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Epidemiology of preeclampsia: Impact of obesity

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Abstract

Preeclampsia is a pregnancy-specific disorder that affects 2 to 8% of all pregnancies and remains a leading cause of maternal and perinatal morbidity and mortality worldwide. Diagnosis is based on new onset of hypertension and proteinuria. Multiple organ systems can be affected with severe disease. The wide range of risk factors reflects the heterogeneity of preeclampsia. Obesity, which is increasing at an alarming rate, is also a risk factor for preeclampsia as well as for later life cardiovascular disease. Exploring common features may provide insight into the pathophysiologic mechanisms underlying preeclampsia among obese and overweight women.

Keywords

pregnancy; preeclampsia; obesity

Introduction

Hypertensive disorders of pregnancy, including preeclampsia, consist of a broad spectrum of conditions which are associated with substantial maternal and fetal/neonatal morbidity and mortality. The incidence is estimated to be between 3 and 10% of all pregnancies.[1, 2] Worldwide, preeclampsia and related-conditions are among the leading causes of maternal mortality.[2] While maternal death due to preeclampsia is less common in developed countries, maternal morbidity is high and is a major contributor to intensive care unit admissions during pregnancy.[2, 3] Approximately 12 to 25% of fetal growth restriction and small for gestational age infants as well as 15 to 20% of all preterm births are attributable to preeclampsia; the associated complications of prematurity are substantial including neonatal deaths and serious long-term neonatal morbidity.[2, 4] Despite major medical advances, the only known cure for preeclampsia remains delivery of the fetus and placenta.

Here, we will review the classification of hypertensive disorders of pregnancy and associated challenges, the global impact of preeclampsia, the epidemiology of risk factors, the effect of obesity – a growing risk factor for preeclampsia, and some insights into pathogenic mechanisms by which obesity may increase the risk in a subset of women.

Classification of preeclampsia

Preeclampsia is a pregnancy-specific syndrome that affects many organ systems and is recognized by new onset of hypertension and proteinuria that occur after 20 weeks' gestation. It is estimated to complicate 2 to 8% of all pregnancies.[2] Although the precise cause is unknown, the pathophysiologic processes underlying this disorder are described in two stages.[5] The first stage is characterized by reduced placental perfusion possibly related

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to abnormal placentation with impaired trophoblast invasion and inadequate remodeling of the uterine spiral arteries. The second stage refers to the maternal systemic manifestations with inflammatory, metabolic, and thrombotic responses converging to alter vascular function which can result in multi-organ damage.[6, 7]

Precise classification of the various hypertensive disorders of pregnancy has remained challenging due to the changing nomenclature as well as the geographic variation in accepted diagnostic criteria. For example, terms such as “toxemia” and “pregnancy-induced hypertension” are now considered outdated. Furthermore, varying diagnostic criteria are used in different regions of the world with disagreement regarding the degree of hypertension, presence/absence of proteinuria, and classification of disease severity.[7] These inconsistencies have led to challenges in comparing and generalizing epidemiologic and other research findings.

The classification system based on the Working Group Report on High Blood Pressure in Pregnancy is most commonly used in the United States in which four major categories are defined: gestational hypertension, preeclampsia- eclampsia, chronic hypertension, and superimposed preeclampsia on chronic hypertension (see Table 1 for criteria).[8] Preeclampsia is defined as new onset of sustained elevated blood pressure (≥140mmHg systolic or ≥90mm Hg diastolic on at least two occasions 6 hours apart) and proteinuria (at least 1+ on dipstick or ≥300mg in a 24 hour urine collection) first occurring after 20 weeks of gestation.

