PREPREGNANCY BMI AND PREECLAMPSIA
Review of the Literature and Public Health Implications

By
Weeda Zabih

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Abstract

Objective: *With increasing prevalence of obesity, there is increased attention on prepregnancy BMI and its relation to pregnancy outcomes. Quantifying the relationship between Body Mass Index (BMI) and preeclampsia may provide rationale for a preconception target for intervention that may affect the incidence of preeclampsia. A review of the literature was performed to explore the relationship between prepregnancy BMI and the risk of preeclampsia.*

Methods: *PubMed, Embase and Google Scholar were searched for epidemiologic studies (with BMI as a main exposure and preeclampsia as one of the main outcomes) in English published between 2000 and 2013. For each study a summary of study characteristics, main findings and methodology were reviewed and summarized.*

Results: *BMI is consistently shown to be significantly associated with increased risk for preeclampsia, with ORs ranging from 1.7 to 7. This association appears independent of race/ethnicity, and the association is stronger as the BMI class increases from overweight to superobese.*

Conclusions: *Prepregnancy BMI is associated with increased odds of preeclampsia. Public health interventions that focus on preconception normalization of BMI in women of reproductive age may impact the incidence of preeclampsia and its associated morbidity.*

Background

Preeclampsia is defined as the new onset of hypertension in pregnancy, with systolic blood pressure > 140 and diastolic blood pressure > 90, starting after 20 weeks of gestation and associated with proteinuria.[1] Each year, an estimated 76,000 maternal and 500,000 child deaths worldwide are attributed to preeclampsia.[2] Preeclampsia occurs in 5-8% of deliveries, affecting one in every 12 women in the US. Globally preeclampsia is one of the main causes of maternal mortality and morbidity accounting for 10-15% of maternal deaths. It is responsible for 18% of all maternal deaths in the US alone and 15% of premature births in developed countries. As the only cure for this condition is delivery, it is one of the main causes of premature delivery and low birth weight.[3]

The exact cause of preeclampsia is not yet known. Abnormal placentation, reduced placental perfusion and inflammation are assumed to be the main mechanisms leading to development of preeclampsia.[57][58] Main risk factors known to be associated with preeclampsia are first pregnancy, obesity (BMI>30), age (under 18 and over 40), history of high blood pressure, diet, family history of preeclampsia, diabetes and paternity.[2]

Due to tremendous financial consequences of managing this disease and its adverse health outcomes for the mother and newborn, preeclampsia is a research priority for health care. While the etiology of preeclampsia remains unclear, known risk factors include previous history of preeclampsia, multiple gestation, chronic hypertension, diabetes, first pregnancy, obesity (BMI 30 or greater), maternal age (over 40 or under 18), autoimmune disorders such as lupus and rheumatoid arthritis, in vitro fertilization, and sickle cell anemia.[4]

Overweight or obese body mass index has been suggested as an independent risk factor for preeclampsia. BMI (calculated as weight {kg} per height squared {m^2}) is an international standard measurement for obesity and is used as a surrogate marker for the status of health and nutrition.[5] Between 1999 and 2003, the proportion of women in the US who delivered a pregnancy who had an overweight or obese BMI at the onset of pregnancy has increased from 37.1 to 40.5%. Given the increased prevalence of obesity and its association with adverse pregnancy outcomes such as preeclampsia, the obesity epidemic can have significant public health implications.

Obesity and risk of preeclampsia

Obesity is associated with significant metabolic and physiologic alterations. Adipose tissue is not simply storage of fat, but rather is a hormonally active tissue producing endocrine mediators such as cytokines and adipokines.[6] These mediators have been associated with a proinflammatory and prothrombotic state, insulin resistance and oxidative stress, all of which have been associated with pathogenesis of preeclampsia, as well as lifetime risk of maternal cardiovascular disease.[7][8] Obesity is associated with increased levels of triglycerides, free fatty acids and reduced levels of HDL (High Density Lipoproteins) and increased or stable LDL (Low Density Lipoproteins).[9] The result of a lower HDL to LDL ratio and hypertriglyceridemia promotes an atherogenic state. Adipose tissue produces proinflammatory mediators such as IL-6 (Interleukin-6), TNF-alpha (Tumor Necrosis Factor Alpha), and CRP (C-Reactive Protein), all noted to be elevated in obese women compared to lean women.[10] CRP is found to be higher in pregnant women who develop preeclampsia [11] and one third of total effect of BMI on risk of

preeclampsia is found to be mediated through triglyceride level and inflammation including levels of CRP.[12] TNF-alpha is produced by adipose tissue, and increases insulin resistance, activates endothelial cells, and is associated with oxidative stress. TNF-alpha has been associated with both preeclampsia and obesity.[13][14] IL-6 is disproportionately elevated in obese and preeclamptic individuals. As IL-6 produced in adipose tissue is responsible for 30% of the overall IL-6 in blood, it is assumed that this chemokine is associated with preeclampsia, insulin resistance and cardiovascular diseases later in life.[15] This chemical is assumed to play a role in vessel wall functioning and produces a prothrombotic state, both inducing vascular damage.[16]

