2277	39	91,514[a]	388	2416
Powers et al, 2010[86]	20	78	383	235	368	—	—	—	—
PlGF (pg/mL)									
Bramham et al, 2020[6]	26–28	14	68[c]	72	193	—	—	90	222
Nzelu et al, 2020[12]	11–13	202		448		—	—	142	
Costa et al, 2016[63]	26–36	13	393	46	478	4	236[a]	27	725
Metz et al, 2014[84]	20	103	N/A	284	N/A	—	—	—	—
Maynard et al, 2013[81]	23–36	6	N/A	16	N/A	—	—	59	N/A
Perni et al, 2012[65,b]	20–36	8	192[c]	73	407	—	—	—	—
Powers et al, 2010[85]	20	78	192	235	222	—	—	—	—
Sunderji et al, 2010[84,b]	20–36	9	18.9[c]	18	364	39	12.1[a]	388	447
sEng (ng/mL)									
Metz et al, 2014[84]	20	103	N/A	284	N/A	—	—	—	—
Maynard et al, 2013[81]	23–36	6	N/A	16	N/A	—	—	59	N/A
Perni et al, 2012[65,b]	20–36	8	31[c]	73	9	—		—	
Powers et al, 2010[85]	20	78	6	235	5	—	—	—	—

N/A, not applicable; *PE*, preeclampsia; *PlGF*, placental growth factor; *sEng*, soluble endoglin; *sFlt-1*, soluble fms-like tyrosine kinase-1.

[a] Significantly different than those without preeclampsia; [b] Preterm preeclampsia only; [c] Significantly different than those without superimposed preeclampsia

Kametas. Screening and diagnosis of superimposed preeclampsia. Am J Obstet Gynecol 2022.

women with chronic kidney disease have a 10-fold increase in the risk of PE compared with a 5-fold increase with chronic hypertension alone.[1,89] Second, it is likely that the mechanism of PE differs among high-risk groups. A woman with chronic hypertension with poorly controlled BP will have a lesser capacity to cope with the endothelial stress of pregnancy than a normotensive woman with previous PE. The latter is likely to require a greater degree of placental impairment than the former to trigger the onset of PE later in pregnancy.[12,74,90]

In summary, alterations in these angiogenic markers may contribute to the risk of superimposed PE in women with chronic hypertension. However, these alterations are not as pronounced compared with new-onset PE and can occur even in the absence of superimposed PE.

Inflammatory biomarkers

Outside of pregnancy, there is substantial evidence to suggest that proinflammatory mediators are not only elevated in patients with chronic hypertension but also associated with later cardiovascular morbidity.[91–93] Several mechanisms have been proposed for the relationship between proinflammatory mediators and hypertension. Stimulation of vascular smooth muscle cells by angiotensin II, a key regulator of BP, which is implicated in chronic hyperetnsion, results in inflammatory activation with increases in the production of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[94] IL-6 then promotes vascular smooth muscle cell proliferation, a hallmark of the early stages of chronic hypertension.[95] TNF-α may also augment the vasoconstrictive effects of

angiotensin II through its up-regulation of its AT1 receptors on smooth muscle cells.[96] In addition, TNF-α enhances the release of another potent vasoconstrictor, endothelin. Significantly higher levels of endothelin have been demonstrated in hypertensive patients and, through its effects on vascular remodeling, has been shown to lead to the development and progression of atherosclerosis.[97] Endothelin is also known to increase the expression of other inflammatory cytokines, such as IL-6, and cell adhesion molecules (CAMs), such as vascular CAM (VCAM).[98]

Similarly, in PE, the physiological inflammatory response observed in normal pregnancy appears to be more exaggerated and associated with an imbalance between proinflammatory and anti-inflammatory cytokines.[39] As with angiogenic factors, uteroplacental hypoxia is proposed to play a central role in shifting the production toward proinflammatory cytokines.[39] Ultimately, this inflammatory response leads to the endothelial dysfunction that is pathognomonic of both chronic hypertension and PE. Thus, proinflammatory cytokines, such as TNF-α, IL-6, and endothelin, and CAMs, such as P-selectin and VCAM, have been investigated for the prediction and diagnosis of superimposed PE in women with chronic hypertension.[99,100]

