

Review Article

Preeclampsia and Its Impact on Long-Term Cardiovascular Risk

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Submitted: 29 August 2017

Accepted: 31 January 2018

Published: 31 January 2018

ISSN: 2373-9258

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Abstract

Preeclampsia, a severe pregnancy associated disorder, is often complicated by impaired fetal growth or preterm delivery and can be associated with long-term maternal mortality and morbidity. Women with a history of preeclampsia have an increased risk of cardiovascular disease later in life. This may be because of both postpartum endothelial dysfunction and asymptomatic structural cardiac alterations. Therefore, lifelong monitoring of cardiovascular risk factors following preeclampsia is advisable.

Keywords

- Preeclampsia
- Cardiovascular disease
- Maternal mortality

ABBREVIATIONS

BMI: Body Mass Index

INTRODUCTION

The underlying pathological cause of cardiovascular diseases is atherosclerosis. Hypertension, smoking, obesity, increased consumption of alcohol, stress, diabetes, physical inactivity and excessive salt consumption are major risk factors.

Patients who experienced preeclampsia often show signs of cardiac dysfunction and have an elevated risk for both development of hypertension and cardiovascular diseases later in life [1,2].

Adequate knowledge regarding cardiovascular abnormalities is important for long-term care during and after pregnancies complicated by preeclampsia and is of crucial importance for both cardiologists and obstetricians.

Preeclampsia as a risk factor

Preeclampsia doubles the risk of ischaemic cardiopathy, stroke and thromboembolism in the 5-15 years following pregnancy. Eighty percent of patients with prior preeclampsia develop arterial hypertension up to 20 years after pregnancy. Furthermore, preeclampsia is often associated with asymptomatic, functional cardiac disorders. Persistent left ventricular hypertrophy one year postpartum increases the risk by 40% for developing arterial hypertension two years after birth [3,4].

Metabolic syndrome as a risk factor

Women having the features of metabolic syndrome, such as arterial hypertension, increased insulin resistance, obesity or hyperlipidemia, often develop preeclampsia during pregnancy. The chronic dysregulation of the maternal metabolism may be responsible for an abnormal utero-placental environment in which the formation of the spiral arteries is restricted (Figure 1). This dysregulation has adverse effects on fetal and maternal

health and may damage the major arteries of the heart, central nervous system and the circulation in the limbs over a longer period of time. The predisposing factors for preeclampsia are interestingly also risk factors for other endothelial diseases, particularly atherosclerosis. Common features of the two diseases are vasomotoric dysfunction, arterial hypertension, activation of platelet aggregation, endothelial damage and increased inflammatory tendency. The vascular lesions in preeclampsia accumulate in the placental blood vessels within a short time, while the atherosclerotic lesions develop over decades. However, the properties of the vascular changes of these two entities are similar.

In studies reported by Ray et al., and Cnattingius et al., a linear association between maternal body-mass-index (BMI), hypertriglyceridemia and the risk of preeclampsia or intrauterine fetal death could be demonstrated [6,7].

The risk of intrauterine fetal death increases with increasing BMI during pregnancy (Table 1). In a population-based cohort study of 167,750 women in Sweden (1992-1993), obese women tended to smoke more often than normal-weight women (28% vs. 24%) and to suffer from pre-existing diabetes mellitus or gestational diabetes (1.1% vs. 0.3%). The risk of developing preeclampsia increases with the maternal BMI (prevalence: 1.8% for underweight women, 2.5% for normal-weight women, 4.2% for overweight women, 7% for obese women) [7].

Maternal overweight and obesity are also associated with hyperlipidemia, which reduces prostaglandin secretion and promotes peroxidase production. This may lead to vasoconstriction and thrombocyte aggregation, which could be an important reason for the increased risk of developing preeclampsia in these women.

An association between hypertriglyceridemia and the development of preeclampsia could also be shown (Table 2).

Other studies, which examined the relationship between preeclampsia/pregnancy-induced hypertension and dyslipi-

demia/hyperlipidemia/hypertriglyceridemia have shown that a significantly increased triglyceride level could be observed in women with preeclampsia compared to women without this complication. The risk of preeclampsia increased with increasing triglyceride levels (Table 2).

Hypertriglyceridemia is associated with chronic inflammatory response, hypercoagulability and endothelial dysfunction. Since hypertriglyceridemia, together with obesity, hypertension and diabetes mellitus, is a component of the metabolic syndrome, which is associated with the development of preeclampsia and can persist up to six months postpartum, these characteristics can influence future pregnancies and the long-term risk of cardiovascular disease in women.

Does preeclampsia unmask pre-existing endothelial dysfunction or vascular disease?