Although the symptoms and signs of preeclampsia occur along a continuum, the syndrome is often categorized as mild or severe to communicate the severity of disease and management approach. Preeclampsia is considered severe when any of the following is present in addition to the defining blood pressure and proteinuria criteria[8]:

- Blood pressure ≥160 mmHg systolic or ≥110 mmHg diastolic
- Urine protein excretion of greater than five grams in a 24 hour collection
- Neurologic disturbances (visual changes, headache, seizures, coma)
- Pulmonary edema
- Hepatic dysfunction (elevated liver transaminases or epigastric pain)
- Renal compromise (oliguria or elevated serum creatinine concentration; creatinine ≥ 1.2 is considered abnormal in women without a history of renal disease)
- Thrombocytopenia
- Placental abruption, fetal growth restriction, or oligohydramnios

Eclampsia refers to seizures that occur in a preeclamptic woman which cannot be attributed to other causes. HELLP syndrome is defined by the presence of hemolysis, elevated liver transaminases, and low platelets. This may or may not occur in the presence of hypertension or proteinuria, but is considered to be along the spectrum of preeclampsia.

The diagnosis of preeclampsia can be particularly challenging in women with pre-existing hypertension and/or renal disease since both blood pressure and urinary protein excretion increase towards the end of pregnancy. Thus, the diagnosis is made based on a sudden increase in blood pressure or proteinuria and/or evidence of end-organ damage (Table 1).[8]

A major criticism of the various classification systems is that none have been independently evaluated for the ability to identify the subgroup of women who are at increased risk of adverse pregnancy outcomes. Recent studies have sought to develop clinically relevant definitions guided by the evidence and based on predictors of adverse outcomes.[9]

Epidemiology of preeclampsia

A systematic review by the World Health Organization indicates that hypertensive disorders account for 16% of all maternal deaths in developed countries, 9% of maternal deaths in Africa and Asia, and as high as 26% in Latin America and the Caribbean.[10] Where maternal mortality is high, most of the deaths are attributable to eclampsia, rather than preeclampsia.[2] Based on data from the United States National Hospital Discharge Survey, the rate of preeclampsia during admission for labor and delivery increased by 25% from 1987 to 2004, while the rate of eclampsia decreased by 22%, albeit not statistically significant.[1] Severe morbidity associated with preeclampsia and eclampsia include renal failure, stroke, cardiac dysfunction or arrest, respiratory compromise, coagulopathy, and liver failure.[2] In a study of hospitals managed by Health Care America Corporation, preeclampsia was the second leading cause of pregnancy-related intensive care unit admissions after obstetric hemorrhage.[3]

Fetal and Neonatal effects

Fetal and neonatal outcomes related to preeclampsia vary around the world. Approximately 12 to 25% of fetal growth restriction and small for gestational age infants as well as 15 to 20% of all preterm births are attributable to preeclampsia. The associated complications of prematurity are substantial including neonatal deaths and serious long-term neonatal morbidity.[2, 4] One quarter of stillbirths and neonatal deaths in developing countries are associated with preeclampsia/eclampsia. Infant mortality associated with preeclampsia is three times higher in low resource settings compared to high income countries, largely due to the lack of neonatal intensive care facilities.[2]

Recurrence in subsequent pregnancies

Studies have reported a 7-20% chance of preeclampsia recurrence in a subsequent pregnancy.[11-13] This risk is further increased if a woman has had two prior preeclamptic pregnancies and is also influenced by gestational age of onset.[14] Estimates of the recurrence of preeclampsia vary widely based on the quality of the diagnostic criteria used. In a study done in Iceland using strict diagnostic criteria for preeclampsia and other hypertensive disorders, the estimated recurrence of preeclampsia or superimposed preeclampsia in a second pregnancy was 13%.[15]

