ORIGINAL ARTICLE

Association of pre-eclampsia with metabolic syndrome and increased risk of cardiovascular disease in women: A systemic review

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Abstract

Background and Objectives: Cardiovascular disease (CVD) is the leading cause of death in women globally. Preeclampsia has been linked to increased risk of developing heart disease later in life. The best approach for the prevention of CVD after preeclampsia is yet unclear. Studies assessing CVD risk post preeclampsia have included metabolic risk factors that define the metabolic syndrome (MS). This review quantifies the association between preeclampsia and CVD in the context of metabolic risk factors that define the MS.

Materials and Methods: PubMed database was searched for relevant articles from 1999 to March 2015. The search phrase was "preeclampsia and MS." After two levels of screening by title and abstract, case–control, cohort, and cross-sectional studies that included at least 50 subjects were selected.

Results: Twenty-four articles that reported the prevalence or odds for MS and its components following a history of preeclampsia and the prevalence of preeclampsia in women with prepregnancy MS were selected. A total of 9 case–control, 11 cohort, and four cross-sectional studies were included. The prevalence of MS ranged from 10.9% to 27.3% after a preeclamptic pregnancy. About 88% of the case–control studies showed a statistically significant difference in prevalence of MS post preeclampsia whereas 75% of the cohort studies reported prevalence values >10% for the prevalence of MS post preeclampsia. The odds for developing MS post preeclampsia ranged from 1.23 to 3.60 and 83% of the studies reported an odds ratio >2. The prevalence of developing preeclampsia in women with prepregnancy MS ranged from 26.7% to 45% compared to 4.7% to 17% among controls.

Conclusion: The prevalence and odds for developing MS after a preeclamptic pregnancy are high suggesting that MS may be involved in the pathogenesis of CVD following preeclampsia. This will provide evidence on the potential health benefits of a modifiable CVD risk screening program for women with a history of preeclampsia.

Key words: Cardiovascular disease risk, metabolic syndrome, preeclampsia

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Introduction

Cardiovascular disease (CVD) that includes heart disease and stroke cause 8.6 million deaths among women

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annually.[1] It is the leading cause of death in women globally, accounting for more mortalities than all cancers, tuberculosis, HIV/AIDS, and malaria combined.[1]

CVD accounts for one of every four female deaths in the United States.[2] In developing countries, women who develop CVD are more likely to die from it than that of women in industrialized nations.[3] In South Africa and Brazil, the proportion of CVD deaths in women aged between 35 and 59 years is 150% and 75% higher, respectively, than that of women in the same age bracket in the United States.[3] Data from Nigeria also show increased morbidity from CVD in women.[4]

Preeclampsia is one of the leading causes of maternal and neonatal morbidity and mortality affecting 5–8% of all pregnancies in the United States.[5] The prevalence of preeclampsia in developing countries ranges from 1.8% to 16.7%.[6]

Preeclampsia is diagnosed when a pregnant woman develops hypertension and significant proteinuria after 20 weeks gestation.[7] The pathophysiology of preeclampsia is still a subject of much speculation, but a common theory involves defective placental development. Defective cytotrophoblast invasion of the uterine spiral arteries in the second trimester to only the superficial layers of the decidua results in reduced uterine perfusion pressure and placental ischemia.[8] The ischemic placental induces the release of bioactive factors that mediate the pathology of preeclampsia.[8]

Clinical features of preeclampsia including endothelial dysfunction, hypertension, and a prothrombotic state share similarities with CVD,[9,10] and recent studies have linked history of preeclampsia to the development of CVD later in life.[11,12]

Metabolic syndrome (MS) is an established risk factor for CVD.[13] Recent data have shown an increase in the number of women with MS, both in industrialized[14] and in low and middle income countries.[15] It is possible that preeclampsia, a disease peculiar to women, may have contributed to this observation.[16]

MS is the occurrence in one individual of a number of cardiometabolic risk factors including hypertension, obesity, insulin resistance, and dyslipidemia[17] most of which are modifiable cardiovascular risk factors. More recently, increased plasma levels of C-reactive protein and plasminogen activator inhibitor-1 have been added to the list of components that make up the MS.[18] It is not clear whether the CVD risk from MS is higher than the simple summation of its individual components, but studies linking preeclampsia and CVD have measured outcomes which include MS and its components.[16,19]

In this review, the association between preeclampsia and CVD is examined in the context of cardiometabolic risk factors which define the MS.

