

Review

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# The link between hypertension and preeclampsia/eclampsia-life-long cardiovascular risk for women

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## Abstract

Cardiovascular diseases remain the main cause of death and morbidity in women. Despite the active preventive measures and the reduction in the total number of morbidity and mortality rates, the rate of cardiovascular morbidity remains high in the population, moreover cardiovascular morbidity is increased in women of 35-54 years. Cardiovascular morbidity has several unique characteristics for women; pregnancy, gestational hypertension, preeclampsia/eclampsia are gender-specific risk-factors for further cardiovascular morbidity in women, it's possible to detect these risk-factors in younger age groups and start prevention as early as possible. Arterial hypertension, which is characterized by genetic polymorphism, is an important and a powerful risk factor for development of both acute and chronic cardiovascular diseases; association of arterial hypertension with different metabolic disorders such as metabolic syndrome, diabetes seems particularly dangerous in pregnancy in terms of peri-pregnancy and life-long morbidity. Preeclampsia shares some common features with atherogenesis and metabolic changes and atherogenesis and metabolic changes, so presence of hypertension during pregnancy increases the risk of cardiovascular diseases and diabetes later in the life. Is pregnancy revealing or predisposing factor of development cardiovascular diseases is not still clear and to answer these questions more and more studies are required.

**Keywords:** Arterial hypertension, women, pregnancy, cardiovascular risk

## INTRODUCTION

Cardiovascular diseases remain the main cause of death and morbidity in women<sup>[1,2]</sup>. Despite the active preventive measures and the reduction in the total number of morbidity and mortality rates, the rate of



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cardiovascular morbidity remains high in the population, moreover cardiovascular morbidity is increased in women at 35-54 years<sup>[3]</sup>. Arterial hypertension is an important, powerful risk factor for cardiovascular acute episodes, is characterized by genetic polymorphism<sup>[4]</sup>; association of arterial hypertension with different metabolic disorders - metabolic syndrome, diabetes is particularly dangerous<sup>[5]</sup>. Moreover, it was found that haemorrhage and hypertensive disorders are major contributors to maternal deaths in developing countries<sup>[2]</sup>.

Preeclampsia/Eclampsia is a multiorgan syndrome associated with pregnancy, which occurs in 2%-8% of pregnant women<sup>[6-9]</sup>. The main characteristics of preeclampsia/eclampsia are pregnancy and elevation of blood pressure. It is considered that the arterial hypertension in pregnancy is clearly associated with cardiovascular morbidity during lifetime<sup>[1,6,7,10,11]</sup>.

Preeclampsia/Eclampsia develops in 3%-5% of pregnancies in developed countries and 7.5%-8% of all over the world<sup>[9,12-14]</sup>. Preeclampsia/eclampsia is clearly linked to gestational age, offspring baby weight, nulliparity, *etc.* The cohort research study in Denmark of 536419 female has shown that delivery at 32-36 weeks of pregnancy increases the risk of next early premature labor from 2.7% to 14.7%, and the risk of preeclampsia from 1.1% to 1.8%. This study also showed that the first childbirth up to 28 weeks of pregnancy increases the risk of premature labour at next pregnancy by 26% and the risk of development of preeclampsia by 3.2%. Preeclampsia during first pregnancy increases the risk of preeclampsia during next pregnancy from 14.1% to 25.3%. Other studies also confirm that there are 3 times rise of cardiovascular morbidity and 7 times the incidence of hypertension in this group of population<sup>[15,16]</sup>.

Excessive weight, hypertension before pregnancy, age, metabolic disorders before pregnancy increases the risk of development of preeclampsia<sup>[6,17,18]</sup>. On the other hand, preeclampsia is clearly associated with the development of metabolic disorders in life, so it is not surprising that women with preeclampsia and eclampsia have a higher risk of cardiovascular morbidity.

## DEFINITION OF HYPERTENSIVE DISORDERS DURING PREGNANCY

Hypertension in pregnancy comprises<sup>[19]</sup>:

- Pre-existing hypertension: precedes pregnancy or develops before 20 weeks of gestation. It usually persists for more than 42 days post-partum and may be associated with proteinuria.
- Gestational hypertension: develops after 20 weeks of gestation and usually resolves within 42 days post-partum.
- Preeclampsia: gestational hypertension with significant proteinuria (> 0.3 g/24 h or Albumin/creatinine ratio  $\geq$  30 mg/mmol). It occurs more frequently during the first pregnancy, in multiple pregnancy, in hydatidiform mole, in antiphospholipid syndrome, or with pre-existing hypertension, renal disease, or diabetes. It is often associated with foetal growth restriction due to placental insufficiency and is a common cause of prematurity.
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria.
- Antenatally unclassifiable hypertension: this term is used when BP is first recorded after 20 weeks of gestation and hypertension is diagnosed; re-assessment is necessary after 42 days post-partum.

