Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 Apr 16; 9(F):137-144.
https://doi.org/10.3889/oamjms.2021.5913
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Narrative Review Article*

Cardiac Biomarkers in hypertensive disorders of pregnancy

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Edited by: Igor Spiroski
Citation: Gencheva D, Nikolov F, Uchikova E, Hristova K, Mihaylov R, Pencheva B. Cardiac Biomarkers in Pregnancies, Complicated by Hypertensive Disorders. Open Access Maced J Med Sci. 2021 Apr 16; 9F:137-144. https://doi.org/10.3889/oamjms.2021.5913
Keywords: Biomarkers; Preeclampsia; Gestational hypertension; Cardiovascular risk; Natriuretic peptides; Troponin; Growth/differentiation factor 15; Suppression of tumorigenicity-2; Galectin-3
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Received: 21-Feb-2021
Revised: 26-Mar-2021
Accepted: 06-Apr-2021

Funding: This research did not receive any financial support.
Competing Interest: The authors have declared that no competing interest exists.

Abstract

In recent years, biomarkers have taken a central place in the assessment of cardiovascular diseases – from prediction to management and prognosis. On the other hand, enough evidence exists to assume that hypertensive disorders of pregnancy share a certain connection with cardiovascular diseases – from common risk factors and underlying mechanisms to the presence of a higher risk for women for the development of a great number of cardiovascular diseases, such as arterial hypertension, coronary atherosclerosis, stroke, peripheral artery disease, venous thromboembolism, and even a higher cardiovascular mortality. The key to a better understanding of the unfavorable cardiovascular profile of women with a hypertensive disorder of pregnancy may lie in their assessment with biomarkers, typically used in the field of cardiology. In this review, we have included studies investigating the use of cardiovascular biomarkers during or after a hypertensive pregnancy, namely, natriuretic peptides, high-sensitivity cardiac troponins, growth/differentiation factor 15 (GDF15), soluble suppression of tumorigenicity-2 (sST2), and galectin-3.

Introduction

Both cardiovascular diseases [1] and hypertensive disorders of pregnancy [2] are socially important entities leading to a considerable disability and mortality in people of active ages. The mechanisms for the development of hypertensive disorders of pregnancy are not completely understood, despite the considerable progress in the field. Poor placentation [3] is now believed to be the triggering event that results in a multisystemic response from the mother that can lead to devastating consequences, such as HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets syndrome), pulmonary edema, renal failure, encephalopathy, eclampsia, disseminated intravascular coagulation, and others [4]. The pregnancy itself is at risk as fetal growth is deterred and premature birth, abruption of the placenta and fetal death are more likely to happen [5]. Although hypertensive disorders induced by pregnancy resolve with the delivery of the placenta or soon after, it is now known that the risk of numerous cardiovascular diseases – arterial hypertension, coronary atherosclerosis, stroke, heart failure, peripheral artery disease, and venous thromboembolism [6], [7] remains higher in those women years after the completion of the pregnancy and even lead to a higher cardiovascular mortality [8]. A very plausible theory – that of hypertensive disorders of pregnancy being a "stress test" [9] unmasking latent endothelial dysfunction and the higher risk for future occurrence of cardiovascular diseases in women, unifies those seemingly different pathologies. Reports of more pronounced changes in the structure and the function of the heart during such pregnancies are not uncommon, such as an increase of the left ventricular mass, dilation of chambers, features of diastolic dysfunction, and occasionally of systolic dysfunction [10].

Indeed, hypertensive disorders of pregnancy share some common pathophysiological mechanisms with cardiovascular diseases as well as risk factors. Preeclampsia is characterized by vasoconstriction and increases in the afterload as a result of a imbalance between vasodilators and vasoconstrictors – there is an increased sensitivity to angiotensin II and less production of nitric oxide [11]. A similar imbalance has been implicated in the mediation of chronic heart failure – the end stage of all severe cardiovascular diseases, where it leads to progressive remodeling and cardiac dysfunction

[12]. Oxidative stress and endothelial dysfunction are also common denominators between those groups of diseases [13]. In hypertensive disorders of pregnancy, there is an exaggerated activation of inflammation as evidenced by the presence of elevated levels of pro-inflammatory cytokines [14] and low-grade inflammation is also known to accelerate the progression of atherosclerosis and is connected to poor cardiovascular outcomes [15]. Hypertensive disorders of pregnancy are also associated with an unfavorable lipid profile [16] and with insulin resistance [17] – both of which are risk factors for the development of cardiovascular diseases. Besides the obstetric risk factors, hypertensive disorders of pregnancy are more common in women presenting with typical cardiovascular risk factors, such as obesity, diabetes, pre-existing arterial hypertension, and thrombophilias [18].

