**Update on preeclampsia**

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**Introduction**

The Australasian Society for the Study of Hypertension in Pregnancy (ASSHP) classifies hypertension-related conditions in pregnancy into several categories. Gestational hypertension is characterised by high blood pressure that develops after 20 weeks of gestation without the multisystem involvement or maternal and fetal features of preeclampsia. Chronic hypertension is identified when high blood pressure is present before the 20th week of gestation, which can be either essential or secondary to another condition. Lastly, there is preeclampsia superimposed on chronic hypertension, where the complexities of both conditions are present in a pregnant individual.

Preeclampsia is a hypertensive disorder in pregnancy characterised by new onset hypertension after 20 weeks gestation (defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on two occasions at least 4 hours apart). Typically, BP returns to the normal range within three months postpartum. Hypertension is often associated with evidence of maternal end-organ dysfunction such as proteinuria ≥300 mg in a 24-hour urine specimen or a urinary protein-to-creatinine ratio ≥0.3). Any organ system, however, may be affected, including the brain, lungs, heart, liver and placenta.

Preeclampsia affects 5-10% of pregnancies, with severe cases occurring in about 1% of pregnancies. It is a leading cause of concern, contributing to 18% of direct maternal deaths. Additionally, preeclampsia is an indication for 2% of caesarean sections and is associated with 6% of perinatal deaths. This condition is recognised as a multisystem disorder, impacting multiple organs and systems within the body, which underscores its severity and the need for careful management during pregnancy.

The condition typically manifests with excessive oedema leading to sudden weight gain, which, unlike normal swelling of pregnancy, may affect the hands and face. The symptoms of preeclampsia arise from core pathologies of vessel wall damage, hypoperfusion and tissue swelling. Depending on the organ systems affected, they may include visual disturbances, headache, epigastric pain, nausea, or vomiting. Seizures, or eclampsia, occur in approximately 0.5-2% of patients. Vascular haemorrhage leading to cerebral stroke is a catastrophic and potentially life-threatening complication.

Treatment strategies often involve antihypertensive medications, close monitoring of maternal and foetal wellbeing, and, in severe cases, expedited delivery to mitigate further maternal morbidity and mortality. The...
PERT test, which stands for “Preeclampsia Risk Estimation Test”, is a predictive tool to assess the risk of preeclampsia in pregnant women. This test involves analysing a range of biomarkers in the blood—such as proteins and enzymes—linked to preeclampsia development. Typically conducted early in pregnancy, the PERT integrates these biomarker readings with personal and family health histories to estimate a woman’s likelihood of developing this condition. The insights from the PERT test allow healthcare providers to accurately classify the risk levels for preeclampsia, enabling them to customise prenatal care appropriately. This might include tailored lifestyle advice, specific medical treatments, or more frequent monitoring for those at higher risk. Importantly, the test is also valuable for identifying women who are less likely to develop preeclampsia, allowing for a more reassuring pregnancy experience and the avoidance of unnecessary interventions.

Early identification through the PERT test facilitates timely interventions to mitigate the severity of preeclampsia and optimises the allocation of healthcare resources. By distinguishing between high-risk and low-risk individuals, the test contributes significantly to improving overall pregnancy outcomes and reducing the incidence and severity of complications associated with preeclampsia.

Historical perspectives

Among the earliest accounts, descriptions of preeclampsia can be traced back to Hippocrates’s era. In these writings, the observations highlighted unwell women, often presenting with swelling, a symptom now recognised as edema. The condition was thought to arise as an imbalance of one or any of the four humours of blood, phlegm, and coloured bile that underscored the human condition. In this context, the swelling seen in such patients was attributed to an excess of fluid in the body, manifesting as disease—a loss of the expected ease of wellbeing.

In the 19th century, the British obstetrician John Lever identified protein in the urine of pregnant women who were symptomatic with this condition. Around the same period, Jean Conrad Amussat, in the 1830s, provided one of the earliest detailed descriptions of eclampsia as a distinct clinical entity, differentiating it from epilepsy. His insights into the sudden development of seizures, described in Greek as “Eklampsis”, laid the foundation for the modern term “eclampsia”. In 1896, the Italian physician Scipione Riva-Rocci introduced the measurement of blood pressure with his invention of the sphygmomanometer. This device allowed accurate blood pressure measurements, establishing a relationship between hypertension and the disease and solidifying the recognition of preeclampsia as a hypertensive disorder of pregnancy.

