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Preeclampsia and Vascular Function: A Window to Future Cardiovascular Disease Risk

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Abstract

Preeclampsia affects ~3%–7% of all pregnancies and is the third leading cause of maternal mortality globally. Growing evidence indicates that preeclampsia results from vascular dysfunction, which also increases the risk for future cardiovascular events. Until recently, preeclampsia was considered a disorder limited to pregnancy, which fully resolved with the delivery of the placenta; however, it is now clear that women with a history of preeclampsia have approximately double the risk of future cardiovascular events compared to women with normotensive pregnancies. The aims of this review were to describe the hemodynamic and vascular changes that occur in normal and preeclamptic pregnancies, to review noninvasive methods to test vascular function, and to discuss the associated increased cardiovascular disease risk related to preeclampsia.

Introduction

Cardiovascular disease (CVD), which includes coronary heart disease and stroke, is one of the leading causes of mortality and morbidity worldwide. In the United States, heart disease remains the leading killer of women; one in four deaths each year is attributable to CVD.[1] Recent evidence indicates that adverse pregnancy outcomes, such as preeclampsia, are associated with a woman's future risk of CVD.[2–4]

Preeclampsia affects ~3%–7% of all pregnancies.[5] For research purposes, the disorder is usually defined as new-onset hypertension with systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg after 20 weeks of gestation accompanied by new-onset proteinuria.[6] Preeclampsia is commonly accompanied by edema and liver function abnormalities. The disorder is dynamic and is considered severe if one or more of the following conditions are met: blood pressure ≥160/110 mmHg, platelet count <100,000/μL (thrombocytopenia), impaired liver function indicated by elevated liver enzymes and/or epigastric pain that cannot be otherwise explained, elevated serum creatinine concentrations, pulmonary edema, or cerebral or visual disturbances.[6] Recent updated guidelines from the American College of Obstetricians and Gynecologists and the International Society for the Study of Hypertension in Pregnancy further define preeclampsia in the absence of proteinuria if new-onset hypertension is paired with thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbances.[6,7]

In the past, preeclampsia was considered a disorder limited to pregnancy that resolved postpartum. However, preeclampsia is now linked to endothelial dysfunction that persists after delivery.[8] Research suggests that women who experience preeclampsia are at a greater risk of developing CVD later in life; however, it is still unclear if this increased risk is caused by preeclampsia[9] or cardiovascular risk factors present before pregnancy.[10] Due to the mounting evidence that women with a history of preeclampsia have an elevated risk of CVD in the decades after pregnancy, in 2011, the American Heart Association identified preeclampsia as a major CVD risk factor for heart disease in women.[11] The aims of this review were to describe the hemodynamic and vascular changes that occur in normal and preeclamptic pregnancies, to describe a noninvasive method to test vascular function during pregnancy, and to discuss future CVD risk in women with a history of preeclampsia.

Physiology of Normal and Preeclamptic Pregnancy

Pregnancy is characterized by dramatic physiological and biochemical changes to supply adequate oxygen and nutrients to the growing fetus and placenta. During pregnancy, maternal heart rate increases by 20% to compensate for the drop in systemic vascular resistance,[12] cardiac output

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increases by 30%–40%,[13,14] and there is an eightfold increase in uterine artery blood flow.[15] Blood pressure (BP) decreases until around week 18 of pregnancy and progressively increases toward term.[16] Furthermore, pregnancy is characterized by a hyperdynamic circulation with an increase in microvascular blood flow[17] and enhanced resting blood flow,[17,18] particularly in the second and third trimesters.[19,20] These changes return to baseline at various rates in the postpartum period. The increase in cardiac output, plasma volume, and heart rate, combined with decreasing BP during pregnancy, can be seen as a cardiovascular stress test; preeclampsia may be a sign of failing the stress test.

Preeclampsia is a complex generalized syndrome that includes increased vascular resistance and vasoconstriction in a number of maternal vascular beds.[18,21] While the cause of preeclampsia is unknown, diffuse maternal endothelial dysfunction is the underlying clinical presentation. Preeclampsia is believed to result from improper implantation of the placenta to the uterine wall.[22] Preeclampsia is also characterized by an imbalance or deficit in growth factors promoting angiogenesis.[23,24] Growing evidence suggests that inadequate trophoblast invasion of the uterine spiral arteries leads to placental ischemia,[25] which, in turn, initiates the release of the antiangiogenic factors, soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). sFlt-1 binds and inhibits angiogenic factors, such as vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF).[26] sEng is thought to play a similar role to sFlt-1, but, instead of VEGF and PlGF, sEng binds to and inhibits transforming growth factor-β (TGF-β) (Fig. 1).[27] Imbalance in these angiogenic factors deprives the maternal vascular endothelium, resulting in systemic endothelial dysfunction, which may culminate in preeclampsia.[26,28] When administered to pregnant rodents, sFlt-1 induces hypertension, proteinuria, and glomerular endotheliosis.[26] sEng has been shown to disrupt the formation of endothelial tubules and to induce hypertension *in vivo*.[27]

These biomarkers may be predictive of preeclampsia. Women with or who go on to develop preeclampsia exhibit low serum concentrations of free PlGF and VEGF and high concentrations of sFlt-1.[23,26] Additional research has also shown that the ratio of sFlt-1 to PlGF is a better marker of preeclampsia than either measure alone, with a higher ratio indicating increased risk.[29,30] A recent study did not find that the assessment of changes in angiogenic markers between first and second trimesters alone improved the prediction of preeclampsia. However, when considered in conjunction with clinical characteristics, such as baseline BP, race, and body mass index (BMI), the predictive power improved for severe (60% sensitivity, 80% specificity) and particularly for early-onset preeclampsia (88% sensitivity, 80% specificity).[31]