Modern-day cardiology makes use of biomarkers, both in acute and chronic situations, as they provide additional information on mechanisms of disease development, facilitate treatment, and define prognosis. The abovementioned poses the question of whether cardiac biomarkers could also be applied successfully in the assessment of women during hypertensive pregnancies. Proper characterization of women during this natural “stress test” could allow for a better understanding of the function of the heart and the vascular system, and therefore provide a more precise risk stratification.

In this review, we aim to summarize the existing evidence of the presence of adverse cardiac biomarker profile in women during or after a hypertensive pregnancy when compared to normotensive pregnancies, and if available to provide information on correlations between the levels of those biomarkers and the clinicopathological characteristics of the women. We have included the following biomarkers – natriuretic peptides, high-sensitivity cardiac troponins, growth/differentiation factor 15 (GDF15), the suppression of tumorigenicity-2 (ST2), and galectin-3. Biomarkers with a primary role in the development of preeclampsia such as placental growth factor (PlGF), soluble FMS-like tyrosine kinase 1 (sFlt-1), and vascular endothelial growth factor (VEGF) are not an object of this review, although they are known to have certain uses in the field of cardiology.

Natriuretic peptides (BNP and NT-proBNP)

The family of natriuretic peptides consists of A-, B-, and C-type natriuretic peptides. The pro-hormone proBNP is secreted mostly by the ventricular cardiomyocytes as a response to the stretching of the myocardial wall due to elevated pressures and then its molecule is halved into the biologically active BNP and the inactive NT-proBNP. BNP stimulates diuresis, natriuresis, and vascular vasodilation and antagonizes the two systems mediating heart failure – the renin–angiotensin–aldosterone system and the sympathetic nervous system [19]. The use of either BNP or NT-proBNP is recommended by the current heart failure documents of the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) for peptides for establishing the diagnosis of heart failure in patients with dyspnea, as well as for prognostic purposes in chronic and acutely decompensated cases with the highest class of recommendation I and level of evidence A. With a lower strength of recommendation and evidence, they can be used for post-discharge prognosis in chronic heart failure and in patients at risk of developing heart failure (IIA, B-N and IIA, B-NR) [20]. It is also worth noting that BNP/NT-proBNP is so far the only biomarkers recommended by the European Society of Cardiology in the setting of heart failure [21].

Higher levels of NT-proBNP and BNP also correlate with a higher all-cause mortality in heart failure patients with preserved and reduced ejection fraction in the 6 months after hospital discharge [22]. BNP is also known to correlate with the degree of the left ventricular diastolic dysfunction, right ventricular systolic dysfunction [23], and also with a larger left ventricular end-systolic and end-diastolic diameter, left atrial diameter, and the degree of mitral insufficiency and lower left ventricular ejection fraction in the setting of acute heart failure, as measured echocardiographically [24]. In a study by Tschöpe *et al*., the levels of NT-proBNP correlated with invasively measured parameters of diastolic dysfunction – left ventricle end-diastolic pressure, dP/dt, Tau, and Pulmonary capillary wedge pressure rest and during exercise; as well as with the NYHA functional class of heart failure [25].

In hypertensive disorders of pregnancy

Elevated levels of natriuretic peptides in hypertensive diseases of pregnancy could be a defense mechanism directed against vasoconstriction, known to happen in those conditions. In a systematic review, Afshani *et al*. [26] selected 12 studies that examined the relationship between BNP levels and preeclampsia, eclampsia, and preterm delivery. The data suggested that levels of BNP remained unaltered in normal pregnancy, but were elevated in the third trimester of preeclamptic women and remained so 3–6 months after the end of the pregnancy. The authors stated that high levels of BNP could be an indicator of cardiovascular complications and preterm delivery, but more investigation on the topic is needed. There was no association between natriuretic peptides and HELLP syndrome and no association with the progression to eclampsia.

