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Review

Hypertension in Pregnancy as an Early Sex-Specific Risk Factor for Cardiovascular Diseases: Evidence and Awareness

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Abstract

Despite being a physiological condition, human pregnancy is known to cause numerous complications that can endanger the life of the mother and the fetus alike. While the majority of complications are mostly limited within the peripartum period, more and more information is available about persistently higher short- and long-term cardiovascular risk after a pregnancy complicated by a hypertensive disorder. There is evidence that women after gestational hypertension or preeclampsia are more likely to develop arterial hypertension, coronary atherosclerosis, myocardial infarction, stroke, peripheral artery disease, and even diabetes mellitus and venous thromboembolism years after the target pregnancy. This has urged some authors to view hypertensive disorders of pregnancy as a "stress test" for the maternal organism that unmasks latent endothelial dysfunction. An explanation is sought in the presence of common risk factors and underlying pathological pathways with cardiovascular diseases, although a certain etiological mechanism for the development of hypertensive disorders in pregnancy has not been established yet. More attention is needed towards the follow-up of women after a hypertensive pregnancy as it could be an opportunity for early prevention of cardiovascular diseases.

Keywords

arterial hypertension, gestational hypertension, preeclampsia, prevention, women's health

INTRODUCTION

Cardiovascular diseases (CVD) lead to severe disability and mortality in a great number of physically active people. Despite the fact that the majority of risk factors are identified and it is possible to modify some of them, CVDs are nowadays the leading cause of mortality worldwide, responsible for the annual death of nearly 18 million people and for 37% of fatal outcomes due to noncommunicable diseases under the age of 70. Myocardial infarction and stroke alone are accountable for 85% of CVD mortality.[1] Although male gender is a classic risk factor, CVDs are women's num-

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ber 1 killer as well[2] - a fact that is somewhat neglected. Much hope is invested in prevention as it is more effective and less expensive than treatment. Particularly optimistic results are available from a study[3] targeting 3154 young people (aged 18 to 30 years) as with proper lifestyle measures low-risk cardiovascular profile can be achieved and this can lead to a significant risk reduction in later life. On the other hand, maternal well-being is prioritized by health organizations worldwide[4], and efforts are made to minimize the risk for the occurrence of hypertensive disorders by the implementation of screenings in early pregnancy[5] and additionally to establish the etiology of fetal death for the benefit of the mother[6,7].

In 2016, the leading cause of death for both men and women in the USA was heart disease as 22% of women lost their lives to it, followed by 21.1% as a result of cancer.[8] A growing number of studies warn about a higher short-term and long-term cardiovascular risk in women, who had a pregnancy complicated by hypertension. Those women are more likely to develop arterial hypertension[9,10], coronary artery disease[11,12], heart failure[13], stroke[14], peripheral artery disease[15], diabetes mellitus[16], and venous thromboembolism[17,18], and have a higher cardiovascular mortality[19,20]. One possible reading of this valuable for women's health information is that of an opportunity to initiate early CVD prevention by controlling the other risk factors of those women.

Cardiovascular changes during normal pregnancy

Normal pregnancy leads to significant changes in the maternal cardiovascular system that aim to adjust the organism to the increased requirements and in preparation for birth. As early as the first trimester, a gradual increase in the intravascular volume starts which causes an increase in the preload, but simultaneously there is a decrease in the systemic vascular resistance. The net effect is a decrease in the arterial blood pressure, both systolic and diastolic, with the lowest values registered during weeks 24 to 26 and normalization to pre-pregnancy values near the end of pregnancy. The heart rate increases and alongside the higher volume and lower afterload results in an increase in the cardiac output. The latter can become nearly double by week 20 of gestation and remain so till the end of the pregnancy.[21,22]