Noninvasive Vascular Testing Measures

Arterial tonometry is a noninvasive method to test vascular function that can be used clinically to measure central BP and arterial stiffness. Research has shown that brachial BP is an imperfect measure of arterial BP,[32] an important variable for predicting CVD outcomes in both men and women.[33,34] In comparison to brachial BP, central pulse pressure (PP) is considered a more direct measure of the aortic pressure

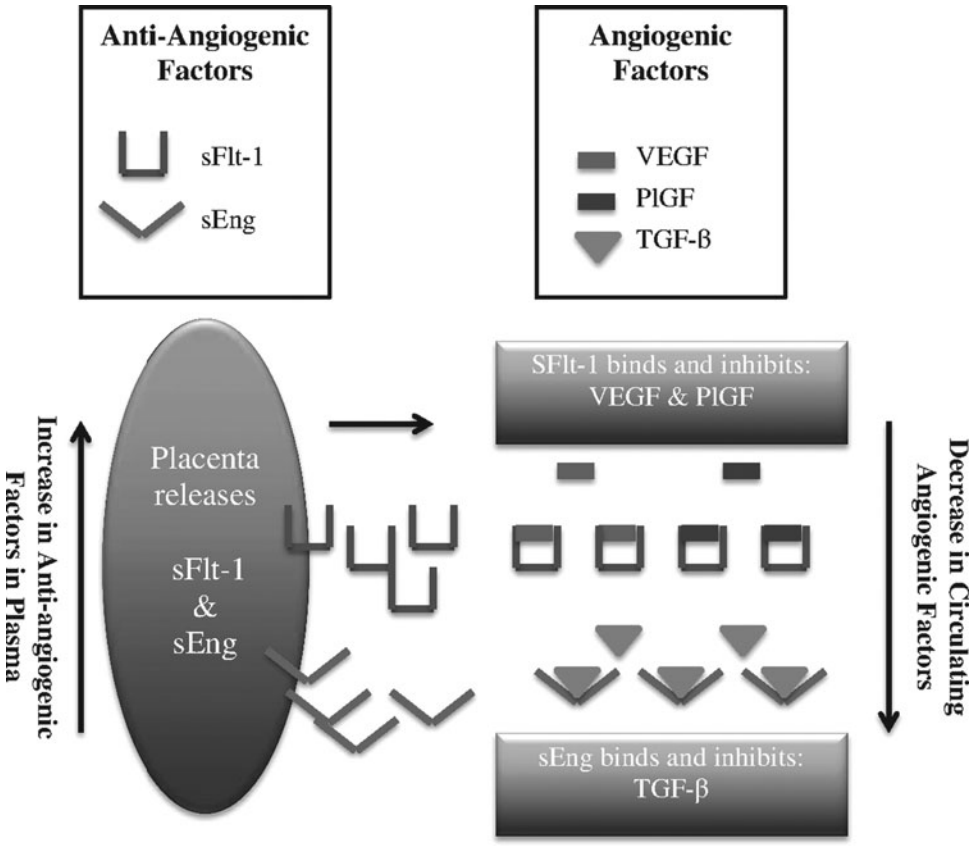

FIG. 1. Current understanding of angiogenic and antiangiogenic factors in preeclampsia. Placental ischemia is thought to promote the release of the antiangiogenic factors, sFlt-1 and sEng. sFlt-1 binds and inhibits VEGF and PlGF. While sEng has been shown to bind and inhibit TGF-β. The overall effect is a decrease in circulating angiogenic factors resulting in systemic endothelial dysfunction. sFlt-1, soluble fms-like tyrosine kinase-1; sEng, soluble endoglin; VEGF, vascular endothelial growth factor; PlGF, placenta growth factor; TGF-β, transforming growth factor-β.

required to circulate blood throughout the body. Parameters measured by arterial tonometry have been found to be associated with the left ventricular hypertrophy,[35] CVD risk factors,[36] CVD events,[37,38] and all-cause mortality.[37,38] Accuracy of arterial tonometry is comparable to traditional invasive vascular testing methods.[39] However, further research is needed before it can be widely used in a clinical setting.[38]

To generate the aortic pressure reading, a tonometer is applied to a peripheral artery, such as the radial artery, to record peripheral pulse waveforms, adjusted for brachial pressure. The result derives a central PP waveform of the ascending aorta. The central PP waveform is the summation of the forward vascular pressure from the heart and backward reflection of the peripheral vasculature.[40] The ability of a vessel to distend and increase volume with increasing pressure is quantified through a pulse wave analysis (PWA), which determines the pressure waveform produced by arterial tonometry. The peak and trough of the PP waveform are central systolic and diastolic BP, respectively (Fig. 2). PWA indices measure vascular compliance and include the following: augmentation pressure (AP), augmentation index (AIx), and AIx75. AP is the additional pressure reflected from peripheral waves back toward the heart that is added to the central systolic peak pressure, while AIx is a ratio of the AP to the central PP (Fig. 2).[40] Given that AIx varies with heart rate, AIx75 is AIx adjusted to a fixed heart rate of 75 bpm.[41] An increase in AIx indicates decreased vascular compliance (*i.e.*, increased arterial stiffness).

