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Review article

# Maternal pre-eclampsia and long-term offspring health: Is there a shadow cast?

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ABSTRACT

Pre-eclampsia is a common pregnancy disorder with important short-term complications for mother and baby. Evidence suggests pre-eclampsia also has implications for the mother beyond pregnancy, as well as long-term effects on offspring health. Limited research has linked pre-eclampsia with changes in offspring blood pressure, BMI, and stroke risk. Underpinning mechanisms are poorly understood, but developmental programming may be involved. Research in this area has been hindered by difficulties in defining pre-eclampsia and problems with study design. Further targeted evaluation through to adulthood is required to determine the long-term impact of pre-eclampsia on offspring disease risk and how this develops.

## 1. Introduction

Pre-eclampsia is a complex syndrome in which there has been debate over diagnostic criteria and lack of clarity on aetiology. Much is known about the acute effects of pre-eclampsia on the mother and newborn, but there is very limited information about the possible long-term effects on offspring. Pre-eclampsia is relatively common affecting 2–8% of all pregnancies [1]. Its precise causes remain largely unknown, but current hypotheses are based on abnormal placentation in early pregnancy and the maternal physiological response to this or abnormal maternal response alone [2,3]. Pre-eclampsia is traditionally defined as new-onset hypertension and proteinuria after 20 weeks of gestation [4]. However, there is ongoing debate over the criteria used to characterise the disease. Recent guidelines no longer require the presence of proteinuria to make the diagnosis of pre-eclampsia, if there is evidence of other maternal organ or utero-placental dysfunction [5]. This reflects the variable clinical presentation of the disorder, which ranges from a seemingly mild asymptomatic condition identified on routine screening to fulminant disease with significant short-term health consequences for both mother and baby.

The difficulties in defining pre-eclampsia must be taken into account when interpreting the available literature. While early research was hampered by all hypertensive disorders of pregnancy being considered together and the changing definition of pre-eclampsia over time, now some authors propose that pre-eclampsia may represent more than one disease [6–8]. This would explain the clinical heterogeneity of the condition. The differences observed between early and late onset disease also support this conclusion. Early onset disease is associated with higher rates of adverse maternal and neonatal outcomes [9,10], and has unique histopathological features with placental vascular lesions consistent with placental insufficiency [8], as well as a distinct biomarker profile [11], compared to late onset disease. For example, early onset pre-eclampsia is associated with increased risk of fetal growth restriction and perinatal death compared to late onset disease [12].

While the immediate health effects of pre-eclampsia are well described, the long-term consequences are only just being recognised. Women who develop pre-eclampsia in pregnancy are at increased risk of cardiovascular disease in later life, with approximately double the risk of developing cardiovascular or cerebrovascular diseases, and three times the risk of hypertension [13–15]. Despite these findings, there has been limited investigation of the long-term health outcomes for the offspring. This review will explore whether children exposed to pre-eclampsia *in utero* are also at risk of cardiovascular disease or other health problems in later life, and will examine possible mechanisms by which this could occur.

*Abbreviations:* BMI, body mass index; CI, confidence interval; HbA1c, glycated haemoglobin

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## 2. What are the short-term consequences of pre-eclampsia for the offspring?

Pre-eclampsia is a well-known cause of offspring morbidity and mortality in the short term [16,17]. While fetal survival has improved with advances in neonatal care that allow for earlier delivery, pre-eclampsia is still associated with a 1.3 times increased risk of stillbirth and twofold increased risk of neonatal death overall (without adjustment for gestational age) [18]. Pre-eclampsia is also an important cause of fetal growth restriction with infants born small-for-gestational-age in almost 20% of term and 60% of preterm cases [12]. Interestingly, Vatten et al. found that while low birthweight was strongly associated with early onset pre-eclampsia, both low and high birthweight were associated with late onset disease [6]. It has been suggested that this finding may be due to differences in pre-eclampsia pathogenesis, with abnormal placentation contributing more to early onset disease with associated fetal growth restriction; whereas in later pregnancy restricted placental growth and perfusion may play a greater role, accounting for more variable effects on birthweight [3].

Pre-eclampsia is also an important cause of prematurity. A recent large multi-centre trial reported a preterm birth rate of 36% [19] compared to approximately 10% across the general population [20,21]. Preterm birth for women with pre-eclampsia may be spontaneous or iatrogenic, but the latter has become increasingly common as delivery remains the only definitive cure for pre-eclampsia and confidence grows in neonatal care and improved neonatal outcomes. For example, a large study in the United States found that pre-eclampsia was the most common indication for medically-indicated preterm birth, accounting for 23% of cases [22]. Although early delivery benefits maternal well-being and allows the offspring to avoid the risks of intrauterine demise and worsening growth restriction, neonates are exposed to all the complications associated with prematurity. Some studies have suggested that infants born preterm after pre-eclampsia may do better in the short term than those born preterm for other reasons, with reduced rates of retinopathy of prematurity [23] and infant mortality [24]. However, results are conflicting, and other studies have found pre-eclampsia makes no difference on the incidence of these outcomes, as well as on other important complications of prematurity such as respiratory distress syndrome, severe intraventricular haemorrhage, and necrotizing enterocolitis [25,26].

