Should Maternal Hemodynamics Guide Antihypertensive Therapy in Preeclampsia?

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Hypertension in pregnancy impacts ≈10% of all pregnancies.[1] Hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension (new-onset hypertension with blood pressure <140/90 after 20 weeks gestation), or preeclampsia (new-onset hypertension with blood pressure <140/90 after 20 weeks gestation with proteinuria or thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral/visual symptoms). On the basis of the timing of clinical presentation or delivery, preeclampsia may be further classified into either early-onset preeclampsia (<34 weeks) or late-onset preeclampsia (34 weeks and beyond).

Hypertensive disorders of pregnancy are a leading cause of maternal morbidity and mortality, accounting for 14% of all maternal deaths worldwide.[2] Gestational hypertension is typically benign; however, 46% of women with gestational hypertension will progress to preeclampsia.[3,4] Although less common, preeclampsia is considered a more severe disease that progresses rapidly and is associated with increased risk of significant maternal and perinatal adverse outcomes, including placental abruption, preterm birth, and low birthweight.[5] Antihypertensive treatment for pregnant women presenting with hypertension must be initiated in a timely manner, as the clinical condition can rapidly deteriorate into a hypertensive emergency that requires hospitalization, stabilization, and close monitoring. If maternal hypertension cannot be controlled, iatrogenic preterm delivery before 34 weeks gestation may be required, with associated significant perinatal risk. Postpartum women who develop hypertension during pregnancy are at significantly higher risk for cardiovascular death, and the offspring of hypertensive pregnancies exhibit significantly elevated blood pressures, compared with normotensive pregnancy.[6,7]

Early diagnosis of hypertension provides an opportunity to initiate antihypertensive therapy before the escalation of clinical symptoms and, most importantly, before the development of significant maternal and fetal adverse outcome.[8] Currently, there is no consensus on the most effective antihypertensive therapy when managing pregnant women presenting with hypertension. A hemodynamic-guided approach to antihypertensive therapy has been investigated in nonpregnant patients.[9,10] Although this approach was demonstrated to improve blood pressure reduction goals, it was never broadly adopted into clinical practice. As pregnant women who subsequently develop early-onset or late-onset preeclampsia exhibit distinct hemodynamic profiles early in pregnancy before the development of clinical hypertension, hemodynamic-guided therapy may improve blood pressure management in women with preeclampsia.[11]

This review will focus specifically on the potential use of maternal hemodynamic-guided therapy for pregnant women with preeclampsia, the more severe hypertensive disorder of pregnancy that has been the subject of intense research in recent years. Hemodynamic-guided therapy for pregnant women with chronic hypertension, gestational hypertension, and preeclampsia superimposed on preexisting hypertension is beyond the scope of this review, as these hypertensive disorders have not been as thoroughly investigated as preeclampsia and there is currently not enough information on maternal hemodynamics in these diseases.

Pathophysiology of Preeclampsia

The maternal cardiovascular system undergoes significant anatomic and functional adaptations throughout normal pregnancy, as the maternal heart adapts to volume expansion.[12] Pro- and antiangiogenic proteins are secreted by the placenta into the maternal circulation, mediating the cardiovascular adaptations to pregnancy. Maternal systemic vascular resistance decreases by ≈25% by the third trimester compared with the nonpregnant state, with significant increases in heart rate, stroke volume, and cardiac output of 15%, 18%, and 32%, respectively.[12] In normal pregnancy, maternal blood pressure decreases early in pregnancy, rising to nonpregnant levels by term. Maternal cardiovascular adaptations that occur during normal pregnancy are disrupted in women with hypertension associated with preeclampsia; however, the nature of the hemodynamic abnormalities is not uniform and is dependent on the timing of onset of preeclampsia.