Prevalence and significance of the hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP) complicate up to 8%–10% of pregnancies worldwide and their prevalence is the highest in developing countries. Based on a vast literature review, Payne et al.[23] estimated that 1% of pregnant women suffer from chronic hypertension, 3% from gestational hypertension, and 2%–4% from preeclampsia. According to a 2014 systematic maternal mortality analysis[24] by WHO encompassing 23 studies between 2003 and 2009 and 417 databases from 115 countries, hypertensive disorders of pregnancy were the second most common cause of death (14%) after hemorrhagic complications (27.1%). Moreover, treatment options during pregnancy are limited with the only definitive treatment being delivery.[22]

Forms of hypertensive disorders of pregnancy

HDPs are nowadays viewed as four main forms:

1. Chronic hypertension – arterial hypertension that exists before pregnancy or is registered before the 20th gestational week. It poses a risk for the development of preeclampsia;

2. Preeclampsia (PE) and eclampsia – preeclampsia is a pregnancy-specific systemic disorder that is characterized by elevated blood pressure (≥140 mmHg systolic and/or ≥90 mmHg diastolic blood pressure) occurring for the first time after the 20th gestational week and the presence of significant proteinuria (defined in pregnancy as >300 mg for 24 hours). Severe forms (systolic blood pressure ≥160 mmHg and/or diastolic ≥110 mmHg) can be further complicated by hemolysis, thrombocytopenia, elevated liver enzymes (HELLP syndrome), vision disturbances, cerebral and pulmonary edema, fetal growth restriction, and intrauterine death. Eclampsia is defined as the appearance of seizures in a woman with preeclampsia when no other reason for the seizures is present. Preeclampsia can be also classified as early onset, beginning before 34 weeks of gestation and associated with more complications and a higher necessity for delivery induction before the 37th week; and late onset - after week 34 of gestation and considered more benign.

1. Preeclampsia imposed on chronic hypertension;

2. Gestational hypertension (GH) – new-onset hypertension occurring after 20 weeks of gestation with a lack of significant proteinuria. Gestational hypertension can progress to preeclampsia.[25]

Pathogenesis and risk factors for HDPs

Although quite common, the etiology and the pathophysiologic mechanisms of hypertensive disorders of pregnancy are not completely clarified. It is currently believed that they develop in two stages. Initially, there is an abnormal remodelling of the spiral arteries leading to placental hypoperfusion, which in its turn triggers a second stage - maternal response aiming to improve the trophy of the fetus. Elevated blood pressure is thought to be part of this response.[22] Contrary to normal pregnancy, in preeclampsia there is an increased

permeability that leads to extravasation of fluid, reduced blood volume, hemoconcentration, vasoconstriction, and an increase in the afterload.[26] According to Silver et al.[27], blood volume is, however, normal in gestational hypertension. Additionally, there is an increased inflammatory response, endothelial dysfunction, and altered balance between pro-angiogenic and antiangiogenic molecules. There are lower concentrations of nitric oxide and prostacyclin and higher concentrations of thromboxane and endothelin, as well as an increased response to angiotensin II.[28] As far as kidney function is concerned, HDPs lead to a moderate decrease in glomerular filtration rate, elevated uric acid and protein excretion with urine, the latter resulting from the changed permeability of the glomerular filter.[29] Virtually any organ can be affected in the course of severe preeclampsia with devastating consequences.[30]

The risk factors are various and heterogeneous. Preeclampsia and gestational hypertension are more common in women with preexisting arterial hypertension, obesity, thrombophilias, diabetes mellitus, a hypertensive disorder in a previous pregnancy, history of preeclampsia in female relatives, maternal age <18 and >35 years, in primiparas, in multiple pregnancy, mola hydatidosa, and in certain ethnicities.[31,32] There is also evidence of a paternal influence on the development of preeclampsia which hampers an unambiguous interpretation of those disorders.[33] It is worth noting that some of those risk factors are also known risk factors for cardiovascular diseases which in turn raises the question of whether HDPs are indeed a separate risk factor for CVDs or simply share some common pathophysiologic mechanisms with them and are therefore a prodrome.

