

Prepregnancy cardiovascular risk factors as predictors for hypertensive pregnancy disorders

Factores de riesgo cardiovascular antes del embarazo como predictores de trastornos hipertensivos del embarazo

202

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Abstract

Hypertensive disorders of pregnancy (HDP) are a group of conditions characterized by abnormally elevated blood pressure during pregnancy. HDP are one of the leading causes of maternal and fetal morbidity and mortality worldwide. There is growing evidence that prepregnancy cardiovascular risk factors significantly increase the risk of HDP. Along these lines, hypertension, diabetes mellitus, obesity, heart failure and hypercholesterolemia appear to be related to HDP. All of these can increase, to a lesser or greater degree, the risk of HDP. Although some of these variables are intertwined, they can also act as independent predictors. A preconceptional predictive tool could improve therapeutic decisions and pregnancy control in high-risk patients. This review aims to analyze the degree of correlation between HDP's incidence and prepregnancy cardiovascular risk factors.

Keywords: Hypertensive disorders of pregnancy, cardiovascular risk factors, hypertension, diabetes, obesity.

Resumen

Los trastornos hipertensivos del embarazo (HDP, por sus siglas en inglés) son un grupo de afecciones caracterizadas por una presión arterial anormalmente elevada durante el embarazo. Los HDP son una de las principales causas de morbilidad y mortalidad materna y fetal en todo el mundo. Cada vez hay más pruebas de que los factores de riesgo cardiovascular previos al embarazo aumentan significativamente el riesgo de HDP. En este sentido, la hipertensión, la diabetes mellitus, la obesidad, la insuficiencia cardíaca y la hipercolesterolemia parecen estar relacionadas con la HDP. Todos ellos pueden aumentar, en mayor o menor grado, el riesgo de HDP. Aunque algunas de estas variables están entrelazadas, también pueden actuar como predictores independientes. Una herramienta predictiva preconcepcional podría mejorar las decisiones terapéuticas y el control del embarazo en pacientes de alto riesgo. Esta revisión tiene como objetivo analizar el grado de correlación entre la incidencia de HDP y los factores de riesgo cardiovascular previos al embarazo.

Palabras clave: Trastornos hipertensivos del embarazo, factores de riesgo cardiovascular, hipertensión, diabetes, obesidad.

Hypertensive disorders of pregnancy (HDP) are a group of conditions characterized by abnormally elevated blood pressure during pregnancy. HDP are one of the leading causes of maternal and fetal morbidity and mortality worldwide¹. The American Congress of Obstetricians and Gynecologists has classified the HDP into four categories: gestational hypertension (GH), preeclampsia/eclampsia, chronic hypertension, and chronic hypertension complicated with preeclampsia/eclampsia². The risk profile of the patient varies depending on the specific condition. Preeclampsia/eclampsia has the most significant risk for adverse outcomes compared to GH³. All management guidelines heavily emphasize the importance of blood pressure monitoring during pregnancy for early diagnosis and, therefore, proper management of the HDP⁴.

Evidence suggests that there has been an increasing trend in HDP incidence during the past decades⁵. The incidence of HDP ranges between 4-25%; further epidemiological aspects of HDP are not well understood, especially in less developed countries⁶. However, prevention and screening remain the best tools to decrease the morbidity and mortality of HDP. Independently of the incidence, HDP are strongly associated with increased offspring mortality and complications and greater maternal mortality. To name a few, HDP increase the risk of fetal growth restriction, preterm labor, postpartum bleeding, postpartum depression, and many more^{7,8}. Individual patient assessment is crucial to predict HDP development; therefore, thorough history assessment and risk analysis are vital in every pregnancy⁴.

It is well known that factors like age and body mass index (BMI) affect the incidence of HDP. Likewise, a history of previous pregnancies with HDP is the most heavily reported risk factor for new episodes of HDP⁹. However, prepregnancy diseases play an essential role in HDP development. There is growing evidence that prepregnancy cardiovascular risk factors significantly increase the risk of HDP. Along these lines, hypertension (HT), diabetes mellitus (DM), obesity, heart failure and hypercholesterolemia appear to be related to HDP^{10,11}. This review aims to analyze the degree of correlation between HDP's incidence and prepregnancy cardiovascular risk factors.

Prepregnancy cardiovascular disease: a new predictor of hypertensive disorders of pregnancy

New-onset HDP occur in nearly 15% of all pregnancies, and are consistently associated with worse pregnancy outcomes, in contrast to normotensive pregnancies (x). Historically, HDP have been associated with an increased risk of developing cardiovascular disease (CVD) after pregnancy. The American Heart Association recognizes GH and preeclampsia as risk factors for CVD (x). However, an inverse correlation has also been proposed, where CVD increases the risk of developing HDP during pregnancy. Prepregnancy comorbidities seem to play a role in the development of HDP. Nonetheless, the extent of this relationship is less well-known (x).

For instance, a study by Hinkosa et al.¹² analyzed the epidemiological profile of new-onset HDP, and found that age, null parity, and positive history of abortion significantly increased the risk of HDP. Conversely, the risk factors with the most significant risk increase were positive history of pre-existing HT, positive family history of HT, and positive history of DM, all of which had odds ratios (OR) greater than 3.5. The authors concluded that women with pre-existing HT had the most significant risk of developing HDP. Thus, unlike normotensive patients, hypertensive patients should receive more appropriate clinical monitoring during pregnancy. Other authors have reported similar results. Although there are some variations regarding the reported risk factors, personal or familiar history of HT prevails as one of the most significant risk factors in developing HDP^{13,14}.