There have been significant advances in the understanding of the pathophysiology of hypertension in early-onset and late-onset preeclampsia, largely driven by research that has defined abnormalities in maternal cardiovascular function and circulating placental-derived angiogenic proteins.[11,13,14] Early-onset preeclampsia seems to be mediated predominantly by placental dysfunction, whereas late-onset preeclampsia more likely relates to maternal constitutional factors associated with the metabolic syndrome and abnormalities in vascular

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function.[15,16] It is hypothesized that early-onset preeclampsia originates from inadequate remodeling of maternal spiral arteries causing abnormal placenta development. It is hypothesized that placental ischemia induces the abnormal production of angiogenic proteins that are secreted by villi and, on entering the maternal circulation, disturb normal endothelial function.[13] Women with early-onset preeclampsia exhibit significantly higher levels of placental-derived antiangiogenic proteins and significantly lower levels of proangiogenic proteins, when compared with healthy pregnant women.[17–19] If placental development is severely compromised, uncontrolled maternal hypertension with end-organ damage and severe fetal growth restriction often dictates preterm delivery before 34 weeks gestation.[8,20] By contrast, late-onset preeclampsia is less frequently associated with placental pathology and more normal levels of placental-derived angiogenic proteins compared with early-onset preeclampsia.[18,21] Consistent with this theory, late-onset preeclampsia is typically associated with more favorable maternal and infant outcomes, with a normal or even large for gestational age birthweight.[22] It has been hypothesized that maternal hypertension in late-onset preeclampsia is a compensatory response to ongoing fetal metabolic demands surpassing the placenta's ability to sustain adequate fetal growth.[23] It is currently unknown whether gestational hypertension is a separate hypertensive disorder from preeclampsia, or if it is simply a mild form of preeclampsia.[8,24]

Hemodynamic Profiles of Pregnant Women With Preeclampsia

Recent investigations have identified striking differences in the maternal hemodynamic profiles of early-onset and late-onset preeclampsia, leading to the hypothesis that these hypertensive disorders of pregnancy most likely arise from different pathoetiologies.[11,25] As early as 8 weeks gestation, women who subsequently develop gestational hypertension or preeclampsia demonstrate significantly elevated blood pressure compared with normotensive women.[25] Interestingly, unique patterns of blood pressure change over the time course of pregnancy are seen in the different hypertensive disorders of pregnancy, with preeclamptic women demonstrating a more rapid increase in blood pressure from 30 weeks onwards compared with women with gestational hypertension. In addition, an investigation assessing the circadian pattern of blood pressure in pregnancy using ambulatory blood pressure monitoring determined that women who develop hypertensive disorders of pregnancy exhibit statistically significant difference in the systolic and diastolic blood pressure circadian variability across all trimesters, compared with normotensive pregnant women.[26] In this study, pregnant women who subsequently develop gestational hypertension or preeclampsia exhibit similar circadian characteristics in the first trimester; however, significant differences are observed across the second and third trimesters.

At 24 weeks gestation, before the clinical presentation of hypertension, women who develop early-onset preeclampsia demonstrate significantly higher blood pressure and systemic vascular resistance with lower heart rate, stroke volume, and cardiac output compared with normotensive pregnant women.[11,14,27] By contrast, pregnant women who subsequently develop late-onset preeclampsia manifest higher stoke volume, cardiac output, and heart rate with significantly lower vascular resistance compared with normotensive pregnant women.[11,14,27] Increased total peripheral resistance during pregnancy has been associated with abnormal plasma levels of angiogenic proteins derived from the ischemic placenta and may also be modified in preeclamptic women by an increased inflammatory response, endothelial dysfunction, and sympathetic overactivity.[8,28–31] A recent study concluded that the assessment of biophysical markers of cardiovascular strain, including blood pressure and total peripheral resistance, and biochemical markers, including placental-derived angiogenic proteins and NT-proBNP (N-terminal pro-B-type natriuretic peptide), in pregnant women presenting with hypertensive disorders of pregnancy and normotensive pregnant women provides further insight into the pathogenesis of these disorders, which in turn may improve prediction and intervention.[32] Prediction of preeclampsia using maternal hemodynamics has been investigated, with total peripheral resistance identified as the best independent predictor of maternal and fetal complications, including preeclampsia.[32,33]

Although maternal and fetal outcomes differ greatly between the hypertensive disorders of pregnancy, the initial common presentation of new-onset hypertension can make early disease differentiation difficult. In addition, disease presentation for these disorders can vary greatly in timing and severity; for example, women with early-onset preeclampsia can present initially with isolated hypertension with no other manifestations of preeclampsia. Information on the maternal hemodynamic profile in the preclinical or latent phase of eclamptic disease could help clinicians anticipate the clinical course of pregnancy and potential hypertensive emergencies. The ability to discriminate between hypertensive disorders of pregnancy early in pregnancy before the development of overt hypertension may be possible, as studies have consistently demonstrated the distinct maternal hemodynamic profiles of these diseases.