Preeclampsia and eclampsia develops before, during and after delivery. It may be firstly developed in the postpartum period, accompanied by manifestations of severe multiorgan impairment. Late postpartum eclampsia can be manifested with severe brain, heart, pulmonary artery impairment in postpartum period<sup>[20]</sup>.

European Society of Cardiology considers arterial blood pressure 140-159/90-109 mmHg as mild and 160/110 mmHg as severely elevated for pregnant women, what is in agreement with other societies as well<sup>[6,19,20]</sup>.

## Risk - factors

The risk factors for preeclampsia and eclampsia are: nulliparity, family history of preeclampsia, multiple gestation, history of diabetes and hypertension, hypertension during pregnancy, rapidly growing hydatidiform mole, mother's age, antiphospholipid syndrome, impaired glucose tolerance, caesarean delivery, race<sup>[6,8,21-23]</sup>. There is evidence that women who smoke are less likely to develop eclampsia, although the reason is not clear<sup>[24]</sup>. Almost all these risk-factors are linked to cardiovascular diseases as well (hypertension, impaired glucose tolerance, age, inflammatory profile, race, *etc.*).

Systematic review and meta-analysis of cohort studies of 25,356,688 pregnancies among 92 studies out of 27 countries<sup>[25]</sup> has shown, that the risk of development of preeclampsia is clearly linked to antiphospholipid antibody syndrome, prior preeclampsia, chronic hypertension, pregestational diabetes, assisted reproductive technology, and BMI > 30. These factors are strongly associated with a high rate of preeclampsia, and presence of any of them will help to reveal the woman with "high risk" of preeclampsia.

## Clinical characteristics

Patients with preeclampsia/eclampsia may develop following complaints<sup>[26,27]</sup>: headache, seizures, visual disturbances (blurred vision, migraine - blinking scotoma), changed mental status, blindness cortical or retinal, shortness of breath, dyspnea, edema, epigastric or pain in the upper right corner of the abdomen, weakness, inability, may be presented signs of haemolytic anemia. It is noteworthy that eclampsia may be developed without prodromal symptoms<sup>[28,29]</sup>.

For a long time it was considered that eclampsia follows the pregnancy, but in recent years information about late (postpartum) eclampsia is growing, and more and more cases of late eclampsia are described and presented. Different authors describe different frequencies of late eclampsia, although the number of complications is not small and varies from 0.3% to 27%<sup>[30,31]</sup>. Almost half of eclampsia cases develop after childbirth<sup>[13,32]</sup>. Seizure is predominantly developing in the first 48 hours after childbirth, although it may occur even at 60 day<sup>[18]</sup>.

Whether early and late preeclampsia/eclampsia have the same pathophysiological mechanisms is not clear. Since pregnancy contains cardiovascular and metabolic stress, response to this stress may represent a woman's personal risk during lifespan, such serious and dangerous complication as venous thromboembolism and pulmonary thromboembolism among others<sup>[33]</sup>.

Late onset postpartum preeclampsia differs clinically from antepartum eclampsia. Thus study conducted on 194 patients with eclampsia (92 antepartum and 92 postpartum) showed, that patients with postpartum preeclampsia were older, multiparous and of lower socio-economic status than patients with antepartum preeclampsia, additionally, patients with postpartum preeclampsia have more clinical symptoms like headache, elevated blood pressure, abnormal vision, nausea/vomiting, seizures, shortness of breath and pedal edema, they also show significantly higher laboratory markers, than patients with antepartum preeclampsia. And additionally, they more often require blood pressure treatment after discharge<sup>[34]</sup>.