Preclampsia and later life cardiovascular disease

Dr. Leon Chesley, a pioneer in the field of preeclampsia, and his co-workers demonstrated that women who had eclampsia in any pregnancy after their first had a mortality risk that was two- to five-fold higher over the next 35 years compared to controls.[16] Following this early report, others have demonstrated an association between preeclampsia and later life cardiovascular disease and related mortality. Cardiovascular disease risk was increased eight-fold in a Scandinavian population of healthy nulliparous women who developed preeclampsia severe enough to necessitate a preterm delivery.[17] In a cohort of women delivering in Jerusalem, there was a two-fold higher risk of mortality at 24-36 year follow-up in women with prior preeclampsia compared to women who did not have this diagnosis.[18] The deaths were largely related to cardiovascular causes. These findings have also been confirmed in other populations.[14, 19] Hypertension, dyslipidemia, insulin resistance, endothelial dysfunction and vascular impairment have all been observed months to years after preeclampsia, further supporting the link between preeclampsia and subsequent cardiovascular disease.[20] It remains unresolved as to whether these common risk factors lead to the development of preeclampsia and later life cardiovascular disease or whether preeclampsia itself may contribute to this future risk. Based on these data, preeclampsia should be considered a cardiovascular risk factor and women with a history of

preeclampsia should have ongoing, close surveillance to prevent and/or detect future cardiovascular disease.

Risk factors for preeclampsia

The epidemiology of preeclampsia reflects a wide range of risk factors as well as the complexity and heterogeneity of the disease. Risk factors can be classified into pregnancy-specific characteristics and maternal pre-existing features (Table 2). The incidence of preeclampsia is increasing in the United States and may be related to the higher prevalence of predisposing disorders such as hypertension, diabetes, obesity, delay in child-bearing, and the use of artificial reproductive technologies with associated increase in multi-fetal gestation.[1, 21]

Pregnancy-specific features

Parity—Nulliparity is a strong risk factor, almost tripling the risk of preeclampsia (odds ratio of 2.91, 1.28 to 6.61) based on a systematic review of controlled studies.[22] It is estimated that two-thirds of cases occur in first pregnancies that progress beyond the first trimester.[23]

New paternity also increases the risk of preeclampsia in a subsequent pregnancy. The association between primiparity and preeclampsia suggests an immunological mechanism such that later pregnancies are protected against those paternal antigens.[24] Supporting this concept, previous pregnancy loss, increased duration of sexual activity prior to pregnancy, or prolonged pre-pregnancy cohabitation confer a lower risk of preeclampsia.[25] Conversely, the risk of preeclampsia is increased with the use of barrier contraceptives, new paternity, and with donor sperm insemination.[25, 26]

Placental factors—Excess placental volume as with hydatidiform moles and multi-fetal gestations is also associated with the development of preeclampsia.[27-29] The disease process may occur earlier and have more severe manifestations in these cases. The risk progressively increases with each additional fetus.[29]

Maternal characteristics

Age—Extremes of childbearing age have been associated with preeclampsia.[1] However, once adjustments for parity are made in the younger age group (since most first pregnancies occur at a younger age), the association between younger age and preeclampsia is lost.[22, 30] Multiple studies demonstrate a higher incidence of preeclampsia among older women independent of parity; however, many of these do not control for pre-existing medical conditions.[1, 22] After controlling for baseline differences, women who were 40 years of age or older had almost twice the risk of developing preeclampsia (risk ratio of 1.68, 1.23 to 2.29 among primiparas and 1.96, 1.34 to 2.87 among multiparas).[31]

Race—The association between African-American merican race and preeclampsia has been confounded by the higher prevalence of chronic hypertension, often undiagnosed, in this group. While some studies demonstrate a higher risk of preeclampsia among African-American women,[32-34] larger prospective studies which controlled for other risk factors and rigorously defined preeclampsia did not find a significant association between preeclampsia and African-American race.[35, 36] More severe forms of preeclampsia may be associated with maternal non-white race.