Recommendations for Management of Hypertension in Preeclampsia

Despite the prevalence and severity of hypertension in the setting of preeclampsia, there is no accepted standard of care for its management. Aspirin has been shown to improve pregnancy outcomes in women at risk of preeclampsia but does not play a role in the management of blood pressure.[34–36] The management of preeclampsia is primarily focused on the therapy of maternal hypertension to reduce the risk of severe hypertensive episodes and to safely prolong gestation. In general, the current standard of care follows the principle that optimum timing and effectiveness of antihypertensive therapy have favorable influence on maternal and fetal outcomes.

Despite evidence that hypertensive disorders of pregnancy do not involve 1 common origin, current recommendations for antihypertensive therapy during pregnancy do not differentiate therapy based on an assessment of maternal hemodynamics, or indeed of any maternal physiological characteristics aside from blood pressure. Rather, antihypertensive medication is merely empirically recommended if blood pressure is above a certain threshold for women with gestational hypertension and preeclampsia, although there is no consensus on what this threshold should be. The National Institute for Health

and Clinical Excellence guidelines in the United Kingdom recommend antihypertensive therapy for preeclamptic women with systolic blood pressures >150 mm Hg or diastolic blood pressures >100 mm Hg, whereas the American College of Obstetricians and Gynecologists recommends that preeclamptic women with severe hypertension initiate antihypertensive therapy when blood pressure is >160 mm Hg systolic or 110 mm Hg diastolic.[37,38] Recommendations from the Society of Obstetrics and Gynaecologists of Canada are not specific to preeclampsia, rather instruct that maternal blood pressure should be lowered to <160 mm Hg systolic and 100 mm Hg diastolic in cases of severe hypertension.[39] In cases of nonsevere hypertension, maternal blood pressure is recommended to be controlled between 130 and 155 mm Hg systolic and 80 and 105 mm Hg diastolic in cases without comorbid conditions, or under 140 mm Hg systolic and 90 mm Hg diastolic in cases with comorbid conditions.[39]

Furthermore, the choice of antihypertensive medications for management of hypertensive disorders of pregnancy is recommended to be primarily based on the physician's familiarity and experience, adverse effects and contraindications to the prescribed drug, local availability, and cost.[38] Labetalol, nifedipine or nicardipine, hydralazine, and methyldopa are recommended in preference to angiotensin-converting enzyme inhibitors, whereas angiotensin receptor blockers and renin inhibitors are not recommended for use during pregnancy. The use of mineralocorticoid receptor antagonists for treatment of hypertension in pregnancy is less clear, with no mention of these agents in the UK and Canadian guidelines, whereas the American guidelines strongly recommended against the use of mineralocorticoid receptor antagonists in pregnancy.[37–39]