The involvement of modifiable cardiovascular risk factors in the pathogenesis of CVD following preeclampsia will provide evidence on the potential health benefits of a modifiable CVD risk screening program for women with a history of preeclampsia, and this may provide a window of opportunity for prevention of future CVD in this population.

Materials and Methods

Search strategy

PubMed database was searched for relevant articles from 1999 to March 2015. The search phrase was "preeclampsia and MS." A total of 245 articles were appeared in PubMed between 1999 and March 2015. At the first level of screening, 144 articles were identified with titles related to preeclampsia and MS. Screening of the abstracts further identified articles that reported the prevalence or odds for the MS and its components before, during, or following a history of preeclampsia.

Selection criteria

Prospective and retrospective studies that had case–control, cohort, or cross-sectional study designs that included at least 50 women with preeclampsia were selected.

Data analysis

The prevalence of MS and the odds ratio (OR) for developing MS were compared between the cases with a history of preeclampsia and controls that had normotensive pregnancy. The prevalence and the OR for developing preeclampsia in the presence of prepregnancy MS were also compared with values from healthy controls.

Results

From a search of the PubMed database from 1999 and March 2015, 24 articles that reported the prevalence or odds for the MS and its components following a history of preeclampsia and the prevalence of preeclampsia in women with prepregnancy MS were selected. A total of nine case–control, 11 cohort, and four cross-sectional studies were included. The prevalence of MS ranged from 10.9% to 27.3% after a preeclamptic pregnancy. Table 1 shows the prevalence of MS following a history of preeclampsia in the case–control studies.

Eight of nine studies (88.8%) showed a statistically significant difference in prevalence of MS following a preeclamptic pregnancy between the cases and controls.

Tables 2 and 3 show the prevalence and odds for MS following a preeclamptic pregnancy in the cohort and cross-sectional studies.

Table 1: The prevalence of metabolic syndrome following a history of preeclampsia from the case-control studies

Author	Prevalence of MS in cases (%)	Prevalence of MS in controls (%)	Remark
Smith *et al*., 2012[20]	18.8	6.78	S
Tam *et al*., 2015[21]	26	4.4	S
Verbeek and Verbeek 2014[22]	17	7	S
Yang *et al*., 2015[19]	27.3	25.4	NS
van Rijn *et al*., 2013[23]	15.2	4.3	S
Hermes *et al*., 2013[24]	25	5	S
Dane *et al*., 2009[25]	27	4.1	S
Cusimano *et al*., 2014[26]	17.4	6.78	S
Poornima 2014[27]	10.9	4.9	S

S=Statistically significant; NS=Not statistically significant; MS=Metabolic syndrome

Table 2: The prevalence of metabolic syndrome following a preeclamptic pregnancy in the cohort and cross-sectional studies

Authors	Prevalence of MS after PET (%)
Veltman-Verhulst *et al*., 2010[16]	14.6
Vallejo Vaz *et al*., 2010[28]	4.1
Stekkinger *et al*., 2009[29]	20
Stekkinger *et al*., 2013[30]	25
Lu *et al*., 2011[31]	27
Scholten *et al*., 2013[32]	15.4
Drobny 2009[33]	4.4
Al-Nasiry *et al*., 2014[34]	13.9

MS=Metabolic syndrome; PET=Preeclampsia

Table 3: The odd ratio for developing metabolic syndrome after a preeclamptic pregnancy

Authors	Odds for MS after PET	95% confidence interval
Tam *et al*., 2015[21]	3.5	1.40-8.80
Al-Nasiry *et al*., 2014[34]	2.11	1.00-4.47
Yang *et al*., 2015[19]	1.23	1.12-1.35
Srinivas *et al*., 2009[35]	2.71	1.10-6.67
Drost *et al*., 2012[36]	2.18	1.34-3.52
Forest *et al*., 2005[37]	3.6	1.40-9.0

MS=Metabolic syndrome; PET=Preeclampsia

Table 4: The prevalence and odds for developing preeclampsia when a woman has metabolic syndrome before pregnancy

Author	Prevalence of PET in cases (%)	Prevalence of PET in controls (%)	Odds ratio
Stekkinger *et al*., 2013[30]	45	17	3.77
Horváth *et al*., 2009[38]	27.3	4.7	7.93
Horvath *et al*., 2013[39]	26.7	5.2	-
Ray *et al*., 2005[40]	-	-	7.7

PET=Preeclampsia

Six of eight studies (75%) reported prevalence values >10% for the prevalence of MS following a preeclamptic pregnancy.

Table 3 shows the OR for developing MS after a preeclamptic pregnancy reported for the cohort and cross-sectional studies.