Another meta-analysis [27], incorporating data from three studies about BNP, concluded that BNP levels were also elevated when comparing severe to mild forms of preeclampsia. A different study discovered higher levels of BNP in early-onset preeclampsia compared to late-onset preeclampsia [28]. Few studies

exist that directly examine the association between the levels of natriuretic peptides and echocardiographic findings in hypertensive pregnancies. A study by Naidoo *et al*. additionally to the increased pre-delivery value of NT-proBNP in preeclamptic women discovered weak positive correlations between NT-proBNP and the tissue Doppler Ea of the mother and the resistance index of the umbilical artery [29]. The serum BNP correlated negatively with ejection fraction and TAPSE and positively with E/Em ratio in the severe preeclampsia group of a 2019 study, but the levels themselves were not increased after adjustment for maternal and gestational age when severe preeclampsia was compared to the controls [30]. Tihtonen *et al*. found a positive correlation between NT-proBNP and systemic vascular resistance index and an inverse one with the cardiac index in preeclamptic women as assessed by whole-body impedance cardiography [31].

As far as gestational hypertension is concerned, in 2016, Sadlecki *et al*. reported that serum NT-proBNP and BMI were independent predictors for the occurrence of gestational hypertension in multivariate logistic regression analysis. They were also indicative for the presence of preeclampsia and correlated inversely with birth weight. The authors suggested the use of NT-proBNP for a better identification and management of such women; however, one limitation of the study was the small sample size (14 women with PE and 26 with GH) [32].

Cardiac troponins

Troponin I and troponin T are muscle proteins that regulate muscle contraction and are highly specific and sensitive for the detection of myocardial injury. Elevated troponin I or T levels are a necessary criterion for the establishment of the diagnosis of myocardial infarction as per the fourth universal definition of myocardial infarction [33] and high-sensitivity assays are useful for the rule-out of myocardial injury in the acute clinical setting. Higher levels are also known to correlate to the size of the myocardial infarction and to predict worse outcomes in acute coronary syndromes [34].

High-sensitivity cardiac troponins are associated with the incidence of coronary heart disease, fatal coronary heart disease, total mortality, and heart failure [35]. The 2017 update of the ACC/AHA/HFSA heart failure guideline recommends the use of high-sensitivity cardiac troponin as a marker of cardiac fibrosis for the prediction of hospitalization and death in heart failure patients, although with a lower class and evidence of recommendation (IIB, B-NR), when compared to the natriuretic peptides [20].

In hypertensive disorders of pregnancy

There are conflicting reports on whether hypertensive pregnancies lead to higher levels of cardiac troponins or not. A systematic review of nine studies of up to 2015 involving 719 women, found that five of the studies indicated significantly higher levels of troponin I in preeclampsia, but the other four did not; and additionally, the authors of the review criticized the lack of consecutive measurements [36]. Fleming *et al*. found higher levels of troponin I in the preeclampsia group compared to the gestational hypertension one in their study [37]. A 2018 study found elevated high-sensitivity troponin I in 25% of the women with preeclampsia and also a significant linear relationship between troponin and mean arterial pressure [38]. In a relatively large prospective study, high-sensitivity cardiac troponin I was an independent predictor of gestational hypertension and preeclampsia during pregnancy and after delivery – with an odds ratio of 9.3 in unadjusted and 11.5 in adjusted models per doubling of its concentrations [39].

Conversely, the authors of a study that did not confirm elevated troponin I in preeclamptic pregnancies advised the exclusion of other reasons for myocardial injury in women with elevated cardiac troponins [40].