Increased AIx is associated with the presence and extent of coronary artery disease[37] and, therefore, may be a useful marker for CVD risk.[36] Interestingly, research has shown that AIx may be especially indicative of CVD risk when utilized in younger populations.[36,42] This may be due to a plateau of AIx values after a certain age, making it more difficult to detect adverse effects on the cardiovascular system.[42]

Pulse wave velocity (PWV) is another noninvasive measure of arterial stiffness derived from arterial tonometry. PWV is defined as the velocity of the pressure wave as it travels between two arteries. Although carotid–femoral PWV is most commonly studied, research has indicated that brachial–ankle indices show similar associations with CVD risk factors and events.[43] Indices are generated by the Moens–Korteweg equation that identifies a relationship between the velocity of the wave and the distensibility of the arterial wall. A higher PWV indicates greater arterial stiffness. For every 1 m/s increase in carotid–femoral PWV, there is an age-, sex-, and risk factor-adjusted increased risk of 14% in total CVD events, 15% in CVD mortality, and 15% in all-cause mortality.[44]

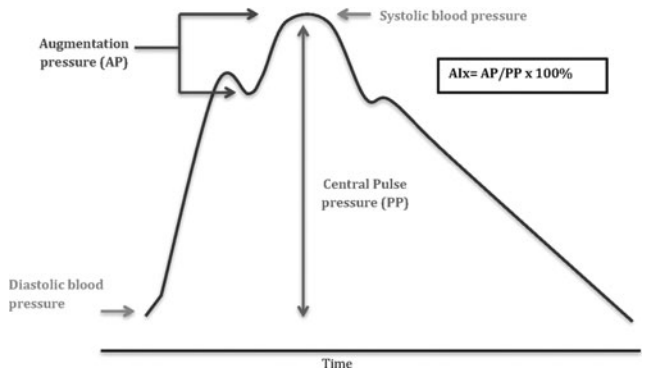

FIG. 2. Central PP wave form of ascending aorta and PWA indices. The peak and trough of the PP waveform are the central systolic and diastolic pressures, respectively. AP accounts for the additional pressure reflected from peripheral waves toward the heart that has an additive effect on the central systolic pressure. AIx is a ratio of the AP to the PP, which indicates the extent to which AP constitutes PP. AIx, augmentation index; AP, augmentation pressure; PP, pulse pressure; PWA, pulse wave analysis.

PWA and PWV can be used as noninvasive diagnostic measures to detect arterial stiffness among patients with and without CVD.[34,45] More recently, these noninvasive measures are being studied to look at vasculature remodeling during pregnancy[46,47] and to determine if they are effective tools for measuring vascular differences between women with and without preeclamptic pregnancies.[48,49]

Noninvasive Vascular Testing During Pregnancy

Normotensive pregnancy

As discussed above, normotensive pregnancy is associated with measurable vascular adaptations to prepare the body for and support the growing fetus. There are a significant amount of vascular changes that occur throughout the entire pregnancy and have been identified as early as 6 weeks of gestation.[46,50] Therefore, it is important to capture changes to the maternal vasculature very early on in the gestational period to understand the full range of adaptations taking place in pregnancy. For example, early in pregnancy, vascular compliance increases (*i.e.*, vascular stiffness decreases) as measured by a decrease in both AIx and BP (Δ brachial systolic: 4 ± 7 mmHg, Δ central systolic: 7 ± 7 mmHg).[46] Interestingly, the changes in AIx and BP occur independent of one another.[47] AIx values decrease in the first and second trimesters and increase during the third trimester, relative to prepregnancy values, and may even exceed prepregnancy levels in the postpartum.[46–48] A greater reduction in central compared to brachial systolic BP has also been identified early in pregnancy.[50] Compared to nonpregnant women, normotensive pregnant women in their third trimester have significantly lower central systolic BP ($p = 0.02$), central PP ($p = 0.02$), AIx ($p = 0.02$), and AP ($p = 0.002$).[51] This trend has been observed in additional cross-sectional analyses, comparing pregnant to nonpregnant women.[52]

There are only a few longitudinal studies that measure arterial function throughout pregnancy within the same population.[46,47,53] Khalil *et al.* were the first to report longitudinal data throughout pregnancy, into the postpartum period, and to evaluate differences between ethnic groups.[47] Analyses showed no significant differences in PWA indices in any trimester between the groups of Caucasian and Afro-Caribbean women.[47] To date, there is only one longitudinal study that offers a look at arterial function from prepregnancy through the postpartum in the same population.[46] Mahendru *et al.* found brachial BP to be 5 ± 8 mmHg and central BP to be 3 ± 8 mmHg lower (mean $\pm$ SD, $p < 0.001$) and AIx $2.5\% \pm 7\%$ higher (mean $\pm$ SD, $p < 0.01$) at 14–17 weeks postpartum than at preconception.[46]

Changes in PWV values follow a similar pattern comparable to the vascular compliance indices measured by PWA, such as AIx. A longitudinal study in normotensive pregnancies found

that PWV decreases during the second trimester, increases from the third trimester through delivery, and then decreases 1 month postpartum.[54] Similar trajectories in PWV indices throughout pregnancy have been replicated in some other studies, further indicating that there are measurable changes in the maternal vasculature that arise in pregnancy.[49,55] Some evidence suggests that the magnitude of the PWV changes across pregnancy is smaller than that of AIx compared to nonpregnant controls.[52] It is possible that differences between study populations in maternal BMI or central BP may account for these conflicting patterns, or lack thereof, in PWV throughout pregnancy.