Increased levels of free fatty acids and inflammation cause a condition known as oxidative stress, where the body is not capable of eliminating harmful oxygen radicals. Decreased levels of antioxidants in obese individuals, has been explained by decreased dietary intake of antioxidants or consumption of it by high levels of reactive oxygen species.[17] The abundance of oxygen free radicals has been associated with further endothelial injury.

Obesity has been suggested as an independent risk factor for development of preeclampsia. The mechanism of how obesity might cause preeclampsia is multifactorial. It is assumed that increase in lipids, cholesterol and triglyceride levels decreases the body's capacity to fight toxicity well enough and increases oxidative stress, which leads to endothelial dysfunction. In addition, increased cardiac output and vasodilation in obese women might also cause endothelial dysfunction.[18]

Life style factors such as diet and physical activity have been associated with obesity and risk of cardiovascular diseases, however the association of these factors

with preeclampsia remains poorly elucidated. Poor nutrition can contribute to cardiovascular diseases and obesity. Diets rich in antioxidants, fruits, vegetables, vitamins, fiber and whole grains are known to reduce the risk of cardiovascular disease.[19] There have been fewer studies about the role of diet in pathogenesis of preeclampsia and how obesity explains that.[20] In some studies deficiencies of certain micronutrients have been found to be negatively associated with BMI and other measures of body fat.[21][22] It is suggested that dietary excess such as increased intake of refined food, as well as some dietary deficiencies explain the association between obesity and preeclampsia.

Physical activity is known to reduce the risk of obesity and cardiovascular diseases. In addition, data from observational studies show that exercise may reduce the risk of preeclampsia. Studies have shown association between physical activity (leisure time and occupational activities) during and before pregnancy to be associated with reduced risk of preeclampsia.[23][24][25] Data from these studies show that physical activity including recreational activities one year before pregnancy and in early pregnancy is associated with reduced risk of preeclampsia. According to these studies, reduced physical activity may explain the association between obesity and risk of preeclampsia as well as cardiovascular diseases risk.

As preeclampsia is associated with significant morbidity and the literature suggests commonalities in the pathogenesis of adverse effects of obesity and preeclampsia, prepregnancy BMI may be a target for pubic health focus to reduce the risk of preeclampsia. The goal of this review is to explore how strongly high BMI is associated with preeclampsia and thus quantify the association of BMI and preeclampsia. This literature review can be used to direct future interventions

targeting preconception health and further studies into the etiology of preeclampsia in relation to prepregnancy BMI.

Methods

PubMed, Embase and Google Scholar were searched during the month of January 2013 using the following search terms: (“body mass index” or “obesity” or “overweight” or “adiposity”) and (“preeclampsia” or “pregnancy induced hypertension” or “eclampsia” or “gestational hypertension”). References from published articles and systematic reviews were also reviewed for recent studies. Criteria for inclusion included English language epidemiologic studies (case series, cohort or interventional trials) published between 2000- 2013, preeclampsia or gestational hypertension as one of its outcomes, and, BMI as the primary exposure studied. Studies were included where, overweight, obese and severely obese were defined as follows: overweight (BMI 25-30), obese (BMI 30-35) and severely obese BMI (>35). Preeclampsia was defined as gestational hypertension and proteinuria. Gestational hypertension defined as two or more measurements of systolic blood pressure persistently ≥ 140mmHg and/or diastolic blood pressure persistently ≥ 90mmHg for the first time after 20 weeks of gestation. Proteinuria was defined as the excretion of > 300mg of protein in 24 hours, a random sample of 2+, a catheterized sample of 1+ or a protein-creatinine ratio > 0.3.

Studies were excluded if they were in languages other than English, were published before 2000 or had fewer than 200 participants studied.

Abstracts were reviewed for potential inclusion and if appropriate, the article was reviewed. Data from the literature review were abstracted on a structured case

report form. The results were reported as OR and adjusted OR for the association of overweight or obese BMI and preeclampsia.