The odds for developing MS following a preeclamptic pregnancy ranged from 1.23 to 3.60. Five of six studies (83.3%) reported an OR >2 for developing MS after a pregnancy complicated by preeclampsia.

The prevalence of developing preeclampsia in a woman with MS before pregnancy ranged from 26.7% to 45% compared to 4.7% to 17% among the controls. The odds for preeclampsia in women with prepregnancy MS ranged from 3.77 to 7.7. Table 4 shows the prevalence and odds for developing preeclampsia when a woman has MS before pregnancy.

The prevalence and odds are higher for developing preeclampsia in women with MS before pregnancy compared to women without prepregnancy MS.

Discussion

A large population-based study by Ray *et al*.[41] established a link between prior history of preeclampsia and increased future risk of CVD. A systematic review and meta-analysis by Brown *et al*. further support this association.[42] The underlying mechanism responsible for the transition from preeclampsia to CVD is multifactorial and is yet to be fully elucidated. This review reports a higher prevalence of MS in women with prior history of preeclampsia compared to women with normotensive pregnancies. The studies reviewed also showed increased odds for developing MS in these women.

The prevalence of MS ranged from 10.9% to 27.3% after a preeclamptic pregnancy. This wide range may be attributed to ethnic/regional differences; different time intervals post preeclampsia at which the women were assessed and the lack of distinction between mild and severe disease in the different studies. One study initially did not find a significant difference in the prevalence of MS post preeclampsia and also reported an OR of 1.23 for the development of MS post preeclampsia.[19] However, after adjusting for age at first pregnancy, women who first became pregnant at ages >35 years and had preeclampsia were found to be at significantly increased likelihood of developing MS later in life (adjusted OR 4.38; 95% confidence interval, 1.62–11.9).[19]

The occurrence of MS post preeclampsia and the eventual culmination in CVD suggest that MS contributes to the

pathophysiologic mechanism linking preeclampsia to future CVD. Pathophysiologic mechanisms underlying preeclampsia include widespread endothelial dysfunction and systemic hypertension,[8] as well as metabolic abnormalities including insulin resistance, dyslipidemia, obesity, and a chronic inflammatory state.[43-45] A clustering of these perturbations, occurring in multiple metabolic pathways, defines the MS, alluding to preeclampsia being the case of MS occurring in the state of pregnancy.[43,46]

Normal pregnancy is associated with anatomic, physiologic, and metabolic adaptations in the mother. Metabolic adaptations include increased insulin resistance, hyperlipidemia, and changes in protein and amino acid metabolism with the aim of providing adequate nutrition for the growing fetus.[47] Preeclampsia appears to be an exaggeration of these biologic adaptations as pregnancies complicated by preeclampsia are characterized by increased insulin resistance, hypertriglyceridemia, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, and high maternal and fetal plasma amino acid concentrations.[47] A study carried out as early as 15 weeks postpartum in pregnancies complicated by preeclampsia[28] showed higher prevalence of MS in these women compared to controls, suggesting that the metabolic perturbations that began during pregnancy have persisted postpartum, marking the onset of MS. MS itself being a clustering of cardiovascular risk factors sets the stage for future CVD in these women. Components of MS are modifiable cardiovascular risk factors. Novel strategies for managing MS have been proposed,[48] but currently lifestyle modification strategies including increased physical activity, diet therapy, reducing alcohol intake, and cessation of smoking have been used with success.[49]

In the sequence of events from preeclampsia to CVD, MS may play a crucial role as a mediator and/or indicator of susceptibility. Some studies report that the presence of MS before pregnancy may predispose women to preeclampsia.[38,40] Reports by Barden[50] from their study of placental syndromes suggest that the absence of the maternal syndrome from pregnancies complicated by IUGR alone is a result of the absence of maternal metabolic perturbations. They concluded that the interplay of defective placentation with maternal metabolic perturbations of insulin resistance, obesity, and dyslipidemia produces the maternal syndrome of preeclampsia,[50] supporting a role for MS as an indicator of susceptibility to preeclampsia.

Conclusion

The prevalence and odds for developing MS after a preeclamptic pregnancy are high suggesting that MS may be involved in the pathogenesis of CVD following preeclampsia. The involvement of modifiable cardiovascular risk factors in the pathogenesis of CVD following preeclampsia will provide evidence on the need to prioritize the establishment of a modifiable CVD risk screening program for women with a history of preeclampsia to footstall progression to CVD.

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Conflicts of interest
There are no conflicts of interest.

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