Historical perspective

Eclampsia is believed to have been scientifically described for the first time in the 17th century.[34] Hypertensive disorders of pregnancy were initially considered to be an entirely obstetric problem, mostly occurring in the first pregnancy and resolving with the delivery or soon after, but with the progress of modern medicine, there was a drastic change of that notion. More and more evidence was accumulated of long-term consequences after a hypertensive pregnancy. In the 1960s and 1970s, the first publications about a connection between preeclampsia and future arterial hypertension and renal dysfunction started to appear.[35,36] Those were quickly followed by numerous retrospective and prospective studies providing evidence of cardiovascular complications in women who had suffered preeclampsia or other hypertensive disorders of pregnancy. From a disease in the expertise of obstetrics and gynecology specialists (ob-gyns), hypertensive disorders of pregnancy started to transform into a risk factor for seriously debilitating cardiovascular events for those women.

Studies indicating a higher risk of arterial hypertension

In a large register-based cohort study with 782 287 women, Lykke et al.[9] discovered that the risk for the occurrence of arterial hypertension is 5.31 times higher after gestational hypertension, 3.61 times after mild preeclampsia, and 6.07 times after severe preeclampsia. If women had two pregnancies complicated with preeclampsia, the risk was even higher - 6 times. The risk was 2.7 times higher if preeclampsia occurred in the first pregnancy only, considering that nulliparity is a classic obstetric risk factor, and much higher if in the second pregnancy only - 4.34 times. The highest estimated risk was if PE was combined with preterm birth and small-for-gestational-age fetus – 7.68 times. The study also assessed the risk for the development of second type of diabetes mellitus - 3.12 times higher after gestational hypertension and 3.68 times higher after severe preeclampsia; for heart failure – 1.67 times after mild PE and 1.71 times after severe PE, but not significantly elevated after gestational hypertension; for thromboembolism – 1.53 times after mild PE; 1.91 times after severe PE, and again not elevated after GH.

In a cohort study, Stuart JJ et al.[10] analysed the data of 58671 participants in Nurses' Health Study II, who had previously given birth and did not have any CVDs or risk factors for such. The follow-up was between 25 and 32 years after the target pregnancy. Compared to women with normotensive pregnancies, those with gestational hypertension were with a hazard ratio (HR) of 2.8 for the presence of arterial hypertension, 1.7 for type 2 diabetes and 1.4 for hypercholesterolemia. Those with preeclampsia had HR 2.2 for chronic hypertension, 1.8 for type 2 diabetes, and 1.3 for hypercholesterolemia. The results showed that the relative risk for arterial hypertension was the strongest up to 5 years after the pregnancy. In those two large studies[9,10], the risk for arterial hypertension was estimated to be higher after gestational hypertension than after preeclampsia, which is worth noting as usually preeclampsia is the one considered to be with a worse prognosis both during and after pregnancy. These findings are far from being isolated as several other authors also found that gestational hypertension is associated with a higher risk for arterial hypertension when compared to preeclampsia.[37-39]

Coronary artery disease

A higher risk for coronary artery disease was found also in the study of Riise et al.[11] who followed prospectively 506350 women from the Norwegian birth register. The hazard ratio for a major coronary event was 2.1 in preeclampsia, but was even higher if preeclampsia was combined with small-for-gestational-age fetus (SGA) and/or preterm delivery – HR 4.3, and was the highest in preeclampsia and preterm delivery – HR 5.38. The risk of CVD death after PE (HR 1.6) was also further elevated by the presence of SGA (HR 3.7) and premature delivery (HR 2.8). A significant

difference for all-cause mortality was not found. Women at the mean age of 59.5±4.6 years with previous preeclampsia more than 30 years ago and no registered CVDs before inclusion were more likely to have Agatston score >50 points according to a study by White et al.[12] Valdés et al.[40] proved that the number of angiographically significant coronary lesions increased by 28% for the women with previous PE compared to those without – 22% (p=0.034) over a 10-year period with a mean age of the participants of 60.9±9.2 years.