Pre-existing conditions—Many of the maternal risk factors for preeclampsia are similar to those for cardiovascular disease. Pre-existing hypertension, diabetes, obesity, and

vascular disorders (renal disease, autoimmune conditions) are associated with preeclampsia.[30, 37] Risk is correlated with the severity of the underlying disorder. Women with underlying chronic hypertension have a 10-25% risk of developing preeclampsia compared to the general population.[13, 38, 39] This risk is increased to 31% in women with a longer duration of hypertension of at least four years or more severe hypertension at baseline.[39] With pre-gestational diabetes, the overall risk of developing preeclampsia is approximately 21%.[40, 41] However, the risk is 11-12% with diabetes of less than 10 years duration, which increases to 36 to 54% among women with longer-standing diabetes associated with microvascular disease.[41, 42] For mild renal disease (serum creatinine of less than 1.5mg/dL), the risk of preeclampsia is estimated at 20 to 25% but greater than 50% for pregnant women with severe renal disease. [43] Preeclampsia also occurs more frequently among pregnant women with autoimmune conditions such as systemic lupus erythematosus and antiphospholipid antibody syndrome.[22]

Obesity—Elevated body mass index (BMI, kg/m^2) is also associated with preeclampsia. Given the obesity epidemic in the United States and around the world, this is one of the largest attributable and potentially modifiable risk factors for preeclampsia. This will be discussed in further detail below.

Family history of preeclampsia—A family history of preeclampsia nearly triples the risk of preeclampsia.[22]

Smoking—Paradoxically, cigarette smoking during pregnancy is associated with a reduced risk of preeclampsia[44-46] possibly due to modulation of angiogenic factors[47].

Obesity and preeclampsia

In the United States, the percentage of women who are overweight or obese has increased by approximately 60% over that last thirty years.[48] The World Health Organization estimates the prevalence of obese and overweight women (body mass index ≥ 25 kg/m^2) to be 77% in the United States, 73% in Mexico, 37% in France, 32% in China, 18% in India, and 69% in South Africa with wide variation within each continent.[49] The high prevalence of obesity and projected increase have substantial implications for pregnancy since obesity is associated with infertility, spontaneous miscarriage, fetal malformations, thromboembolic complications, gestational diabetes, stillbirth, preterm delivery, cesarean section, fetal overgrowth and hypertensive complications.[50]

Obesity increases the overall risk of preeclampsia by approximately 2- to 3-fold.[51] The risk of preeclampsia progressively increases with increasing BMI, even within the normal range. Importantly, it is not only the late or mild forms of preeclampsia that are increased, but also early and severe preeclampsia, which are associated with greater perinatal morbidity and mortality.[52, 53] The increased risk is present in both Caucasian and African-American women.[52] The association between preeclampsia risk and obesity has also been demonstrated in varying populations across the globe.[54, 55] Supporting the concept that obesity may play a causal role is the finding that weight loss reduces the risk of preeclampsia.[56] Some studies suggest that excessive maternal weight gain is associated with the risk of preeclampsia, although these may be confounded by the increase in fluid retention with preeclampsia contributing to the higher weight.[57] Although weight loss is discouraged in pregnancy, obesity is a potential modifiable risk factor for preeclampsia. Weight loss prior to pregnancy is encouraged in overweight and obese women to decrease the risk of adverse outcomes.[50] In our population (Pittsburgh, Pennsylvania), it is estimated that 30% of the preeclampsia risk is attributable to obesity.

Obesity is a risk factor for both preeclampsia and cardiovascular disease.[58] Exploring common mechanisms may provide insight into the pathophysiology of preeclampsia, potential areas for further investigation, and possible targets for therapy. Here, we will briefly highlight a few features that are shared by these conditions including insulin resistance, inflammation, oxidative stress and vascular dysfunction, adipokines, and angiogenic factors (see reference 58, for a detailed discussion).

Insulin resistance

Insulin resistance is estimated to be present in two-thirds of obese individuals. It is also a risk factor for cardiovascular disease and type 2 diabetes. Insulin resistance is more common with preeclampsia and can persist for as long as seventeen years after a preeclamptic pregnancy, thus increasing cardiovascular risk.[59, 60] Features of the metabolic syndrome (obesity, hypertension, insulin resistance, impaired glucose tolerance and dyslipidemia) are also observed more commonly with preeclampsia.[59] With metabolic syndrome, it has been proposed that obesity contributes to hypertension by multiple mechanisms including reduction in available nitric oxide due to oxidative stress, increase in sympathetic tone, and increased angiotensinogen by adipose tissue.[61] Dyslipidemia and the increase in free fatty acids released from adipocytes have also been posited to contribute to oxidative stress and insulin resistance.

