Pre-eclampsia and the risk of cardiovascular disease

ANNEMARIE HENNESSY MB BS, PhD, FRACP
ANGELA MAKRIS MB BS, PhD, FRACP

Hypertension in pregnancy (including pre-eclampsia and eclampsia) occurs in 10% of pregnancies in Australia. Although pre-eclampsia was largely thought to be a reversible condition, evidence is mounting that it and other hypertensive diseases of pregnancy are potential risk factors for coronary artery disease, stroke and hypertension later in the woman's life. Significantly, identification of early cardiovascular risk factors has the potential to target this population for intervention and thereby prevent future morbidity and mortality in these women.

Hypertension is the most common maternal medical condition seen in Australia, occurring in about 10% of pregnancies.[1] The death rate is low in Australia,[2] but worldwide the hypertensive disorders of pregnancy (including pre-eclampsia and eclampsia) account for around 75,000 deaths each year, most due to the poor availability of adequate antenatal services in many developing countries.

Pre-eclampsia or 'toxaemia' is hypertension in pregnancy associated with a toxic endothelial reaction, resulting in renal, liver, brain and cardiac dysfunction and growth restriction of the baby. This complex syndrome is best explained by endothelial damage or dysfunction, which was largely thought to be reversible.[3] The dysfunction arises from placental failure due to inadequate placental invasion of the maternal uterine arteries[4] and therefore resolves when the placenta is delivered. A more recent theory, however, holds that the endothelial dysfunction may well remain.[5]

Clinical features of pre-eclampsia

The clinical features of pre-eclampsia range in severity from a mild, asymptomatic increase in blood pressure, to proteinuria, peripheral oedema and worsening hypertension and then to organ failure, seizures and maternal death. In the more severe cases, there may be evidence of maternal organ (renal, brain and liver) dysfunction, which is likely to be due to the more severe endothelial dysfunction. 'Eclampsia' is the development of neurological seizures in the woman due to uncontrolled pre-eclampsia. It carries a high mortality for the mother and, when it occurs before delivery, for the baby also.

Pre-eclampsia occurs after 20 weeks' gestation and may last for days or weeks, depending on the maternal and fetal effects resulting from the condition. The cure is achieved by delivery, but delivery may need to be delayed to prolong gestational time and allow fetal growth and maturity.[6] Delivery is indicated when the blood pressure is acutely uncontrollable despite medication; when organ function is threatened (as indicated by elevated levels of liver transaminases, decreasing platelet count or elevated serum creatinine level); when the mother is becoming symptomatic (especially with neurological manifestations such as altered mental state, focal cerebral dysfunction or seizures); and when there is evidence of compromise of fetal wellbeing or progressive fetal growth retardation.

A longer duration of maternal endothelial damage occurs when delivery is delayed. This may lead to longer term endothelial dysfunction.

Key points

- **There is a clear link between endothelial dysfunction that manifests as pre-eclampsia and subsequent maternal cardiovascular disease (CVD).**
- **Identification of early cardiovascular (CV) risk factors in pregnant women enables intervention and thereby prevention of future CV morbidity and mortality.**
- **Babies who have suffered in utero growth restriction from pre-eclampsia and other causes have higher rates of later development of CVD, hypertension and diabetes.**

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Professor Hennessy is the Foundation Professor of Medicine at the University of Western Sydney, and Director of Vascular Immunology Research at the Heart Research Institute, Sydney. Dr Makris is an Obstetric and Renal Physician at Liverpool Hospital, Sydney, NSW.

Risk factors for pre-eclampsia

There are many established risk factors for the development of pre-eclampsia. These include obstetric conditions (such as multiple pregnancy), immunological disease (such as systemic lupus erythematosus) and cardiovascular conditions. CV risk factors include chronic hypertension (a 5 to 30% increased risk), renal disease, diabetes mellitus and insulin resistance, gestational diabetes, obesity and hypercholesterolaemia.[7-12] These are also important risks factors for the development of cardiovascular disease in later life.[13]

Hypertension complicating underlying renal disease has been identified in up to 30 to 40% of women with severe early-onset pre-eclampsia (under 32 weeks' gestation).[14] Several studies attribute pre-eclampsia to hypercholesterolaemia. It has been demonstrated that higher total cholesterol levels and increased levels of low density lipoproteins are associated with an increased risk of hypertension in pregnancy.[15] High lipid levels have been associated with increased diastolic blood pressure.[12] Dyslipidaemia identified in early pregnancy is presumed to be present prior to pregnancy. Pregnancy itself leads to changes in levels of total cholesterol, serum triglycerides and blood glucose, particularly in the second and third trimesters.[16] An association between hypertension (both before and during the pregnancy) and increased levels of lipoprotein (a) and triglycerides has been described.[17,18] Diabetes and gestational diabetes are also linked to hypertension in pregnancy, probably due to endothelial dysfunction associated with insulin resistance and the metabolic syndrome.[10]

Table 1. Comparative risk ratios for the main causes of coronary artery disease[5,20,21]