## 3. Are there long-term consequences of pre-eclampsia for the offspring?

### 3.1. Cardiovascular disease

There is some evidence that pre-eclampsia has long-term consequences for offspring cardiovascular health. Kajantie et al. reported an almost twofold increase in the risk of stroke among individuals whose mothers had pre-eclampsia [27]. In the same study, there was no evidence of an increased risk of coronary heart disease in the offspring, but the authors commented that a small effect could not be excluded due to sample size. This result must be interpreted with caution. The data were derived from adults born in Finland between 1934 and 1944. Thus, a number of factors may have independently influenced the outcome, such as the medical care available at this time, in particular how pre-eclampsia was defined and treated, as well as other stressors that study participants born in this era may have been exposed to.

In contrast, most studies have examined cardiovascular risk factors (rather than disease) and almost all available data are from cohorts of children and young adults. The literature has tended to focus on blood pressure, and an association between maternal pre-eclampsia and a small but significant increase in offspring blood pressure has been consistently demonstrated [27–32]. For example, a recent meta-analysis from ten available studies showed that pre-eclampsia was associated with a 2.39 mmHg (95% CI: 1.74–3.05; $p < .0001$) increase in systolic and a 1.35 mmHg (95% CI: 0.90–1.80; $p < .0001$) increase in diastolic blood pressure in childhood and young adulthood [29]. Blood pressure differences persisted with adjustment for birth weight and gestational age [29], and have been shown to be independent of familial adiposity [31]. It could be argued that these blood pressure differences are not clinically significant. On the other hand, if raised blood pressure was to progress with age this could help to explain an increased stroke risk for offspring in later life. There is some evidence to support this. Palmsten et al. [28] found that maternal pregnancy-related hypertension was associated with an increased risk of being prescribed anti-hypertensives in adult offspring at 34 to 44 years of age. In addition, Kajantie et al. reported a risk of hypertension that was 1.5 times higher among people aged 60–70 years who were born from pregnancies complicated by 'severe pre-eclampsia,' which the study defined as a systolic blood pressure greater than 160 mmHg after 20 weeks [27].

Maternal pre-eclampsia has also been associated with increased offspring body mass index (BMI) in two systematic reviews and meta analyses; one in children and young adults that showed a 0.62 $kg/m^2$ (95% CI: 0.41–0.84; $p < .0001$) increase in BMI [29], and the other in adults that found a 0.44 $kg/m^2$ (95% CI: 0.09–0.78) increase [33]. Note that BMI remained significantly increased when male and female offspring were considered separately, and among offspring born at term with normal birth weight [29]. Again, this difference in body composition is of questionable clinical significance. However, if progressive, or as one of a number of metabolic derangements associated with pre-eclampsia, such a difference could contribute to an increased risk of cardiovascular disease in offspring.

There has been limited investigation of the effect of pre-eclampsia on offspring glucose metabolism. A 2015 study found that insulin sensitivity, estimated using a surrogate measure (the Quantitative Insulin Sensitivity Check Index – QUICKI), did not differ between the offspring of pre-eclamptic and normotensive mothers at 12 years of age [34]. Other studies have found no significant differences in fasting insulin and glucose levels in adolescents and young adults compared to controls [35–39]. However, it is imprecise to assess insulin sensitivity in adolescence because pubertal development in this age group is variable, and puberty is associated with a significant decrease in insulin sensitivity, making results difficult to interpret [40]. Furthermore, the one-time measurements of insulin used in all of these studies are not the optimal approach for assessment of insulin sensitivity, which is yet to be studied using validated models in children born to mothers with pre-eclampsia. In adults, Thomas et al. [41] reported a significantly higher prevalence of raised HbA1c ($\geq 6\%$) in offspring exposed to pre-eclampsia at 45 years of age. This study also found an association between pre-eclampsia and raised HbA1c and type 2 diabetes in logistic regression analyses that persisted after adjustment for birth weight and adiposity, but the association was not statistically significant after adjustment for all important confounders [41]. Similarly, the findings of another small study suggested a possible association between maternal pre-eclampsia and risk of type 2 diabetes in the offspring in their 40s [42].

Further, there have been no consistent differences in lipid profile observed in the offspring, beyond acute changes in cord blood samples [43,44]. Kvehaugen et al. found *in utero* exposure to pre-eclampsia was associated with higher total cholesterol levels [45], but the majority of studies have found no difference in fasting lipid profiles in young offspring [34,35,38,39,46,47].

### 3.2. Other health problems

There is also evidence linking *in utero* exposure to pre-eclampsia with other long-term health outcomes in the offspring. In a large population-based cohort study, Wu et al. [48] found that children born at term exposed to pre-eclampsia but who were not small-for-gestational-age had an increased risk of hospitalisation for a number of conditions.