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Chapter

Preeclampsia: From Etiopathology to Organ Dysfunction


Abstract

Preeclampsia is a hypertensive disorder of pregnancy affecting 6–12% of the population. There are various risk factors for the development of preeclampsia, ranging from advanced maternal age to genetics. The proposed etiologies for preeclampsia are abnormal placentation, immunological intolerance, endothelial damage, and genetic inheritance. The pathogenesis includes endothelial activation and dysfunction leading to vasospasm. Preeclampsia is divided into two stages: asymptomatic and symptomatic stages. Preeclampsia causes multiple organ involvement, namely central nervous system, respiratory, cardiovascular, hematological dysfunction, HELLP (hemolysis elevated liver enzymes, low platelets) syndrome, endocrine, renal, hepatic, and uteroplacental dysfunction. These organ dysfunctions increase morbidity and mortality in preeclamptic pregnant patients.

Keywords: abnormal placentation, etiology, endothelial dysfunction, epidemiology, hypertensive disorders of pregnancy, HELLP syndrome, long-term impact, multiple organ dysfunction, preeclampsia, risk factors, uteroplacental malfunction

1. Introduction

Hypertension is a common pregnancy-specific medical disorder, which is a significant cause of maternal and perinatal mortality [1]. There is disproportionate risk to the mother and fetus for further complications and long-term sequelae.

Preeclampsia is a hypertensive disorder of pregnancy causing multi-organ dysfunction syndrome with placental dysfunction occurring in the latter half of pregnancy, with major cause of maternal morbidity, maternal intensive care admissions, Cesarean section, end-organ damage, and fetal complications.
Preeclampsia

2. Definition

Preeclampsia is defined as new onset of hypertension with or without proteinuria or new onset hypertension with evidence of end organ dysfunction after 20 weeks gestation or postpartum in a previously normotensive woman [2].

Classification of hypertension in pregnancy by ACOG (American College of Obstetrician and Gynecologist) 2013 task force:

• Preeclampsia
  ○ Preeclampsia without severe features
  ○ Severe preeclampsia with severe features

Progress of preeclampsia is divided into two stages:

2.1 Asymptomatic first stage

It occurs early in pregnancy with impaired remodeling of the spiral arteries and abnormal placentation. This failure of normal angiogenesis results in superficial placentation.

2.2 Symptomatic second stage

It presents in late second or third trimester and is characterized by signs and symptoms distinguished by the release of excess of antiangiogenic factor from intervillous space into the maternal circulation, which causes widespread maternal endothelial dysfunction and accentuated systemic inflammatory response specific to each organ system.

3. Epidemiology

It affects 6–12% of all pregnant women worldwide, with preeclampsia in 5–8% of pregnancy [3, 4]. The WHO (World Health Organization) has identified hypertension as the second most common cause of maternal death among the triad of hemorrhage and sepsis [5]. It is responsible for 70,000 maternal deaths (major cause of maternal morbidity and mortality) and 500,000 fetal deaths worldwide every year [5]. Nulliparous women are prone to develop preeclampsia, while older women are at higher risk of chronic hypertension with superimposed preeclampsia.

Hypertension is well known in pregnancy worldwide, including chronic, gestational, and possible dangerous preeclampsia [6]. It is considered as high-risk pregnancy when unfavorable conditions prevail for the well-being of mother, fetus, or both.

Effective antenatal care with good surveillance minimizes the risk of complications. Hypertensive disorders of pregnancy can result in life-threatening multisystem pathology, affecting nervous, hematological, renal, hepatic, and respiratory systems.

Preeclampsia presents with maternal features of hypertension, proteinuria, and systemic dysfunction with or without fetal syndrome. Thus, proteinuria is an objective marker and reflects the system-wide endothelial leak that characterizes the preeclampsia syndrome.
There has been an alarming 30% increase in incidence of hypertensive disorders of pregnancy [7], which is explained by the demographics of increase in maternal age, obesity, and increase in use of assisted reproductive techniques, which alters the maternal-fetal immune response. It is also influenced by genetic predisposition, race, and ethnicity.

4. Risk factors

Numerous preconceptional and pregnancy-related risk factors are identified and classified in development of preeclampsia.