Risk factor	Risk ratio for coronary artery disease	95% Confidence interval for risk ratio	Study reference
Smoking	2.1	1.5–2.9	Kramer et al, 2006[20]
Hypertension	2.12	1.4–3.0	Wilson et al, 1998[21]
Low density lipoprotein (>4.1 mmol/L)	1.68	1.17–2.4	Wilson et al, 1998[21]
Pre-eclampsia	2.16	1.86–2.52	Bellamy et al, 2007[5]

Pre-eclampsia and future cardiovascular disease

Recent analyses of the long-term effects of pre-eclampsia have determined that the endothelial dysfunction may have long-term consequences for the mother. Women who have had pre-eclampsia have a higher rate of coronary artery disease independent of other risk factors than women who have not had pre-eclampsia.[19] The degree of future CVD risk conferred by pre-eclampsia appears to be comparable with the traditional risk factors of coronary artery disease (Table 1).[5,20,21]

An association between pre-eclampsia and CVD later in life was first identified in 1961 and has been the focus of more recent epidemiology studies that have been reviewed.[5,22] These studies demonstrate that a woman whose pregnancy was complicated by pre-eclampsia had an increased risk of hypertension, coronary heart disease, ischaemic heart disease, cerebrovascular disease, stroke and death compared with women whose pregnancies were not complicated by pre-eclampsia (Table 2).[5,23-29] Structural cardiac changes are seen after pre-eclampsia, particularly global diastolic dysfunction and left ventricular remodelling, but the reversibility of these changes is unknown.[30]

Several studies have demonstrated a 'degree–response effect' of the pre-eclampsia.[5,28] The more severe the pre-eclampsia, the greater the future risk of cardiac disease.

Table 2. Pre-eclampsia and future risk of cardiovascular disease[5,23-29]

Study reference	Number of participants	Years to follow up	Outcome	Relative risk (95% CI)
Bellamy et al, 2007[5]	198,252 (meta-analysis)	5 to 33	Hypertension	3.7 (2.7–5.05)
Hannaford et al, 1997[23]	23,000	33	Hypertension	2.35 (2.08–2.65)
Bellamy et al, 2007[5]	198,252 (meta-analysis)	5 to 33	Coronary artery disease	2.16 (1.86–2.52)
Kestenbaum et al, 2003[24]	807,010	7 to 8	Cardiovascular disease	2.2 (1.3–3.6)
Smith et al, 2001[25]	129,920	12 to 19	Ischaemic heart disease	2.0 (1.5–2.5)
Wilson et al, 2003[26]	3593	15 to 19	Cerebrovascular disease	2.1 (1.0–4.3)
Brown et al, 2006[27]	682	10 to 14	Stroke	1.63 (1.02–2.62)
McDonald et al, 2008[28]	116,175 (meta-analysis)	7 to 40	Stroke	2.03 (1.54–2.67)
Irgens et al, 2001[29]	626,272	13	Death due to cardiovascular disease	1.65 (1.01–2.7)

Severe pre-eclampsia (as determined by presence of proteinuria as well as hypertension – defined as blood pressure of 160 mmHg or higher systolic or 110 mmHg or higher diastolic with proteinuria of 0.3 g or more per day,[24] or 110 mmHg or higher diastolic with proteinuria of 5.0 g or more per day[31]) was associated in these studies with a greater risk of ischaemic heart disease than was milder pre-eclampsia. An even greater risk was identified when the pregnancy was associated with pre-eclampsia before 37 weeks' gestation.

In addition to the proposed effect of pre-eclampsia on CVD, the likelihood of the development of renal disease and the eventual need for renal biopsy has been identified in women with a history of the condition.[32,33]

In utero events for the fetus may be associated with future CV risk. There is evidence that babies who have suffered in utero growth restriction (regardless of cause) have a higher rate of later development of hypertension, CV disease and diabetes – this is known as the 'Barker Hypothesis', or 'DOHaD' (the Developmental Origins of Health and Disease).[34,35,]

Treating pre-eclampsia

Treatment targets for blood pressure in pregnancy need to be viewed with regard to both potential obstetric complications and the possible long-term CV benefits.

The effects of endothelial dysfunction after a pregnancy complicated by severe pre-eclampsia may be corrected or curtailed with adequate blood pressure control. The roles of blood pressure management and other CV risk factor management in and after the pregnancy are yet to be determined. It has been shown that the identification and follow up in general practice of women with persistent hypertension after pre-eclampsia is variable.[36] This could be improved through better insights into the nature and effect of hypertension in pregnancy, and specifically pre-eclampsia.

Risk factors for CV disease and CVD itself (especially ischaemic heart disease) are both increased in women who have had pre-eclampsia. Further research is needed to determine if correction of these risk factors in pregnancy decreases the future CV risk.

Conclusion

There is a clear link between endothelial dysfunction that manifests as pre-eclampsia and subsequent maternal CV disease. Further research needs to clarify whether limitation of the maternal endothelial dysfunction (by expediting delivery) and aggressive treatment of risk factors after delivery will significantly affect the mother's long-term risk. Babies who have suffered in utero growth restriction from pre-eclampsia and other causes have been shown to have higher rates of later development of CVD and also hypertension and diabetes. CT

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