First trimester. A meta-analysis of the studies on first-trimester IL-6 and TNF-α levels concluded that the existing data were insufficient to determine whether there was a difference between pregnancies later complicated by PE and those that remained normotensive.[101] Of the 3 studies that demonstrated a difference in first-trimester TNF-α, 2 reported a detection rate of 67.8%[102] and 75.0%,[103] at a false positive rate of 10%, for the prediction of PE using first-trimester TNF-α alone. In contrast, a third study found that TNF-α alone was not predictive of PE but in combination with other inflammatory mediators, such as IL-8, it provided a detection rate of 55%.[104] No significant association between first-trimester IL-6 and subsequent development of PE has been reported.[101]

In the general obstetrical population, there is a positive correlation between first-trimester endothelin and the later development and severity of PE.[105] As with TNF-α, first-trimester endothelin alone performs poorly in the prediction of PE with a detection rate of 55.5%.[105] Furthermore, in uncomplicated pregnancies, a significant association between first-trimester endothelin level and BPs within the normal range has been demonstrated.[106]

There is only 1 study that has evaluated first-trimester levels of IL-6, TNF-α, endothelin, and VCAM in women with chronic hypertension. Compared with the normotensive controls, the findings in women with chronic hypertension in this study demonstrated that at 11 0/7 to 13 6/7 weeks of gestation, serum levels of endothelin was increased, but TNF-α, IL-6, and VCAM were not significantly different.[107] Within the group of women with chronic hypertension, only serum levels of VCAM were higher in those who developed superimposed PE than in those who did not. However, in women with chronic hypertension, first-trimester serum levels of VCAM provided poor prediction of superimposed PE.[107]

Second and third trimesters. There are 3 studies evaluating soluble TNF (sTNF) receptors, considered to be a proxy of TNF activity, in a heterogeneous cohort at high risk of developing PE, including those with chronic hypertension, multiple gestation, previous PE, and pregestational diabetes.[84,108,109] One study found significantly higher levels of sTNF receptor I from the second trimester of pregnancy onward only in those who later developed PE with intrauterine fetal growth restriction and/or severe features.[108] The second study demonstrated significantly higher levels of sTNF receptor II in the second trimester of pregnancy in those who later developed PE.[109] Although these differences remained after adjustment for chronic hypertension,[109] neither study performed a separate subgroup analysis for the 13 and 303 women with chronic hypertension included, respectively.[108,109] As with the angiogenic factors, such an approach has limitations. A subgroup analysis by Metz et al[84] found considerable variation in the differences in levels of biomarkers, such as TNF-α and its receptor, between those who did and did not develop PE within each high-risk subgroup. Levels of TNF-α and its receptor were higher only in those with chronic hypertension who developed superimposed PE than in those who did not.[84]

As with cytokines, CAMs, in particular VCAM and P-selectin, have also been implicated in the pathophysiology of chronic hypertension and PE. The endothelial expression of CAMs promotes leucocyte recruitment and rolling, extravasation into the perivascular tissue leading to increased endothelial permeability and dysfunction.[98,110,111] In a study of women with chronic kidney disease, of which over half had coexisting chronic hypertension, significantly higher levels of VCAM in the second trimester of pregnancy were observed in those who developed superimposed PE than in those who did not.[112] Similarly, second-trimester P-selectin was found to be increased in women with chronic hypertension who subsequently developed superimposed PE compared with those who did not.[84]

In summary, none of the proinflammatory mediators examined to date are useful in the prediction of superimposed PE in women with chronic hypertension. As inflammation plays a key role in the endothelial dysfunction characteristic of both chronic hypertension and PE, it may be that the existing studies are underpowered to identify subtle differences and further evaluation is still needed.

Cardiac biomarkers

Pro—B-type natriuretic peptide (NT-proBNP) is regarded as a sensitive marker of early cardiac dysfunction and has been found to correlate with volume expansion and pressure overload.[113] Low NT-proBNP levels typically seen in uncomplicated pregnancies suggest that the increased intravascular volume in late pregnancy is handled without an

increase in left ventricular end diastolic pressure.[114] Conversely, in pregnancies complicated by PE, the pressure overload that develops within a few week has been correlated to elevated levels of NT-proBNP.[114] Despite this correlation, in the general obstetrical population, the performance of NT-proBNP in the prediction of PE is modest with AUCs of 0.55[115] and 0.69[116] in the first and third trimesters of pregnancy, respectively.