Umazume *et al*. made serial measurement of high-sensitivity troponin I accompanied by echocardiographic assessment of women with hypertensive disorders of pregnancy and found that the serum levels correlated negatively with the maternal e-wave in the third trimester and 1 month postpartum. The authors found an area under the curve of 0.82 and 0.81, respectively, for the prediction of reduced left ventricular relaxation in those periods [41]. Muijsers *et al*. measured high-sensitivity troponin I levels 9–10 years after an early-onset preeclamptic pregnancy and while there was no difference compared to women with a normotensive pregnancy in that time period, currently, hypertensive women with a history of early-onset preeclampsia had higher levels than normotensive women with early-onset preeclampsia. Higher troponin levels were also associated with a higher blood pressure [42].

Soluble suppression of tumorigenicity-2 (sST2)

A relatively novel biomarker in the cardiovascular field, the suppression of tumorigenicity-2 (ST2) is a member of the interleukin-1 family, with a circulatory form – soluble ST2 (sST2) that binds to IL-33 and thus promotes inflammation, hypertrophy, fibrosis, and ventricular dysfunction [43]. The biomarker is secreted by the cardiac myocytes and fibroblasts and is increased under mechanical stress [44]. The biomarker has a promising role in the prognosis and management of heart failure [45], Eisenmenger's syndrome [46], and major adverse cardiac events and is also associated with the complexity of coronary atherosclerotic lesions [47].

The current ACC/AHA/HFSA update on the Heart Failure Guideline also recommends its use in

heart failure as it could provide additional prognostic information and risk stratification to the use of natriuretic peptides with a class of recommendation IIB, B-NR [20]. In a direct comparison study between sST2, galectin-3, and high-sensitivity troponin T in chronic heart failure patients with reduced ejection fraction, out of the three biomarkers, only the serial measurements of sST2 predicted reserve myocardial modeling and independently added to the risk model for adverse cardiovascular events [48]. In patients with heart failure with preserved ejection fraction, sST2 levels were associated with the presence of diabetes mellitus, atrial fibrillation, systemic congestion, and kidney failure. It also correlated with worse exercise tolerance and higher NT-proBNP levels, C-reactive protein, and high-sensitivity troponin [49].

In hypertensive disorders of pregnancy

Soluble ST2 has also been examined in the setting of preeclampsia, although large studies are not available. In a longitudinal study of 160 uncomplicated pregnancies and 40 preeclamptic ones, maternal plasma sST2 concentrations were elevated 6 weeks before the clinical presentation of preeclampsia, which the authors attributed to an exaggerated inflammatory response or a misbalance between humoral and cellular immunity [50]. Higher concentrations of sST2 were found in women with preeclampsia compared to normotensive pregnancies and the difference was more pronounced in early onset and in severe preeclampsia. There were no correlations with the uterine or umbilical Doppler findings. In addition, there was a negative correlation with the placental growth factor – a pro-angiogenic factor which is necessary for proper placentation and is pathologically reduced in preeclampsia [51]. In a recent, relatively, but small study sST2 levels were elevated in 24 women with severe preeclampsia 24 h before delivery, but not 1 year afterward, compared to healthy pregnant controls and additionally in the preeclampsia group, there was an inverse correlation with echocardiographic markers of the left ventricular diastolic function, but not with the systolic ones [52].

Galectin-3

Galectin-3 is a protein with an established role in inflammation, immunity, and oncogenesis. It is secreted by the activated macrophages and its main function is associated with the activation of the fibroblasts that form collagen and fibrotic tissue [53]. Experimental animal studies prove its role in cardiac remodeling as a result of pressure overload [54]. In human studies, its upregulation has been established in patients with the left ventricular hypertrophy [53] and heart failure [55]. Its levels correlated with the number of hospitalizations for heart failure [56] and were also elevated in pulmonary hypertension, where they correlated with the prognosis, regardless of etiology [57]. In a 2016 study, there was a significant correlation between galectin-3 levels and the thickness of the ventricular septum, the left ventricular posterior wall, and the left ventricular mass in arterial hypertension. In the same study, its levels were elevated even in newly diagnosed hypertensive patients [58]. In a non-pregnant population, a negative correlation was discovered between galectin-3 levels and some parameters of the right ventricular function – TAPSE and the tricuspid S-wave, in patients with reduced left ventricular function, but the levels were not associated with the left-sided parameters themselves [59]. The recommendation of its use for additional risk stratification by the ACC/AHA/HFSA in chronic heart failure is IIB, B-NR, similarly to that of high-sensitivity troponin and sST2 [20].

