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Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test?

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Keywords

preeclampsia; hypertension in pregnancy; cardiovascular outcomes; female gender; eclampsia; endothelial dysfunction; coronary heart disease; stroke

Introduction

It is estimated that about 10% of pregnancies are affected by hypertension worldwide. Hypertension in pregnancy includes a spectrum of conditions,[1] including preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension, chronic hypertension and gestational hypertension (Table 1). Unlike other hypertensive pregnancy disorders, preeclampsia is a multisystem disease, its distinctive feature being either sudden onset or worsening of pre-existing proteinuria.

Approximately one-half of all hypertensive pregnancy disorders are due to preeclampsia. In a recent study [2] examining all maternal deaths after the 20th week of pregnancy, preeclampsia and eclampsia were responsible for 790 of 4024 deaths between 1979 and 1992. The overall preeclampsia-eclampsia case-fatality rate was 6.4 cases per 10,000 cases at delivery. The burden is even higher in developing countries. Over the last 50 years, much progress has been made in improving the treatment of preeclampsia with respect to blood pressure control and prevention of eclamptic seizures. However, the etiology of this condition remains elusive, resulting in a failure to develop specific screening, preventive, and treatment strategies. Delivery remains the mainstay of therapy for severe forms and anticipated life threatening complications. As severe forms of preeclampsia commonly develop before the full term pregnancy, labor induction under these circumstances typically results in a preterm delivery, low-birth weight, and related neonatal complications.

Hypertensive pregnancy disorders have an impact on public health well beyond the affected pregnancies. Children born to preeclamptic mothers commonly have a low-birth weight, which is known to be associated with an increased risk for cardiovascular mortality in adulthood. [3] An inverse relationship between maternal risk for CVD mortality and infant birth weight is well-recognized. [4, 5]

Over the past decades, it has become increasingly clear that women with a history of preeclamptic compared to normotensive pregnancies are at increased risk for cardiovascular disease later in life. The purpose of this review is to highlight some of the recent work regarding this risk, and to discuss some of the relevant physiology providing a basis for these findings.

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Preeclampsia in the spectrum of hypertensive pregnancy disorders

The diagnosis of hypertension in pregnancy, and the distinctions among different hypertensive pregnancy disorders are not straightforward, despite the clearly defined criteria. Hypertension in pregnancy is defined by a BP ≥ 140/90 mm Hg on 2 determinations performed 6 hours apart. However, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, individuals with a systolic blood pressure of 120–139 mm Hg, and/or a diastolic blood pressure of 80–89 mm Hg should be considered as prehypertensive. [6] This suggests that the diagnostic threshold of 140/90 mm Hg may be too high for any population and particularly high for young females of childbearing age, potentially leading to the underestimation of hypertensive pregnancy disorders. Furthermore, as blood pressure decreases in midpregnancy, even in patients with chronic hypertension, [7] women with preexisting hypertension may be labeled as hypertensive for the first time towards the end of pregnancy when blood pressure increases to pre-pregnancy levels. Consequently, these women are diagnosed with chronic hypertension only in retrospect, i.e., after their “gestational hypertension” fails to normalize after delivery.

These disorders are classified according to clinical presentation. While these conditions appear as a spectrum of disease, ranging from mild gestational hypertension to severe convulsive eclampsia, significant differences have been reported as to the physiologic bases of these disorders. Preeclampsia may occur *de novo*, i.e., in a previously healthy woman, or superimposed on chronic hypertension. It is believed to result from inadequate placentation resulting in the elaboration of various vasoactive peptides, exemplified by the soluble receptor for vascular endothelial growth factor, commonly referred to as soluble FMS-like tyrosine kinase 1, or sFlt-1. [8] Recent research indicates that the elevation of sFlt-1 seen in preeclampsia and eclampsia is not present in gestational hypertension, [9] indicating that differences in the clinical presentations among preeclampsia and other hypertensive disorders (Table 1) likely are due to different underlying mechanisms that may have different implications for later CVD.