In women with chronic hypertension, pressure overload because of increased intravascular volume (preload) or increased peripheral vascular resistance (afterload) is likely to predate the pregnancy.[117] As an indicator of this left ventricular strain, elevated NT-proBNP has been demonstrated outside of pregnancy in patients with chronic hypertension.[117] It has been proposed that because NT-proBNP reflects the impaired hemodynamics of women with chronic hypertension, it may also give insight into their risk of developing superimposed PE. One study has demonstrated significantly elevated NT-proBNP in women with chronic hypertension throughout all trimesters of pregnancy compared with normotensive controls. In women with chronic hypertension who develop superimposed PE, NT-proBNP was significantly elevated compared with those who did not at 16 weeks of gestation.[118] Another study reported that in women with superimposed PE, levels of NT-proBNP did not decrease with advancing gestation, as normally expected, compared with normotensive controls and women with chronic hypertension but no superimposed PE.[66] However, in the latter study, NT-proBNP, at any point in pregnancy, was not predictive for the development of superimposed PE.[66]

We have previously stratified women with chronic hypertension according to first-trimester BP control, with those with suboptimal BP control despite antihypertensive medications at the highest risk of developing superimposed PE.[15] We proposed that these groups are likely to represent 3 hemodynamic profiles at different stages of cardiovascular disease.[15] Those with mild impairment in vascular function demonstrate physiological adaptation to early pregnancy with normalization in BP, whereas those with more severe impairment in vascular function and thus less capacity for adaptation are persistently hypertensive.[119] The inclusion of markers of cardiac function may, aside from BP thresholds, provide additional value in identifying women with chronic hypertension who fall into this latter strata.

Uterine artery Doppler velocimetry

Second-trimester Doppler examination of the uterine arteries has been advocated as a screening test for PE, particularly in those considered at high risk, such as women with chronic hypertensions.[120−123] Studies have confirmed a significant association between abnormal uterine artery resistance index (RI) and presence of a diastolic notch with the later development of superimposed PE in women with chronic hypertension.[121,122] However, the performance of these indices in the prediction of superimposed PE remains modest with a reported AUC of 0.73.[121] This finding along with the similarly modest predictive performance of first-trimester PlGF in women with chronic hypertension supports the hypothesis that where there is preexisting endothelial dysfunction, placental impairment plays a smaller role in the onset of superimposed PE.

Conclusion

In women with chronic hypertension, there are differences in uric acid, the renin-angiotensin aldosterone system, angiogenic factors, proinflammatory markers of endothelial dysfunction, and NT-proBNP between those who develop superimposed PE and those who do not. However, none of these biomarkers have been shown to be useful in the screening and diagnosis of superimposed PE. ■

REFERENCES

1. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol 2017;50:228–35.
2. Rezk M, Gamal A, Emara M. Maternal and fetal outcome in de novo preeclampsia in comparison to superimposed preeclampsia: a two-year observational study. Hypertens Pregnancy 2015;34:137–44.
3. Valent AM, DeFranco EA, Allison A, et al. Expectant management of mild preeclampsia versus superimposed preeclampsia up to 37 weeks. Am J Obstet Gynecol 2015;212:515.e1–8.
4. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. Hypertension 2018;71:e13–115.
5. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 203: chronic hypertension in pregnancy. Obstet Gynecol 2019;133:e26–50.
6. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20:IX–XIV.
7. Morgan JL, Nelson DB, Roberts SW, Wells CE, McIntire DD, Cunningham FG. Association of baseline proteinuria and adverse outcomes in pregnant women with treated chronic hypertension. Obstet Gynecol 2016;128:270–6.
8. Caetano ER, Zatz R, Saldanha LB, Praxedes JN. Hypertensive nephrosclerosis as a relevant cause of chronic renal failure. Hypertension 2001;38:171–6.
9. Brown MA, Buddle ML. What's in a name? Problems with the classification of hypertension in pregnancy. J Hypertens 1997;15:1049–54.
10. Tranquilli AL, Dekker G, Magee L, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. Pregnancy Hypertens 2014;4:97–104.
11. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 202: gestational hypertension and preeclampsia. Obstet Gynecol 2019;133:e1–25.
12. Nzelu D, Biris D, Karampitsakos T, Nicolaides KK, Kametas NA. First trimester serum angiogenic and anti-angiogenic factors in women with chronic hypertension for the prediction of preeclampsia. Am J Obstet Gynecol 2020;222:374.e1–9.
13. Lecarpentier E, Tsatsaris V, Goffinet F, Cabrol D, Sibai B, Haddad B. Risk factors of superimposed preeclampsia in women with essential chronic hypertension treated before pregnancy. PLoS One 2013;8:e62140.
14. Sibai BM, Lindheimer M, Hauth J, et al. Risk factors for preeclampsia, abruptio placentae, 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.