Results

A total of 50 articles were identified for this study. Of this only 10 met the inclusion criteria. Table (1) gives an overview of each study characteristics. Table (2) summarizes ORs for three BMI categories in each study:

Table (1) Characteristics of studies examining the relationship between prepregnancy Body Mass Index and preeclampsia

#	Study	Country	Type of study Study size	Study Size	Maternal inclusion criteria	Maternal exclusion criteria
1	Effect of prepregnancy maternal overweight and obesity on pregnancy outcome. Ovesen et al. 2011[26]	Denmark	Prospective cohort	369,347	Singleton pregnancy	Incorrect or missing data on BMI,
2	Associations of maternal obesity with blood pressure and the risks of gestational hypertensive disorders. The generation R study Gaillard et al. 2011[27]	Netherlands	Prospective cohort	6902	Low risk pregnancy	No data on BMI and blood pressure, history of hypertension, fetal deaths, induced abortion and twin pregnancies,
3	Determinants of preeclampsia: a case control study in a district hospital in south India. Kumar et al. 2010[28]	India	Case control study	100 cases 100 controls	Diagnosed with preeclampsia	No information provided

4	Prepregnancy body mass index, gestational weight gain, and risk of hypertensive pregnancy among Latina women. Fortner R.T et al., 2009[29]	US	Prospective cohort	1043	Latina women prior to 24 weeks gestation.	Multiple gestation, Diabetes Mellitus, hypertension, heart disease, chronic renal disease, medications affecting glucose tolerance, <16 or >40,
5	Prepregnancy weight status and the risk of adverse pregnancy outcomes. Haugher M.S et al., 2008[30]	Argentina	Prospective cohort	46,964	Pregnancy	Congenital malformations, multiplets,
6	Prepregnancy body mass index and adverse pregnancy outcomes. Driul L et all, 2008[31]	Italy	Prospective cohort	916	Singleton pregnancy,	Twins, chronic hypertension, history of preterm delivery before 37 weeks, history of neonatal death, diabetes and gestational diabetes in the current or previous pregnancies, elective Caesarean section.

7	Prepregnancy body mass index and the occurrence of severe hypertensive disorders of pregnancy. Bodnar L.M et al., 2007[32]	US	Prospective cohort	38188	Singleton pregnancy	Chronic hypertension or elevated blood pressure before 24 weeks' gestation
8	Effect of prepregnancy body mass index categories on obstetrical and neonatal outcomes. Haim A et al., 2007[33]	Canada	Retrospective cohort	18,643	Pregnancy	No information
9	The risk of preeclampsia rises with increasing prepregnancy body mass index. Bodnar L.M et al.. 2005 [34]	US	Prospective cohort of	1179	Primiparous pregnancy less than 16 weeks gestation	Chronic hypertension, diabetes mellitus, or HIV infection, or a positive toxicology screen spontaneous or therapeutic abortion
10	Adult weight change, weight cycling, and prepregnancy obesity in relation to risk of preeclampsia. Frederick I.O et al. 2006[35]	US	Prospective cohort of	1644 women	Multiparous and nulliparous pregnancy	Abortion or fetal demise before 28 weeks of gestation pregestational diabetes chronic or essential hypertension

Table (2) Odds Ratios and Confidence Intervals reported for three BMI categories			
Study	**Overweight BMI (25-30) Odds Ratio 95% CI**	**Obese BMI (30-35) Odds Ratio 95% CI**	**Severely obese BMI (>35) Odds Ratio 95% CI**
Effect of prepregnancy maternal overweight and obesity on pregnancy outcome.	1.9 (1.79–1.95)	3 (2.86–3.17)	4.4 (4.17–4.72)
Associations of maternal obesity with blood pressure and the risks of gestational hypertensive disorders. The generation R study	1.82 (1.16–2.83)	2.49 (1.29–4.78)	3.40 (1.39–8.28)
Determinants of preeclampsia: a case control study in a district hospital in south India.	.	7.56 (1.32-43.37)	.
Prepregnancy body mass index, gestational weight gain, and risk of hypertensive pregnancy among Latina women.	.	2.7 (1.2-5.8)	.
Prepregnancy weight status and the risk of adverse pregnancy outcomes.	1.55 (1.30-1.86)	3.10 (2.54- 3.78)	.
Prepregnancy body mass index and adverse pregnancy outcomes.	1.457 (0.576–3.689)	5.68 (2.524-12.815)	.
Prepregnancy body mass index and the occurrence of severe hypertensive disorders	Whites vs Blacks		
	1.7 (1.1–2.5)	3.4 (2.1–5.6)	7.6 (4.2–13.7)

