EDITORIAL

Hemodynamic Prediction and Stratification of Hypertensive Disorders of Pregnancy: A Dream That Is Coming True?

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Hypertensive disorders of pregnancy (HDP) are a major cause of maternal and fetal morbidity and death.[1] To date, the prediction of these disorders and their complications has been based on many clinical characteristics, hemodynamics, and placental indicators (either with Doppler evaluation of uterine artery and/or levels of circulating angiogenic proteins).[2–11] Early identification of asymptomatic women more likely to develop HDP and other complications would help clinicians in planning appropriate monitoring during pregnancy, potentially treating the condition with preventive strategies before the blood pressure actually increases, and with a possible delay or mitigation of its consequences.

Pregnancy is usually associated with a reduction of uterine artery resistance attributable to a correct trophoblast invasion, inducing a reduction of total vascular resistance (TVR).[12] This process reaches its nadir in the second trimester. When these mechanisms fail, uterine artery resistance and TVR do not fall and HDP and/or other complications of pregnancy, such as fetal growth restriction, may develop.

Many methods have been used in the past for the prediction of HDP. The first one has been the uterine artery Doppler interrogation in the second trimester, and has been introduced since the past 2 decades of the past century.[1] Lately, biochemical and central hemodynamic parameters have been used to refine and improve the classification and the prediction of HDP.[2–11,13]

In this issue of the *Journal of the American Heart Association* (*JAHA*), McLaughlin et al[13] propose an interesting study to identify, through a hieratical cluster analysis, phenotypes of pregnant women with different risk of developing HDP: low-, moderate-, and high-risk patients.

The authors use different methods, such as clinical characteristics of the mothers, local (uterine artery resistance) and central (TVR) hemodynamics, and placental biochemical indicators, to identify the best predictive approach to the HDP.

The study included 46 normotensive women, of whom 20 were at low risk and 26 were at high risk of developing HDP. The high-risk group was selected through abnormal placental biochemistry, abnormal placental shape or texture, abnormal uterine artery Doppler, and abnormal clinical risk factor score. The authors added to the evaluation a noninvasive hemodynamic assessment performed between 22 and 26 weeks' gestation through transthoracic bioreactance. The statistical approach was interesting for identifying clusters of parameters predicting the different class of risk for HDP.

Interestingly, although no woman was hypertensive at the time of the hemodynamic evaluation in the second trimester, the high-risk group showed low stroke volume (SV) and a high peripheral resistance hemodynamic profile with lower placental growth factor levels.

Strikingly, the higher the risk of developing HDP, the higher is the hemodynamic compromise: in women in the cluster of high and moderate risk of developing HDP, TVR was 45% and 24% higher, respectively, than in the low-risk cluster. One of the strengths of the study was the normotensive profile of women at the time of the hemodynamic evaluation, so that blood pressure was at best in the high normal level. Nevertheless, if we look at mean arterial pressure in the 3 clusters of risk, we can notice that is higher as the risk increases, although the absolute levels of blood pressure suggest that blood pressure measurements are unlikely to predict satisfactorily the hypertensive disorders that have yet to appear. Instead, the markedly elevated TVR was reflected in significantly reduced cardiac output (CO), mainly because of a low SV. These data thus indicate a vascular dysfunction in the preclinical phase of HDP during the second trimester of pregnancy.

The inclusion of maternal hemodynamics in combination with well-established clinical and biochemical parameters

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routinely used for the prediction of HDP is the important novelty of this study. In particular, 14 different clinical, biochemical, and hemodynamic parameters were included in the analysis. Lately, many groups of researchers have used different methods for the detection of hemodynamic parameters in pregnancy: echocardiography[8–11]; UltraSonic Cardiac Output Monitor and Non-Invasive Cardiac Output Monitor (noninvasive Doppler method to determine hemodynamic values with a nonimaging continuous-wave Doppler transducer)[14]; and impedance cardiography and thermodilution.[13,15] Many of the latest studies have shown that, among the hemodynamic parameters, TVR and CO represent a cornerstone for the understanding of the preclinical and clinical stages of the HDP. McLaughlin et al,[13] in accordance with other reports, found in their study that maternal TVR was the best single predictive factor for the development of hypertension in pregnancy, followed by endoglin, mean arterial pressure, placental growth factor, and soluble Fms-like tyrosine kinase-1. TVR represents the equilibrium between SV, blood pressure, and heart rate. The noninvasive detection of TVR with one of the above-mentioned techniques in the second trimester of pregnancy would provide physicians valuable data to consider a possible preventive approach, for those women in the moderate- or high-risk clusters. The clinical use of this approach, however, requires much larger studies.