Cardiovascular disease in women

Despite significant advances in diagnostic and treatment strategies for CVD in the 1980’s, the decline in cardiovascular mortality in men was not accompanied by the same rate of decline in women. [10, 11] The reasons for the gender differences observed with respect to overall cardiovascular disease (CVD) risk profiles and clinical course are not well understood. In addition to sex-based disparities in the delivery of health care, they likely include gender-specific factors, which may influence the onset and diagnosis of CVD, its clinical course, efficacy of therapy and, ultimately, prognosis. While many risk factors are similar between the genders, such as obesity and smoking, the role of female-specific conditions frequently is not accounted for. Estrogen exposure, pregnancy, menopause and possible subsequent hormone use may have modifying effects on many risk factors, such as lipid profiles and timing of the onset of disease. In addition, the history of female specific conditions such as preeclampsia and eclampsia are not included in traditional risk models, despite a growing body of evidence suggesting that women with a history of these conditions may be at a higher risk for CVD than those who had normotensive pregnancies. [12] These two conditions do share several common risk factors, such as diabetes and obesity that may lead to preeclampsia and CVD at different times of a woman’s life. An alternative explanation, although less plausible in the absence of supporting data, is that preeclampsia itself may induce irreversible vascular and metabolic changes that my increase the overall risk for CVD. Either way, women who develop preeclampsia appear to be at higher risk for CVD later in life. Therefore, a history of preeclampsia may help identify women at CVD risk early in life, thus offering an opportunity for timely screening, and preventive and treatment strategies.

Preeclampsia and cardiovascular disease: common mechanisms

Preeclampsia seems to originate from complex interactions among maternal constitutional factors, including pre-existing metabolic abnormalities, placenta-derived products, and the exaggerated adaptive mechanisms that normally occur during pregnancy, which are strikingly similar to abnormalities associated with CVD (features of the metabolic syndrome, an inflammatory response, and a hypercoagulable state). In addition, similar to cardiovascular diseases, endothelial dysfunction plays a critical role in the pathogenesis of preeclampsia.

Endothelial Dysfunction

Several potent mediators of endothelial cell dysfunction have been shown to be upregulated in preeclampsia, including cellular fibronectin, [13] von Willebrand factor, [14] cell adhesion molecules: P-selectin, [15] vascular endothelial adhesion molecule-1 (VCAM-1) and inter-cellular adhesion molecule -1 (ICAM-1), [16] and cytokines: interleukin-6 (IL-6) [17] and tumor necrosis factor-α (TNF-α). [18] Relative nitric oxide deficiency may contribute to the generalized vasoconstriction seen in preeclampsia. [19] While it remains unclear whether dysregulation of these substances causes endothelial dysfunction, or whether their upregulation represents merely a marker of endothelial injury, the sum effect of these abnormalities is a state of systemic vasoconstriction, systemic ischemia, and multisystem dysfunction. Recent studies have provided evidence that preeclampsia is associated with elevated levels of the soluble receptor for vascular endothelial growth factor (VEGF), commonly referred to as sFlt-1 (from fms-like tyrosine-kinase receptor-1). By antagonizing the pro-angiogenic effects of VEGF, increased levels of sFlt-1 can induce endothelial dysfunction, and thus hypertension and proteinuria. [8] The interplay among endothelial dysfunction and ongoing oxidative stress, inflammation and the hypercoagulable state that are present in preeclampsia appears quite complex as these mechanisms may potentiate each other, resulting in cumulative vascular damage.

Metabolic abnormalities

CVD and preeclampsia, as mentioned previously, share several common metabolic abnormalities as risk factors. These include obesity, insulin resistance, and lipid abnormalities. [20, 21] Patients who are obese before pregnancy are at a greater risk for preeclampsia. [22] In diabetic pregnancies, the risk for hypertension in pregnancy and/or preeclampsia is double when compared to normal, non-diabetic controls. [23] The pattern of increased small, dense low-density lipoprotein (LDL) and triglycerides (pattern B) is known as particularly atherogenic and has been described in patients with coronary artery disease [24] and in women with preeclampsia. [25, 26] Notably, a picture of “acute atherosis” in the placental bed, which is characteristic for preeclampsia, is due to oxidized LDL taken up preferentially by macrophages to form lipid-laden macrophages, or foam cells, and closely resembles atherosclerotic plaques. Similarly, leptin, an adipocyte-derived hormone, [27] a marker of increased risk for CVD, [28] has been shown to be increased significantly in preeclamptic mothers. [29] Elevated levels of leptin are suggestive of resistance to its metabolic effects and may promote platelet aggregation, [30] thus further contributing to a hypercoagulable state of preeclampsia.