Inflammation

Inflammation is a common feature of obesity, cardiovascular disease and preeclampsia. Adipose tissue generates several inflammatory mediators that can alter endothelial function and are produced more actively in obese individuals. C-reactive protein (CRP), an inflammatory mediator produced by the liver as well as adipocytes, is higher in obese individuals and associated with cardiovascular morbidity. Circulating CRP is elevated early in pregnancy prior to the development of preeclampsia and appears to have a stronger association with preeclampsia among obese women.[62, 63] Interleukin-6 is another potent inflammatory mediator that can lead to vascular damage and is associated with obesity, insulin resistance and later life cardiovascular disease.[64] Circulating concentrations are also higher with obesity and with preeclampsia, indicating a potential link.[65] Tumor necrosis factor alpha (TNF-α) is also produced in adipose tissue and associated with insulin resistance, endothelial damage and oxidative stress. Circulating levels are increased with obesity as well as with preeclampsia.[66] However, studies demonstrate that TNF-α is not higher in obese pregnant women compared to non-obese controls.[67, 68]

Oxidative stress

In preeclampsia, oxidative stress is postulated to lead to altered endothelial function and resulting vascular dysfunction.[59] Obesity is also associated with oxidative stress possibly secondary to increased inflammation and free fatty acids as well as lower concentration of circulating anti-oxidants.[6169] Thus, oxidative stress may be a factor that predisposes obese women to developing preeclampsia.

Adipokines

Leptin and adiponectin, two substances produced by adipose tissue, affect metabolism have been linked with cardiovascular disease. Obesity is associated with elevated leptin and decreased adiponectin concentrations.[70] Circulating leptin is increased in preeclampsia and correlates with maternal BMI.[60, 71, 72] Of note, leptin is also produced by the placenta and is likely a major contributor to circulating concentrations during pregnancy. Adiponectin, has insulin sensitizing effects, is decreased with obesity, and inversely correlated with cardiovascular risk. There is not yet a consensus on adiponectin concentrations in

preeclampsia, as studies have reported higher as well as lower concentrations.[73-75] Based on the mechanism of action and association with cardiovascular disease and obesity, these adipokines s may be relevant in preeclampsia, particularly among obese and overweight women.

Angiogenic factors

The balance of circulating angiogenic factors is altered in preeclampsia compared to normal pregnancy, even weeks prior to development of the clinical condition.[76] Placental growth factor (PGF), a member of the vascular endothelial growth factor (VEGF) family, is lower in preeclamptic women. This is likely due to higher circulating concentrations of soluble Flt-1, an anti-angiogenic factor that binds and inactivates PGF and VEGF.[77] Some studies have demonstrated that sFlt-1 and PGF are both lower in obese pregnant women,[78] while others have shown that higher BMI is associated with higher sFlt-1 concentrations and a higher sFlt-1/PGF ratio indicative of an anti-angiogenic milieu even in early pregnancy.[79] Although findings are not consistent across studies, the altered angiogenic milieu with obesity may have implications in the development of preeclampsia.

Lifestyle factors such as diet, sleep disorders, and physical activity are also associated with obesity and cardiovascular disease. Many of these factors have also been implicated with preeclampsia; thus, raising the possibility of a mechanistic link whereby obesity may increase the risk of preeclampsia.[58]