4.1 Advanced maternal age

There has been variation of maternal age of pregnancy from teenage to women who are 40 years or older, as compared with women between 20 and 29 years [8] of age, with approximately twofold increase in risk of preeclampsia. Hispanic ethnicity may be at increased risk of developing preeclampsia [9]. Women with advancing age and delayed childbirth show a substantial increase in chronic hypertension during pregnancy and are at increased risk of preeclampsia.

4.2 Genetic factors

Maternal and fetal genetic factors carry strong risk for preeclampsia, with one-third attributable to maternal genetic factors [10]. Women are twice as likely to develop the disorder if they have a family history of preeclampsia, [11] and the risk increases with multiple affected pregnancies [12], potentially carrying high-risk outcomes of placental abruption and fetal growth restriction. Women with history of preeclampsia in previous pregnancy are at increased risk in subsequent pregnancy, particularly in the early onset of preeclampsia.

Partner-related risk factors are long considered a disease of primigravida in women due to limited paternal sperm antigens exposure before conception, which suggests an immunological role in pathophysiology of preeclampsia, with its incidence approximately threefold higher as compared to parous women [13]. A significant contribution of paternal genes (in the fetus) was identified as risk, with one-fifth of the variance in liability conferred through fetal genes in preeclampsia [14].

4.3 Metabolic factors

With worldwide increase in prevalence of obesity, risk of preeclampsia escalates with increasing body mass index (BMI) [15]. A systemic review found that an increase in BMI of 5–7 Kg/m was associated with a twofold increased risk of preeclampsia; it also has strong association with insulin resistance and chronic hypertension, elevating the risk of preeclampsia [16].

Other maternal medical conditions with recognized risk factors for preeclampsia are chronic renal disease, antiphospholipid antibody syndrome, and systemic lupus erythematosus [17] and pregnancy-related conditions with increased placental mass, including multiple fetal gestation and hydatidiform mole, are associated with higher rates of preeclampsia as well [18].

Associated metabolic syndrome, chronic disorders hypertension, preexisting diabetes, and renal diseases that cause endothelial injury are risk factors for preeclampsia. This explains the similar tendency of endothelial dysfunction and
common factor for association of preeclampsia with increased future cardiovascular diseases [19].

4.4 Behavioral factors

Cigarette smoking during pregnancy decreases the risk of preeclampsia [20] by 30–40% as compared to women who do not smoke although biological mechanism remains unknown but probable mechanism may include nicotine inhibition of thromboxane A2 synthesis [21], simulation of nitric oxide release, or combination of both.

4.5 Recreational physical activity

Physical activity during pregnancy is associated with decreased risk for preeclampsia in non-obese women [22]. This occurs by decreasing oxidative stress, enhancing endothelial function, and modulating the immune and inflammatory response.

5. Evtiology

The exact cause of initiation and progress of the disease process is not known, with placenta being the focus in pathogenesis.

Following theories have been proposed to explain mechanics causing preeclampsia.

- Abnormal placentation with failure of trophoblast invasion of uterine vessels.
- Immunological intolerance between maternal, paternal (placental), and fetal tissues.
- Vascular endothelial damage.
- Genetic-inherited predisposition and polygenic disorders.

5.1 Abnormal placentation

In physiological pregnancy, embryo-derived endovascular cytotrophoblast invades the decidual (10–12 weeks) and myometrial (16–18 weeks) segment of spiral arterioles of uteroplacental bed, replacing endothelial lining [23] and causing remodeling of vascular smooth muscles and inner elastic lamina (Figure 1). These physiological changes lead the maternal spiral arterioles to distend the luminal diameter fourfold, resulting in creation of tortuous and funnel-shaped flaccid [23] tubes that provide a low-resistance, low-pressure, high-capacitance, high-flow pathway into intervillous space, which gets further remodeled and unresponsive to vasoactive stimuli. These alterations in maternal vasculature ensure adequate blood flow to nourish the growing fetus and placenta.

In preeclampsia, endovascular cytotrophoblast invasion may be incomplete [24] and only the decidual vessels undergo change, while the deeper myometrial arterioles do not lose their endothelial lining and musculoelastic tissue, resulting in narrowing of maternal spiral arterioles (Figure 1), thus impairing placental blood flow and remaining hyperresponsive to vasoactive stimuli. Inadequate spiral arteriolar remodeling leads to narrowing of maternal vessels and relative placental ischemia.
The severity of the disease correlates with the magnitude of defective trophoblastic invasion [25]. Atherosclerotic changes in maternal radial arteries that supply decidua are observed in preeclampsia. Decidual vasculopathy lesions have high association in preeclampsia with placental insufficiency, including intrauterine growth restriction and small for gestational age [26]. These changes correspond to symptomatic second stage of the preeclampsia syndrome with systemic inflammatory response [27].

