

# Long-term Cardiovascular Health after Hypertensive Disorders of Pregnancy

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## Lay Summary

### What are hypertensive disorders of pregnancy (HDP)?

Hypertensive disorders of pregnancy (HDP) are complications of pregnancy affecting around 2-8% of pregnancies. It is classified into: pre-eclampsia, gestational hypertension, chronic hypertension, white coat hypertension and masked hypertension. Although most HDP resolve after pregnancy, they have been linked with increased chances of developing heart disease in later life.

### Impact on long term blood pressure measurements

Women who have had pre-eclampsia have double the risk of developing high blood pressure, stroke and heart disease, as well as quadruple the risk of heart failure in the future, compared to women who did not have pre-eclampsia. Women who had pre-eclampsia *more than once* also have a higher risk of developing long term health issues. Although the increase in relative risk is the highest within the first year after delivery, these risks persist decades after the pregnancy (when the absolute risks for older women are greater than for women immediately after delivery.)

### Other long-term complications

Women who had pre-eclampsia have a 6-fold increased risk of renal disease and double the risk of diabetes and venous thromboembolism (VT). VT is when a blood clot forms in a deep vein (deep vein thrombosis, DVT) breaks free and travels in the circulation to the lungs (pulmonary embolism) in later life. Women who had gestational hypertension have a 1.4-fold increased risk for future stroke and coronary heart disease, which is lower than that for women who had pre-eclampsia. HDP and future Cardio Vascular Disease (CVD)

The association between HDP and future Cardio Vascular Disease (CVD) are now well established, however, many women with HDP miss out on appropriate postnatal cardiovascular screening due to either lack of awareness in healthcare professionals or among the women themselves.

There are several international guidelines that advocate the incorporation of HDP in the cardiovascular risk assessment of women to prevent future disease. The American Heart Association (AHA) CVD prevention guidelines (2011) consider women with a history of HDP as 'at

risk' and recommend lifestyle modifications, such as giving up smoking, increasing regular physical activity, eating healthily and monitoring of blood pressure.

Long term prevention of strokes and diabetes

If cholesterol levels are found to be high, women are advised to take medication to lower them. The AHA/American Stroke Association (ASA) stroke prevention guidelines (2014) recommend considering the evaluation and treatment of women with a history of pre-eclampsia/eclampsia for cardiovascular risk factors including high blood pressure, obesity, smoking, and high cholesterol, starting from 6 months to 1 year after delivery. Pre-eclampsia has been included as a risk-enhancing factor for consideration of treatment in the American College of Cardiology (ACC)/AHA guideline on the management of blood cholesterol (2018) and the ACC/AHA CVD guideline on the primary prevention of CVD (2019). The European Society of Cardiology (ESC) CVD prevention guidelines (2021) suggest that in women with a history of HDP, screening for high blood pressure and diabetes might be useful.

#### Postnatal monitoring

There has been increasing recognition that a collaborative multidisciplinary approach is needed from pre-conception, through pregnancy and postpartum and at-risk women are monitored closely by obstetricians in the immediate postpartum period. This monitoring would then be followed up in primary care with referral to long term cardiology if monitoring is needed. In addition to high blood pressure and cholesterol management, lifestyle modification may help to reduce the risk of developing Cardio Vascular Disease in later life.

## Technical Summary

Hypertensive disorders of pregnancy (HDP) is a leading cause of maternal morbidity and mortality worldwide and is classified into pre-eclampsia, gestational hypertension, chronic hypertension, white coat hypertension and masked hypertension.<sup>1</sup> Pre-eclampsia affects 2-8% of all pregnancies,<sup>2,3</sup> but its pathogenesis remains poorly understood. Pregnancy is a physiologic stress test to the heart. During pregnancy, there are adaptive changes designed to provide adequate uteroplacental circulation for the optimal growth of the developing fetus.<sup>4</sup> Insufficient hemodynamic changes may result in adverse pregnancy outcomes, such as HDP. Even after these acute issues resolve, some studies have shown an association between adverse pregnancy outcomes and cardiovascular disease (CVD) after the reproductive years.

