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In Utero Exposure to Preeclampsia and Cardiometabolic Risk: A Review of Literature

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ABSTRACT

Preeclampsia is a hypertensive disorder that occurs during pregnancy, affecting 3-5% of pregnancies globally and is an independent cardiovascular risk factor for the mother, and recent studies reveal that offspring of affected pregnancies may also have an increased risk for developing cardiovascular diseases (Karrar and Hong, 2022). This is referred to as foetal programming and is said to be related to several factors (Davies et al., 2017). Therefore, this study focuses on the cardiometabolic risks endured by offspring of preeclamptic pregnancies.

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INTRODUCTION

According to O'Hearn et al. (2022), long-term health outcomes are thought to be significantly influenced by cardiometabolic health, which encompasses the intricate interplay between cardiovascular and metabolic systems. These outcomes are shaped by early-life factors, specifically those encountered during the perinatal period. With maternal disorders like preeclampsia emerging as strong contributors to altered health trajectories in perinates, the notion of developmental programming emphasises the impact of the intrauterine environment on the trajectory of health and disease risk (Stojanovska et al., 2016). Preeclampsia, a hypertensive disorder of pregnancy, affects 3-5% of pregnancies globally. This disease is responsible for 2% to 8% of pregnancy-related complications, more than 50,000 maternal deaths, and over 500,000 foetal deaths worldwide (Karrar and Hong, 2022). Wagner (2004) defines the initial diagnostic criteria for preeclampsia as a systolic blood pressure of 140 mmHg or higher or a diastolic blood pressure of 90 mmHg or higher on two separate occasions, at least 4 hours apart. As an alternative, a shorter interval timing of 110 mmHg or higher for the diastolic blood pressure or 160 mmHg for the systolic blood pressure, all of which need to be reported after 20 weeks of gestation (Lim, 2022). Preeclampsia has been linked to long-term cardiometabolic risks for both mothers and their offspring, in addition to its immediate complications. Recent reports have shown that neonates exposed to preeclampsia in utero have increased predisposition to cardiovascular conditions and metabolic dysfunction, such as hypertension, insulin resistance and dyslipidaemia (Stojanovska et al., 2016). These findings are consistent with the Barker hypothesis, which suggests that unfavourable intrauterine conditions can result in permanent physiological changes with lifelong health implications (Stojanovska et al., 2016). This review of the literature examined the primary risks associated with in utero exposure to preeclampsia and the potential long-term consequences. Additionally, the importance of proper follow-up for these offspring will be emphasised, even after childbirth.

Normal placentation

The aetiology of preeclampsia remains elusive; however, it has been reported to be preceded by poor placentation (Jung et al., 2022). The placenta is a multifaceted, transient organ that develops gradually over the first three months of pregnancy, growing in parallel with the growth of the uterus (Burton et al., 2021). It mediates all nutrient and oxygen supply to the foetus, sustaining its normal growth potential. The development of this organ is of great importance, as it is a significant determinant of the well-being of the developing foetus (Braun et al., 2022). This intricate biological process begins with the fertilisation of the egg and progresses through several key stages, each playing a pivotal role in ensuring the proper growth and nourishment of the developing foetus. These stages include trophoblast differentiation and invasion, chorionic villi formation, vascularisation and blood flow, as well as placental barrier formation (Burton et al., 2021).