A systematic review and meta-analysis assessed the impact of chronic hypertension and pregnancy outcomes. Women with a history of chronic hypertension had a relative risk (RR) of 7.7 to develop superimposed preeclampsia; however, the RR for superimposed eclampsia was only 1.3 compared to the general population. Despite the disparities, the authors concluded that the increased risk of preeclampsia was enough to justify an optimization of preconceptional maternal health in women with chronic HT¹⁵. Considering the impact of prepregnancy hypertension, current guidelines advise in favor of appropriate preconceptional counseling. In light of the above, it is suggested that new evidence-based and patient-centred models of prepregnancy counseling are needed to properly manage comorbidities like chronic HT to decrease fetal and maternal morbidity and mortality¹⁶.

Other authors suggest that not only HT increases the risk of pregnancy complications but any sort of vascular dysfunction. Assessment of vascular dysfunction markers is not routinely performed, but evidence suggests that it could help make better pregnancy outcome predictions. For example, Hale et al.¹⁷ analyzed the predictive power of two well-known markers of vascular dysfunction: pulse wave velocity (PWV) and soluble vascular cell adhesion molecule (sVCAM-1). Results

suggested that the lower the values of PWV, the lower the chances of developing pregnancy complications like HDP. Similarly, the sVCAM-1 level was significantly lower in the group without pregnancy complications. The authors concluded that these markers of vascular dysfunction may be useful prepregnancy discriminators for assessing the risk of preeclampsia.

Separately, type 1 and type 2 DM (DM1 and DM2, respectively) are known to increase the incidence of HDP, as well as the risk of developing severe preeclampsia and eclampsia^{18,19}. This increased risk may be due to several factors, including but not limited to endothelial dysfunction, oxidative distress, chronic inflammation, advanced glycation end products, and abnormal placental development²⁰. Lisonkova et al.²¹ analyzed the risk factors associated with early (<34 weeks) and late-onset (\geq 34 weeks) preeclampsia. Patients with DM had a higher risk of developing both early and late-onset preeclampsia, but the association was more robust with the latter.

In comparison to the incidence of preeclampsia in non-diabetic women (2-7%) (22), preeclampsia is diagnosed nearly three times more frequently in women with DM1 (15-20%) and twice as much in DM2 (10-14%)^{23,24}. However, DM persisted as a risk factor after adjusting for BMI, meaning DM is an independent risk factor for preeclampsia²⁵. Similar adjustments for confounders have been made for microalbuminuria, nephropathy, retinopathy, and other diabetic comorbidities. Even in the absence of all comorbidities, the risk of preeclampsia is still increased by the presence of DM¹⁹. Furthermore, other authors have found that a family history of DM significantly increases the risk of developing HDP. There were no differences between maternal and paternal family history, but when combined, the risk was significantly greater²⁶.

On the other hand, obesity has also been reported to increase the incidence of HDP²⁷. For example, GH was significantly more common in obese patients, with a 2.9-fold higher risk of developing it than in the control group²⁸. Furthermore, a systematic review and meta-analysis of 23 studies found that overweight and obese women had a greater risk of preeclampsia (OR= 1.73 and OR=3.15, respectively). The authors concluded that there was enough evidence that excessive BMI was significantly associated with an increased risk of preeclampsia after adjusting for confounders²⁹.

Previously, other authors have reported that the increased risk of preeclampsia follows a linear correlation with BMI. It has been reported that each 5-7 kg/m² increment in BMI above the normal weight doubles the risk of preeclampsia³⁰. A recent study reported that for every increment of 5 kg/m², the risk of preeclampsia increases almost strictly parallel. However, the most remarkable association was found in late-onset preeclampsia, whereas age was the main predictor for

early-onset preeclampsia³¹. The latter might explain why in high-income countries, where DM prevalence is higher, late-onset preeclampsia is more prevalent than its counterpart.

Lastly, evidence suggests that hyperlipidemia may be a causative or additive factor in the pathogenesis of preeclampsia. Serum levels of triglycerides (TG), total cholesterol (TC), and low-density cholesterol (LDL-c) seem to increase the risk of preeclampsia³². A meta-analysis reported that preeclampsia was associated with elevated TC, elevated non-high-density lipoprotein (non-HDL-c), and elevated triglycerides, regardless of the gestational age at the time of blood sampling. Meta-regression analyses suggested that the differences in BMI could explain the difference across the studies. Nevertheless, the authors concluded that preeclampsia patients were more likely to have elevated TC, triglycerides, and non-HDL-c during all trimesters of pregnancy and prior to the pregnancy³³.

The mechanisms that link hyperlipidemia and preeclampsia are not well understood. Some authors suggest that endothelial dysfunction and placental ischemia are worsened by hypertriglyceridemia, which is the lipid parameter that correlates the most with an increased risk of preeclampsia³². Despite the lack of well-founded pathophysiologic mechanisms, authors suggest that preconceptional lipid screening should be performed to predict the likelihood of developing preeclampsia during pregnancy since lipid profiling is not routinely performed according to current guidelines^{32,34}.

Conclusions

HDP are a common complication of pregnancy associated with higher maternal and fetal morbidity and mortality. Current guidelines suggest screening for these conditions in the early stages of pregnancy to provide proper treatment and decrease the associated outcomes. However, available evidence suggests that these diseases can be predicted through preconceptional variables. As a result, there is growing research regarding the impact of prepregnancy risk factors as predictors for HDP. The most well-studied predictors are cardiovascular variables, like preconceptional HT, DM, obesity, hyperlipidemia, and many others. All of these can increase, to a lesser or greater degree, the risk of HDP. Although some of these variables are intertwined, they can also act as independent predictors. A preconceptional predictive tool could improve therapeutic decisions and pregnancy control in high-risk patients.

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