Although no trial of antihypertensive therapy has demonstrated a definitive benefit on maternal or fetal pregnancy outcome, the therapy of hypertension in the setting of preeclampsia remains a clinical standard. The important question that remains is which pharmacological approach would be associated with the best outcome. Tighter overall control of maternal blood pressure (target diastolic blood pressure, 85 mm Hg) reduced the risk of severe maternal hypertension in pregnant women with preexisting or gestational hypertension, compared with less-tight control (target diastolic blood pressure, 100 mm Hg); however, such control does not reduce pregnancy loss, high-level neonatal care, or serious maternal complications.[40] Tighter blood pressure control was also associated lower incidence of elevated liver enzymes and thrombocytopenia. A Cochrane review comparing antihypertensives in pregnant women with severe hypertension concluded that there did not seem to be differences in blood pressure control between the commonly prescribed hydralazine, labetalol, and nifedipine.[41] However, no differentiation was made between underlying hypertensive disorders of pregnancy being treated. Because there were insufficient data to evaluate the superiority of antihypertensives, as the majority of trials were small (<100 women), with few studies reporting outcomes beyond blood pressure control, the hypothesis that goal-directed antihypertensive therapy could confer significant benefit has yet to be tested.[41] More recently, a randomized controlled trial investigating choice of antihypertensive therapy for pregnant women with chronic hypertension concluded that both labetalol and nifedipine effectively controlled maternal blood pressure to treatment target.[42] An additional Cochrane review determined that antihypertensive therapy in pregnant women with mild to moderate hypertension significantly reduced the subsequent progression to severe hypertension, but did not impact the development of preeclampsia, fetal death, or small for gestational age babies.[43] Interestingly, β-blocker and calcium channel blocker antihypertensive therapy was associated with reduction in the risk of proteinuria/preeclampsia development, when compared with methyldopa therapy (risk ratio, 0.73; 95% confidence interval, 0.54–0.99). The risk of proteinuria/preeclampsia development in pregnant women with mild to moderate hypertension was significantly reduced with β-blocker therapy (risk ratio, 0.73; 95% confidence interval, 0.57–0.94), as assessed in 8 trials with 883 women, and was significantly increased with calcium channel blocker therapy, as assessed in 4 trials with 725 women (risk ratio, 1.40; 95% confidence interval, 1.06–1.86), when compared with no treatment with these agents.[43]

However, the trials assessed in this review were small with heterogeneous patient populations, leading authors to conclude that there are currently insufficient data to assess if antihypertensive therapy is worthwhile for pregnant women with mild to moderate hypertension. Despite significant advancements in understanding disease pathophysiology and cardiovascular function of hypertensive disorders of pregnancy, there has been no parallel progress toward optimizing antihypertensive therapies for women with hypertensive disorder of pregnancy.

Hemodynamic-Guided Antihypertensive Therapy in Nonpregnant Patients

In the nonpregnant population, hypertension is managed empirically, with most therapeutic approaches designed to reduce inappropriately elevated peripheral vascular resistance. This approach is successful in the large majority of patients with hypertension. As such, antihypertensive therapy is relatively straightforward, except in rare cases where there are secondary causes or in the setting of accelerated hypertension.

Nearly 40 years ago, an individualized strategy of antihypertensive therapy for essential hypertension was based characterizing and classifying disease phenotype according to renin–angiotensin–aldosterone system activity, categorizing patients into those with increased plasma volume versus those with increased peripheral resistance.[44] The majority of hypertensive patients were found to have elevated plasma renin and considered to have hypertension mediated through increased vascular resistance. These patients were preferentially designated to antirenin therapy, at that time primarily β-blockers, followed by angiotensin-converting enzyme inhibitors. The minority of patients were characterized by low plasma renin levels and considered to have sodium-mediated hypertension with a favorable response to diuretic therapy.[45] The first report of such a strategy determined that the effectiveness of propranolol in hypertensive patients was determined to closely correlate with plasma renin levels, with the greatest reduction in diastolic blood pressure in patients with high renin activity, suggesting a neurogenic mechanism of action.[46] Furthermore, patients with hypertension characterized by vasoconstriction

and elevations in renin were shown to be at significantly higher risk of myocardial infarction.[47] Therefore, plasma renin activity was determined to be an effective indicator of essential hypertension origin, predicts blood pressure responses to antihypertensive therapy, and directs appropriate, effective antihypertensive therapy. Despite potential use, this neurohormonal approach to guide antihypertensive therapy has never been broadly applied, in part because reliable assays for plasma renin were not routinely available in the clinical setting.

The strategy of individualized antihypertensive therapy using noninvasive hemodynamic assessments based on thoracic bioimpedance or bioreactance has been investigated in a limited number of studies in nonpregnant patients. This approach to the management of hypertension was recently reviewed.[48] Overall, this approach to hemodynamic-guided antihypertensive therapy of uncontrolled hypertension was more effective for blood pressure control in nonpregnant hypertensive patients, when compared with specialist care alone. In one of the reviewed trials, a predefined hemodynamic-based, antihypertensive therapy protocol was developed for patients with resistant or refractory hypertension, such that patients presenting with low cardiac index and high vascular resistance (as typically observed in early-onset preeclampsia) were prescribed a calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or direct vasodilator, accompanied by a reduction in β-blocker use.[10] Conversely, patients with high cardiac index and low systemic vascular resistance index were prescribed a β-blocker with a reduction in vasodilators. Blood pressure control was more effective in patients where hemodynamic-guided therapy was used when compared with patients where therapy was guided by physician preference.[10] Similar results were obtained in another study where hemodynamic-driven therapy led to greater reductions in blood pressure in nonpregnant patients with uncontrolled hypertension, with higher control rates when compared with standard care (77% versus 57%, $P<0.01$).[9] In this case, systemic vascular resistance index was significantly reduced in the hemodynamic monitoring cohort, compared with the control group.[9] Significantly more patients in the hemodynamic-driven arm became hemodynamically normal, based on blood pressure, cardiac index, and systemic vascular resistance index, when compared with those receiving standard antihypertensive care.