of pregnancy.	2.1 (1.4–3.2)	3.2 (2.1–5.0)	5.3 (2.9–9.7)
Effect of prepregnancy body mass index categories on obstetrical and neonatal outcomes.	2.28 (1.88–2.77)	4.65 (3.71–5.83)	6.26 (3.48-11.26)
The risk of preeclampsia rises with increasing prepregnancy body mass index.	26 2.1 (1.4, 3.4) 28 2.6 (1.5, 4.5)	30 2.9 (1.6, 5.3) 35 2.8 (1.4, 5.7)	40 2.3 (0.80, 6.4)
Adult weight change, weight cycling, and prepregnancy obesity in relation to risk of preeclampsia.	2.1 (0.6-7.0)	0.6 (0.1-4.6)	.

Interpretation of findings

Prepregnancy BMI was consistently shown to be associated with preeclampsia. ORs for this association ranged from 1.7 – 7 in different BMI categories. The risk of preeclampsia increased with higher BMI categories. This finding was consistent in all studies reviewed. Bodnar et al.[36] reported that compared to women with BMI of 21, the risk of preeclampsia was double for BMI of 26 and almost tripled for women with BMI 30. Also this study found that the risk of preeclampsia rises even within each traditional BMI category, e.g., within obese BMI category (30-35), women with BMI 35 have higher risk of preeclampsia compared to women with BMI 30 or 31. In addition, women at the age of 18 and classified as overweight had 2.1 fold increased risk of preeclampsia compared with women of same age and normal BMI. Every 1kg/m^2 in prepregnancy BMI resulted in an 8% increased risk of preeclampsia. A history of intentional weight cycling (defined as intentional weight loss and unintentional weight gain) was associated with 1.5 increase in risk of preeclampsia.[37]

Apart from preeclampsia, some of the studies additionally reported increased risk for other maternal and newborn adverse outcomes for higher BMI categories. Obesity was shown to be associated with increased risk of cesarean section,[38][39] gestational hypertension and preterm birth.[40] Two of the studies [41][42] reported increased risk of fetal macrosomia (≥ 4000g) in overweight (OR= 1.96), and obese (OR=2.58) women.

The importance of socioeconomic status and health disparities were highlighted in at least two of the studies that studied the association between BMI

and maternal adverse outcomes including preeclampsia in minority populations such as blacks and Latinas. One of the studies[43] found preeclampsia to be more common among Blacks (4.5%) than whites (2.7%). Adjusted ORs ranged from 0.7-4.9 for mild preeclampsia and 0.8- 7.6 for severe preeclampsia among Blacks compared to Whites with ORs of 1-4.2 for mild preeclampsia and 1.4-5.3 for severe preeclampsia for different age groups (17-35). Black women were found to be of low socioeconomic status, be 21 or younger, and obese compared to white women. In this study race/ethnicity was found to play a role in the relationship between BMI and preeclampsia as an effect modifier. Another study[44] was conducted to understand this relationship in Latina women. The results of this study reported that Latina women with prepregnancy obesity have 3-fold risks for hypertensive disorders and preeclampsia compared to normal weight women.

Limitations of the review/studies

The main methodological limitations for reviewed studies were self-reported prepregnancy weight, small sample size and unmeasured confounding variables, which might have biased the results. In order to obtain women's prepregnancy BMI, information on women's weight prior to pregnancy was obtained through self-report using questionnaires and interviews. Only one of the studies reported verification of this information with medical records. This kind of information collection is always subject to recall bias and might cause misclassification of subjects into inaccurate categories.[45] In addition, information about socio-demographic and behavioral variables such as diet, physical activity

before pregnancy, family history of preeclampsia, smoking etc. before pregnancy was also collected through self-reports for all the studies. In addition, none of the studies adjusted for possible confounders such as prepregnancy dietary intake, access to health services, maternal and paternal genetic factors. Small sample size[46] made it challenging in some of these studies to calculate the risk of preeclampsia in all BMI categories.[47]

Other limitations included: inappropriate measurement of blood pressure in obese women and lacking data on other surrogates of prepregnancy adiposity such as prepregnancy waist circumference or skinfold measurements, which might have served as more robust measures of adiposity and its association with hypertensive disorders of pregnancy. Some studies reported [48] residual confounding; self reported data, small sample size [49] and lack of generalizability of the results [50][51] as limitations for the study. Due to small sample size in these studies and heterogeneity of preeclampsia as a disease condition, study participants were too homogenous (for instance studying preeclampsia only in diabetic patients or clients of a specific health facility) thus the results of these studies cannot be generalized to other populations of women with possible risk of preeclampsia.[52][53][54]