It is known that eclampsia and preeclampsia increases the risk of cardiovascular morbidity at 2-4 times in lifetime and reaches the level of risk related to tobacco consumption<sup>[3]</sup>. In this group of population is manifested life-long increase of incidence of arterial hypertension and metabolic disorders. Thus, after two years of observation of women with preeclampsia and eclampsia had been shown the increase the risk of cardiovascular disease<sup>[11]</sup>; Hypertension during pregnancy is associated with rise of 10 year cardiovascular risk in women<sup>[35]</sup>, women with preeclampsia who remain having hypertension after delivery have a twofold rise of risk of developing CVD in the next 10-30 years<sup>[36]</sup>, particularly during their fifth decade<sup>[37]</sup>. That's why

the American Heart Association is considering eclampsia and preeclampsia as gender-specific risk factors of CVD<sup>[3]</sup>.

Preeclampsia itself is the risk factor for the other complications, including life-threatening complications. A population based study conducted in Sweden of 1,003,489 deliveries showed that preeclampsia, multiple childbearing, caesarean deliveries are important risk factors for pulmonary embolism and stroke<sup>[33,38]</sup>; On the background of preeclampsia increases the incidence of pulmonary embolism and stroke 3-12 times in late pregnancy, at delivery, and in the puerperium, and similar increases in risks were also observed for multiple pregnancies and caesarean delivery. At the time of pregnancy physiologically develops hypercoagulation state, rise of D-dimer; continuous rise of these markers can lead to or is associated with vein thrombosis and pulmonary thromboembolism<sup>[39]</sup>.

Hypertension can occur firstly in postpartum period as well, the pathophysiology of this condition is not clear. In retrospective study of 988 women showed that women with postpartum hypertension have clinical risk factors and an antepartum plasma angiogenic profile similar to those found in women with preeclampsia what could be sign of subclinical or unresolved preeclampsia<sup>[40]</sup>.

Development of hypertension later in the life seems is clearly linked to complications and hypertension during pregnancy; thus a population-based study of 146,748 women showed that hypertension during pregnancy was associated with an elevated risk of future CVD or hypertension during life-time, irrespective of time of development of hypertension<sup>[41]</sup>.

### Physiology

Normal physiologic changes during pregnancy are expressed in rise of cardiac output (CO) up to 20%-50% starting by 6 week of gestation and reaching maximum by 16-28 weeks (usually around 24 week); all of this is followed by rise of heart rate and stroke volume. It remains near peak levels up to 30 week<sup>[42]</sup>. CO is rising by another 30% during labor but then rapidly drops after delivery and reaches 15%-25% above normal level because of contraction of the uterus. Then continues gradual reduction (mostly over the next 3 to 4 weeks) and reaches the pre-pregnancy level at about 6 week postpartum. The rise of CO during pregnancy is mostly determined by increased requirements of the utero-placental circulation; Rise of cardiac output is determined also by the needs of skin to regulate the temperature and kidneys to excrete fetal wastes as well. Changes in cardiac function are associated with changes in renal function, thus glomerular filtration rate (GFR) rises by 30%-50%, reaching maximum again by 16-24 week gestation, and remains at same level almost until term<sup>[42-44]</sup>.

Gestational Hypertension and Preeclampsia/Eclampsia are associated with impairment of cardiac function longer than in normal pregnancy. A prospective longitudinal case-control study showed that in one year postpartum, preeclampsia is associated with diastolic dysfunction, asymptomatic left ventricular moderate-severe dysfunction/hypertrophy, functional/geometric abnormality, which is even more expressed in women with preterm preeclampsia (56%) than with term preeclampsia (14%) or matched controls (8%;  $P < 0.001$ )<sup>[45]</sup>. This study showed that majority of preterm preeclamptic women have stage B asymptomatic heart failure postpartum, and 40% develop essential hypertension within 1 to 2 years after pregnancy.

Fibrinoid necrosis with a perivascular mononuclear cell infiltrate vessel wall in early phase of preeclampsia, later lipophages are found in vessels of these women<sup>[46]</sup>. These changes are quite close to atherosclerotic process. Acute atherosclerosis is not found in normal pregnancies including normal pregnancies in diabetic women, but can develop in vessels of women with preeclampsia or in women with small-for-gestational-age infants, or both.

Pregnancy leads to response from endocrine glands as well, partly because the placenta produces hormones and partly because most hormones circulate in protein-bound forms and this protein binding increases

during pregnancy what affects response from endocrine glands. Thus, during pregnancy levels of estrogen, progesterone, thyroid hormones, aldosterone, cortisol are rising<sup>[47]</sup>, changes in insulin-resistance are developing. Each of these factors participate in atherogenesis and impairment of metabolic profile.