In association with defective remodeling of uteroplacental vasculature, there may be presence of agonistic autoantibodies to the angiotensin receptor-1 (AT1) [28]. These autoantibodies activate AT1 receptors, endothelial cells, and vascular smooth muscle cells [29]. The autoantibodies appear to block trophoblastic invasion and may induce the production of reactive oxygen species that plays a significant role in the pathogenesis of preeclampsia at several different stages [29].

### 5.2 Immunological factors

Maternal immune tolerance to parentally derived placental and fetal antigens is lost at maternal-placental interface, which is suggestive of acute graft rejection. The abnormal uteroplacental development is not clearly understood but is likely due to complex interaction of immunologic, vascular, environmental, and genetic factors. The theory of immune maladaptation may play a central role in predisposition to abnormal placentation and subsequent preeclampsia, suggesting that long-term exposure to paternal antigens in sperm is protective.

In preeclamptic women, extravillous trophoblast in early pregnancy expresses reduced amounts of immunosuppressive non-classic human leukocyte antigen G (HLA G). These changes contribute to defective placental vascularization in stage 1 of preeclampsia syndrome [30].
Excess macrophages in the decidua are associated with impaired trophoblast invasion and impaired placentation, signifying excess inflammation. NK cells interact with fetal trophoblast cell markers via killer immunoglobulin receptors (KIR) to influence trophoblastic invasion. Specific genotypic combinations of maternal KIR and trophoblastic human leukocyte antigen C (HLA-C) may increase the risk for preeclampsia. Systemic review of 22 studies examining association between HLA type and risk of preeclampsia suggests that HLA-DR correlates with preeclampsia, but it is unclear if this or any other HLA genotype is casually related to preeclampsia risk; further large sample size studies are called to examine maternal-fetal HLA combinations and risk of preeclampsia [30].

Etiology of preeclampsia is summarized in Figure 2.

6. Pathogenesis

6.1 Endothelial activation or dysfunction causing vasospasm

Inflammatory changes are said to be a continuation of stage 1 alternation. Placental factors are released in response to ischemia, and a cascade of events is provoked in response to antiangiogenic and metabolic factors and other inflammatory leukocyte mediators, commonly called endothelial cell activation or dysfunction. Systemic endothelial cell injury with intense vasospasm is from imbalance of vasodilators (PGI, NO), vasoconstrictors (Angiotensin-II, Thromboxane A2, and Endothelin-II), oxidative stress, and inflammatory mediators (Figure 3). Vasospasm exerts a damaging effect on blood vessels and causes endothelial cells to contract and, together with hypoxia, leads to hemorrhage, necrosis, and compromised end-organ function.

In preeclampsia, inflammatory mediators contributed by systemic oxidative stress are tumor necrosis factor [31] alpha (TNF-Alpha) and interleukins that in turn lead to formation of lipid peroxidases [32], producing toxic radicals that injure systemic vascular endothelial cells.

Mechanisms are precisely understood but proposed theory discussed are as follows:

• Increase in circulatory pressor substances.
Preeclampsia

7.10 Renal dysfunction

Defining component of preeclampsia is proteinuria, with its renal manifestations of persistent proteinuria, changes in glomerular filtration rate, renal blood flow, and hyperuricemia. In preeclampsia serum markers, blood urea nitrogen BUN, creatinine, and uric acid reflect a decrease in renal functions. Hyperuricemia (elevated uric acid levels) is one of the recognized early predictors of preeclampsia, with the primary mechanism of decreased renal clearance [51]. High level of serum uric acid correlates with the severity of the disease. Glomerular endotheliosis is the main feature of the preeclamptic kidney defined by endothelial swelling and glomerular capillary narrowing.

Oliguria is a probable late manifestation and parallels the severity of preeclampsia. Persistent oliguria (< 500-mL urine output in 24 hours) requires immediate attention for evaluation of intravascular volume status.

Major pathological process of acute renal failure in preeclampsia (83–90%) is from prerenal and intrarenal pathology (most commonly acute tubular necrosis), which resolves completely after delivery.

7.11 Hepatic dysfunction

Reduced blood flow to the liver may lead to periportal necrosis and are at risk of periportal hemorrhage, fibrin deposit, subcapsular bleeding, and hepatic rupture.