Policy implications/recommendations and significance for Maternal and Child Health

- Overweight and obese BMI is associated with preeclampsia as a dose-response association and thus may be a target to reduce the incidence of preeclampsia.[34]
- Life style intervention programs may be key to overcoming the challenge of obesity and weight gain during pregnancy.[30] This can be accomplished through raising awareness of women about weight gain, healthy eating during pregnancy, promoting overall healthy lifestyle habits and organizing preconception counseling for reproductive age women. Such initiatives may not only lower the risk of preeclampsia, but also prevent other adverse health conditions and chronic diseases such as diabetes and hypertension.
- Specific studies should be designed to evaluate interventions that focus on women who enter pregnancy with high BMI. These women can be recognized as high risk and targeted for interventions, such as lifestyle interventions (others may include medication use such as low dose aspirin to prevention preeclampsia).
- Preeclampsia is a heterogeneous condition with possibly sub-classifications of the disease such as early onset and late onset having different etiologies. Future research should focus on larger sample sizes studying these sub-classifications of the disease, in relationship to prepregnancy BMI.[55]

- Considering the racial/ethnic disparities in the incidence of preeclampsia in one of the studies, more studies can be conducted to understand the racial/ethnic interactions with prepregnancy adiposity and elucidate mechanisms causing these differences.[32]
- Public health campaigns are recommended to target young adults (specifically women of reproductive age) who might have risk factors for developing preeclampsia. These campaigns can promote behavior and dietary changes to improve reproductive health outcomes and long-term health condition.

Conclusions

Maternal body fat was assumed to be associated with preeclampsia as long ago as 1810.[56] Obesity is shown to be strongly associated with increased mortality and morbidity during labor and delivery as well as puerperium. Obese women need more intensive care during labor and are likely to end up having C-sections and as a result are at higher risk for surgical complications such as bleeding, thrombophlebitis, infections, etc.

The exact mechanism of relationship between BMI and preeclampsia is yet not clearly understood. There is possibly more than one mechanism associated with development of preeclampsia.[57] It is assumed that reduced placental perfusion as a result of abnormal placentation is the main feature. However, evidence shows that not all women who have reduced placental perfusion end up developing preeclampsia. This finding has led scientists to assume that for development of preeclampsia apart from placental hypo-perfusion, some maternal genetic, environmental and behavior characteristics need to be present. In such women, a predisposing factor such as obesity can trigger endothelial dysfunction, oxidative stress, and initiation of coagulation cascade and finally cause preeclampsia.[58]

In a literature review of 10 epidemiologic studies higher BMI before pregnancy was consistently shown to be associated with increased risk of preeclampsia. ORs ranged from 1.2-2.28 for overweight, from 2.49-7.56 for obese and from 3.4-7.6 for severely obese individuals. One of the studies [57]

reported that a 1.6kg/m^2 lowering of prepregnancy BMI from 29 to 27.4, the equivalent of 4.5kg in women whose heights are 65 inches could reduce the risk of preeclampsia by 50%. These studies showed that obese women have not only higher risk for preeclampsia, but also increased risk for other adverse outcomes such as gestational hypertension, cesarean section and diabetes. In addition, prepregnancy BMI was found to be associated with adverse neonatal outcomes such as macrosomia and preterm birth. Furthermore, one of the studies reported higher risk of preeclampsia among black women who have higher BMI compared to white women.

Obesity is an important health problem in the United States ranked as the second leading cause of death.[59] Obesity is also associated with various morbidity and chronic health conditions such as hypertension, cardiovascular diseases and diabetes. Almost 6-7% of national health expenditures in the US are spent for obesity. Maternal obesity is associated with life threatening conditions and morbidities for both mother and the newborn. [58] With increased prevalence of obesity in the world in recent years,[59] more research and interventions need to be geared towards overcoming the problem of obesity and its associated adverse outcomes for women of reproductive age.

In the context of Maternal and Child Health Pyramid, different interventions at different levels may help overcome the challenge of obesity in women of reproductive age. At the level of population-based services, life style modification interventions with an emphasis on public education and preconception counseling may lower the risk of preeclampsia in women of

reproductive age. Public health programs can promote healthy eating habits and losing weight. These interventions can target women of reproductive age in general and women with higher BMI in particular with appropriate programs. At the level of enabling services, women with higher BMI entering pregnancy can be identified and targeted for health education and family support services. At the level of infrastructure building services, more research with larger sample sizes might provide scientifically reliable conclusions for subcategories of this heterogeneous disease. Further research can follow to evaluate the efficacy, effectiveness and longer-term impact of interventions and programs implemented.

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