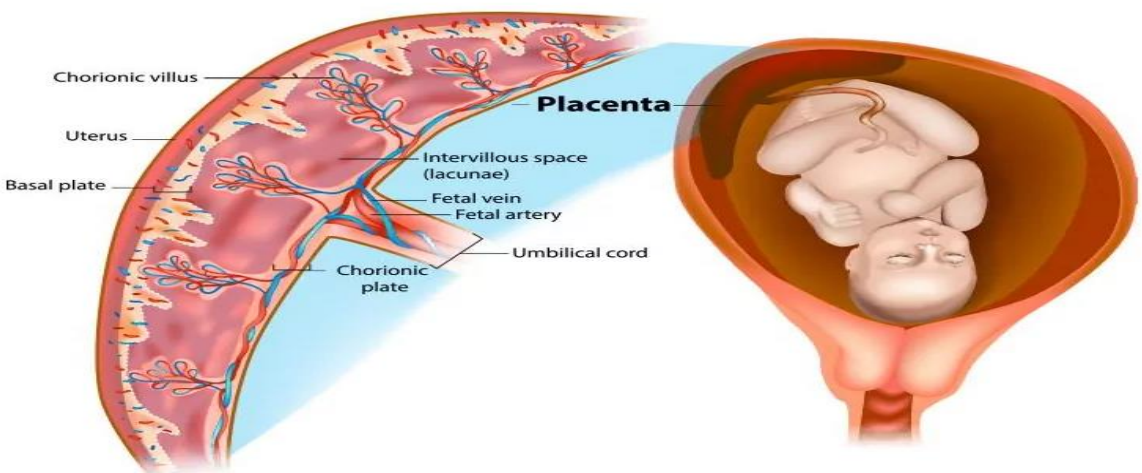

Figure 1. The placenta growing parallel to the foetus

Trophoblast Differentiation and Invasion

The placenta originates from the trophoblast, a layer of cells surrounding the fertilised egg (Vidal et al., 2014). These trophoblast cells differentiate into two distinct layers: the cytotrophoblast and the syncytiotrophoblast. The syncytiotrophoblast, an outer layer of multinucleated cells, plays a crucial role in nutrient and gas exchange (Marsh et al., 2022). Trophoblast cells also invade the maternal endometrium, allowing the uterine spiral arteries to remodel into high-volume, low-pressure conducting vessels, and ultimately facilitating the establishment of the placenta.

Placentation in Preeclampsia

In the case of early-onset pre-eclampsia, vascular remodelling of the spiral arteries is abnormal: only the superficial endometrial parts are invaded. Thus, the spiral arteries remain narrow with high pressure, leading to hypoperfusion and predisposition to reperfusion damage and ischaemia (Bokslag et al., 2016; Burton et al., 2019). Local hypoperfusion and oxidative stress of the syncytiotrophoblast lead to the release of proinflammatory cytokines and antiangiogenic agents into the maternal circulation. These trigger endothelial dysregulation, a generalised hyperinflammatory state and systemic maternal disease, resulting in placental insufficiency (Steegers et al. 2010, Burton et al. 2019). The imbalance between antiangiogenic and proangiogenic factors caused by abnormal placentation results in a widespread endothelial dysfunction affecting maternal organ systems and foetal growth (Gathiram and Moodley, 2020). Vasoconstriction and immune dysregulation are the main effects of this imbalance, which is mainly mediated by soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) (Ives et al. 2020). Ischaemia and reperfusion damage of the spiral arteries impede the delivery of oxygen and nutrients to the foetus (Burton et al. 2019). It is this hypoxia and undernutrition that cause oxidative stress and foetal growth restriction and consequently increase the offspring's risk for cardiovascular diseases.