15. Nzelu D, Dumitrascu-Biris D, Nicolaides KH, Kametas NA. Chronic hypertension: first-trimester blood pressure control and likelihood of severe hypertension, preeclampsia, and small for gestational age. Am J Obstet Gynecol 2018;218:337.e1–7.
16. Giannubilo SR, Dell'Uomo B, Tranquilli AL. Perinatal outcomes, blood pressure patterns and risk assessment of superimposed pre-eclampsia in mild chronic hypertensive pregnancy. Eur J Obstet Gynecol Reprod Biol. 2006 May 1;126:63–7.
17. Sibai BM. Chronic hypertension in pregnancy. Obstet Gynecol 2002;100:369–77.
18. Nakanishi S, Aoki S, Nagashima A, Seki K. Incidence and pregnancy outcomes of superimposed preeclampsia with or without proteinuria among women with chronic hypertension. Pregnancy Hypertens 2017;7:39–43.
19. Ono Y, Takagi K, Seki H, et al. Neonatal outcome in infants of chronically hypertensive mothers. J Obstet Gynaecol Res 2013;39:1142–6.
20. Homer CS, Brown MA, Mangos G, Davis GK. Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension. J Hypertens 2008;26:295–302.
21. Schiff E, Friedman SA, Kao L, Sibai BM. The importance of urinary protein excretion during conservative management of severe pre-eclampsia. Am J Obstet Gynecol 1996;175:1313–6.
22. Thangaratinam S, Coomarasamy A, O'Mahony F, et al. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. BMC Med 2009;7:10.
23. Morton A, Burke M, Jarvis E, Kumar S. Changes in proteinuria and diagnosing pre-eclampsia in CKD pregnancy. Pregnancy Hypertens 2020;20:92–5.
24. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension 2018;72:24–43.
25. Bainbridge SA, Roberts JM. Uric acid as a pathogenic factor in preeclampsia. Placenta 2008;29(SupplA):S67–72.
26. Thangaratinam S, Ismail KM, Sharp S, Coomarasamy A, Khan KS. Tests in Prediction of Pre-eclampsia Severity Review Group. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. BJOG 2006;113:369–78.
27. Salahuddin S, Lee Y, Vadnais M, Sachs BP, Karumanchi SA, Lim KH. Diagnostic utility of soluble fms-like tyrosine kinase 1 and soluble endoglin in hypertensive diseases of pregnancy. Am J Obstet Gynecol 2007;197:28.e1–6.
28. Nisell H, Kublickas M, Lunell NO, Pettersson E. Renal function in gravidas with chronic hypertension with and without superimposed preeclampsia. Hypertens Pregnancy 1996;15:127–34.
29. Malha L, Sison CP, Helseth G, Sealey JE, August P. Renin-angiotensin-aldosterone profiles in pregnant women with chronic hypertension. Hypertension 2018;72:417–24.
30. Lim KH, Friedman SA, Ecker JL, Kao L, Kilpatrick SJ. The clinical utility of serum uric acid measurements in hypertensive diseases of pregnancy. Am J Obstet Gynecol 1998;178:1067–71.
31. August P, Helseth G, Cook EF, Sison C. A prediction model for superimposed pre-eclampsia in women with chronic hypertension during pregnancy. Am J Obstet Gynecol 2004;191:1666–72.
32. Parrish M, Griffin M, Morris R, Darby M, Owens MY, Martin JN Jr. Hyperuricemia facilitates the prediction of maternal and perinatal adverse outcome in patients with severe/superimposed preeclampsia. J Matern Fetal Neonatal Med. 2010;23:1451–5.
33. Gennari-Moser C, Khankin EV, Escher G, et al. Vascular endothelial growth factor-A and aldosterone: relevance to normal pregnancy and preeclampsia. Hypertension 2013;61:1111–7.
34. Verdonk K, Visser W, Van Den Meiracker AH, Danser AH. The renin-angiotensin-aldosterone system in pre-eclampsia: the delicate balance between good and bad. Clin Sci (Lond) 2014;126:537–44.
35. Zhou CC, Ahmad S, Mi T, et al. Autoantibody from women with preeclampsia induces soluble fms-like tyrosine kinase-1 production via angiotensin type 1 receptor and calcineurin/nuclear factor of activated T-cells signaling. Hypertension 2008;51:1010–9.