Throughout this time, the term “toxaemia” was extensively used, reflecting the then-prevailing hypothesis that toxins caused the condition. However, from the 1950s onwards, the nomenclature gradually shifted towards “preeclampsia”. This change underscored a broader understanding of the condition’s complex aetiology, moving away from the simplistic notion of toxins to embrace an understanding of placental dysfunction and vascular health.

Today, preeclampsia is recognised as a multifaceted condition involving intricate pathophysiological mechanisms. While the term “eclampsia” remains to describe the severe progression involving seizures, the majority of cases that remain unencumbered by this complication are described under the broader classification of preeclampsia.

Aetiology

Preeclampsia is unique to pregnancy. In other words, it is a condition that only occurs in the setting of pregnancy, or more specifically, in the setting of pregnancy with placental tissue in situ. The condition will resolve when the pregnancy ends, and the placenta is delivered. This critical role of the placenta is highlighted by conditions of abnormal placental growth or differentiation, such as molar pregnancy, where the risk of preeclampsia still prevails despite not having a baby and may be as high as 10% to 30% of women compared to a rate of between 2 and 8% in otherwise normal pregnancy.

The placental aetiology of preeclampsia is complex and multifactorial. In non-molar pregnancy, the condition appears consequent to some effect of abnormal placental function. Studies suggest that this fault arises at the time of implantation, where early invasion or migration of trophoblast cells into the maternal decidua of the uterus sets the stage for vascular arterial remodelling that will eventually allow increased perfusion to the placental as the pregnancy develops. If this process is compromised, the efficacy of the placenta as an interface supporting maternal foetal exchange is
limited. The onset and evolution of symptoms characterising preeclampsia will depend on the extent of this limitation; the more compromised placental function is, the more severe the symptoms will be and the earlier they will arise\(^1,3,6\).

**Primary pathology**
Abnormalities of early placentation lead to inadequate remodelling of maternal spiral arteries, resulting in reduced blood flow to the placenta and subsequent placental ischemia. This ischemic insult triggers the release of various factors into the maternal circulation, such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng), which contribute to systemic endothelial dysfunction, hypertension, and proteinuria—the hallmark features of preeclampsia\(^1\).

**Secondary pathology**
As a result of factors released into the maternal circulation, secondary pathology arises due to systemic vascular endothelial and circulatory dysfunction. There is impaired vasodilation and an exaggerated response to circulating vasoconstrictors, leading to widespread microvascular damage\(^2\). This results in increased permeability with tissue oedema and perfusion disorder that can affect any organ system. It may include renal impairment with subsequent proteinuria, as seen in historical accounts, hepatic dysfunction, neurological complications, and coagulopathy. These secondary effects contribute to the clinical manifestations of preeclampsia, such as oedema, visual disturbances, headaches, epigastric pain, hyperreflexia and fitting.

**Tertiary pathology**
Refers to the severe and potentially life-threatening complications that can arise from preeclampsia. Eclampsia, characterised by the onset of seizures, is probably the most recognised. HELLP syndrome, an acronym for haemolysis, elevated liver enzymes, and low platelets can also occur either as an extension of preeclampsia or as a separate entity. Vascular haemorrhage can be the most catastrophic complication because it can lead to abruption or cerebral infarction and stroke\(^1\).

**Risk factors**
The risk factors for preeclampsia are varied and complex, reflecting both genetic and environmental influences and individual health conditions. First pregnancies often carry a higher risk of preeclampsia compared to subsequent ones. Moreover, a history of preeclampsia in previous pregnancies considerably raises the risk of recurrence, underscoring the unpredictable nature of the condition and its proclivity to provoke exacerbation depending on individual susceptibility. Each pregnancy with a new paternal partner may increase the risk of developing preeclampsia, suggesting that maternal exposure to new paternal antigens affects immune tolerance developed during pregnancy. This immunological hypothesis is supported by evidence pointing to aberrant maternal immune responses to paternal antigens presented by the fetus and placenta, which can lead to systemic inflammation and endothelial dysfunction\(^1,4\).