The question arises whether women who are predestined for preeclampsia have a pre-existing metabolic dysbalance or whether the metabolic abnormalities and vascular damages are

caused by preeclampsia itself.

It is very likely that the etiology is a combination of both situations. The presence of pre-existing risk factors for preeclampsia may contribute to the development of postpartum cardiovascular disease, but a link between preeclampsia and cardiovascular diseases can also be explained by a pre-existing metabolic dysfunction [8].

Figure (2) shows that during pregnancy the risk of vascular disease increases due to metabolic and vascular changes. After childbirth the risk decreases again, but does not return to pre-pregnancy levels, so that the risk increases incrementally with every pregnancy. Sattar et al., have shown that the concentrations of lipids and coagulation factors in patients with preeclampsia are higher in the postpartum period and specific defects of vascular function can be found in these women compared to those with uneventful pregnancies, regardless of prior blood pressure levels or insulin resistance [9].

Several studies have shown a link between coronary disease

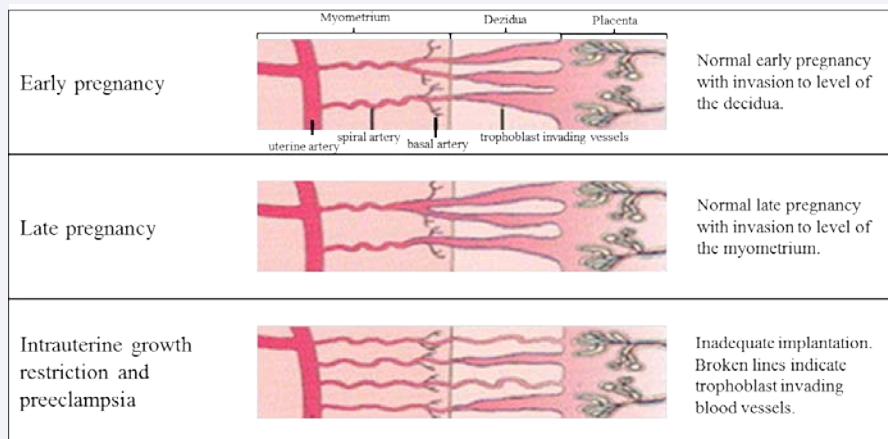


Figure 1 Invasion of the maternal circulation by trophoblasts. Modified according to Greer et al. [5].

Table 1: Association between BMI and late death or early neonatal death.

BMI	No. of births	Late fetal death		Early neonatal death	
		No. of cases N=466	Odds Ratio (95%CI)	No. of cases N=309	Odds Ratio (95%CI)
<19.9	22,634	46	1	36	1
20.2-24.9	101,266	257	1.2 (0.9-1.7)	184	1.1 (0.8-1.6)
25.0-29.9	22,428	109	1.6 (1.1-2.3)	69	1.3 (0.9-1.9)
>30	10,412	54	2.6 (1.7-3.8)	20	1.2 (0.7-2.1)

Maternal BMI before pregnancy and the risk of adverse pregnancy outcome. Modified according to Cnattingius S et al. [7]

Table 2: Prevalence of preeclampsia according to maternal triglyceride concentration.

Study design	Citation	Plasma or serum triglyceride concentration (mmol)				Number of woman with pre-eclampsia within each triglyceride concentration category			
		1	2	3	4	1	2	3	4
cohort	17	<1.5	1.5-2.4	>2.4		37/1148	23/834	11/175	
	22	<1.0	1.0-1.5	>1.5		9/175	19/189	29/203	
Case control	18	<1.0	1.0-1.3	1.3-1.5	>1.5	19/169	29/74	35/81	90/135
	26	<2.1	2.6-3.2	2.6-3.2	>3.2	14/59	20/65	29/74	62/106

Modified according to Ray JG et al.[6]

and multiple pregnancies [10]. However, it is assumed that this is due, among other things, to maternal weight gain and a greater risk of developing type 2 diabetes with increasing age.

Preterm (<37 weeks of gestation) preeclampsia increases cardiovascular risk

A prospective Norwegian study using data from the country's national birth registry was conducted which included both multiparous as well as nulliparous / primigravid women from 1967 – 2002 [11]. It could be demonstrated that of the 836.147 women included, 23.000 had died by 2009, of whom 3.891 women had died from cardiovascular disease.

Primigravidity complicated by preterm preeclampsia was associated with an increased risk of cardiovascular death, with a hazard ratio of 9.2 (6.5-13.7), while women who had previously given birth had clearly lower risk, with a hazard ratio of 2.4 (1.5-3.9). Patients with preeclampsia at term were also at a lower risk, with a hazard ratio of 3.4 (2.6-4.6) [11].

