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How much does hypertension in pregnancy affect the risk of future cardiovascular events?

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Hypertensive disorders in pregnancy (HDP) include essential (or secondary) hypertension occurring before 20 weeks of gestation or in women already on antihypertensive therapy prior to pregnancy, gestational hypertension, developing after 20 weeks of gestation without significant proteinuria, and pre-eclampsia or AH onset after 20 weeks of pregnancy in the presence of proteinuria. The development of HDP is associated with a higher incidence of long-term cardiovascular (CV) adverse events, such as myocardial infarction, heart failure, stroke, and CV death. Women who develop high blood pressure in their first pregnancy have an increased risk of complication in a subsequent pregnancy. In the years following delivery, pregnant women with hypertensive disorders develop subclinical atherosclerosis and alterations of cardiac structure and function that may lead to CV disease and heart failure. Thus, it is recommended to monitor these changes over time and subject in pregnant women with these characteristics to CV surveillance through structured and multidisciplinary interventions for CV prevention.

Gestational hypertension: epidemiology and pathophysiology definitions

Arterial hypertension (HA) in pregnancy is a relatively common condition, affecting ~10% of pregnant women.[1] It includes both chronic hypertension diagnosed before pregnancy and pregnancy-related hypertension. Accordingly with main guidelines,[2–4] the current classification includes the following conditions which are often grouped under the term of hypertensive disorders in pregnancy (HDP):

- Chronic hypertension: Essential (or secondary) AH present before the 20th week of gestation or already on antihypertensive therapy before pregnancy.
- Gestational hypertension: AH arising after the 20th week of gestation, without significant proteinuria. It usually resolves within 6 weeks of delivery. Gestational Arterial Ipertension (AI) is considered a form of secondary AI.
- Pre-eclampsia: AH onset after 20 weeks of pregnancy concomitant with proteinuria (proteinuria/creatininuria ratio ≥30 mg/mmol or albuminuria/creatinineuria ratio ≥8 mg/mmol or ≥1 g/l[2] dipstick or other organ dysfunction of the woman (hepatic, renal, neurological, haematological complications) or uteroplacental dysfunction (foetal growth retardation, umbilical artery Doppler waveform abnormalities, or intrauterine foetal death).
- Pre-existing hypertension plus gestational hypertension superimposed with proteinuria.
- Unclassifiable prenatal hypertension: This term is used when blood pressure is recorded for the first time after 20 weeks of gestation and hypertension is diagnosed; re-evaluation is required 42 days postpartum.

If not promptly diagnosed and treated, hypertension in pregnancy can lead to serious consequences for both the woman (increased risk of stroke) and the child (e.g. low birth weight, increased risk of access to neonatal intensive care).

The pathophysiological mechanisms of the development of gestational AI and those of pre-eclampsia and eclampsia are not fully understood, even if the pathophysiological hypotheses are not lacking. These include poor development of uterine placental spiral arterioles (which reduce uteroplacental blood flow in late pregnancy), genetic, immunological, and/or placental ischaemia or infarction.[4] Lipid peroxidation of cell membranes, induced by free

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radicals, could contribute to the onset of pre-eclampsia. Diffuse or multifocal vasospasms can cause maternal ischaemia and lead to target organ damage in the brain, kidney, and liver. Factors that may favour vasoconstriction are an imbalance in endothelial production between prostacyclin (decreased) and endothelin (increased) and an increase in circulating receptor for soluble vascular endothelial growth factor Flt-1.[4,5] Pre-eclampsia increases the risk of placental abruption in current pregnancy, probably because both disorders are related to uteroplacental insufficiency. Placental dysfunction causes the release of anti-angiogenic factors, leading to subsequent multiorgan dysfunction.[5] The activation of the coagulation system, probably secondary to endothelial dysfunction, determines platelet activation and favours the development, in 10–20% of cases of severe pre-eclampsia or eclampsia, of the HELLP syndrome (haemolysis, elevated liver function tests, and low platelets) with a reported incidence of ∼100 times that of all pregnancies (1–2/1000). Most pregnant women with HELLP syndrome have hypertension and proteinuria, but some have neither condition.[4]

From an epidemiological point of view, the incidence of pre-eclampsia has increased by 25% in the last decade with a growing trend explained in part by the more advanced maternal age and the coexistence of a greater number of associated comorbidities.[4] Pre-existing hypertension is associated with an increased risk of developing pre-eclampsia which can complicate up to 25% of cases. Pre-eclampsia is associated with a four-fold increase in heart failure and hypertension and a two-fold increase in the risk of IHD, stroke, and cardiovascular (CV) deaths.[6]

The long-term risk of gestational hypertension

In addition to the poor prognosis of blood pressure disorders in pregnancy, there are growing data demonstrating that the development of AI in pregnancy is associated with a higher incidence of long-term adverse CV events, such as myocardial infarction, heart failure, stroke, and death from CV causes.[6–8] Women who develop hypertension in their first pregnancy have a higher risk of recurrence in a subsequent pregnancy, but are also at greater risk of hypertension, stroke, and ischaemic heart disease in late adulthood.[3,7–11] The European Society of Cardiology's 2021 Cardiovascular Prevention guidelines report that pre-eclampsia occurs in 1.2% of all pregnancies and is associated with an increased relative risk (RR) of CV disease (CVD) by 1.5–2.7 times compared with all women. RR of developing hypertension increased three-fold and that of developing diabetes mellitus 2.1-fold compared with women without AI in pregnancy. Whether the increased risk of CVD after pre-eclampsia occurs independently of CV risk factors has not been established. The associated risk of late CVD is lower than that of pre-eclampsia, but always remains high (RR 1.7–2.5).[12]