Pre-existing medical conditions are also significant contributors to the risk of developing preeclampsia. Conditions such as hypertension, diabetes, and kidney disease prior to pregnancy are all implicated. Additionally, autoimmune disorders like lupus and rheumatoid arthritis are linked with higher rates of preeclampsia, reflecting the intricate interplay between autoimmune responses and pregnancy. Obesity exacerbates the risk as well, with higher body mass indexes correlated with increased incidences of preeclampsia\(^2,6\).

Maternal age is another critical factor, with increased susceptibility observed in very young mothers and those over 35, likely due to the different physiological stresses associated with these age groups. Similarly, multiple pregnancies, such as those involving twins or triplets, significantly raise the likelihood of preeclampsia, highlighting the additional strain placed on the mother’s body. Methods of conception also influence risk; pregnancies achieved through in vitro fertilisation (IVF) show higher rates of preeclampsia, which could be linked to the underlying fertility issues or the procedures involved in IVF\(^6\).

The spacing between pregnancies is another factor; both closely and widely spaced pregnancies increase the risk, suggesting that optimal interpregnancy intervals might mitigate this risk. Additionally, socioeconomic and environmental factors, including limited access to healthcare and lower socioeconomic status, contribute to increased risk, likely due to disparities in healthcare access, nutritional status, and stress levels; because of this or the effect of the factors mentioned above, the risk of preeclampsia appears to be shared across families where a history of previous disease in relatives will lead to a higher predisposition\(^1,4,7\).
Mortality and incidence

Preeclampsia is a significant global health concern, contributing significantly to maternal and perinatal morbidity and mortality. According to the World Health Organization (WHO), it affects approximately 2% to 8% of all pregnancies worldwide. The mortality rates associated with preeclampsia vary widely depending on factors such as access to healthcare, quality of prenatal care, and socioeconomic conditions. In low-resource settings with limited access to medical care, it is estimated to account for approximately 14% of all maternal deaths. In higher-resource settings with better access to medical care, mortality rates are lower, but the condition still poses significant risks to maternal and foetal health.

With prompt diagnosis and appropriate management, the mortality rate can be reduced. However, complications such as eclampsia HELLP syndrome and vascular compromise can still lead to adverse outcomes. In Australia, mortality rates are relatively lower compared to some low-resource settings. Mild preeclampsia occurs in 5-10% of pregnancies, and severe preeclampsia in 1-2% of pregnancies. Australia benefits from a well-developed healthcare system with access to prenatal care, which helps in the early detection and management of preeclampsia. However, disparities in healthcare access and outcomes still exist, particularly among marginalised populations.

Vanguards of current care

The management of preeclampsia is a complex and multifaceted approach that aims to safeguard both maternal and fetal health through preventive measures, targeted medical interventions, and comprehensive monitoring.

The administration of low-dose aspirin is a cornerstone of prevention for those at high risk of developing preeclampsia. The U.S. Preventive Services Task Force (USPSTF) recommends initiating low-dose aspirin therapy between 12 and 16 weeks of gestation, typically at a daily dosage of 100 mg, and continuing no later than the 28th week. This intervention is crucial for women with high-risk factors such as a history of preeclampsia, particularly those with severe or recurrent cases, as well as those with multiple gestations, chronic hypertension, diabetes, kidney disease, or autoimmune disorders like systemic lupus erythematosus or antiphospholipid syndrome. Research supports the efficacy of this approach, showing a 17% reduction in the risk of developing preeclampsia, with the number needed to treat (NNT) being 72. This reduction is even more significant in the high-risk group. Additionally, low-dose aspirin therapy is associated with an 8% reduction in preterm birth and a 14% reduction in fetal and neonatal death, highlighting its potential benefits even though it has yet to be recommended as standard practice.

Antenatal care plays a crucial role in the management and treatment of preeclampsia, emphasising the importance of comprehensive monitoring and assessment to safeguard maternal and fetal health. A thorough risk factor assessment from the patient’s medical history is vital. Regular monitoring of blood pressure and urine protein levels is essential, alongside evaluations of fetal wellbeing that may include foetal movement, fundal height, CTG and Ultrasound assessments of fetal growth and biophysical profile.