Preeclamptic pregnancy

Several studies have demonstrated vascular dysfunction during and after preeclampsia using noninvasive measures of arterial function.[48,49] Preeclamptic women present with differences in arterial stiffness and vascular function relative to women with normotensive pregnancies; these differences are measurable by PWA and PWV. Although research is limited, preeclampsia is consistently related to higher AIx both at the time of diagnosis[48,49] and in the third trimester compared to normal pregnancy.[56,57] While increased PWV readings have also been observed in preeclamptic compared to normal pregnancy,[49,56] the increases are much less remarkable and often do not reach statistical significance.[48,58]

Maternal vasculature may be altered even after delivery of the fetus and placenta. Arterial stiffness indices have been found to be elevated from a few weeks[49] up to 3 years postpartum.[59] One recent study measured traditional CVD risk factors, AIx and PWV, in women 10 years after a preeclamptic pregnancy.[60] Women with a history of preeclampsia had higher PWV compared to normotensive pregnant controls matched on age and time since delivery; however, there was no difference in AIx between groups.[60] Previously, preeclamptic women were also more likely to be hypertensive and have a higher waist–hip ratio, indicating that an adverse cardiovascular risk profile persists after delivery.[60] Tests of vascular dysfunction after preeclampsia may help to understand why former preeclamptics are at elevated CVD risk and may help to distinguish which preeclamptics go on to develop CVD.

Severity and time of onset of the preeclamptic disorder have also been found to affect arterial stiffness indices during and after pregnancy. At 33 weeks of gestation, one study found that women with severe preeclampsia [defined as high BP (≥160 mmHg systolic or ≥110 mmHg diastolic), oliguria (500 mL in 24 hours), proteinuria (≥5 g/L in a 24-hour urine collection or ≥3 g/L on two random urine samples), cerebral or visual disturbances, pulmonary edema or cyanosis, impaired liver function, epigastric or right upper quadrant pain, and fetal growth restriction] had significantly higher AIx, PWV, BP, and cardiac outputs than women with preeclampsia who do not have severe cases.[61] Arterial stiffness indices taken as early as 3 months up to 2 years postpartum are also significantly elevated in women who had pregnancies complicated with early-onset preeclampsia (<34 weeks) compared to women with normotensive or late-onset preeclamptic pregnancies (≥34 weeks).[48,62] Furthermore, while AIx values were elevated during early- and late-onset preeclampsia at the time of diagnosis, both AIx and PWV were elevated at 3–6 months after delivery among those with early-onset preeclampsia,[48] suggesting that only women with a history of early-onset preeclampsia exhibit impaired vascular functioning postpartum. The differences in arterial stiffness indices observed in early- and late-onset preeclampsia may be connected to distinguishable angiogenic imbalances. A study comparing angiogenic factors in early- and late-onset preeclampsia found that while the sFlt-1 concentration and sFlt-1/PlGF ratio increased for all cases from diagnosis to time of delivery, the increase was much higher for early-onset preeclampsia (SFlt-1: 11% vs. 3% per day, $p < 0.05$, and sFlt-1/PlGF ratio: 23% vs. 8% per day, $p < 0.05$).[63]

Noninvasive arterial tonometry may also be useful for identifying women who are at risk for preeclampsia. AIx75 and PWV readings, for example, have provided evidence of arterial stiffness at the 11- to 13-week mark in women who subsequently develop preeclampsia.[64] In addition, results of one study found that PWA measured between 11(+0) and 13(+6) weeks of gestation was able to predict 79% of women who developed preeclampsia and 88% of women who developed severe early-onset preeclampsia, with a false-positive rate of 11%.[65] PWV may be especially useful for predicting preeclampsia in high-risk women. A recent study looked at the detection rate of five potential diagnostic markers for preeclampsia in high-risk women between 22 and 26 weeks of gestation as follows: PWV, serum levels of sFlt-1 and uric acid, and 24-hour calcium and protein excretion.[66] Results showed that PWV had the highest detection rate for all cases of preeclampsia (81%) and for early onset (82%) with a false-positive rate of 10%, and when combined with sFlt-1 serum levels, detection rates rose to 90% and 92%, respectively.[66] These findings suggest that both arterial stiffness indices (PWV) and measures of endothelial dysfunction (sFlt-1) combined have the highest diagnostic power for both early- and late-onset preeclampsia. In the same study, univariate analysis showed a strong correlation between PWV and sFlt-1 ($r = 0.408$; $p < 0.001$), and a multivariate adjusted regression model revealed SFlt-1 to be a major determinant of PWV.[66] These findings provide evidence that endothelial dysfunction measured by circulating angiogenic factors is associated with increased arterial stiffness measured by PWV.

Arterial tonometry with its various measures, including AIx and PWV, may offer a simple and accurate approach for evaluating arterial stiffness during pregnancy.[61] These methods may be useful for identifying changes to maternal vasculature during pregnancy and contribute to our understanding of the pathophysiology of preeclampsia. These tests may help to determine the existence and extent of arterial dysfunction before, during, and after pregnancy, as well as identify which factors (*i.e.*, early onset, severity, prepregnancy health) modify the association with future CVD risk. This will give us a window into options for the best treatment of women with preeclampsia and perhaps help us ''type'' preeclampsia with respect to future CVD risk.