The question that arises, and that McLaughlin et al[13] try to discuss, is related to the usefulness of the hemodynamic monitoring of pregnancy for directing a preventive treatment. In normotensive high-risk patients and gestational hypertensive women, elevated TVR early in pregnancy strongly correlates with subsequent severe complications (ie, preeclampsia, severe hypertension, fetal growth restriction, abruption placentae, and Hemolysis, Elevated Liver enzymes, and Low platelet count [HELLP] syndrome).[8,9] Some interesting studies have noted that, in established gestational hypertension with high TVR, the intervention based on a hemodynamic approach may be useful for the reduction of severe complications during pregnancy.[16,17] In particular, a reduction of TVR by >20% in hypertensive patients appears to reduce severe complications[16]; other reports have also demonstrated that a hemodynamic approach to the antihypertensive therapy versus standard care may significantly reduce the rate of severe maternal hypertension.[17] On the other hand, some authors pose some caution on the basis of a well-done meta-analysis[18] that evidenced how an excessive reduction of mean blood pressure could be harmful for the baby because of a reduction of placental perfusion. In this meta-analysis,[18] however, no data on CO were taken into account. The standard care and the international guidelines, in fact, only look at the blood pressure levels, without any definitive evidence on the superiority of this approach for maternal and fetal outcomes in pregnancy hypertension.[19] Actually, the way we achieve TVR reduction during gestational hypertension, when this is high, should be the focus of our pharmacological intervention. The reduction of TVR may be achieved in different ways: (1) a reduction of blood pressure alone; (2) an increase in CO (increasing heart rate, SV, or both); or (3) a combination of blood pressure reduction and CO increase. The reduction of blood pressure alone might be ineffective in reducing TVR significantly, in particular when the circulation is underfilled and the high blood pressure becomes essential in maintaining placental perfusion. That is why when reducing blood pressure in a patient with high TVR–low CO gestational hypertensive status, we need to induce an increase of SV-CO to avoid placental underperfusion. In this view, the datum of maternal hemodynamic profile (derived from echocardiography; transthoracic bioimpedance; Doppler noninvasive techniques, such as UltraSonic Cardiac Output Monitor or Non-Invasive Cardiac Output Monitor; or any other technique) appears to be crucial. This information differentiates patients with high blood pressure and high TVR–low SV-CO, who need a reduction of blood pressure associated with an increase in CO-SV, from those with high blood pressure and low or normal TVR (mainly characterized by high SV-CO), for whom our target of treatment might be represented almost exclusively by the blood pressure levels. Therefore, heart rate, SV, and blood pressure (the 3 parameters accounting for the maternal hemodynamic profile included in TVR) should be taken into account together when choosing a pharmacological treatment for pregnant hypertensive patients.

McLaughlin et al[13] go further, posing another question in the discussion: if hemodynamic profile identifies patients likely to develop HDP in the latent phase, is it then possible to act on the hemodynamics with preventive strategies to delay or mitigate the consequences of the disease? This question opens ethical problems and requires a careful evaluation of the advantages and disadvantages of a preventive strategy in patients who are still not hypertensive (do not show high blood pressure) and would not require a treatment according to any guideline. On the other hand, this is the real core and the real question when the physicians face any kind of disease. In the present study, although the numbers were small, principal component analysis gave back 4 variables into maternal characteristics in the second trimester (peripheral resistance, placental growth factor, CO, and endoglin) with an area under the curve of 0.975. If these results are confirmed in larger studies, the identification of patients with this model might become so reliable that the preventive strategies could have no, or only minor, disadvantages. The answer that comes from McLaughlin et al[13] is not conclusive, and much work has yet to be done by researchers, but the data on hemodynamics are more and more encouraging and seem to push toward this direction. Considering that, in normotensive patients with

previous early preeclampsia, high TVR in the nonpregnant state precedes the recurrence of preeclampsia during a second pregnancy,[20] this preventive approach might be extended also to this group of women.

In summary, McLaughlin et al[13] provide a stratification of patients in whom maternal hemodynamic characteristics gain a double role:

1. A role in the identification of patients who will subsequently develop HDP, next to placental growth factor and endoglin.
2. A role in a possible "preventive approach" of the HDP in which the pathological condition is not represented by the high blood pressure, but by the altered hemodynamic variable that precedes the elevation of blood pressure and its potentially dramatic consequences.

Hemodynamics can easily be detected with noninvasive methods. This tool may become, in the future, essential for the stratification and, possibly, the preventive treatment of HDP. Is this dream coming true? Much work clearly remains to be done.

Disclosures

None.

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