Cerebrovascular disease

Based on the data from the Stroke Prevention in Young Women Study, Brown et al.[14] established a higher risk for stroke in women after a pregnancy with preeclampsia compared to those after normotensive pregnancies even after adjustment for age, race, education status, and parity. In another study[41], women with preeclampsia were at a higher risk for stroke during pregnancy and within the first year after the pregnancy with an adjusted relative risk of 10.68 for hemorrhagic stroke and 40.86 for ischemic stroke within 3 months before birth; 6.45 and 34.71 within the first three days postpartum and 19.90 and 4.35 from the 6th till the 12th month postpartum.

Diabetes mellitus

Diabetes mellitus is known to cause histopathological changes in the placenta[42] and is an independent risk factor for adverse pregnancy outcomes[43]. A retrospective cohort study of more than 1 million women conducted by Feig DS et al.[16] was specifically designed to discover whether preeclampsia and gestational hypertension posed a greater risk for the development of diabetes after pregnancy and whether the combination of PE/GH with gestational diabetes elevated the risk of postpartum diabetes. Both preeclampsia and gestational hypertension held a higher risk with an incidence of 6.47 and 5.26 per 1000 person-years respectively, while women with neither had an incidence of 2.81. Both hypertensive conditions proved to be risk factors for diabetes (HR 2.08 for PE and HR 1.5 for GH), but the risk was not as high as that of gestational diabetes (HR 12.77). The combination of gestational diabetes with either GH or PE yielded the highest risk - HR 15.75 and 18.49, respectively. The authors recommended diabetes screening in those women.

In another study[44], women with type 1 diabetes who suffered preeclampsia were more likely to develop diabetic nephropathy. No such connection existed with gestational hypertension. The odds ratio of preeclampsia for the development of diabetic nephropathy was higher (OR 7.7) than that of HbA1 (OR 2.0). Another study[45] proved worsening of diabetic retinopathy in women with type 1 diabetes if they developed PE during the pregnancy.

Venous thromboembolism

Several studies also found a relationship between HDPs and venous thromboembolism (VTE). In one study[17], the risk was 2.2 times higher when compared to normotensive pregnancies. The authors, however, did not recommend anticoagulant prophylaxis for those women, but advised caution towards them. Olié et al.[18] proved an association between preeclampsia and VTE after the pregnancy, but not during the pregnancy itself, after analysing data for nearly 4.5 million women.

Other CVDs (peripartum cardiomyopathy and peripheral artery disease)

Bello et al.[46] performed a literature review and meta-analysis that included 22 studies and 979 patients and found that the incidence of preeclampsia in women with peripartum cardiomyopathy was ~22%, which is much higher than its incidence in the general population. The authors suggested an overlap between the two conditions possibly due to similar pathogenesis. Women after a hypertensive pregnancy were also more prone to the occurrence of peripheral artery disease later in life as assessed by the ankle-brachial index with an OR 1.63 even after adjustment for the majority of other confounders - age, race, height, heart rate, smoking, hypertension, diabetes, dyslipidemia, coronary artery disease, and BMI.[15]

Mortality risk

Another study[19], besides the elevated risk for arterial hypertension and stroke, found also a higher mortality from all causes, stroke, and ischemic heart disease for women after gestational hypertension and preeclampsia/eclampsia. Brown et al.[20] also confirmed a higher risk of CVDs, mortality from CVDs and of cerebrovascular disease and arterial hypertension from a systematic review of 50 articles and 43 meta-analyses, but did not find a connection between premature birth in preeclampsia and future CVDs. Another meta-analysis[13] encompassing 22 studies and 6.4 million women, more than 258 000 of whom with preeclampsia, found that preeclampsia was independently associated with the occurrence of heart failure, fatal CVDs, stroke, and future coronary artery disease even after adjustment for confounders.