Preeclampsia and CVD Risk

Women with a history of preeclampsia are at increased risk of CVD compared to women with a history of normotensive pregnancies.[3,8] It is still unclear whether this relationship reflects a vascular injury from the preeclamptic episode or an

elevated CVD risk profile before pregnancy, making women more susceptible to both preeclampsia and CVD risk factors and events after delivery. Preeclampsia and CVD have shared risk factors, including BMI, hypertension, and diabetes,[67] suggesting that CVD risk, at least in part, may precede preeclampsia. Although a limited number of publications exist, current evidence suggests that CVD risk factors before pregnancy predict preeclampsia[68] and are positively associated with CVD risk after pregnancy.[10] However, one study found that, even in the absence of traditional CVD risk factors, women with a history of new-onset hypertension in pregnancy (with or without proteinuria) are at risk for CVD.[69] This could reflect unmeasured common risk factors or it might suggest a causal impact of preeclampsia on CVD risk. Another study looked at CVD risk factors 10 years after preeclampsia in otherwise healthy women, defined as no diabetes, rheumatic disease, hypertension, renal disease, CVD, or previous preeclamptic pregnancies.[70] While preeclampsia in previously healthy women was not associated with more traditional risk factors, such as BMI, intima–media thickness, and fat mass, these women were more likely to have lower high-density lipoprotein cholesterol and elevated markers of endothelial dysfunction (urate and sFlt-1), supporting the association of preeclampsia, vascular dysfunction, and future CVD risk in women.[70]

After pregnancy, women with a history of preeclampsia display a wide range of differences in CVD risk compared to women with a history of normotensive pregnancies.[71] A meta-analysis of 15 studies found that women with a history of hypertension in pregnancy had elevated biochemical CVD risk factors, including glucose (10 studies), insulin (5 studies), total cholesterol (11 studies), low-density lipoprotein (10 studies), and triglycerides (10 studies).[72] Most of the larger systematic reviews and meta-analyses assessing CVD risk markers following pregnancy do not differentiate between women with preeclampsia and other hypertensive disorders of pregnancy, such as gestational hypertension (without proteinuria). However, a few studies that have looked specifically at women with a history of preeclampsia have shown elevated CVD risk markers.[71,72] In addition, metabolic syndrome and hypertension are common in women with a history of preeclampsia.[72–74] One larger longitudinal study that differentiated between preeclampsia and gestational hypertension found a larger number of CVD risk factors in women with a history of preeclampsia, suggesting that preeclampsia may be a stronger indicator of future CVD than gestational hypertension.[3]

A history of preeclampsia is linked to adverse cardiac outcomes, including hypertension,[75,76] diabetes mellitus,[77] ischemic heart disease,[76] peripheral arterial disease,[78] stroke,[75,76] and CVD death.[78,79] A recent meta-analysis found that women with a history of preeclampsia have three times the risk of developing hypertension (RR = 3.13, 95% CI 2.51–3.89) and double the risk of developing both CVD (OR = 2.28, 95% CI 1.87–2.77) and cerebrovascular events (OR = 1.77, 95% CI 1.43–2.21).[4] These results are similar to other large meta-analyses, which also show increased CVD risk at a relatively young age, further indicating that women with a history of preeclampsia should be monitored closely and early on for CVD.[76,78]

Differences in CVD risk are also observed between subgroups of previously preeclamptic women, with early-onset cases having the highest risk of future CVD.[76] A recently published study found that women with a history of early-onset preeclampsia have significantly increased CVD risk factors and an overall worse CVD risk profile compared to late-onset preeclampsia cases and those with gestational hypertension alone.[80] Furthermore, when looking at the prevalence of hypertension across these three groups of women, almost half of early-onset cases developed hypertension compared to 39% and 25% of women in the gestational hypertension and late-onset groups, respectively.[80] Evidence from studies that compare CVD risk between early- and late-onset preeclampsia all points to a consistent relationship between early-onset preeclampsia and elevated BP.[81,82] This is highlighted in a publication comparing the prevalence of chronic hypertension and the estimated future CVD risk for women with a history of early-onset preeclampsia, late-onset preeclampsia, and normotensive pregnancies.[82] The results of this study showed that only increased prevalence of hypertension significantly contributed to an increased risk for future CVD, while other traditional risk factors did not.[82] In addition, researchers found that only former preeclamptic women with chronic hypertension and those with early-onset preeclampsia (the group with highest prevalence of hypertension) had increased risk for later CVD, indicating that the increased risk of future CVD seen in preeclampsia is likely due to prolonged elevation in BP.[82]

Effectiveness-based guidelines for the prevention of CVD in women in 2011 were updated to include the following three categories of CVD risk: high risk, at risk, or ideal cardiovascular health based on modifiable and nonmodifiable risk factors.[11] A history of preeclampsia alone classifies a woman as ''at risk.'' The guidelines recommend that clinicians ask women about complications related to pregnancy, including gestational diabetes, gestational hypertension, and preeclampsia, to identify women with increased risk for CVD.[11] Furthermore, other pregnancy-related complications are being studied to determine if they increase CVD risk in women, such as premature delivery,[83] fetus size,[84] and delivering a term low-birth-weight infant.[85]

Summary and Future Directions

Vascular dysfunction has been implicated in the pathogenesis of both preeclampsia and CVD, and a shared pathway may explain the association of preeclampsia with CVD events decades later. Preeclampsia is categorized by vascular and biochemical changes that present differently than in normotensive pregnancy. What is not known, however, is whether women enter pregnancy with normal vascular function or if vascular dysfunction predates a preeclamptic pregnancy. The answer to this question is important. If preeclampsia arises in women with normal prepregnancy vascular function, then it may be possible that a causal relationship exists and the stress of the preeclamptic episode, *per se*, results in vascular dysfunction leading to increased CVD risk. However, if preeclampsia is merely an early ''stress test'' unveiling vascular dysfunction, then utilizing biomarkers and vascular screening will help identify women at high risk for preeclampsia as well as future CVD.