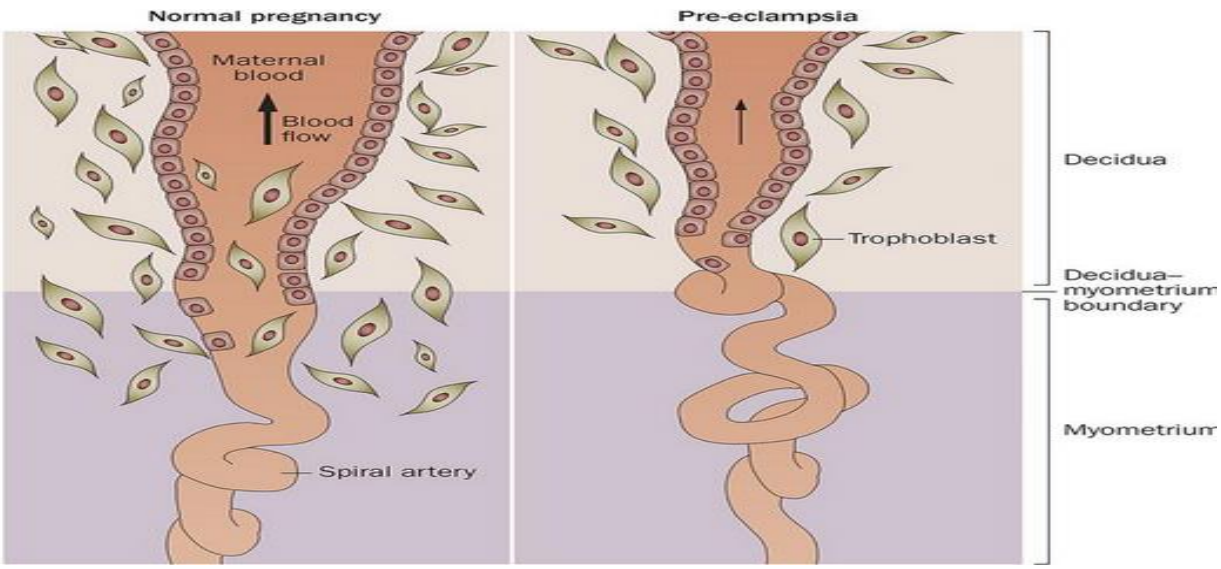

Figure 2. Uterine spiral artery remodelling in the healthy state and in preeclampsia

Definitions and risk factors

Pre-eclampsia is a pregnancy-specific disorder that complicates 3% to 5% of pregnancies globally (Mol et al. 2016). According to the International Society for the Study of Hypertension in Pregnancy, pre-eclampsia is defined as hypertension >140/90mmHg occurring after 20 weeks of gestation, combined with one of the following new-onset conditions: proteinuria >300mg/d, other maternal dysfunction such as renal insufficiency, liver involvement, haematological or neurological complication, or evidence of uteroplacental dysfunction or insufficiency or intrauterine growth restriction (Tranquilli, 2014). Previously, proteinuria was

required for confirmation of preeclampsia. However, two subtypes have been suggested:

- Early preeclampsia: onset at < 34 weeks' gestation and
- Late-onset preeclampsia: onset at ≥ 34 weeks' gestation (reviewed in Burton et al. 2019).

Pre-eclampsia is one of the main causes of maternal and foetal mortality, especially in low- and middle-income countries (Steegers et al. 2010, Mol et al. 2016). Various maternal factors, such as older age, obesity, chronic hypertension, type 1, type 2 and gestational diabetes , antiphospholipid syndrome, chronic renal disease, nulliparity, multifetal pregnancy, hyperandrogenism, previous or familial pre-eclampsia, previous stillbirth or intrauterine growth restriction (IUGR), low socioeconomic status, and specific ethnic backgrounds (i.e. African-American and Filipino) can predispose to pre-eclampsia (Steegers et al. 2010, Burton et al. 2019). Although the cause of pre-eclampsia remains largely unknown, a genetic contribution has been recognised (Roberts and Cooper 2001, Burton et al. 2019). Pre-eclampsia may recur across generations, and both maternal and paternal genes contribute to the risk (Skjærven et al. 2005, Petry et al. 2014, Burton et al. 2019). Heritability of pre-eclampsia has been estimated to be over 30% (Nilsson et al. 2004). Early-onset pre-eclampsia is considered to have primarily a placental cause, whereas in the late-onset form, interactions between senescence of the placenta and maternal genetic predisposition to cardiometabolic diseases have been suggested (Burton et al. 2019).

Epigenetic alterations induced by hypertensive disorders of pregnancy

The phenomenon "epigenetics" is defined as the changes in gene expression that are heritable and do not particularly alter the DNA sequence. These changes are mainly governed by mechanisms like histone modification, non-coding RNAs, and DNA methylation (Kazmi et al., 2019). They can be influenced by environmental factors, such as in-utero exposure to hypertensive disorders of pregnancy (HDP).

Preeclampsia, which is a form of hypertensive disorders of pregnancy, is known to disturb placental formation and function, leading to maternal oxidative stress, systemic inflammation, and ultimately obstructing oxygen and nutrient delivery to the developing foetus. Some epigenetic changes in the developing foetus, specifically in genes involved in metabolic and cardiovascular function, can be triggered by this adverse gestational milieu (Talpur et al., 2024). Altered DNA methylation patterns affecting hemodynamic regulation, glucose and lipid metabolism have been noted in cord blood from preeclamptic pregnancies (Zhu et al., 2024).

