Obesity and Preeclampsia: A Literature Review

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Abstract

As the main cause of worldwide fetal mortality and morbidity, the risk factors of preeclampsia need to be addressed. The number of obesities has been increasing in a manner like the growth in preeclampsia. As both topics have been mentioned related on some research, this literature review aims to collect data and articles of the topics.

Keywords: obesity; preeclampsia; risk factors; literature review

1. Introduction

Preeclampsia has approximately 5-7% worldwide incidences which cause 70.000 maternal death yearly. Preeclampsia is the main cause of worldwide fetal mortality and morbidity by causing around 500.000 fetal death yearly [1]. Each year, this illness kills 500 000 newborns and 76 000 women worldwide. Preeclampsia and hypertensive disorders of pregnancy are also more common in low-resource countries than in high-resource ones, putting these women at greater risk than their counterparts there. Due to nutritional disparities, poor food, obesity, and diabetes (both before and during pregnancy), which increase the risks of pregnancy problems, especially pre-eclampsia, vulnerable populations have historically been afflicted by socioeconomic, educational, and environmental disadvantages. [2].

2. Overview of Preeclampsia

Preeclampsia is a multisystemic disease in pregnancy associated with the new onset of hypertension that typically occurs after 20 weeks of gestation and close to term with the presence of proteinuria in a patient who was previously normotensive, as defined by American College of Obstetrics and Gynecology [3]. If proteinuria is undetectable, the target organ damage may still be present with systemic symptoms such low platelets or high liver enzymes.

International Society for the Study of Hypertension (ISSHP) defined preeclampsia as a systolic blood pressure of less than 140 mmHg and/or diastolic blood pressure of less than 90 mmHg on at least two occasions measured four hours apart in previously normotensive women who also have at least one of the following new-onset conditions at or after 20 weeks of pregnancy:

- Proteinuria: 24-hour urine protein less than 300 mg/day; spot urine protein/creatinine ratio less than 30 mg/mmoL or less than 0.3 mg/mg; or urine dipstick testing more than two.

- other abnormalities of maternal organs, including acute renal injury (creatinine 90 mol/L; >1.1 mg/dL); liver involvement (such as increased liver transaminases >40 IU/L) with or without right upper quadrant or epigastric discomfort; neurological problems (such as eclampsia, altered mental status, blindness, stroke, or more frequently hyperreflexia when accompanied by clonus, severe headaches, and persistent visual scotomas); and hematological complications (thrombocytopenia–platelet count <150 000/µL, disseminated intravascular coagulation, hemolysis); uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery doppler wave form or stillbirth) [2].

2.1. Etiology

The underlying etiology of preeclampsia is poorly understood, despite the fact that clinical presentation, diagnostic standards, and therapy of preeclampsia are all widely used today. Despite these challenges, it has been demonstrated that defective placentation, which causes aberrant spiral artery remodeling, placental ischemia, hypoxia, and oxidative stress, is the well-supported etiologic origin of preeclampsia [4;5].

2.2. Classifications of Preeclampsia

Due to the shifting nomenclature and regional differences in accepted diagnostic standards, it is still difficult to classify the numerous hypertensive diseases of pregnancy precisely. For instance, phrases like "toxemia" and "pregnancy-induced hypertension" are currently regarded as archaic. Furthermore, there is dispute about the degree of hypertension, the presence or absence of proteinuria, and the classification of illness severity throughout different parts of the world due to different diagnostic criteria [6]. Due to these discrepancies, comparing and generalizing epidemiologic and other study data has proven difficult.

Table 1. Classification of Preeclampsia [7]

Classification	Criteria
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'
Moderate Preeclampsia (criteria mentioned above, plus item 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

2.3. Pathophysiology

The precise cause of preeclampsia is still shrouded in considerable ambiguity. Preeclampsia is caused by two major pathophysiologic mechanisms, the first of which is an impaired placentation that occurs in the first trimester and the second of which is a maternal syndrome that manifests throughout the remainder of pregnancy and is characterized by an excess of antiangiogenic factors.

The failure of cytotrophoblasts to undergo transformation during poor placentation results in an incomplete remodeling that causes the narrowing of the maternal arteries and relative placental ischemia. The placental flow is further hampered by atherosclerosis in the small spiral arteries. Uterine artery Doppler investigations can be used to pinpoint the placental ischemia. Systolic and diastolic uterine artery flows are shown to be healthy during normal pregnancy, however preeclampsia is characterized by an impairment of diastolic flow with a notch in the waveform that occurs prior to the clinical signs and symptoms of the maternal syndrome of preeclampsia.

By opposing VEGF and TGF- 1 signaling, the sENG and sFLT1 contribute to the imbalance of circulating angiogenic factors that results in endothelial dysfunction. [1].