Hepatic involvement frequently presents as right upper quadrant or epigastric pain and accounts for 32% maternal mortality rate [50].

Rupture of a subcapsular hematoma of the liver is a life-threatening complication that can manifest as abdominal pain, which worsens over time and becomes localized to the epigastric area or right upper quadrant associated with nausea, vomiting, and headache. Alarming hypotension and shock develop with enlarged and tender liver. Diagnosis of liver subcapsular hematoma is confirmed by ultrasonography, computerized tomography (CT), or magnetic resonant imaging (MRI). The most common cause of death is coagulopathy. Conservative management is recommended for subcapsular hematoma or intraparenchymal hemorrhage without capsular rupture in stable women with an important component to avoid all potential trauma to the liver.

7.12 Uteroplacental malperfusion

Uteroplacental perfusion can be impaired in pregnancies complicated by preeclampsia with increased downstream resistance in the uteroplacental bed, decreased diastolic flow velocity, and increased systolic-diastolic flow velocity ratio [51]. Reduced uteroplacental malperfusion is considered one of the major causes of fetal compromise (IUGR, premature birth, and perinatal death). Risk of placental abruption is increased threefold with increased perinatal morbidity and mortality in preeclampsia women [51].

8. General principles and management

- Definite treatment of preeclampsia is termination of pregnancy to prevent disease progression and reduce maternal complications and neonatal morbidity. Time of delivery is based on gestational age, severity of preeclampsia, and maternal and fetal condition.
• Birth of infant who can then thrive subsequently.

• Most patients with preeclampsia with or without severe features can be delivered vaginally. Cesarean delivery is indicated for obstetric indications.

• Fluid balance must be titrated closely to avoid excessive administration and avoid pulmonary edema.

• Expectant management of women with preeclampsia without severe features of disease process may be considered in tertiary care center setting with maternal-fetal medicine specialist (frequent laboratory monitoring, and clinical assessment of mother and fetus).

• Complete restoration of mother’s health.

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<th>Cardiovascular</th>
<th>Neurovascular</th>
<th>Metabolic</th>
<th>Renal</th>
<th>Central nervous system</th>
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<td>Stroke</td>
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<td>Glomerular dysfunction</td>
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<td>Retinal detachment</td>
<td>Metabolic syndrome</td>
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Table 1. Long-term impact of preeclampsia.

9. Long-term consequences

Table 1 describes long-term complications of preeclampsia syndrome.

10. Conclusion

Preeclampsia is one of the hypertensive disorders of pregnancy with increased morbidity and mortality. It occurs in up to 12% of pregnancies. Advanced maternal age, genetic factors, obesity, and chronic renal impairment increase the risk of preeclampsia in pregnant patients. Abnormal placentation, immunological changes, endothelial injury and activation, and increased pressor response are the pathogenesis of preeclampsia.

Due to these generalized endothelial changes, the preeclampsia patients develop multiple organ dysfunction, including PRES (posterior reversible encephalopathy) syndrome, pulmonary edema, HELLP syndrome, acute kidney injury, and uteroplacental insufficiencies.

Management of preeclampsia is supportive therapy, blood pressure control, and seizures prevention and delivery of the fetus. Long-term effects of preeclampsia are chronic hypertension, stroke, and chronic kidney disease.
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Author details

Nissar Shaikh1, Seema Nahid2, Firdous Ummunnisa3, Ifrah Fatima4, Mohamad Hilani3, Asma Gul4, A. Al Basha4, W. Yahia2, F. Al Hail2, H. Elfil1, E. Abdalla1, M.M. Nainthramveetil2, M.A Imraan3, Muhammad Zubair3, Sibghatulla Khan2, N. Korichi2, S. Alkhawaga4, H. Ismail4, S. Yaqoob4 and Mashael Abdulrahman M. S. Al Khelaifi4

1 Surgical Intensive Care Unit: Hamad Medical Corporation, Doha, Qatar
2 Department of Anesthesia/ICU and Perioperative Medicine: Hamad Medical Corporation, Doha, Qatar
3 Dr. Halima Al Tamimi, Obstetrics and Gynaecology Centre, Doha, Qatar
4 Women Wellness and Research Center: Hamad Medical Corporation, Doha, Qatar

*Address all correspondence to: nissatfirdous99@gmail.com

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