Accurate noninvasive testing may prove useful in both cardiovascular and obstetric practices to gain a clearer understanding between preeclampsia and CVD risks. After a preeclamptic pregnancy, identifying the timing and

pathophysiology of CVD risk as it emerges is also essential to designing novel screening and prevention protocols tailored to a young woman's CVD risk profile. Future studies should focus on measuring the prevalence of CVD risk factors and vascular function from postpartum onward to better facilitate the understanding of when the increased risk manifests. More research is needed to test the accuracy and predictive value of arterial tonometry and its measures of arterial stiffness in pregnancy and postpregnancy.[21,47,57,86]

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Author Disclosure Statement

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References

1. Kochanek KD, Xu J, Murphy SL, Minino AM, Kung HC. Deaths: Final data for 2009. Natl Vital Stat Rep 2011;60:1–116.
2. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: An underused opportunity to improve women's health? Epidemiol Rev 2014;36:57–70.
3. Fraser A, Nelson SM, Macdonald-Wallis C, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: The Avon Longitudinal Study of Parents and Children. Circulation 2012;125:1367–1380.
4. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: Systematic review and meta-analysis. Eur J Epidemiol 2013;28:1–19.
5. Rich-Edwards JW, Ness RB, Roberts JM. Chapter 3- Epidemiology of pregnancy-related hypertension. In: Lindheimer RNTMRGCD, ed. Chesley's hypertensive disorders in pregnancy, 4th ed. San Diego: Academic Press, 2015:37–55.
6. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–1131.
7. 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.
8. Agatisa PK, Ness RB, Roberts JM, Costantino JP, Kuller LH, McLaughlin MK. Impairment of endothelial function in women with a history of preeclampsia: An indicator of cardiovascular risk. Am J Physiol Heart Circ Physiol 2004;286:H1389–H1393.
9. Berks D, Hoedjes M, Raat H, Duvekot JJ, Steegers EA, Habbema JD. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: A literature-based study. BJOG 2013;120:924–931.
10. Romundstad PR, Magnussen EB, Smith GD, Vatten LJ. Hypertension in pregnancy and later cardiovascular risk: Common antecedents? Circulation 2010;122:579–584.
11. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: A guideline from the American Heart Association. J Am Coll Cardiol 2011; 57:1404–1423.
12. Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. Am J Obstet Gynecol 1993;169:1382–1392.
13. Lees MM, Taylor SH, Scott DB, Kerr MG. A study of cardiac output at rest throughout pregnancy. J Obstet Gynaecol Br Commonw 1967;74:319–328.
14. Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989;161:1439–1442.
15. Palmer SK, Zamudio S, Coffin C, Parker S, Stamm E, Moore LG. Quantitative estimation of human uterine artery blood flow and pelvic blood flow redistribution in pregnancy. Obstet Gynecol 1992;80:1000–1006.
16. Macdonald-Wallis C, Lawlor DA, Fraser A, May M, Nelson SM, Tilling K. Blood pressure change in normotensive, gestational hypertensive, preeclamptic, and essential hypertensive pregnancies. Hypertension 2012;59: 1241–1248.
17. Anim-Nyame N, Sooranna SR, Johnson MR, Gamble J, Steer PJ. A longitudinal study of resting peripheral blood flow in normal pregnancy and pregnancies complicated by chronic hypertension and pre-eclampsia. Cardiovasc Res 2001;50:603–609.
18. Bowyer L, Brown MA, Jones M. Forearm blood flow in pre-eclampsia. BJOG 2003;110:383–391.
19. Dorup I, Skajaa K, Sorensen KE. Normal pregnancy is associated with enhanced endothelium-dependent flow-mediated vasodilation. Am J Physiol 1999;276:H821–H825.
20. Williams DJ, Vallance PJ, Neild GH, Spencer JA, Imms FJ. Nitric oxide-mediated vasodilation in human pregnancy. Am J Physiol 1997;272:H748–H752.
21. Lampinen K, Ronnback M, Kaaja R, Groop P. Impaired vascular dilatation in women with a history of pre-eclampsia. J Hypertens 2006;24:751–756.

22. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. Obstet Gynecol Annu 1972;1:177–191.
23. Sahay AS, Patil VV, Sundrani DP, et al. A longitudinal study of circulating angiogenic and antiangiogenic factors and AT1-AA levels in preeclampsia. Hypertens Res 2014;37:753–758.
24. Reuvekamp A, Velsing-Aarts FV, Poulina IE, Capello JJ, Duits AJ. Selective deficit of angiogenic growth factors characterises pregnancies complicated by pre-eclampsia. Br J Obstet Gynaecol 1999;106:1019–1022.
25. Matijevic R, Johnston T. In vivo assessment of failed trophoblastic invasion of the spiral arteries in pre-eclampsia. Br J Obstet Gynaecol 1999;106:78–82.
26. 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;111:649–658.
27. Venkatesha S, Toporsian M, Lam C, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med 2006;12:642–649.
28. Sugimoto H, Hamano Y, Charytan D, et al. Neutralization of circulating vascular endothelial growth factor (VEGF) by anti-VEGF antibodies and soluble VEGF receptor 1 (sFlt-1) induces proteinuria. J Biol Chem 2003;278:12605–12608.
29. Verlohren S, Galindo A, Schlembach D, et al. An automated method for the determination of the sFlt-1/PIGF ratio in the assessment of preeclampsia. Am J Obstet Gynecol 2010;202:161.
30. Buhimschi CS, Norwitz ER, Funai E, et al. Urinary angiogenic factors cluster hypertensive disorders and identify women with severe preeclampsia. Am J Obstet Gynecol 2005;192:734–741.
31. Myatt L, Clifton RG, Roberts JM, et al. Can changes in angiogenic biomarkers between the first and second trimesters of pregnancy predict development of pre-eclampsia in a low-risk nulliparous patient population? BJOG 2013;120:1183–1191.
32. Safar ME, Blacher J, Protogerou A, Achimastos A. Arterial stiffness and central hemodynamics in treated hypertensive subjects according to brachial blood pressure classification. J Hypertens 2008;26:130–137.
33. Guray Y, Guray U, Altay H, et al. Aortic pulse pressure and aortic pulsatility are associated with angiographic coronary artery disease in women. Blood Press 2005;14:293–297.
34. Safar ME, Blacher J, Pannier B, et al. Central pulse pressure and mortality in end-stage renal disease. Hypertension 2002;39:735–738.
35. Hashimoto J, Nichols WW, O'Rourke MF, Imai Y. Association between wasted pressure effort and left ventricular hypertrophy in hypertension: Influence of arterial wave reflection. Am J Hypertens 2008;21:329–333.
36. Xiao WK, Ye P, Luo LM, Liu DJ, Wu HM. [Radial augmentation index is associated with cardiovascular risk and arterial stiffness]. Zhonghua Nei Ke Za Zhi 2011;50:831–835.
37. Weber T, O'Rourke MF, Lassnig E, et al. Pulse waveform characteristics predict cardiovascular events and mortality in patients undergoing coronary angiography. J Hypertens 2010;28:797–805.
38. Xu Y, Arora RC, Hiebert BM, et al. Non-invasive endothelial function testing and the risk of adverse outcomes: A systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging 2014;15:736–746.
39. Meidert AS, Huber W, Muller JN, et al. Radial artery applanation tonometry for continuous non-invasive arterial pressure monitoring in intensive care unit patients: Comparison with invasively assessed radial arterial pressure. Br J Anaesth 2014;112:521–528.
40. Nichols WW, O'Rourkey MF. McDonald's blood flow in arteries: Theoretical, experimental and clinical principles, 5th ed. London: Hodder Arnold, 2005.
41. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol 2000;525:263–270.
42. Fischer-Rasokat U, Brenck F, Zeiher AM, Spyridopoulos I. Radial augmentation index unmasks premature coronary artery disease in younger males. Blood Press Monit 2009;14:59–67.
43. Tanaka H, Munakata M, Kawano Y, et al. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. J Hypertens 2009;27:2022–2027.
44. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318–1327.
45. Weber T, Auer J, O'Rourke MF, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation 2004;109:184–189.
46. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. J Hypertens 2014;32:849–856.
47. Khalil A, Jauniaux E, Cooper D, Harrington K. Pulse wave analysis in normal pregnancy: A prospective longitudinal study. PLoS One 2009;4:e6134.
48. Franz MB, Burgmann M, Neubauer A, et al. Augmentation index and pulse wave velocity in normotensive and preeclamptic pregnancies. Acta Obstet Gynecol Scand 2013;92:960–966.
49. Robb AO, Mills NL, Din JN, et al. Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness. Hypertension 2009;53:952–958.
50. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. Maternal cardiovascular changes from prepregnancy to very early pregnancy. J Hypertens 2012;30:2168–2172.
51. Wykretowicz M, Krauze T, Guzik P, et al. Arterial stiffness, central hemodynamics and wave reflection in normal pregnancy and control nonpregnant women. Eur J Obstet Gynecol Reprod Biol 2011;159:49–52.
52. Macedo ML, Luminoso D, Savvidou MD, McEniery CM, Nicolaides KH. Maternal wave reflections and arterial stiffness in normal pregnancy as assessed by applanation tonometry. Hypertension 2008;51:1047–1051.
53. Fujime M, Tomimatsu T, Okaue Y, et al. Central aortic blood pressure and augmentation index during normal pregnancy. Hypertens Res 2012;35:633–638.
54. Oyama-Kato M, Ohmichi M, Takahashi K, et al. Change in pulse wave velocity throughout normal pregnancy and its value in predicting pregnancy-induced hypertension: A longitudinal study. Am J Obstet Gynecol 2006;195:464–469.