### *Association between Hypertensive Disorders of Pregnancy and Cardiovascular Disease*

Pre-eclampsia is associated with a two-fold increased risk in future hypertension, stroke and coronary heart disease, as well as a four-fold increase in future heart failure,<sup>5,6</sup> with recurrent pre-eclampsia having the highest risk.<sup>7-9</sup> Although the relative risk is the highest within the first year after delivery,<sup>8</sup> the risks persist decades after the pregnancy when the absolute risks are greater than those immediately postpartum.<sup>9</sup> Even after adjusting for some potential confounders such as age, body mass index and diabetes, these increased future risks for CVD remained statistically significant. However, as no study to date has fully adjusted for all potential confounding factors for CVD, it is unclear whether these associations are mainly due to worse clinical risk factor profile in patients with pre-eclampsia. In addition to CVD, women who had pre-eclampsia are at risk of other diseases. Meta-analyses have shown that they have a 6-fold increased risk of end-stage renal disease<sup>10</sup> and double the risk of diabetes<sup>11</sup> and venous thromboembolism in the future.<sup>6</sup> There is evidence suggesting gestational hypertension alone is also associated with future hypertension and CVD, though to a lesser extent than pre-eclampsia itself. There is a 1.4-fold risk for stroke and coronary heart disease, compared to women without HDP.<sup>12,13</sup>

Table 2| Relative risk\* of future cardiovascular morbidity in women with hypertension in previous or current pregnancy

Risk of future cardiovascular disease	Type of hypertension in current or previous pregnancy			
	Any hypertension	Pre-eclampsia	Gestational hypertension	Chronic hypertension
Major adverse cardiovascular event	Risk increased (up to ~2 times)	Risk increased (~1.5-3 times)	Risk increased (~1.5-3 times)	Risk increased (~1.7 times)
Cardiovascular mortality	Risk increased (up to ~2 times)	Risk increased (~2 times)	No data	No data
Stroke	Risk increased (up to ~1.5 times)	Risk increased (~2-3 times)	Risk may be increased	Risk increased (~1.8 times)
Hypertension	Risk increased (~2-4 times)	Risk increased (~2-5 times)	Risk increased (~2-4 times)	Not applicable

\* Risks are overall estimates—summarised from risk ratios, odds ratios, and hazard ratios—compared with the background risk in women who did not have hypertensive disorders during pregnancy. Absolute risks will vary considerably depending on follow-up time (from 1 to 40 years postpartum).

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### *Potential mechanisms*

The underlying mechanism for the association between HDP and future CVD remains to be fully investigated. It remains unclear whether HDP itself initiates a pathway that results in CVD or if HDP uncovers a woman’s predisposition to CVD.

HDP and CVD share risk factors. Women with pre-eclampsia and gestational hypertension have a greater prevalence of hypertension, kidney disease, dyslipidaemia,<sup>14</sup> obesity,<sup>15-17</sup> insulin resistance,<sup>18,19</sup> metabolic abnormalities, heightened inflammatory responses, hypercoagulable states and endothelial dysfunction.<sup>20</sup> Therefore, shared risk factors has been considered as a potential mechanism. Alternatively, pre-eclampsia and gestational hypertension may be independent risk factors for future CVD as the post-pregnancy body may not fully recover from the damage to the microvascular, endothelial, cardiac, coronary, and metabolic systems during pregnancy. Therefore, following further systemic injury over time, the damage sustained during pregnancy may present as cardiovascular events in later life.<sup>21</sup> Other hypotheses include genetic factors and multifactorial mechanisms.