In hypertensive disorders of pregnancy

Galectin-3 is not much studied in pregnancy-induced hypertension or its complications. However, we managed to identify a couple of relevant studies. In a 2019 study by Taha *et al*. [60], the Galectin-3 levels were significantly higher in preeclamptic women and additionally indicated a worse lipid profile – they showed a positive correlation with the total, VLDL, LDL cholesterol, and triglycerides and a negative one with HDL cholesterol. A positive correlation was also present with maternal and gestational age of the women. Jeschke *et al*. [61] found an upregulation of both galectin-1 and galectin-3 in the extravillous trophoblast of eight preeclamptic placentas and five placentas of women with HELLP syndrome when compared to placentas of healthy women. In another study, there was also a higher galectin-3 expression in the umbilical cord of small-for-gestational-age infants when compared to appropriate-for-gestational-age ones [62].

Growth/differentiation factor 15 (GDF15)

GDF-15 is a protein from the transforming growth factor-β superfamily that is normally secreted in small quantities by many organs, but in much higher concentrations from the placenta in pregnancy. It is involved in apoptosis, inflammation, oncogenesis, and the metabolism, but its role in pregnancy is not entirely clear [63]. It is now known to participate in cardiac ischemia [64] and in the formation of the atherosclerotic plaque [65]. High concentrations are present in heart failure and in different forms of coronary artery disease and are related to the progression of the disease, ventricular remodeling, plaque burden, and the severity of ischemia [66]. A large study proved that it can be used in the prediction of all-cause, cardiovascular, and non-cardiovascular mortality with better predictive abilities for all-cause mortality than the popular predictors NT-proBNP and the C-reactive protein [67].

In hypertensive disorders of pregnancy

In normal pregnancy, serum levels of GDF-15 were elevated with the progression of the pregnancy, but were reduced in the third trimester in 34 women with preeclampsia, especially if the preeclampsia was late onset. It, however, could not be used as an early prediction (11–13 gestational week), as the levels did not differ in women who later on developed preeclampsia [68]. Results from other studies, however, showed the opposite – higher concentrations in hypertensive pregnancies. Sugulle *et al*. [69] examined GDF-15 concentrations in preeclampsia to test the hypothesis that the placental oxidative stress is causing elevation of its levels. According to their results, maternal serum GDF-15 concentrations were higher in preeclamptic pregnancies at term compared to controls, and additionally, levels were elevated in the fetal circulation and the amniotic fluid in cases of preeclampsia and superimposed preeclampsia. The placental GDF-15 mRNBA was also elevated in preeclampsia. The authors viewed their finding as a confirmation of the presence of oxidative stress and ischemia in preeclamptic pregnancies. In the same study, the levels were also higher in women with diabetes mellitus. Another group of authors [70] also found significantly elevated concentrations in preeclampsia and the highest levels of GDF-15 were in its early-onset forms. There was a positive correlation with the systolic and diastolic blood pressure and a negative one with the gestational age of delivery and the birth weight. Those results were explained with the production of GDF-15 in the setting of cytokine-mediated endothelial injury.

Conclusion

The use of cardiac biomarkers in pregnancy is unfortunately not a widely researched area, but a progress in it could lead to a better understanding of the mechanisms behind the development of hypertensive disorders of pregnancy. In addition, research could provide an explanation for the higher cardiovascular risk in affected women both during and years after a hypertensive pregnancy. The growing evidence of cardiac biomarkers being altered during hypertensive pregnancies necessitates a more thorough cardiologic assessment of affected women and could be promising for risk stratification for future cardiovascular events. More pronounced changes in the biomarker levels could indicate a worse cardiovascular profile. The identification of such women can facilitate health-care provision and prophylaxis, therefore improving the management of women's health issues. The information on the topic, however, remains somewhat scarce, especially when correlations of biomarkers with cardiac structural or functional changes are sought after. Larger studies are needed, especially with more information about gestational hypertension as this group of women tends to be underexamined when compared to preeclampsia, while the risk of further cardiovascular complications is far from negligible.

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