Oxidative stress

Oxidative stress due to free radical generation also contributes to endothelial dysfunction both in preeclampsia and atherosclerosis. [31] Evidence for oxidative stress in preeclampsia includes increased lipid peroxidation, coupled with the diminished activities of antioxidant enzymes (superoxide dismutase and glucose 6-phosphate-dehydrogenase), [32] decreased plasma ascorbate levels, [33] and an increased capacity of preeclamptic placental cells to generate reactive oxygen species. [34] While a pilot study evaluating the efficacy of antioxidant treatments with vitamins C and E showed a significant reduction in the biomarkers of preeclampsia, and a decreased rate of preeclampsia in treated patients, [35] a follow-up randomized, placebo-

controlled, adequately powered trial in women at increased risk showed that vitamins C and E not only did not prevent preeclampsia, but increased the risk for a low infant birth weight. [36] Likewise, the data on the use of antioxidants in the primary prevention of coronary heart disease are conflicting. [37, 38]

Inflammatory response

During normal pregnancy, the maternal immune reaction to fetal antigens manifests as an exaggerated inflammatory response. [39, 40] This inflammatory response is further potentiated in preeclampsia, as evidenced by elevated levels of markers of neutrophil activation compared to normal pregnancy. [17, 18][41, 42, 43, 44][45] Similar to CVD, elevated C-reactive protein levels have been associated with an increased risk for preeclampsia. [46] Likewise, and similar to atherosclerosis, [47] leukocyte adhesion to endothelium plays an important role in promoting inflammation that may contribute to the development of preeclampsia.

Hypercoagulability

Compared to women with histories of normal pregnancies, those with histories of preeclampsia have a higher incidence of activated protein C resistance, protein S deficiency, anticardiolipin antibodies, factor V Leiden and hyperhomocysteinemia [48]. Similarly, an increased risk for cardiovascular disease has been associated with elevated levels of pro-coagulants, most notably homocysteine [49] and PAI-1. [50] In preeclampsia, the hypercoagulable state of normal pregnancy is further potentiated, as evidenced by an imbalance between fibrinolysis and coagulation in favor of the latter. Procoagulant proteins such as tissue plasminogen activator (tPA), plasminogen activator inhibitor (PAI-1), von Willebrand factor, [14] fibronectin, [51] homocysteine, [52] and thrombomodulin [53] are upregulated in preeclampsia, while levels of the anticoagulant proteins, including anti-thrombin III, protein C and protein S [54] are reduced. Conceivably, the presence of a maternal hypercoagulable state, in the setting of low-pressure placental blood flow, may trigger deposition of fibrin and formation of thrombi, further worsening endothelial dysfunction and placental ischemia. [55]

Preeclampsia and chronic hypertension later in life

Increasing evidence suggests that women with a history of preeclamptic pregnancies are at increased risk of chronic hypertension later in life. An association between preeclampsia and the future development of hypertension and renal disease was first recognized in the early 19th century. Several studies in the 1960's and 1970's offered further support. [56, 57] In the early 1970's, Chesley and colleagues reported that primiparous preeclamptic women are not different from controls with respect to the development of hypertension, overall mortality, or mortality secondary to cardiovascular disease. [58, 59] This study had several serious limitations: the control group consisted of women from previously published epidemiologic studies and therefore was not entirely comprised of normotensive pregnancies, and most likely included some women with hypertensive pregnancy disorders. Its results, however, had far-reaching effects and led to the conclusion that hypertensive diseases of pregnancy are limited to the affected pregnancy, and have few, if any, long term maternal effects.

More recently, there has been renewed interest in the field, due perhaps to the steadily increasing rates of CVD in women. In 1986, Sibai et al [60] reported a significantly higher incidence of hypertension in patients with histories of preeclampsia or eclampsia during their first pregnancies compared to matched controls who had had normotensive first pregnancies. The risk was particularly high for patients with a history of recurrent preeclampsia or eclampsia, and in those who presented with the condition before 30 weeks' gestation. Importantly, most of the differences were noticed in individuals who had been followed up for at least 10 years. The importance of the follow-up interval was further supported by the work of Selvaggi, et al,

[61] in which half of the participating women with a history of preeclampsia were hypertensive 10 years after delivery compared with only one-third who were hypertensive 5 years earlier.