Within this group, multiparous women with preeclampsia at term, in contrast to primiparous women had a lower hazard ratio of 1.5 (1.2-2.0).

It seems unlikely that further pregnancies can reverse the endothelial changes that occurred during the first pregnancy. The findings in this study could have been affected by confounding variables, such as premature maternal death, which would obviously prevent further pregnancies. However, increased maternal mortality in the first years after pregnancy was not found, therefore this could not have been a factor which could have affected the results. Another reason that might prevent women from having more children could be the presence of other diseases which might lead physicians to advise against future pregnancies. It is certainly possible that women with preeclampsia and pre-existing diabetes often decide against future pregnancies.

Cardiovascular health after pregnancy-induced diseases

Pregnancy-induced hypertension, miscarriage and placental insufficiency often have common pathophysiologic mechanisms.

Table 3: Risk of maternal premature cardiovascular disease, according to type of maternal placental syndrome and concomitant presence of poor fetal growth or intrauterine fetal death.

Maternal disease during pregnancy	Hazard Ratio(95%) for cardiovascular disease
Maternal placenta syndrome (n=75380)	2.0 (1.7-2.2)
Placenta abruption (n=11156)	1.7 (1.3-2.2)
Gestational hypertension (n=20942)	1.8 (1.4-2.2)
Pre-eclampsia (n=36982)	2.1 (1.8-2.4)
Maternal placenta syndrome and poor fetal growth (n=4390)	3.1 (2.2-4.5)
Maternal placenta syndrome and intra uterine fetal death (n=1171)	4.4 (2.4-7.9)

Modified according to Ray JG et al. [12]

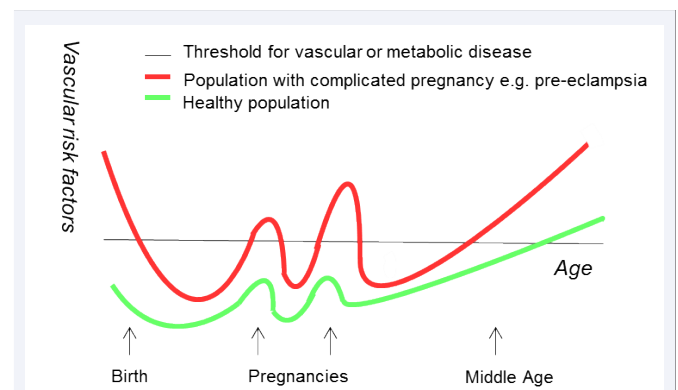


Figure 2 Schematic representation of vascular risks during a lifetime. Modified according to Rodie VA et al. [8].

Women with these pregnancy related complications frequently have risk factors for cardiovascular diseases such as obesity, pre-existing hypertension, diabetes or hyperlipidemia.

Ray et al., demonstrated in a retrospective Canadian cohort study, which included over one million women without cardiovascular disease before the first documented birth, that the risk of early onset cardiovascular disease is significantly increased when maternal placental syndrome (which includes preeclampsia, pregnancy-induced hypertension and placental insufficiency) and fetal growth retardation/intrauterine fetal death had occurred (Table 3) [12].

Sattar et al., also state that a low birth weight due to intrauterine growth restriction entails an increased risk of vascular disease in later life [9].

A retrospective study by Smith et al. showed that women who gave birth to a child with a birth weight below 2500 g had a seven to 11 times higher risk of dying from cardiovascular disease compared to women whose children had a birth weight over 3500 g [13]. This observation suggests an association between maternal risk factors for coronary heart disease and fetal programming. Intrauterine growth retardation could be due to a maternal genotype and phenotype associated with increased cardiovascular risk, allowing these risk factors to be passed through generations. The genotype cannot be altered, but by improving the maternal metabolic profile, e.g. through increased physical activity, weight loss and avoidance of nicotine, an improvement of fetal growth and development and a reduction of vascular risks may be achieved.

CONCLUSION

In patients with preeclampsia, a follow-up concept regarding evaluation for cardiovascular diseases later in life should be established and pre-existing conditions should be excluded. Despite a generally low risk in young women for cardiovascular disease, it has been shown that they have an up to 7-fold increased risk when early-onset preeclampsia, prematurity and intrauterine growth retardation occur [13]. In the case of cardiac dysfunction, therapeutic interventions should already be initiated during the asymptomatic phase, as the long-term prognosis can be effectively improved.

ACKNOWLEDGEMENTS

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Cite this article

Veit J, Lapaire O (2018) Preeclampsia and Its Impact on Long-Term Cardiovascular Risk. *Ann Clin Exp Hypertension* 6(1): 1053.