Additionally, uterine artery Doppler imaging is a diagnostic ultrasound technique used during pregnancy to evaluate the blood flow through the uterine arteries, which supply the placenta. In a normal pregnancy, the uterine arteries undergo significant changes known as vascular remodelling. This process involves the arteries becoming wider and more elastic to accommodate the increased blood flow necessary for the growing fetus. However, these changes may be inadequate or impaired in conditions such as preeclampsia. By assessing the resistance to blood flow within these arteries (often measured as the Resistance Index or Pulsatility Index), we can help identify pregnancies at high risk of preeclampsia, intrauterine growth restriction, or other placental insufficiencies.

Maternal serum screening is another critical component of prenatal care, providing valuable insights into the fetus’s health and development and the mother’s wellbeing. Among the various biomarkers used in this screening, low levels of Pregnancy-Associated Plasma Protein-A (Papp-A), which is produced by the placenta in early pregnancy, can be indicative of preeclampsia, intrauterine growth restriction, and even chromosomal abnormalities like Down syndrome. Together, these measures facilitate timely interventions and continuous monitoring, which are key to managing the complexities of preeclampsia.

Support and encouragement of lifestyle modification play a significant role in managing preeclampsia, focusing on reducing risk factors and improving overall health.
maternal health. Dietary and lifestyle changes, including nutritional supplements such as calcium, while not curative, can help manage symptoms and potentially stabilise the mother’s condition. Antioxidants such as Vitamins C and E and fish oils have not been shown to be effective.

Antihypertensive medications, such as labetalol, nifedipine, and methyldopa, are prescribed to control blood pressure and prevent the escalation of symptoms\(^2\). It is important to acknowledge that they do not stop the underlying condition but rather aim to prevent sequelae such as hypertensive crises, including the risk of cerebral bleeding. Additionally, magnesium sulphate may be administered to manage severe preeclampsia and prevent eclamptic seizures, a major risk factor for maternal morbidity and mortality.

The definitive cure for preeclampsia involves the delivery of the placenta, linking delivery planning as a crucial management endpoint. The decision to deliver the baby – and, by extension, the placenta – must carefully balance the benefits of prolonging the pregnancy to achieve greater fetal maturity against the risks of continued exposure to preeclampsia\(^4\). In scenarios where early delivery is indicated, corticosteroids may be administered to enhance fetal lung maturity and reduce complications associated with prematurity, including respiratory distress syndrome, neurological issues such as intraventricular haemorrhage, and gastrointestinal complications like necrotising enterocolitis\(^5\). These necessitate advanced neonatal care in neonatal intensive care units (NICUs) to address immediate and long-term health needs.

Managing blood pressure is critical during labour, with parenteral therapy recommended if systolic pressure reaches 170 or higher, or if diastolic pressure is 110 or greater. Blood pressure should be monitored at least every 30 minutes. Biochemical tests, including surveillance of platelets and coagulation status, may be required regularly. Strict fluid management is essential to prevent overload and risks of iatrogenic harm. Patients with severe disease may require monitoring in a critical care environment to allow central venous (CV) or arterial pressure lines to prevent pulmonary edema. Epidural anaesthesia may be considered, except in cases of coagulopathy/thrombocytopenia or severe fetal distress that requires immediate delivery. General anaesthesia may pose challenges due to potential airway edema. Active management of the third stage of labour is necessary, avoiding the use of syntometrine or ergometrine due to the risk of potentiating a hypertensive crisis. Regarding the mode of delivery, a term fetus usually tolerates labour and vaginal delivery well under continuous monitoring. However, in cases of a preterm fetus or severe preeclampsia, a caesarean delivery is often the preferred option\(^1\).

Postpartum care is equally important, as preeclampsia can persist or emerge after childbirth. Women are advised to remain vigilant for symptoms such as high blood pressure, headaches, and visual changes and to maintain regular postpartum check-ups. Each management strategy is carefully tailored to the individual’s condition severity, gestational age, and overall health to mitigate immediate and long-term risks effectively. This comprehensive management strategy ensures that both mother and child receive optimal care tailored to their specific needs and the dynamics of the condition\(^1\).