Stuart *et al.*[13] examined the impact of HDP on long-term CV outcome and their correlation with traditional cardiometabolic risk factors in a cohort of 57 000 women from the Nurses' Health Study II, a registry of more than 100 000 nurses in the USA. Nulliparous women, women with a history of hypertension, dyslipidaemia, diabetes, or CV events before pregnancy, and women who had their first pregnancy after age 40 were excluded from the initial cohort. Outcomes included acute myocardial infarction, stroke, and fatal coronary events. Approximately 10% of women included in the registry developed HDP during their first pregnancy. Women with HDP did not show significant differences compared with normotensive women in terms of clinical characteristics; however, more frequently, they presented a positive family history of an early CV event and a BMI >30 kg/m^2 during the first pregnancy. At the end of 34 years of follow-up, women with HDP during their first pregnancy had a 63% increased risk of developing CV events compared with normotensive women, with a higher cumulative risk for pre-eclampsia [hazards ratio (HR): 1.72; 95% confidence interval (CI): 1.42–2.10] compared with gestational hypertension (HR 1.41; 95% CI: 1.03–1.93). Women with only one pregnancy complicated by HDP had a 43% increase in the incidence of CV events; those with multiple pregnancies complicated by HDP increased the risk by a further 2.3-fold. In women with HDP, CVD risk was independent of the length of pregnancy and CV events occurred earlier and at a significantly lower age: between 40 and 49 years and then increased further in the following two decades. Furthermore, while pre-eclampsia showed a significant association with coronary events (HR 2.2; 95% CI: 1.7–2.8), gestational hypertension was more closely related to future stroke development (HR 1.6; 95% CI: 1.0—2.4).

The latter observation is consistent with the greater weight of AH as a risk factor for cerebrovascular events, while pre-eclampsia appears to show a multifactorial genesis. These results also confirm many previous observations. A 2017 meta-analysis including 22 studies and more than 250 000 women with pre-eclampsia suggested that hypertension started before pregnancy played a key role in the subsequent development of CVD. Furthermore, the risk of developing stroke, heart failure, and ischaemic heart disease was highest in 1–10 years postpartum, suggesting that many women with a history of HDP may develop adverse cardiac events before middle age.[14] A further meta-analysis published in 2019, which included over 220 000 women followed for over 7 years of follow-up, demonstrated that in the subgroup of patients with HDP, the presence of chronic hypertension determined a 64% risk of future CV events.[10] This and other evidence is reported in the 2021 European consensus document on the management of disorders in pregnancy.[6]

Pathophysiology of hypertensive disorders in pregnancy

While gestational hypertension appears to represent a pure hypertensive phenotype, the underlying pathophysiology of pre-eclampsia is more heterogeneous, resulting from abnormal placentation resulting in endothelial dysfunction, systemic vascular impairment, vasoconstriction, and organ ischaemia during pregnancy.[4,5,14] In the years and decades following childbirth, women with a history of pre-eclampsia present with endothelial dysfunction, alterations in cardiac structure and function, and an early vascular 'aging' phenomenon that favours the development of subclinical atherosclerosis.[15] More than 80% of the increased risk of CVD among women with gestational

hypertension was due to the development of chronic hypertension after pregnancy. Although most of the pre-eclampsia–CVD association was explained by traditional risk factors, ~40% of the association remained unexplained. This suggested that pre-eclampsia may increase CV risk through non-traditional and/or unrecognized risk factors.[10,13,14] The development of HDP also leads to structural and functional changes of the myocardium, and is associated with an increase in left ventricular wall thickness, concentric remodelling, and even long-term (8–10 years) diastolic dysfunction after delivery.[16,17]

Preventive interventions for hypertensive disorders in pregnancy

Current guidelines and consensus documents form scientific societies recommend to identify as early as possible the subgroups of women at risk to be referred to primary CV prevention treatments.[1,3,4,6,11,12,18]

A recent review[19] pointed out not only the CV risk related to the development of HDP, drawing up a follow-up path structured through five steps: educational, scheduled postpartum visits, monitoring, risk stratification, and a team-based approach aimed at reducing exposure to modifiable risk factors and lifestyle changes, involving cardiologists, gynaecology dieticians, and psychologists (lifestyle coaching). Primary prevention of CVD should begin early in the postpartum period and continue throughout the woman's life. The approach involves an immediate postpartum visit, assessment of risk factors, and multidisciplinary lifestyle intervention at 6–12 weeks and 1 year postpartum, followed by an annual follow-up visit and a final assessment at 50 years of age. In the future, the phenotypes at risk will have to be part of the common interventions in primary prevention through increasingly close links between hospital and territorial specialists and with the involvement of general practitioners and other health professionals.

Conclusions

Hypertensive disorders in pregnancy are associated with an increased risk of developing long-term CV events. Although the mechanism is not clear, pregnancy can underlie subclinical CV risk factors and generate complications through mechanisms such as endothelial dysfunction and the development of subclinical atherosclerosis, structural and functional alterations of the myocardium, leading on the one hand to diastolic left ventricular dysfunction, myocardial hypertrophy, and clinical heart failure, and on the other hand to heart attack, stroke, and CV death. The development of risk factors and markers of CV risk begins early after delivery. The most vulnerable period for the development of CV events occurs in the decade following delivery. Screening of women at risk and application of CV prevention strategies is recommended by guidelines and scientific consensus documents.

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Data availability

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