Utilization of the "stress test": evidence-based guidelines vs. reality

In 2005, Finnish authors[47] published a vast literature review of articles from 1990 to 2005 dealing with the con-

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nection between pregnancy and chronic conditions and reached the conclusion that the physiological changes that occur during the period of pregnancy could unmask latent pathological conditions, which later on could manifest as diseases. The notion of hypertension in pregnancy as a "stress test" towards the female organism started to emerge. Endothelial dysfunction is revealed at an early stage in women with gestational hypertension and preeclampsia and could eventually develop into the aforementioned cardiovascular diseases. This at the same time can be used as a natural screening to identify high-risk women and to allows for an early prevention.[47-49]

Based on the available evidence, the American Heart Association officially acknowledged preeclampsia and gestational hypertension as risk factors for cardiovascular diseases in their 2011 guidelines for CVD prevention in women.[50] In the guidelines, the occurrence of preeclampsia, gestational hypertension, and gestational diabetes is equalized to the risk that smoking, arterial hypertension, obesity, metabolic syndrome, poor physical activity and diet, subclinical atherosclerosis, dyslipidemia (defined as total cholesterol ≥5.3 mmol/l or HDL-cholesterol ≤1.2 mmol/l), and systemic autoimmune collagen-vascular disease pose for adverse CVD events for women. Follow-up of those women by a primary care physician or a cardiologist is recommended as well as efforts to improve lifestyle risk factors.

Similar, but more concise are the recommendations from the European Society of Cardiology in the current guidelines for the management of cardiovascular diseases during pregnancy (2018)[51] and for arterial hypertension (2018)[52] – the long-term cardiovascular risk is acknowledged and monitoring of blood pressure and metabolic factors are encouraged. The latter guidelines[52] also stresses the importance of taking anamnesis about preeclampsia or elevated blood pressure during pregnancy for risk assessment.

The necessity of measures directed towards women at risk is obvious considering the role of CVDs for poor quality of life and mortality worldwide. Moreover, two-thirds of those deaths happen in low and middle-income countries, where hypertensive disorders of pregnancy are also with a higher prevalence.[1] In its "Global action plan for the prevention and control of NCDs 2013-2020"[53], WHO endorses the prevention and control of non-communicable diseases, stressing the importance of reducing the burden of arterial hypertension and the need for early detection and control of modifiable risk factors.

The European Society of Cardiology Prevention guideline[54] supports the use of the SCORE Risk Charts to evaluate the 10-year risk of fatal CVDs, based on the classic risk factors from the Framingham Heart Study – male sex, age, smoking, total cholesterol, and systolic blood pressure. While women do have a lower risk when compared to men, it does not equal low mortality, but simply that the risk is postponed for a decade. In countries with very high risk such as Bulgaria where the mortality from CVDs is more than 2 times higher than in the countries with low risk (>450/100 000 for men and >350/100 000 for women), there is also a lower ratio between male and female mortality. This indicates an even higher risk for women living in those countries as compared to women living in other parts of the world.

Although women with HDPs do not fall into the classical risk categories, it is stated in the guidelines that screening them for eventual arterial hypertension and diabetes is not without merit as their relative risk is higher. Results from the Avon Longitudinal Study of Parents and Children[55] suggested an association with an odds ratio of 1.31 with the calculated 10-year CVD Framingham risk score for preeclampsia, which proves the presence of an independently increased CVD risk for those women. The study also verified that growth restriction and preterm delivery were associated with higher blood pressure years after the pregnancy.