**Innovations to current practice: the PERT test**

The Preeclampsia Ratio Test (PERT) represents a significant advancement in prenatal screening, particularly for women at high risk of developing preeclampsia, including those with a history of the condition or who present new symptoms. Developed by a team led by Professor Shaun Brennecke at the Royal Women’s Hospital, the PERT test utilises key protein biomarkers produced by the placenta in association with Pulse Wave Velocity (PWV) and Uterine Artery Doppler Ultrasound to help predict the risk of preeclampsia in asymptomatic women. Maternal blood sampling measures Placental Growth Factor (PIGF), a protein critical to placental development, where lower levels often indicate a higher risk of preeclampsia\(^8\). Another key biomarker is Soluble fms-like tyrosine kinase-1 (sFlt-1), an antagonist that binds to and inhibits PIGF and other growth factors. Elevated levels of sFlt-1 are also linked to an increased risk of preeclampsia. The ratio of sFlt-1 to PIGF can be used to predict the likelihood of a woman developing preeclampsia within the next four weeks. A PERT ratio below 38 indicates a very high negative predictive value of 99.3\%, effectively ruling out the development of preeclampsia in the near term and allowing clinicians to avoid unnecessary hospital admissions for intensive monitoring. Conversely, a ratio above 38, while indicating an increased risk, has a lower positive predictive
value of 36.7%, suggesting it is more reliable in excluding the disease rather than confirming it. PlGF alone, with levels below 100pg/ml, can also serve as a sensitive indicator, showing high sensitivity and negative predictive value.

Surveillance, using monthly PERT tests from as early as the 20th week of gestation in high-risk women, may provide critical data for ongoing clinical decision-making. This testing strategy not only helps in diagnosing preeclampsia and predicting its onset – even in cases lacking overt symptoms – but also significantly alleviates patient anxiety. Healthcare providers can concentrate resources and interventions on those who truly need them by accurately identifying those not at risk and optimising maternal and fetal outcomes.

Moreover, the PERT test’s utility extends to monitoring disease progression. Elevated or rapidly increasing PERT levels correlate with the swift progression of the disease and an elevated risk of severe maternal complications, such as acute lung edema, HELLP syndrome, placental abruption, renal failure, and refractory hypertension. These levels are also predictive of adverse fetal outcomes, including growth restriction and prematurity. This predictive capacity supports a tailored, comprehensive approach to antenatal care, crucial for safeguarding maternal and fetal health.

The application of the PERT test is not confined to singleton pregnancies. Despite variations in normal test levels between singleton and twin pregnancies, the PERT test remains a valuable tool in making informed clinical decisions across different pregnancy types. Its implementation in prenatal care routines marks a pivotal shift towards more individualised and effective management of pregnancies at risk for preeclampsia.

**Conclusion**

Preeclampsia remains a complex and potentially severe medical condition that significantly impacts maternal and fetal health worldwide. The management of preeclampsia requires a proactive and comprehensive approach, combining antenatal care, strategic delivery planning, and rigorous postpartum monitoring to effectively mitigate risks and enhance outcomes for both mother and baby.

From initiating low-dose aspirin therapy in the first or early second trimester for high-risk individuals to carefully managing blood pressure and symptoms using antihypertensive medications and lifestyle modifications, each aspect of care is designed to stabilise the mother’s health and prepare for safe delivery. Innovations such as the Preeclampsia Ratio Test (PERT) provide new insight to enhance further our ability to predict and manage the disease, allowing for more precise and individualised care, empowering and revolutionising the anticipatory management of this complex condition.

Delivery, while being the definitive cure for preeclampsia by removing the placenta, is carefully timed to balance fetal maturity with maternal and fetal risks. The use of corticosteroids to enhance fetal lung maturity and the advanced care provided in neonatal intensive care units are critical in managing the risks associated with premature delivery.

Postpartum care is crucial, as the risk of preeclampsia can extend beyond delivery, requiring continued vigilance and care to prevent and manage late-onset complications. Through a combination of advanced screening techniques, targeted medical interventions, and personalised care plans, healthcare providers can significantly improve the prognosis for women with preeclampsia and their babies, demonstrating the evolution and effectiveness of current management strategies in facing this challenging medical condition.

**References**

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