These changes may increase the offspring's risk for developing cardiometabolic disorders, such as dyslipidaemia, insulin resistance, childhood obesity and cardiovascular diseases. DNA methylation patterns that seem to deviate from accepted standards, as well as histone modifications, have been associated with obstructed metabolic pathways and vascular function, further increasing predisposition to cardiometabolic diseases in later life (Deng et al., 2024). In response to preeclampsia, non-coding RNAs like microRNAs also play a significant role in modulating gene expression, further influencing cardiometabolic outcomes.

Metabolic and Cardiovascular effects of preeclampsia on the offspring

Dyslipidaemia

Altered lipid and lipoprotein profiles have increasingly been recognised in the offspring of preeclamptic pregnancies, suggesting early-life programming of dyslipidaemia and future cardiovascular risk. A prospective case–control study by Alahakoon and colleagues measured maternal and foetal lipid panels in normotensive, preeclamptic (PE), foetal growth–restricted (FGR), and combined PE+FGR pregnancies. While maternal PE was associated with elevated triglycerides (TG), foetal total cholesterol (TC), HDL, and LDL levels did not differ by group. However, cord-blood apolipoprotein B (ApoB) was significantly higher in PE, FGR, and PE+FGR foetuses than in controls, indicating an atherogenic shift at birth that may predispose to later dyslipidaemia.

Stadler et al. profiled HDL subclasses and functional parameters in patients with early- and late-onset PE. In PE mothers, large HDL-cholesterol decreased, and small HDL increased, accompanied by increased TG content and altered antioxidant capacity. Importantly, neonates from early-onset PE displayed higher TC. In contrast, those from late-onset PE had markedly reduced HDL cholesterol-

efflux capacity — an impaired anti-atherogenic function that may set the stage for dyslipidaemia in childhood and beyond.

Mechanistic work has implicated dysregulations in placental lipases such as lipoprotein lipase (LPL) and endothelial lipase (EL), and oxidative stress in PE, with altered foetal lipoprotein assembly and hepatic lipid metabolism. These lipases play a crucial role in modulating foetal lipid profiles and energy metabolism, as well as facilitating foetal uptake of free fatty acids (FFA). In preeclampsia, placental dysfunction alters the expression and activity of these enzymes, which is reflected in the cord blood lipid profiles. Furthermore, epigenetic modifications of genes governing cholesterol synthesis and clearance have been reported in offspring exposed to preeclampsia. This provides a plausible link to persistent alterations in LDL and HDL homeostasis, as well as an increased risk of dyslipidaemia later in life.

Insulin resistance

Perinates exposed to hypertensive disorders of pregnancy in utero often present altered glucose homeostatic control after birth. Due to foetal hyperinsulinemia triggered by placental insufficiency, these neonates may exhibit transient hypoglycaemia at birth. This is consistent with recent reports suggesting that in utero exposure to preeclampsia may predispose offspring to insulin resistance and related metabolic disturbances later in life. A 2023 review by Koulouraki et al. highlights that the placental dysfunctions and inflammatory milieu characteristic of preeclampsia can induce epigenetic changes that affect the insulin signalling pathway in the foetus. These alterations may persist postnatally, contributing to impaired glucose metabolism and increasing risks of metabolic syndromes in childhood and adolescence.

Studies have shown that children born from a preeclamptic pregnancy exhibit higher fasting insulin levels, elevated homeostasis model assessment of insulin resistance score (HOMA-IR), and altered adipokine profile, even when adjusted for birth weights and gestation ages. These findings support the hypothesis that foetal programming during preeclamptic pregnancies may disrupt pancreatic β-cell function and insulin sensitivity, independent of postnatal environmental factors.