2.4. Complications

Preeclamptic patients in the late preterm period who delay delivering the fetus run a higher risk of developing severe hypertension, which can lead to serious complications like eclampsia, HELLP syndrome, pulmonary edema, myocardial infarction, acute respiratory distress syndrome, stroke, renal and retinal injury, and fetal complications like growth restriction, placental abruption, or fetal or maternal death. [4;8]

2.5. Treatment

Early diagnosis and intervention are the first steps in managing preeclampsia, with an emphasis on effective blood pressure management and seizure prevention. Using beta-blockers like labetalol or calcium-channel blockers like nifedipine, blood pressure can be controlled. Additionally, antenatal testing such as non-stress tests and biophysical profiles, as well as ultrasound of the amniotic fluid index and estimated fetal weight, should be included in the examination of the fetus. Delivery vs expectant treatment for preeclamptic patients may be significantly influenced by the fetal state of the patient.

The delivery of the fetus is, in the end, the only effective treatment for preeclampsia. The dangers of expectant management persist, even if continuous observation is permitted for preterm gestations in patients

with either well-controlled gestational hypertension or preeclampsia without severe symptoms in the context of normal antepartum testing. Serial ultrasonography, weekly antepartum tests, diligent surveillance of symptoms, blood pressure, and laboratory values should all be used if expectant treatment is started in stable individuals. [9]

3. The Effect of Obesity in the Occurrence of Preeclampsia

Obesity and preeclampsia have been closely correlated in research. Over the past 25 years, obesity prevalence has increased in a manner like the growth in preeclampsia. There has been an approximate 60% increase in the proportion of overweight or obese women in the United States. [10]. The prevalence of obese and overweight women (body mass index 25 kg/m2) is estimated by the World Health Organization 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 significant regional variation. [11]. Given that obesity is linked to infertility, spontaneous miscarriage, fetal malformations, thromboembolic complications, gestational diabetes, stillbirth, preterm delivery, cesarean section, fetal overgrowth, and hypertensive complications, the high prevalence of obesity and projected increase have significant implications for pregnancy. [12]

Obesity roughly doubles to triples the risk of preeclampsia overall. [13]. Even within the normal range, preeclampsia risk increases over time as BMI rises. Importantly, preeclampsia in its early and severe forms, which are linked to higher maternal morbidity and mortality, is also elevated, not just the late or mild variants. [14;15]. Both Caucasian and African-American women are at a higher risk. [14]. In numerous populations around the world, it has also been shown that obesity increases the risk of preeclampsia. [16, 17]. Further contributing to the relationship between preeclampsia and obesity, a study found that weight loss reduces the risk of developing preeclampsia [18]. Despite the fact that weight loss is not recommended during pregnancy, studies have found that excessive maternal weight gain is correlated with an increased risk of preeclampsia [19], thus weight loss is recommended in women with obesity or overweight that are planning to be pregnant [12]

Preeclampsia first manifests as an altered invasion of fetal-origin cytotrophoblast cells into the uterus and spiral arterioles, which leads to lessened remodeling of these arterioles and, as a result, lessened blood supply to the placenta [20]. In hypoxic conditions, the placenta releases a variety of substances into the mother's bloodstream, including pro-inflammatory substances like tumor necrosis factor alpha (TNF-), which is linked to maternal endothelial dysfunction, and anti-angiogenic substances like soluble fms-like tyrosine kinase 1 (sFlt-1) [21]. We have shown that preeclamptic women have higher levels of these factors in their plasma [22;23]. Clinical and experimental evidence suggests that obesity may affect placental function and perfusion through some of the metabolic changes associated with obesity, such as hyperlipidemia, hyperinsulinemia, or hyperleptinemia; however, the exact mechanisms are not well-known. This series of changes is one of the proposed mechanisms linking obesity to the risk of preeclampsia [24;25]. It is known that these metabolic indicators are raised in the plasma of obese pregnant women, and they are significantly higher in preeclamptic women. Additionally, it has been noted that the total serum cholesterol levels in the first and second trimesters of pregnancy predict the onset of preeclampsia [26], and we have reported lipid profile changes in preeclamptic women, including elevated levels of low-density lipoproteins (LDLs), low HDL levels, and elevated triglyceride levels [27; 28]. LDL is said to inhibit extra villous cytotrophoblast migration and encourage trophoblast death [29]. Additionally, preeclampsia is associated with raised levels of free fatty acids and triglycerides, which are both increased in obesity and enhance the likelihood of developing the condition [30]. Peroxisome proliferator-activated receptor (PPAR) is known to be stimulated by these two

circumstances. Preeclamptic placentas exhibit enhanced PPAR- expression, and higher concentrations of this receptor reduce the invasiveness of trophoblast cells [31].

We have demonstrated that hyperinsulinemia and insulin resistance precede the clinical presentation of preeclampsia, making them two of the most significant aspects of obesity [32]. According to experimental research, nitric oxide (NO) generation is affected by hyperinsulinemia, which also causes a shallower implantation site and intrauterine growth limitation [33]. Additionally, Granger and colleagues' team discovered that raising insulin levels at the end of pregnancy causes rats' blood pressure to rise [34]. When considered collectively, these clinical and experimental evidence support the idea that one of the common pathways tying obesity to preeclampsia is insulin resistance, which plays a critical role [35; 32].

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