Despite all recommendations listed above, the implementation of women's specific risk factors in clinical practice seems to be less than desired. Roth et al.[56] conducted a scoping review about the awareness of women and physicians of the association between CVDs and HDPs. The general conclusion was that both health-care providers and women lacked an adequate level of knowledge about the problem. Most health-care practitioners recognized the risk for arterial hypertension, but in one study[57], a great number of internists did not recognize the risk for ischemic heart disease (56%), stroke (48%), and decreased life expectancy (79%); while the percentage was respectively 23%, 38%, and 77% for obstetrician-gynecologists. Only 5% of internists and 42% of ob-gyns asked about preeclampsia when taking history. The majority of both internists (88%) and ob-gyns (79%) did not know whether preeclampsia was officially included in the AHA guidelines as a risk factor for CVDs. Risk-reduction advice for those women was provided by only 9% of internists and 38% of ob-gyns. Another survey[58] from Nigeria showed a relatively satisfactory knowledge of the risk of preeclampsia, ischemic heart disease, stroke, and kidney disease (87%, 63%, 69% and 73%, respectively), but only 46% of health care workers actually asked about past preeclampsia and provided counsel on future CVD risk. A survey by Hird et al.[59] found that 41% of healthcare practitioners did not inform more than half of the women with a previous diagnosis of preeclampsia of higher CVD risk and called this result a "research-to-practice gap".

Women themselves had limited knowledge of the risk they face after such a pregnancy. Surveys, which are included in the review[56], did not have a large number of participants as 5 out of 7 included less than 20 women. In a Portuguese survey[60], 70% of 78 women stated that they were not made aware of future CVD risk after preeclampsia. In a USA survey[61] with 146 participants, 65% of the women with severe features of PE were aware of the increased CVD risk and only 43% of those without such features. To aggravate the situation further, only 54% of American women realized that they were most likely to die from a cardiovascular event in a survey with 2300 participants by Mosca et al.[62] from 2009. The

authors, however, considered this result an improvement as in their previous study[63] from 1997, only 30% of women were aware of the problem. Conversely, another group of authors[64] found a decline in the awareness of women about the leading cause of death among them in the span of the last decade: from 65% in 2009 to 44% in 2019.

CONCLUSIONS

There is overwhelming evidence that hypertensive disorders of pregnancy are an early sign of predisposition of the female organism to endothelial dysfunction and to future cardiovascular events. Hence, in a way, what was initially considered a pregnancy-exclusive problem has evolved into a sex-specific risk factor for some of the most lethal diseases in the modern world. Considering the importance of prevention and its cost-effectiveness in the cardiovascular field, efforts should be made to use this knowledge as current studies show less than optimal awareness of healthcare workers and women alike.

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Артериальная гипертензия при беременности как ранний фактор риска сердечно-сосудистых заболеваний, зависящий от пола: доказательства и осведомлённость

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Резюме

Известно, что беременность у человека, несмотря на то, что это физиологическое состояние, вызывает многочисленные осложнения, которые могут угрожать жизни как матери, так и плода. В то время как большинство осложнений в основном ограничены перинатальным периодом, появляется всё больше информации о постоянно более высоком краткосрочном и долгосрочном сердечно-сосудистом риске после беременности, осложнённой гипертонической болезнью. Имеются данные о том, что у женщин после гестационной гипертензии или преэклампсии более вероятно развитие артериальной гипертензии, коронарного атеросклероза, инфаркта миокарда, инсульта, заболеваний периферических артерий и даже сахарного диабета и венозной тромбоэмболии спустя годы после намеченной беременности. Это побудило некоторых авторов рассматривать гипертензивные нарушения беременности как «стресс-тест» для материнского организма, выявляющий скрытую эндотелиальную дисфункцию. Объяснение ищут в наличии общих факторов риска и фоновых патологических путей при сердечно-сосудистых заболеваниях, хотя определённый этиологический механизм развития гипертензивных расстройств при беременности до сих пор не установлен. Необходимо уделять больше внимания последующему наблюдению женщин после гипертензивной беременности, поскольку это может быть возможностью для ранней профилактики сердечно-сосудистых заболеваний.

Ключевые слова

артериальная гипертензия, гестационная гипертензия, преэклампсия, профилактика женского здоровья