We recently reported that women with histories of preeclampsia had a higher prevalence of future hypertension (48.5%) in their fifties (25 years after their preeclamptic pregnancies, on average) than those with histories of normotensive pregnancy (22%). [62] A major strength of our study draws from rigorous medical chart review to confirm the presence or absence of the diagnostic criteria of preeclampsia. Similar to previous published reports, our study sample was relatively small, consisting of 103 cases and 100 controls.

As most of the published studies have been clearly underpowered, Bellamy, et al [63] recently performed a systematic review and meta-analysis assessing the risks of CVD in women with histories of preeclampsia and eclampsia. They conducted a search of Medline and Embase between 1960 and December 2006; both positive and negative studies were included in the analysis. A total of 13 studies involving 21,030 women examined the risk of hypertension subsequent to a preeclamptic or eclamptic pregnancy. Over a mean follow-up of 14.1 years, the authors found that 1885 of 3658 women with preeclampsia developed hypertension later in life, providing a relative risk of 3.7. These findings illustrate that the bulk of the available the data supports a significant risk for preeclamptic women to become hypertensive later in life.

Hypertension in pregnancy and coronary heart disease

Over the last decade, several population-based studies have provided evidence suggesting adverse long-term cardiovascular outcomes in women with histories of preeclampsia. It is noteworthy that these published studies suffer from several limitations related to their retrospective designs, inadequate durations of follow-up, difficulties in establishing the diagnosis of preeclampsia in a retrospective fashion, and changes in the definition of and diagnostic criteria for hypertensive pregnancy disorders over time. Therefore, distinctions among different categories of hypertension in pregnancy, and particularly contrasting preeclampsia to other hypertensive pregnancy disorders, may be challenging. The following discussion will focus on the specific long-term effects of preeclampsia on future CVD. Studies looking at composite CVD outcomes (hypertension, coronary heart disease, cerebrovascular disease, and disorders of the peripheral vascular system) are further elaborated in Table 2 and Table 3.

Jonsdottir, et al noted a significant increase in mortality from ischemic heart disease (IHD) in patients with histories of hypertensive pregnancies compared to population data from public health and census reports. [64] The relative risk (RR) of dying from IHD was significantly higher among eclamptic women, RR=2.61, 95% confidence interval (CI) 1.11–6.12, and those with preeclampsia, RR=1.90 (95% CI 1.02–3.52), than those with hypertension alone, RR=1.20 (95% CI 1.01–1.42). This increased risk further was supported by a Scottish study that reported a risk ratio of 2.0 (95% CI 1.5–2.5) for the association between preeclampsia and later maternal risk of IHD admission or death. [65] Data from the Royal College of General Practitioners (RCGP) oral contraception study showed that women with histories of preeclampsia, compared to those with normotensive pregnancies, had an increased RR to 2.24 (95% CI 1.42–3.53) for acute myocardial infarction. [66] Irgens, et al using the Norwegian medical birth registry, found that mothers with preeclampsia, compared to those who didn't develop this condition during their pregnancies, had a higher risk for all-cause death. The risk further increased in those who had a pre-term delivery and was the highest for cardiovascular death. Those who had a preterm delivery had a hazard ratio of death secondary to cardiovascular causes of 8.12 (95% CI 4.31–15.33). [67] A recent population-based retrospective cohort study of 1.03 million women who were free from CVD before their first documented delivery, reported an incidence of CVD of

500 per million person-years in women who had had maternal placental syndrome, which included preeclampsia and gestational hypertension, in addition to placental abruption and infarction, compared to 200 per million in women who had not (adjusted hazard ratio 2.0, 95 CI 1.7–2.2). [68]

Several factors were identified that further increased the risk of CVD, if concomitant with preeclampsia. These included smoking, [69] parity, [64] pre-term delivery, [67] and older age. [70] Most importantly, several studies indicated that women with severe forms of preeclampsia had worse outcomes than those who suffered from gestational hypertension only, [64, 71, 72]