55. Karkkainen H, Saarelainen H, Valtonen P, et al. Carotid artery elasticity decreases during pregnancy—the Cardiovascular Risk in Young Finns study. BMC Pregnancy Childbirth 2014;14:98.
56. Elvan-Taspinar A, Franx A, Bots ML, Bruinse HW, Koomans HA. Central hemodynamics of hypertensive disorders in pregnancy. Am J Hypertens 2004;17:941–946.
57. Ronnback M, Lampinen K, Groop PH, Kaaja R. Pulse wave reflection in currently and previously preeclamptic women. Hypertens Pregnancy 2005;24:171–180.
58. Hausvater A, Giannone T, Sandoval YH, et al. The association between preeclampsia and arterial stiffness. J Hypertens 2012;30:17–33.
59. Paez O, Alfie J, Gorosito M, et al. Parallel decrease in arterial distensibility and in endothelium-dependent dilatation in young women with a history of pre-eclampsia. Clin Exp Hypertens 2009;31:544–552.
60. Christensen M, Kronborg CJ, Knudsen UB. [139-POS]: Preeclampsia and arterial stiffness—A 10-year follow up of previous preeclamptic women. Pregnancy Hypertens 2015;5:72–73.
61. Oylumlu M, Oylumlu M, Yuksel M, et al. A simple method for the assessment of arterial stiffness in pre-eclamptic patients. Clin Exp Hypertens 2014;36:531–537.
62. Yinon Y, Kingdom JC, Odutayo A, et al. Vascular dysfunction in women with a history of preeclampsia and intrauterine growth restriction: Insights into future vascular risk. Circulation 2010;122:1846–1853.
63. Schaarschmidt W, Rana S, Stepan H. The course of angiogenic factors in early- vs. late-onset preeclampsia and HELLP syndrome. J Perinat Med 2013;41:511–516.
64. Khalil A, Akolekar R, Syngelaki A, Elkhouli M, Nicolaides KH. Maternal hemodynamics at 11–13 weeks' gestation and risk of pre-eclampsia. Ultrasound Obstet Gynecol 2012; 40:28–34.
65. Khalil A, Cooper D, Harrington K. Pulse wave analysis: A preliminary study of a novel technique for the prediction of pre-eclampsia. BJOG 2009;116:268–276.
66. Katsipi I, Stylianou K, Petrakis I, et al. The use of pulse wave velocity in predicting pre-eclampsia in high-risk women. Hypertens Res 2014;37:733–740.
67. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. BMJ 2005;330:565.
68. Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: Population based cohort study. BMJ 2007;335:978.
69. Mannisto T, Mendola P, Vaarasmaki M, et al. Elevated blood pressure in pregnancy and subsequent chronic disease risk. Circulation 2013;127:681–690.
70. Sandvik MK, Leirgul E, Nygard O, et al. Preeclampsia in healthy women and endothelial dysfunction 10 years later. Am J Obstet Gynecol 2013;209:569.
71. Smith GN, Walker MC, Liu A, et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol 2009;200:58 e51–e58.
72. van Rijn BB, Nijdam ME, Bruinse HW, et al. Cardiovascular disease risk factors in women with a history of early-onset preeclampsia. Obstet Gynecol 2013;121:1040–1048.
73. Aykas F, Solak Y, Erden A, et al. Persistence of cardiovascular risk factors in women with previous preeclampsia: A long-term follow-up study. J Investig Med 2015;63:641–645.
74. Gaugler-Senden IP, Berends AL, de Groot CJ, Steegers EA. Severe, very early onset preeclampsia: Subsequent pregnancies and future parental cardiovascular health. Eur J Obstet Gynecol Reprod Biol 2008;140:171–177.
75. Wilson BJ, Watson MS, Prescott GJ, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: Results from cohort study. BMJ 2003;326:845.
76. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Preeclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. BMJ 2007; 335:974.
77. Magnussen EB, Vatten LJ, Smith GD, Romundstad PR. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol 2009;114:961–970.
78. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses. Am Heart J 2008;156:918–930.
79. Funai EF, Friedlander Y, Paltiel O, et al. Long-term mortality after preeclampsia. Epidemiology 2005;16:206–215.
80. Veerbeek JH, Hermes W, Breimer AY, et al. Cardiovascular disease risk factors after early-onset preeclampsia, late-onset preeclampsia, and pregnancy-induced hypertension. Hypertension 2015;65:600–606.
81. Lazdam M, de la Horra A, Diesch J, et al. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. Hypertension 2012;60:1338–1345.
82. Breetveld N, Ghossein-Doha C, van Kuijk S, et al. Cardiovascular disease risk is only elevated in hypertensive, formerly preeclamptic women. BJOG 2015;122:1092–1100.
83. Perng W, Stuart J, Rifas-Shiman SL, Rich-Edwards JW, Stuebe A, Oken E. Preterm birth and long-term maternal cardiovascular health. Ann Epidemiol 2015;25:40–45.
84. Skjaerven R, deRoo L, Klungsoyr K, Morken NH, Rich-Edwards J, Wilcox AJ. [77-OR]: Preeclampsia and maternal mortality, the importance of size of the fetus. Pregnancy Hypertens 2015;5:41.
85. Dietz PM, Kuklina EV, Bateman BT, Callaghan WM. Assessing cardiovascular disease risk among young women with a history of delivering a low-birth-weight infant. Am J Perinatol 2013;30:267–273.
86. Everett TR, Mahendru AA, McEniery CM, Wilkinson IB, Lees CC. Raised uterine artery impedance is associated with increased maternal arterial stiffness in the late second trimester. Placenta 2012;33:572–577.

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