### *Cardiovascular risk prediction*

As women with a history of HDP are at risk for CVD, they may benefit from atherosclerotic CVD (ASCVD) risk reduction efforts before the onset of adverse cardiovascular events. Several national guidelines recommend the evaluation of adverse pregnancy outcomes, in addition to traditional CVD risk factors such as as hypertension and hyperlipidemia, in the ASCVD risk assessment in women. For example, the American Heart Association (AHA) CVD prevention guidelines (2011) consider women with a history of HDP as at risk and recommends lifestyle modification (e.g. smoking cessation, regular physical activity, weight management and healthy eating), blood

pressure control and LDL-C lowering therapy if LDL-C  $\geq$ 190mg/dL.<sup>22</sup> The AHA/American Stroke Association (ASA) stroke prevention guidelines (2014) recommend to consider the evaluation and treatment of women with a history of pre-eclampsia/eclampsia for cardiovascular risk factors including hypertension, obesity, smoking, and dyslipidaemia, ? starting from 6 months to 1 year post-partum.<sup>21</sup> Pre-eclampsia has been included as a risk-enhancing factor for consideration of therapy in the American College of Cardiology (ACC)/AHA guideline on the management of blood cholesterol (2018)<sup>22</sup> and the ACC/AHA CVD guideline on the primary prevention of CVD (2019).<sup>23</sup> The European Society of Cardiology (ESC) CVD prevention guidelines (2021) suggest that in women with a history of HDP, periodic screening for hypertension and diabetes mellitus should be considered.<sup>24</sup>

<b>Guideline</b>	<b>Pre-eclampsia or HDP</b>	<b>Follow-up</b>	<b>Assessment</b>	<b>Intervention</b>
AHA CVD prevention in women 2011 in adults 2019	HDP	Refer to cardiology PP	Other risk enhancing factor	Lifestyle modification
ASA/AHA Stroke prevention 2014	Pre-eclampsia / eclampsia	6m to 1yr PP	Risk factor	Evaluate and treat risk factors (HTN, obesity, smoking, dyslipidaemia)
ACC/AHA Cholesterol management 2018	HDP	---	Risk enhancing factor	If intermediate risk (7.5 - $\leq$ 20%), favour statin
ACOG Postpartum care 2018 HTN in pregnancy 2020	HDP	---	ASCVD risk assessment with attention to effect of social determinants of health	Long-term follow-up and lifestyle modification

NICE HTN in pregnancy 2019	HDP	---	---	Lifestyle modification
ESC CVD prevention 2021	HDP	Periodic	Risk modifier	Screen for HTN and DM

ACC, American College of Cardiology. ACOG, American College of Obstetricians and Gynaecologists. AHA, American Heart Association. ASA, American Stroke Association. ASCVD, atherosclerotic cardiovascular disease. CVD, cardiovascular disease. DM, diabetes mellitus. ESC, European Society of Cardiology. HDP, hypertensive disorders of pregnancy. HTN, hypertension. NICE, National Institute for Health and Care Excellence. PP, postpartum.

Furthermore, there has been an increasing recognition that a collaborative multidisciplinary approach is essential from pre-conception, through pregnancy and postpartum, such that at-risk women are monitored closely by obstetricians in the immediate postpartum period and then followed up in primary care with referral to cardiology if required in the long term. There is also an increasing interest in the field of Cardio-Obstetrics and the need to improve Cardio-Obstetric knowledge in obstetricians and cardiologists.

Innovative approaches to bridging gaps in care are needed to capture this high-risk group of women. Future directions should include improved pre-pregnancy counselling, postpartum follow-up and hypertension management, and engaging women themselves in lifestyle modification. Future research should focus on further understanding of the proteomic, metabolomic and epigenomic profiles of women with hypertensive disorders of pregnancy to understand the underlying biological mechanisms that link between hypertensive disorders of pregnancy and adverse cardiovascular outcomes, this will feed into refining the CVD prediction models to reflect the additional risk of hypertensive disorders of pregnancy and design of population studies that include women of reproductive age.

In summary, HDP is associated with adverse cardiovascular outcomes, including CVD, coronary heart disease, and stroke, as well as hypertension, diabetes, end-stage renal disease and thromboembolism. The mechanism for the association remains unclear. However, this high risk group of women should be assessed and followed up postnatally, in order to reduce their risk of CVD.

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