Endothelial dysfunction

Preeclampsia is characterised by maternal endothelial dysfunction, reduced nitric oxide (NO) bioavailability, and vascular stiffness. Emerging evidence suggests that these vascular impairments may be mirrored in the offspring, potentially predisposing them to future cardiovascular disease. Tashie et al. (2020) demonstrated that preeclamptic pregnancies are associated with reduced NO and L-arginine/ADMA ratios, alongside elevated levels of asymmetric dimethylarginine (ADMA) and 3-nitrotyrosine. These markers indicate impaired endothelial NO synthesis, a key regulator of vascular tone and anti-inflammatory signalling. Osol et al. (2017) emphasised that reduced NO signalling in PE stems from oxidative stress, endothelial nitric oxide synthase (eNOS) uncoupling, and elevated anti-angiogenic factors like sFlt-1 and sEng. These disruptions may impair foetal vascular development and endothelial programming.

Chambers et al. (2001) found that women with prior PE had reduced flow-mediated dilation (FMD), a surrogate marker of endothelial function. This vascular phenotype may be inherited or epigenetically programmed in offspring, contributing to early arterial stiffness. Hayden (2025) linked decreased NO bioavailability to vascular arterial stiffening (VAS) and atherosclerosis. These processes begin early in life and are exacerbated by endothelial dysfunction, suggesting a mechanistic bridge between in utero exposure and later cardiovascular risk. Riaz et al. (2025) reported significantly lower NO levels and impaired FMD in hypertensive pregnancies in Pakistan. These findings reinforce the global relevance of endothelial dysfunction and its measurable impact on vascular health in diverse populations.

Growth abnormalities

Two key outcomes—small for gestational age (SGA) and preterm birth—are frequently observed in pregnancies complicated by PE and are independently linked to elevated cardiometabolic risk in offspring.

PE impairs uteroplacental blood flow, leading to a restriction of nutrients and oxygen that compromises foetal growth. Elevated anti-angiogenic factors (e.g., sFlt-1, sEng) and oxidative stress in PE disrupt placental vascular development, contributing to foetal growth restriction (FGR) and

early delivery. Vakil et al. (2022) reviewed 23 studies and found that infants exposed to PE had lower birth weight, length, and BMI at 2 years compared to controls. Some showed accelerated postnatal catch-up growth, which may predispose to obesity and insulin resistance in later life. Jańczewska et al. (2023) reported that preterm birth and low birth weight are associated with elevated blood pressure, altered vascular structure, and increased risk of metabolic syndrome in adolescence and adulthood. Hooijschuur et al. (2015) found that women with PE and SGA infants had the highest prevalence of metabolic syndrome postpartum, suggesting shared maternal–foetal cardiometabolic vulnerability.

Childhood obesity

Recent studies have shown that children who are exposed to preeclampsia in utero may have an increased risk for obesity in later life. One observational study from Iran found that gestational hypertension was significantly associated with overweight and obesity in 2–7-year-old children (OR=1.88, 95% CI=1.46–2.68). This suggests that an adverse intrauterine environment may disrupt foetal metabolic programming and promote excessive weight gain postnatally.

Another cohort study by Palma dos Reis et al. examined the association between preeclampsia and childhood obesity at age 10. Although initial analysis showed higher BMI z-scores in exposed offspring, the association was not statistically significant after adjusting for maternal BMI, parity and smoking.

Furthermore, Byberg et al. reported that exposure to severe preeclampsia was associated with altered growth trajectories, including increased waist-to-height ratios and BMI in girls by adolescence. These results support the hypothesis that severity of exposure and sex-specific factors may influence obesity risk.

Childhood hypertension

A recent meta-analysis shows that exposure to preeclampsia in utero was associated with higher systolic and diastolic blood pressure in offspring during childhood and adolescence. The pooled estimate indicated an increase of 2.0 mm Hg (95% CI: 1.2–2.8 mm Hg) for systolic BP and 1.4 mm Hg (95% CI: 0.9–1.9) for diastolic BP in exposed children compared to controls. However, heterogeneity was moderate ($I^2 \approx 55\%$), suggesting that study-level factors may influence the magnitude of effect. This means that the study characteristics themselves may be driving some of that variability, rather than every study pointing to the same effect size. For example, here in this study, age at follow-up and the BP measurement method modify the observed effect measure (differences in systolic and diastolic BP).