Cerebrovascular and venous thromboembolic disease

Few studies have been performed assessing the relationships between hypertension in pregnancy and either cerebrovascular or peripheral vascular disease. Most of the data are from the World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. A history of hypertension in pregnancy was identified as a risk factor for both venous thromboembolic disease [73] and cerebrovascular events [74] in patients taking oral contraceptives later in life, i.e. years after an affected pregnancy. Subsequent studies showed that women with a history of preeclampsia were 60% more likely to have a non-pregnancy related ischemic stroke [75] and that they were at an increased risk for death from stroke, adjusted relative risk 3.59 (95% CI 1.04–12.4), [76] compared to women without such a history. While the immediate risk for stroke in preeclamptic pregnancies is well-recognized, these studies indicate that an association between a history of preeclampsia and ischemic stroke persists later in life.

Conclusion

Increasing evidence suggests that hypertension in pregnancy in general, and preeclampsia in particular, is an under-recognized risk factor for CVD, as these women, compared to those with normotensive pregnancies, are at higher risk for cardiovascular and cerebrovascular events, and demonstrate a less favorable overall CVD risk profile years after their affected pregnancies. One possible mechanism for this relationship is that (preeclampsia and CVD share several common risk factors (obesity, diabetes mellitus, and renal disease) or, alternatively, preeclampsia may induce long-term metabolic and vascular abnormalities that may increase overall risk for CVD later in life. From the standpoint of scientific study, it is important to elucidate whether preeclampsia itself increases the future risk of CVD or whether it serves as a marker for women at risk. As it relates to the care of individual patients, it is important to recognize that women with histories of preeclampsia are at increased risk of future CVD, and, regardless of mechanism, need to be counseled and screened appropriately. Pending large-scale studies further supporting this association, women with a history of preeclampsia need to be monitored closely for asymptomatic CVD and treated aggressively for modifiable risk factors.

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Table 1

Hypertension in Pregnancy: Classification and Definitions

Preeclampsia- eclampsia	Preeclampsia is a pregnancy-specific disorder characterized by hypertension and proteinuria of 300 mg or greater in a 24-hour urine. Eclampsia is a convulsive form of preeclampsia that affects 0.1 % of all pregnancies.
Chronic hypertension	BP greater than or equal to140/90 mm Hg prior to pregnancy, or before the 20^{th} week of gestation.
Preeclampsia superimposed on chronic hypertension	Up to 30% of women with chronic hypertension develop preeclampsia, heralded by proteinuria, which occurs for the first time in the third trimester.
Gestational hypertension	Hypertension occurring for the first time during the second half of pregnancy in the absence of proteinuria. It includes i) women with preeclampsia who have not yet developed proteinuria ii) those with hypertension only, and iii) a subset of patients in whom blood pressure remains elevated after delivery, leading to the diagnosis of chronic hypertension.

Table 2

The association between cardiovascular events and history of hypertensive pregnancy disorders

Author, Year, Country	Study design	Study group	Control group	Outcomes: study vs control group.
Mann, [77]1976, UK	Case-control study, 1968–1972	Women treated for MI, under 45 years of age	Age-matched, treated for conditions other than MI	MI: RR 3.0 for PE
Croft, [69]1989, UK	Nested case-control study, the RCGP Oral Contraceptive Study	Women with acute MI	Women without acute MI	MI: RR 2.8 (1.7–4.8) for toxemia [1]
WHO, [73]1995, worldwide	WHO collaborative, case-control study, 21 centers in 17 countries	Women with VTE	Aged-matched, without VTE	VTE OR 1.66 (1.20–2.29) for HTN in pregnancy in Europe vs. 1.16 (0.89–1.52) in developing countries
WHO, [74]1996, worldwide	WHO collaborative, case-control study, 21 centers, 17 countries	Women with CVA	Age-matched, without CVA	CVA OR 1.94 (1.26–2.97) for HTN in pregnancy in Europe vs. 2.54 (2.01–3.20) in developing countries
Brown, [75]2006, USA	Population-based case-control study, the Stroke Prevention in Young Women Study, 1992–1996.	Women with CVA	Women without CVA	CVA OR 1.63 (1.02–2.62) for PE

[1]Toxemia, a synonym that was used in the 1960's for preeclampsia.

