

## Obesity as Risk Factor for Preeclampsia

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### Introduction

Preeclampsia is a common, yet incompletely understood, complication of pregnancy. Women with preeclampsia usually develop hypertension, proteinuria, and varying degrees of ischemic end-organ damage, caused by widespread endothelial dysfunction. Preeclampsia is also associated with abnormalities of coagulation system, disturbed liver function, renal failure and cerebral ischemia [1]. Preeclampsia is characterized by vasospasm, increased peripheral vascular resistance, and thus reduced organ perfusion [1,2]. It complicates an estimated 2–30% of pregnancies and it is a major cause of maternal morbidity, prenatal death and premature delivery, although outcome for most women is good [2,3].

According to the criteria established by The National High Blood Pressure Education Program Working Group, in pregnant women, hypertension is defined as a systolic blood pressure level of 140 mmHg or higher or a diastolic blood pressure level of 90 mmHg or higher that occurs after 20 weeks of gestation in a woman with previously normal blood pressure. As many as one quarter of women with gestational hypertension will develop proteinuria, ie, preeclampsia [4].

Mild Preeclampsia was defined by the occurrence of two or more systolic pressure  $\geq 140$  mmHg and/or diastolic pressure  $\geq 90$  mmHg, diastolic blood pressure measurements, with the first elevated blood pressure occurring after 20 weeks gestation up to 24 hours after delivery, combined with proteinuria at least 0.3g or "1+ protein" per 24 hours [5].

Severe preeclampsia was defined as a systolic blood pressure of 160 mmHg or greater and diastolic blood pressure of 110 mmHg or greater on at least two occasions at least 4 hours apart or on one occasion if antihypertensive therapy was administered. Severe proteinuria was defined with a 24-hour urine sample containing  $\geq 3.5$ g of protein or two urine samples of "3+ protein" or greater taken at least 4 hours apart. The syndrome of haemolysis elevated liver enzymes, and low platelets and eclampsia was also categorized as severe PE [5].

The pathogenesis of preeclampsia is complex. It has been suggested that preeclampsia is a two-stage disease: Stage 1: asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency. This in turn leads to symptomatic, stage 2, wherein the pregnant women develops characteristic hypertension, renal impairment, and proteinuria and is at risk for the HELLP syndrome, eclampsia and other end-organ damage [6]. Pregnancy per se is a state of oxidative stress arising from the increased metabolic activity in placenta mitochondria and the reduced scavenging power of antioxidants [7]. The aetiology of preeclampsia is still not completely understood, although many facts of the disease have been illuminated. Endothelial cell dysfunction would seem to be the common denominator in the various stages of preeclampsia and appears to be present from the first trimester of pregnancy [8,9]. The physiological response of pregnancy represents a transient excursion into a metabolic syndrome where several components are acquired: a relative insulin resistance, significant hyperlipidemia and an increase in coagulation factors [10].

Preeclampsia is associated with accentuation of many features of the metabolic syndrome, including insulin resistance, hypertriglyceridemia, elevated FFA and LDL, low HDL cholesterol, hyperuricemia and abnormalities in the fibrinolytic system [7,11].

Numerous studies have shown that high maternal pre-pregnancy body mass index (BMI; weight (kg)/height (m)<sup>2</sup>) is a strong risk factor for preeclampsia. Overweight is associated with alterations in lipid concentrations and an activation of inflammatory markers and both of these metabolic abnormalities are characteristic of preeclamptic pregnancies before the onset of clinically evident disease [12-14]. Pre-pregnancy BMI was categorized as: underweight (<19.9), normal (20.0-24.9), overweight (25.0-29.9) or obese (>30.0) [15]. Total maternal weight gain during pregnancy was recorded on admission to delivery ward.

Cigarette smoking is associated with lower maternal sFlt-1 concentrations during pregnancy and PE. Based on this data, cigarette smoke exposure may decrease the risk of PE in part by moderating the anti-angiogenic phenotype observed in syndrome [16].

The prevalence of overweight has increased among women in many countries in recent decades. Pre-pregnancy obesity is becoming a common occurrence in obstetric management. Changes in the treatment of obesity-related infertility have resulted in more of these women achieving a pregnancy. Furthermore, as estimated by the World Health Organization in 2000, 30 million people worldwide are clinically obese. In the United States, the obesity is reported to have risen from 13-27% between 1980 and 1999 [17]. American trends are now being seen among the European population with the prevalence of obesity in women in England rising from 16.4 in 1993 to 23.8% in 2004 [18]. Women who developed preeclampsia had higher rates of overweight prior to pregnancy and gained more weight during pregnancy.

BMI and obesity is a validated and independent risk factor for preeclampsia, but the mechanism of how it imparts increased risk is not completely understood. Obesity might act through its association with insulin resistance, a syndrome of metabolic derangement characterized by hyperinsulinemia, hyperlipidemia, hypertension, and endothelial dysfunction [8-10].

Women who developed preeclampsia have an increased risk of ischemic heart disease, hypertension, stroke venous thromboembolism, and mortality over the long term [19]. Greater weight gain, and the increased risk of overweight and obesity in middle age, is associated with an increased risk of cardiovascular disease, diabetes, cancers, and overall mortality. There appears to be linear association between increasing BMI (from 20) and adverse health outcome [20]. Increased mean arterial pressure over 85 mmHg in first or over 90 mmHg in second trimester, predicted preeclampsia, late in pregnancy [21].

CRP levels and concentration of triglycerides during pregnancy, especially in first and second trimester at <20 weeks may be important mediator of the "BMI-preeclampsia" association. The collection of blood specimens in early pregnancy, measuring concentration of CRP, triglycerides, insulin, glucose and inflammatory markers, alongside anthropomorphic assessment, and then followed by a thorough assessment of clinical outcome through a large cohort study, might optimally address the role lipids and the metabolic syndrome in the causation of preeclampsia. These data provide further rationale to examine the potential benefit of preconception weight loss and antenatal exercise [22-24].

At present no management strategy that effectively prevent preeclampsia. It is very important to detect risk women for preeclampsia, especially to differentiate between mild and severe forms, because early or severe preeclampsia is associated with raised rates of maternal and perinatal morbidity and mortality. Women with preeclampsia had higher pre-pregnancy BMI and gain greater amount of weight than women without preeclampsia. We may conclude that pre-preg



pregnancy BMI in combination with blood pressure measurement (especially MAP) appear to be fairly weak predictor for preeclampsia. BMI and blood pressure measurement are virtually free of cost, non-invasive, and ubiquitously available [25].

Future research should concentrate on the development of algorithms that combine biochemical and biophysical markers, including blood pressure measurement-a diagnostic process used in clinical care [25]. These may help improve the predictive accuracy of the tests to clinically important values. An integrated first hospital visit at first trimester combining data from maternal characteristics and history and maternal blood pressure measurement can define the patient at risk for PE.

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