36. Saxena AR, Karumanchi SA, Brown NJ, Royle CM, McElrath TF, Seely EW. Increased sensitivity to angiotensin II is present postpartum in women with a history of hypertensive pregnancy. Hypertension 2010;55:1239–45.
37. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol 2011;204:193–201.
38. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol 1989;161:1200–4.
39. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol 2014;10:466–80.
40. Wheeler T, Evans PW, Anthony FW, Godfrey KM, Howe DT, Osmond C. Relationship between maternal serum vascular endothelial growth factor concentration in early pregnancy and fetal and placental growth. Hum Reprod 1999;14:1619–23.
41. Wheeler T, Elcock CL, Anthony FW. Angiogenesis and the placental environment. Placenta 1995;16:289–96.
42. Evans PW, Wheeler T, Anthony FW, Osmond C. A longitudinal study of maternal serum vascular endothelial growth factor in early pregnancy. Hum Reprod 1998;13:1057–62.
43. Ni Y, May V, Braas K, Osol G. Pregnancy augments uteroplacental vascular endothelial growth factor gene expression and vasodilator effects. Am J Physiol 1997;273:H938–44.
44. Bausero P, Ben-Mahdi M, Mazucatelli J, Bloy C, Perrot-Applanat M. Vascular endothelial growth factor is modulated in vascular muscle cells by estradiol, tamoxifen, and hypoxia. Am J Physiol Heart Circ Physiol 2000;279:H2033–42.
45. Barleon B, Siemeister G, Martiny-Baron G, Weindel K, Herzog C, Marmé D. Vascular endothelial growth factor up-regulates its receptor fms-like tyrosine kinase 1 (FLT-1) and a soluble variant of FLT-1 in human vascular endothelial cells. Cancer Res 1997;57:5421–5.
46. Fan X, Rai A, Kambham N, et al. Endometrial VEGF induces placental sFLT1 and leads to pregnancy complications. J Clin Invest 2014;124:4941–52.
47. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004;350:672–83.
48. Akolekar R, Zaragoza E, Poon LC, Pepes S, Nicolaides KH. Maternal serum placental growth factor at 11 + 0 to 13 + 6 weeks of gestation in the prediction of pre-eclampsia. Ultrasound Obstet Gynecol 2008;32:732–9.
49. Chaiworapongsa T, Romero R, Korzeniewski SJ, et al. Plasma concentrations of angiogenic/anti-angiogenic factors have prognostic value in women presenting with suspected preeclampsia to the obstetrical triage area: a prospective study. J Matern Fetal Neonatal Med 2014;27:132–44.
50. Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation 2013;128:2121–31.
51. O'Gorman N, Wright D, Poon LC, et al. Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2017;49:751–5.
52. Wright D, Tan MY, O'Gorman N, et al. Predictive performance of the competing risk model in screening for preeclampsia. Am J Obstet Gynecol 2019;220:199.e1–13.
53. Wright A, Wright D, Syngelaki A, Georgantis A, Nicolaides KH. Two-stage screening for preterm preeclampsia at 11-13 weeks' gestation. Am J Obstet Gynecol 2019;220:197.e1–11.
54. Gallo DM, Wright D, Casanova C, Campanero M, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19-24 weeks' gestation. Am J Obstet Gynecol 2016;214:619.e1–7.
55. Tsiakkas A, Saiid Y, Wright A, Wright D, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 30-34 weeks' gestation. Am J Obstet Gynecol 2016;215:87.e1–17.
56. Ciobanu A, Wright A, Panaitescu A, Syngelaki A, Wright D, Nicolaides KH. Prediction of imminent preeclampsia at 35-37 weeks gestation. Am J Obstet Gynecol 2019;220:584.e1–11.
57. Maynard SE, Min JY, Merchan J, 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.
58. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med 2016;374:13–22.
59. Romero R, Nien JK, Espinoza J, et al. A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. J Matern Fetal Neonatal Med 2008;21:9–23.