All above mentioned are well-known factors associated with normal pregnancy and impairment in one of them may have influence on others as well.

Preeclampsia (Eclampsia) is condition related to ischemia of placenta. There are studies that confirm the link between preeclampsia and gestational arterial hypertension with endocrine and metabolic diseases-preeclampsia is considered as a risk-factor of hypothyroidism, diabetes mellitus, and dyslipidaemia<sup>[48-50]</sup>. Each of them independently increases the incidence of cardiovascular morbidity.

Healthy pregnancy is driven into a growing of pro-atherogenic metabolic state<sup>[51,52]</sup>. Shortly after conception pregnant women develops a high cardiac output<sup>[53]</sup>, hypercoagulability<sup>[54]</sup>, and increased inflammatory activity<sup>[55]</sup>. After 20 weeks there is insulin resistance<sup>[52,56]</sup> and hyperlipidaemia<sup>[57]</sup>. Healthy women responds adequately and tolerates well physiologic changes during pregnancy, but woman with inherited or acquired predisposition to different chronic diseases may not tolerate pregnancy induced hormonal or hemodynamic changes<sup>[57]</sup>. These gestational changes are usually more pronounced in women who later develop preeclampsia. The effect of coexisting risk-factors are clearly confirmed in several studies. This is partly due to pre-existing, subclinical inflammatory and/or cardiovascular risk factors in “healthy” women who go on to develop preeclampsia<sup>[58]</sup>. These women are more likely to be overweight<sup>[59,60]</sup> have higher lipid levels, higher blood pressure, insulin resistance and are more likely to have a thrombophilia, compared with women who go on to have a normotensive pregnancy.

Angiogenic factors also contribute to development of preeclampsia. Seems that maternal diseases (or predisposition) is related to anti-angiogenic factors sFlt-1 and sEng, released by an affected placenta. Are these anti-angiogenic proteins involved in development of the maternal diseases later is not clear, however could indicate the predisposition of development of cardiovascular abnormalities<sup>[22]</sup>.

Preeclampsia is associated with impairment of vascular function, impaired endothelial function, share some common features of development of atherosclerosis. The 498 women from the Epidemiology of Coronary Artery Calcification Study were evaluated for presence of subclinical coronary atherosclerosis using logistic regression model, up to 10.4% had history of hypertension during pregnancy, what also was associated with impairment of kidney function and coronary artery calcium score later during lifespan<sup>[22,61]</sup>.

Insulin resistance is developing physiologically in healthy pregnant women, however may remain after delivery and even progress in certain women with predisposition (because of acquired or inherited factors). In a population-based, retrospective cohort study for 1,010,068 pregnant women was determined two-fold rise of risk of development of diabetes during up to 16.5 years after pregnancy, even in the absence of gestational diabetes. The presence of preeclampsia or gestational hypertension in women with gestational diabetes also significantly rises the lifelong risk of diabetes compared to gestational diabetes without preeclampsia or gestational diabetes<sup>[21,62]</sup> which is independent risk for future cardiovascular events.

Vascular wall seems that is responding to preeclampsia. Thus study preformed showed that Carotid Artery Intima-media thickening is reliably higher in women with preeclampsia, is reducing after delivery, but remain significantly higher in a year after delivery in women with previous preeclampsia<sup>[63]</sup>.

## CONCLUSION

Cardiovascular morbidity is multifactorial, preclinical stage is starting in early ages, is linked to multiple risk-factors. Cardiovascular morbidity has several unique characteristics for women; pregnancy, gestational

hypertension, preeclampsia/eclampsia are gender-specific risk-factors for further cardiovascular morbidity in women, which is possible to reveal in young ages and start prevention as early as possible. Seems abnormalities detected during pregnancy are linked to life-long cardiovascular morbidity, so pregnancy-related morbidity starts to exceed concerns of obstetricians and takes the important part of primary care physicians and cardiologists as well. Is pregnancy just revealing or predisposing factor of development cardiovascular diseases is not still clear and to answer these questions more and more studies are required.

## DECLARATIONS

### Authors' contributions

Study design: Vakhtangadze T

Data collection: Gakhokidze N

Manuscript writing: Vakhtangadze T, Gakhokidze N

Manuscript review: Vakhtangadze T

Serching and evaluating the references: Khutsishvili M, Mosidze S

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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