A narrative review by Kanata et al. described that children born after pregnancies complicated by hypertensive disorders, including preeclampsia, presented with a higher prevalence of clinical hypertension by school age. They reported that early-onset or severe forms of preeclampsia carry the most significant risk, with some cohorts showing up to a 1.8-fold increase in hypertension diagnoses before 18 years old. These observations support the notion that placental insufficiency has a lasting impact on vascular structure.

One prospective cohort from the Boston Birth Cohort found that maternal preeclampsia was associated with about a 5.3 percentile higher systolic BP in offspring between 3 and 18 years of age. Significantly, this association was attenuated in children whose cord blood 25-hydroxyvitamin D levels were in the highest quartile. This suggests that in utero vitamin D status may not only modulate but also mitigate the later blood pressure programming, offering a potential avenue for intervention.

Epigenetic and endothelial dysfunction pathways have been proposed to explain why preeclampsia exposures predispose to childhood hypertension. Koulouraki et al. highlighted that anti-angiogenic factors released by the diseased placenta can induce long-term changes in offspring vascular reactivity and renal sodium handling. These mechanistic frameworks help explain clinical observations of early vascular remodelling and elevated peripheral resistance.

Abad et al. (2024) highlight that neonates exposed to PE are particularly vulnerable to oxidative stress due to immature antioxidant systems and high metabolic demands. Reactive oxygen species (ROS) generated by placental ischemia-reperfusion injury can overwhelm foetal defences, leading to lipid peroxidation, protein damage, and mitochondrial dysfunction. These changes are implicated in neonatal complications such as renal injury and retinopathy and may prime vascular tissues for

future dysfunction.

Inflammatory and oxidative stress markers

Kurmanova et al. (2025) report elevated levels of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and immune activation markers (e.g., CD16+, CD56+, HLA-DR+) in maternal and neonatal blood from PE pregnancies. Conversely, anti-inflammatory cytokines like IL-10 were reduced in placental tissue, suggesting a dysregulated immune environment. This imbalance may contribute to vascular remodelling defects and long-term endothelial vulnerability.

Afrose et al. (2022) conducted a meta-analysis identifying ischemia-modified albumin (IMA), uric acid (UA), and malondialdehyde (MDA) as reliable oxidative stress biomarkers in PE. These markers not only reflect acute placental and foetal stress but may also serve as early indicators of cardiovascular risk in offspring.

Businge et al. (2021) explored inflammatory and oxidative stress pathways in PE among South African women. Elevated serum ferritin, gamma-glutamyl transferase (GGT), and high-sensitivity C-reactive protein (hs-CRP) were associated with endothelial dysfunction and immune activation. These findings underscore the relevance of oxidative-inflammatory mechanisms in African populations and their potential link to early-onset CVD.

Conclusion

Preeclampsia represents a significant perinatal insult with far-reaching consequences for offspring cardiometabolic health. Altering the intrauterine milieu through hypertension and systemic inflammation activates developmental programming pathways that permanently reshape vascular and metabolic set-points.

Abnormal spiral artery remodelling and resultant placental hypoxia trigger the release of anti-angiogenic factors and proinflammatory cytokines, driving endothelial dysfunction and oxidative stress. These events impair nutrient and oxygen delivery and induce epigenetic modifications — such as DNA methylation changes and microRNA dysregulation — that persist postnatally and influence gene networks governing lipid and glucose metabolism.

Clinically, individuals exposed to preeclampsia in utero exhibit higher risks of dyslipidaemia, insulin resistance, obesity, and elevated blood pressure throughout childhood and adolescence. A population-based cohort study demonstrated a 28% increased hazard of dyslipidaemia in those prenatally exposed to preeclampsia, while additional data link early insulin signalling disruptions and altered adipokine profiles to later metabolic syndrome features.

These insights underscore the need for longitudinal, mechanistic studies to delineate severity- and sex-specific trajectories of cardiometabolic risk. Early identification of at-risk offspring and targeted interventions — whether nutritional , pharmacological , or lifestyle-based — could mitigate long-term sequelae. Future research should integrate multi-omics approaches and randomised prenatal or postnatal modifiers' trials to translate these findings into
preventive strategies.

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