MI, myocardial infarction; PE, preeclampsia; RCGP, Royal College of General Practitioners; RR, relative risk; WHO, World Health Organization; VTE, venous thromboembolism that includes deep venous thrombosis and/or pulmonary embolism; HTN, hypertension; CVA, cerebrovascular accident; OR, odds ratio.

Table 3

Patients with hypertensive pregnancy disorders and their later-in-life cardiovascular events and outcomes: Population and registry based studies, single- and multi-center cohorts.

Author, Year, Country	Study design	Study group	Outcomes: study vs. control group [1]
Jonsdottir, [64]1995, Iceland	Retrospective review, the maternity records 1931–1947 and IHD death	1. Eclampsia 2. PE 3. HTN in pregnancy	1. IHD death RR 2.61 (1.11–6.12) 2. IHD death RR 1.90 (1.02–3.52) 3. IHD death RR 1.47 (1.05–2.02)
Hannaford, [66]1997, UK	Retrospective analysis, a subgroup of women from the RCGP Oral Contraceptive Study who never used contraceptives	Women with history of toxemia [2]	HTN RR 2.35 (2.08–2.65) Acute MI RR 2.24 (1.42–3.53) Venous thromboembolism RR 1.62 (1.09–2.41)
Irgens, [67]2001, Norway	Population-based study, the Norwegian medical birth registry, 1967–1992.	PE, either term or preterm deliveries [3]	All-cause death HR 1.2 (1.02–1.37) CV death for term PE, HR 1.65 (1.01–2.70) CV death for preterm PE, HR 8.12(4.31–15.33)
Smith, [65]2001, Scotland	Population-based study, the Scottish morbidity record system, 1981–1985.	PE	IHD HR 2.0 (1.5–2.5)
Kestenbaum [71]2003, USA	Population-based study, the Washington State Birth Event Record data base, 1987–1998.	1. Gestational HTN 2. Mild PE 3. Severe PE	1. Acute CVD event HR 2.8 (1.6–4.8) 2. Acute CVD event HR 2.2 (1.3–3.6) 3. Acute CVD event HR 3.3 (1.7–6.5)
Wilson, [76]2003, Scotland	Population-based study, the Aberdeen maternity and neonatal databank 1951–1970.	PE, eclampsia	HTN OR 3.98 (2.82–5.61) Stroke (fatal) IRR 3.59 (1.04–12.4)
Arnadottir, [70]2005, Iceland	Case-control study, University Hospital Reykjavik, 1931–1947	Gestational HTN, PE, eclampsia	IHD death RR 1.66 (1.27–2.17) CVA death RR 1.46 (0.94–2.28)
Funai, [78]2005, Israel	Population-based study, the Jerusalem Perinatal Study, 1964–1976.	PE	All-cause death RR 2.13 (1.79–2.53) CVD death RR 3.07 (2.18–4.34)
Wikstrom, [72]2005, Sweden	Cross-sectional population study, the Swedish Medical Birth Register, 1973–1982.	1. Gestational HTN 2. Mild PE 3. Severe PE	1. IHD IRR 1.6 (1.3–2.0) 2. IHD IRR 1.9 (1.6–2.2) 3. IHD IRR 2.8 (2.2–3.7)
Ray, [68]2005, Canada	Population-based study, the Ontario Health Insurance Plan, 1990–2004.	1. MPS [4] 2. PE	1. CVD HR 2.0 (1.7–2.2) 2. CVD HR 2.1 (1.8–2.4)

[1] Where numbered, the outcomes correspond to a difference between the respective study group (labeled with the same number) and its control. For all studies, the control group consisted of women with normotensive pregnancies, with the exception of the study by Jonsdottir, et al. in which the outcomes were compared to those from the general population

[2] Toxemia, a synonym that was used in the 1960's for preeclampsia

[3] Term delivery: delivery at ≥ 37 gestational weeks; preterm delivery: delivery at 16–36 gestational weeks

[4] MPS, maternal placental syndromes: gestational HTN, preeclampsia, placental abruption, and placental infarction

IHD, ischemic heart disease; PE, preeclampsia; HTN, hypertension; RR, relative risk; RCGP, Royal College of General Practitioners; MI, myocardial infarction; HR, hazard ratio; OR, odds ratio; IRR, incidence rate ratio; CVD, cardiovascular disease