60. Foidart JM, Munaut C, Chantraine F, Akolekar R, Nicolaides KH. Maternal plasma soluble endoglin at 11-13 weeks' gestation in pre-eclampsia. Ultrasound Obstet Gynecol 2010;35:680–7.
61. Crovetto F, Figueras F, Triunfo S, et al. Added value of angiogenic factors for the prediction of early and late preeclampsia in the first trimester of pregnancy. Fetal Diagn Ther 2014;35:258–66.
62. Tsiakkas A, Duvdevani N, Wright A, Wright D, Nicolaides KH. Serum soluble fms-like tyrosine kinase-1 in the three trimesters of pregnancy: effects of maternal characteristics and medical history. Ultrasound Obstet Gynecol 2015;45:584–90.
63. Costa RA, Hoshida MS, Alves EA, Zugaib M, Francisco RP. Preeclampsia and superimposed preeclampsia: the same disease? The role of angiogenic biomarkers. Hypertens Pregnancy 2016;35:139–49.
64. Powers RW, Jeyabalan A, Clifton RG, et al. Soluble fms-Like tyrosine kinase 1 (sFlt1), endoglin and placental growth factor (PlGF) in preeclampsia among high risk pregnancies. PLoS One 2010;5:e13263.
65. Perni U, Sison C, Sharma V, et al. Angiogenic factors in superimposed preeclampsia: a longitudinal study of women with chronic hypertension during pregnancy. Hypertension 2012;59:740–6.
66. Bramham K, Villa PM, Joslin JR, et al. Predisposition to superimposed preeclampsia in women with chronic hypertension: endothelial, renal, cardiac, and placental factors in a prospective longitudinal cohort. Hypertens Pregnancy 2020;39:326–35.
67. Dwyer BK, Krieg S, Balise R, et al. Variable expression of soluble fms-like tyrosine kinase 1 in patients at high risk for preeclampsia. J Matern Fetal Neonatal Med 2010;23:705–11.
68. Felmeden DC, Spencer CG, Belgore FM, Blann AD, Beevers DG, Lip GY. Endothelial damage and angiogenesis in hypertensive patients: relationship to cardiovascular risk factors and risk factor management. Am J Hypertens 2003;16:11–20.
69. Stumpf C, Jukic J, Yilmaz A, et al. Elevated VEGF-plasma levels in young patients with mild essential hypertension. Eur J Clin Invest 2009;39:31–6.
70. Marek-Trzonkowska N, Kwieczyńska A, Reiwer-Gostomska M, Koliński T, Molisz A, Siebert J. Arterial hypertension is characterized by imbalance of pro-angiogenic versus anti-angiogenic factors. PLoS One 2015;10:e0126190.
71. Belgore FM, Blann AD, Li-Saw-Hee FL, Beevers DG, Lip GY. Plasma levels of vascular endothelial growth factor and its soluble receptor (SFlt-1) in essential hypertension. Am J Cardiol 2001;87:805–7. A9.
72. Zeeman GG, Alexander JM, McIntire DD, Byrd W, Leveno KJ. Inhibin-A and superimposed preeclampsia in women with chronic hypertension. Obstet Gynecol 2003;101:232–6.
73. Sibai BM, Koch MA, Freire S, et al. Serum inhibin A and angiogenic factor levels in pregnancies with previous preeclampsia and/or chronic hypertension: are they useful markers for prediction of subsequent preeclampsia? Am J Obstet Gynecol 2008;199:268.e1–9.
74. Panaitescu AM, Akolekar R, Kametas N, Syngelaki A, Nicolaides KH. Impaired placentation in women with chronic hypertension who develop pre-eclampsia. Ultrasound Obstet Gynecol 2017;50:496–500.
75. Baumann MU, Bersinger NA, Mohaupt MG, Raio L, Gerber S, Surbek DV. First-trimester serum levels of soluble endoglin and soluble fms-like tyrosine kinase-1 as first-trimester markers for late-onset preeclampsia. Am J Obstet Gynecol 2008;199:266.e1–6.
76. Vatten LJ, Eskild A, Nilsen TI, Jeansson S, Jenum PA, Staff AC. Changes in circulating level of angiogenic factors from the first to second trimester as predictors of preeclampsia. Am J Obstet Gynecol 2007;196:239.e1–6.