Exploring common mechanisms

Perturbation in the nitric oxide (NO) synthesis and bioavailability leading to vascular dysfunction has been a key mechanistic pathway that has garnered attention in the context of cardiovascular disease and obesity.[80] Asymmetric dimethylarginine (ADMA) is a competitive agonist of L-arginine, the precursor of nitric oxide synthesis. ADMA functions as a nitric oxide synthase inhibitor resulting in reduced NO production and increased superoxide generation. Elevated ADMA concentrations are associated with inflammation, insulin resistance, dyslipidemia, obesity, and cardiovascular disease.[80] Interestingly, circulating ADMA has been shown to decrease with weight loss.[81, 82] Several studies have demonstrated higher concentrations of ADMA with preeclampsia and even prior to the onset of disease at mid-gestation.[83, 84] L-arginine has been used to reverse some of the effects of ADMA in clinical studies. It has been used safely in pregnancy.[85] One randomized controlled trial demonstrated that preeclampsia was reduced with administration of a combination of arginine and anti-oxidant therapy in a high risk population compared to placebo or anti-oxidants alone.[86] Further study is needed to elucidate the effects of L-arginine administration on the risk of preeclampsia in other populations including obese women. Thus, a better understanding the relationship between obesity, preeclampsia and cardiovascular disease may shed light on common mechanisms and potential targets for therapy.

In summary, the impact of preeclampsia on women and their babies is profound. The wide range of risk factors highlights the heterogeneity of this syndrome. Obesity, a growing problem worldwide, is a risk factor for both preeclampsia and later life cardiovascular disease. Further exploration into the mechanism underlying these links has potential to reveal important pathophysiologic mechanisms leading to preeclampsia as well as potential targets for therapy.

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Table 1

Classification of hypertensive disorders of pregnancy

Mild preeclampsia	• New onset of sustained elevated blood pressure after 20 weeks' gestation in a previously normotensive woman (≥140 mm Hg systolic or ≥90 mm Hg diastolic on at least 2 occasions 6 hours apart • Proteinuria of at least 1+ on a urine dipstick or ≥300 mg in a 24 hour urine collection after 20 weeks'
Severe preeclampsia (above criteria plus any of the items listed)	• Blood pressure ≥160 mmHg systolic or ≥110 mmHg diastolic • Urine protein excretion of at least 5 grams in a 24 hour collection • Neurologic disturbances (visual changes, headache, seizures, coma) • Pulmonary edema • Hepatic dysfunction (elevated liver transaminases2 or epigastric pain) • Renal compromise (oliguria or elevated serum creatinine concentration, ≥ 1.2 is considered abnormal in women with no history of renal disease) • Thrombocytopenia • Placental abruption, fetal growth restriction, or oligohydramnios
Eclampsia	• seizures that occur in a preeclamptic women that can not be attributed to other causes.
Superimposed preeclampsia	• sudden and sustained increase in blood pressure with or without substantial increase in proteinuria. • new onset proteinuria (≥300 mg in a 24 hour protein collection) in a woman with chronic hypertension and no proteinuria prior to 20 weeks'* • sudden increase in proteinuria or a sudden increase in blood pressure in a woman with previously well controlled hypertension in a women with elevated blood pressure and proteinuria prior to 20 weeks of gestation* • Thrombocytopenia, abnormal liver enzymes, or a rapid worsening of renal function • *Precise diagnosis is often challenging and high clinical suspicion is warranted given the increase maternal and fetal/neonatal risks associated with superimposed preeclampsia**
HELLP syndrome	• presence of *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelets. This may or may not occur in the presence of hypertension and is often considered a variant of preeclampsia
Gestational hypertension	• New onset of sustained elevated blood pressure after 20 weeks' gestation in a previously normotensive woman (≥140 mm Hg systolic or ≥90 mm Hg diastolic on at least 2 occasions 6 hours apart • No proteinuria

Table 2

Common risk factors for preeclampsia

Pregnancy-specific issues
• nulliparity
• Partner-related factors (new paternity, limited sperm exposure (e.g., barrier contraception)
• multifetal gestation
• hydatidiform mole
Maternal pre-existing conditions
• Older age
• African-American race
• Higher body mass index
• Pregestational diabetes
• Chronic hypertension
• Renal disease
• Antiphospholipid antibody syndrome
• Connective tissue disorder (e.g.,systemic lupus erythematosus)
• Family history or preeclampsia
• Lack of smoking