Therefore, the use of hemodynamic-guided approach has proven feasible to improve the ability of the practitioner to achieve blood pressure reduction goals in the nonpregnant hypertensive population; however, to date, no studies have compared the long-term impact of a standard empirical approach versus a tailored hemodynamic assessment approach on meaningful clinical outcomes. Trials designed to assess differences in clinical outcomes with the application of a tailored approach to therapy in nonpregnant patients with systemic hypertension would have been impractical, as the low event rates in this population would have necessitated large sample sizes and extensive follow-up periods. However, the situation is very different for hypertensive disorders of pregnancy, particularly those patients who are suspected to have preeclampsia. In these cases, adverse events for mother and fetus are common, and effective antihypertensive therapy must be initiated promptly. In some cases, if antihypertensive therapy is not effective and there are other signs of maternal and fetal risk, premature delivery may be mandated.

Hemodynamic-Guided Antihypertensive Therapy in Preeclampsia

There are clear differences in the hemodynamic characteristics of pregnant women presenting with hypertension, with early-onset preeclampsia characterized by elevated systemic vascular resistance, and late-onset preeclampsia characterized by increased cardiac output with relatively reduced vascular resistance.

Although the theory of guiding antihypertensive treatment in pregnancy through hemodynamic assessment is not novel, only a small number of trials have evaluated maternal hemodynamics in pregnant women receiving antihypertensive therapies.[49] In severe preeclamptic women experiencing a hypertensive emergency, the calcium channel blockers nifedipine and nicardipine decreased mean arterial pressure and significantly reduced maternal vascular resistance while increasing cardiac index, as assessed through thoracic electric bioimpedance and transthoracic Doppler echocardiography.[50,51] In a similar population of women with severe preeclampsia, labetalol decreased mean arterial pressure and heart rate but had no effect on cardiac index and did not reduce systemic vascular resistance.[52] In a randomized, placebo-controlled trial, atenolol decreased the incidence of late-onset preeclampsia in nulliparous women with a high cardiac output hyperdynamic state (the typical late-onset preeclampsia hemodynamic profile), compared with placebo treatment.[53] More recently, pregnant women presenting with any type of hypertension who were unresponsive to labetalol were characterized as being more likely to be of black ethnicity and to have higher blood pressure and total peripheral resistance and lower heart rate and cardiac output at the time of clinical presentation, as assessed through thoracic bioreactance.[54] Furthermore, these unresponsive women also delivered significantly earlier in pregnancy with lower fetal birthweight, were twice as likely to develop preeclampsia and over 10× as likely to develop severe hypertension. Finally, antihypertensive therapy for pregnant women presenting with any type of hypertension being referred for antihypertensive therapy that was guided by hemodynamic monitoring significantly reduced the rates of severe maternal hypertension from 18% to 3.8%.[55] A retrospective review of pregnant women at risk of preeclampsia treated with atenolol early in pregnancy who had subsequent antihypertensive therapy guided by maternal hemodynamics determined that this strategy was generally effective for preventing maternal hypertension and preterm birth.[56] These studies are hypothesis raising but require confirmation in larger scale studies powered to determine if such tailored hemodynamic approaches to blood pressure management can favorably modify maternal and fetal outcomes.