77. Erez O, Romero R, Espinoza J, et al. The change in concentrations of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters in risk assessment for the subsequent development of preeclampsia and small-for-gestational age. J Matern Fetal Neonatal Med 2008;21:279–87.
78. Thadhani R, Mutter WP, Wolf M, et al. First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia. J Clin Endocrinol Metab 2004;89:770–5.
79. Akolekar R, de Cruz J, Foidart JM, Munaut C, Nicolaides KH. Maternal plasma soluble fms-like tyrosine kinase-1 and free vascular endothelial growth factor at 11 to 13 weeks of gestation in preeclampsia. Prenat Diagn 2010;30:191–7.
80. Odibo AO, Rada CC, Cahill AG, et al. First-trimester serum soluble fms-like tyrosine kinase-1, free vascular endothelial growth factor, placental growth factor and uterine artery Doppler in preeclampsia. J Perinatol 2013;33:670–4.
81. Maynard SE, Crawford SL, Bathgate S, et al. Gestational angiogenic biomarker patterns in high risk preeclampsia groups. Am J Obstet Gynecol 2013;209:53.e1–9.
82. Minhas R, Young D, Naseem R, et al. Association of antepartum blood pressure levels and angiogenic profile among women with chronic hypertension. Pregnancy Hypertens 2018;14:110–4.
83. Sunderji S, Gaziano E, Wothe D, et al. Automated assays for sVEGF R1 and PlGF as an aid in the diagnosis of preterm preeclampsia: a prospective clinical study. Am J Obstet Gynecol 2010;202:40.e1–7.
84. Metz TD, Allshouse AA, Euser AG, Heyborne KD. Preeclampsia in high risk women is characterized by risk group-specific abnormalities in serum biomarkers. Am J Obstet Gynecol 2014;211:512.e1–6.
85. Powers RW, Roberts JM, Cooper KM, et al. Maternal serum soluble fms-like tyrosine kinase 1 concentrations are not increased in early pregnancy and decrease more slowly postpartum in women who develop preeclampsia. Am J Obstet Gynecol 2005;193:185–91.
86. Moore Simas TA, Crawford SL, Bathgate S, et al. Angiogenic biomarkers for prediction of early preeclampsia onset in high-risk women. J Matern Fetal Neonatal Med 2014;27:1038–48.
87. Shaker OG, Shehata H. Early prediction of preeclampsia in high-risk women. J Womens Health (Larchmt) 2011;20:539–44.
88. Diguisto C, Piver E, Gouge AL, et al. First trimester uterine artery Doppler, sFlt-1 and PlGF to predict preeclampsia in a high-risk population. J Matern Fetal Neonatal Med 2017;30:1514–9.
89. Williams D, Davison J. Chronic kidney disease in pregnancy. BMJ 2008;336:211–5.
90. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science 2005;308:1592–4.
91. Blankenberg S, Rupprecht HJ, Bickel C, et al. Circulating cell adhesion molecules and death in patients with coronary artery disease. Circulation 2001;104:1336–42.
92. Luvarà G, Pueyo ME, Philippe M, et al. Chronic blockade of NO synthase activity induces a proinflammatory phenotype in the arterial wall: prevention by angiotensin II antagonism. Arterioscler Thromb Vasc Biol 1998;18:1408–16.
93. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. J Hum Hypertens 2005;19:149–54.
94. Kranzhöfer R, Schmidt J, Pfeiffer CA, Hagl S, Libby P, Kübler W. Angiotensin induces inflammatory activation of human vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 1999;19:1623–9.
95. Ikeda U, Ikeda M, Oohara T, et al. Interleukin 6 stimulates growth of vascular smooth muscle cells in a PDGF-dependent manner. Am J Physiol 1991;260:H1713–7.
96. Sasamura H, Nakazato Y, Hayashida T, Kitamura Y, Hayashi M, Saruta T. Regulation of vascular type 1 angiotensin receptors by cytokines. Hypertension 1997;30:35–41.
97. Schiffrin EL, Deng LY, Sventek P, Day R. Enhanced expression of endothelin-1 gene in resistance arteries in severe human essential hypertension. J Hypertens 1997;15:57–63.

98. Ishizuka T, Takamizawa-Matsumoto M, Suzuki K, Kurita A. Endothelin-1 enhances vascular cell adhesion molecule-1 expression in tumor necrosis factor alpha-stimulated vascular endothelial cells. Eur J Pharmacol 1999;369:237–45.
99. Wolff K, Nisell H, Carlström K, et al. Endothelin-1 and big endothelin-1 levels in normal term pregnancy and in preeclampsia. Regul Pept 1996;67:211–6.
100. Szarka A, Rigó J Jr, Lázár L, Beko G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. BMC Immunol 2010;11:59.
101. Lau SY, Guild SJ, Barrett CJ, et al. Tumor necrosis factor-alpha, interleukin-6, and interleukin-10 levels are altered in preeclampsia: a systematic review and meta-analysis. Am J Reprod Immunol 2013;70:412–27.
102. Gomaa MF, Naguib AH, Swedan KH, Abdellatif SS. Serum tumor necrosis factor-α level and uterine artery Doppler indices at 11-13 weeks' gestation for preeclampsia screening in low-risk pregnancies: a prospective observational study. J Reprod Immunol 2015;109:31–5.
103. Hamai Y, Fujii T, Yamashita T, et al. Evidence for an elevation in serum interleukin-2 and tumor necrosis factor-alpha levels before the clinical manifestations of preeclampsia. Am J Reprod Immunol 1997;38:89–93.
104. Salazar Garcia MD, Mobley Y, Henson J, et al. Early pregnancy immune biomarkers in peripheral blood may predict preeclampsia. J Reprod Immunol 2018;125:25–31.
105. Shaarawy M, Abdel-Magid AM. Plasma endothelin-1 and mean arterial pressure in the prediction of pre-eclampsia. Int J Gynaecol Obstet 2000;68:105–11.
106. Lygnos MC, Pappa KI, Papadaki HA, et al. Changes in maternal plasma levels of VEGF, bFGF, TGF-beta1, ET-1 and sKL during uncomplicated pregnancy, hypertensive pregnancy and gestational diabetes. In Vivo 2006;20:157–63.
107. Nzelu D, Dumitrascu-Biris D, Karampitsakos T, Nicolaides KK, Kametas NA. First trimester inflammatory mediators in women with chronic hypertension. Acta Obstet Gynecol Scand 2020;99:1198–205.
108. Schipper EJ, Bolte AC, Schalkwijk CG, Van Geijn HP, Dekker GA. TNF-receptor levels in preeclampsia—results of a longitudinal study in high-risk women. J Matern Fetal Neonatal Med 2005;18:283–7.
109. Sibai B, Romero R, Klebanoff MA, et al. Maternal plasma concentrations of the soluble tumor necrosis factor receptor 2 are increased prior to the diagnosis of preeclampsia. Am J Obstet Gynecol 2009;200:630.e1–8.
110. Ferrara N. Role of vascular endothelial growth factor in regulation of physiological angiogenesis. Am J Physiol Cell Physiol 2001;280:C1358–66.
111. Watson C, Whittaker S, Smith N, Vora AJ, Dumonde DC, Brown KA. IL-6 acts on endothelial cells to preferentially increase their adherence for lymphocytes. Clin Exp Immunol 1996;105:112–9.
112. Wiles K, Bramham K, Seed PT, et al. Diagnostic indicators of superimposed pre-eclampsia in women with CKD. Kidney Int Rep 2019;4:842–53.
113. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. Eur J Heart Fail 2004;6:257–60.
114. Tihtonen KM, Kööbi T, Vuolteenaho O, Huhtala HS, Uotila JT. Natriuretic peptides and hemodynamics in preeclampsia. Am J Obstet Gynecol 2007;196:328.e1–7.
115. Pihl K, Sørensen S, Stener Jørgensen F. Prediction of preeclampsia in nulliparous women according to first trimester maternal factors and serum markers. Fetal Diagn Ther 2020;47:277–83.
116. Verlohren S, Perschel FH, Thilaganathan B, et al. Angiogenic markers and cardiovascular indices in the prediction of hypertensive disorders of pregnancy. Hypertension 2017;69:1192–7.
117. Buckley MG, Markandu ND, Miller MA, Sagnella GA, MacGregor GA. Plasma concentrations and comparisons of brain and atrial natriuretic peptide in normal subjects and in patients with essential hypertension. J Hum Hypertens 1993;7:245–50.
118. Giannubilo SR, Cecchi S, Tidu E, Ciavattini A. Maternal NT-proBNP in chronic hypertensive pregnancies and superimposed preeclampsia. Int J Cardiol 2014;176:1227–9.
119. Lee RM, Dickhout JG, Sandow SL. Vascular structural and functional changes: their association with causality in hypertension: models, remodeling and relevance. Hypertens Res 2017;40:311–23.
120. Rovida PL, Pagani G, Gerosa V, et al. PP173. The role of mean artery blood pressure in the prediction of pre-eclampsia in pregnancies complicated with chronic hypertension. Pregnancy Hypertens. 2012;(3):333–4.
121. Roncaglia N, Crippa I, Locatelli A, et al. Prediction of superimposed preeclampsia using uterine artery Doppler velocimetry in women with chronic hypertension. Prenat Diagn 2008;28:710–4.
122. Frusca T, Soregaroli M, Zanelli S, Danti L, Guandalini F, Valcamonico A. Role of uterine artery Doppler investigation in pregnant women with chronic hypertension. Eur J Obstet Gynecol Reprod Biol 1998;79:47–50.
123. Zeeman GG, McIntire DD, Twickler DM. Maternal and fetal artery Doppler findings in women with chronic hypertension who subsequently develop superimposed pre-eclampsia. J Matern Fetal Neonatal Med. 2003;14:318–23.