It is well known that noninvasive hemodynamic assessments have limitations in terms of accuracy and reproducibility. Hemodynamic assessment using Doppler echocardiographic techniques in pregnant women is limited by lack of uniform access to highly trained sonographers, as well as the technical challenges associated with pregnancy.[57] Nonimaging Doppler

approaches have been developed that are less demanding in terms of technical staff but still require training, are operator dependent, and have not been widely adopted.[58,59] However, routine noninvasive hemodynamic assessment can be more widely applied using techniques based on thoracic bioimpedance or bioreactance. Commercial systems are available that have been validated in nonpregnant patients when compared with other techniques used in the measurement of cardiac output, most commonly thermodilution.[60–63] Importantly, validation of thoracic bioimpedance and bioreactance technology compared with thermodilution in the setting of pregnancy is not available and is unlikely to be forthcoming. However, the reporting of true cardiac output by a noninvasive device may not be necessary to establish clinical validity, as long as a device is repeatable, able to differentiate between distinct populations and detect changes in hemodynamics.[64]

A Proposal for Future Research

Thoracic bioimpedance and bioreactance technology can provide the hemodynamic information necessary to individualize antihypertensive disorders in patients with preeclampsia. The assessment of maternal hemodynamics in addition to standard blood pressure measurements could be used to provide a physiological basis for the choice of antihypertensive therapy of pregnant women at high risk of or presenting with preeclampsia. Current recommendations for antihypertensive therapy in pregnancy do not differentiate treatment based on maternal hemodynamic data, despite distinct origins of hypertension between hypertensive disorders of pregnancy. Although not widely used in standard clinical care, a tailored, hemodynamic-guided approach using an ambulatory device has proven effective for controlling blood pressure in nonpregnant hypertensive populations. We hypothesize that hemodynamic-guided screening would stratify pregnant women presenting with preeclampsia, distinguishing between the hypertensive disorders of pregnancy and guide antihypertensive therapy. This approach could be further augmented by the assessment of placental-derived angiogenic markers, which establish a placental basis for systemic maternal vascular dysfunction.[28,65] This concept of individualized therapy has the potential to improve blood pressure control, placental perfusion, and perinatal outcomes in hypertensive preeclamptic women. After initiation of antihypertensive therapy, continued hemodynamic monitoring is recommended to observe maternal response to therapy and detect any abrupt deviations from the initial hemodynamic profile observed, as has previously been described in women with preeclampsia.[66]

Hypertension in the setting of pregnancy is associated with high maternal and fetal event rates. As such, although still a substantial organizational challenge, it is possible to launch multi-centered clinical trial programs with adequate sample sizes. Clinical trials that evaluate hemodynamic-guided therapy for the selection of appropriate antihypertensive therapy and blood pressure management in preeclamptic women based on individual hemodynamics mediating hypertension would serve to answer many outstanding clinical questions and could be of great clinical value. First, they would be able to define which antihypertensive agents provide the best blood pressure control in preeclampsia. Hemodynamic-guided therapy could also be valuable for selection and timing of a second antihypertensive agent, in the setting of resistant hypertension. Second, they could define whether the choice of antihypertensive therapy has a significant impact on maternal and fetal outcome. Third, longitudinal hemodynamic assessments may further evaluate the predictive capacity of the hemodynamic profile in differentiating between normotensive pregnancy versus early- and late-onset preeclampsia; this will likely directly impact clinical management in pregnancy. These clinical programs would confirm the effectiveness of noninvasive assessment of hemodynamics in the setting of hypertensive disorders of pregnancy.

Ideally, the optimization of hypertension management in preeclampsia should be a collaborative effort involving obstetrics and hypertension specialists. Though cardiologists are typically not consulted when pregnant women present with hypertension, this collaboration may broaden both the approach to research and improve patterns of clinical care. When compared with a nonpregnant hypertensive patient, women with preeclampsia represent a unique population with rapid onset of hypertension that typically resolves with delivery, requiring the precarious challenge of balancing maternal and fetal health. The addition of hemodynamic monitoring, along with specialist care, may improve the effectiveness of antihypertensive therapy, compared with specialist judgment alone.

Conclusions

In summary, there remains no definitive evidence on the superiority of antihypertensive therapies for maternal and fetal outcomes in preeclamptic women. A focus on normalizing maternal hemodynamic function in addition to reducing maternal blood pressure based on unique hypertensive disorders of pregnancy could be a future therapeutic strategy.

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