folia medica

Folia Medica 65(4):539-545
DOI: 10.3897/folmed.65.e99159

Review

White-Coat Hypertension in Pregnant Women: Risk Factors, Pregnancy Outcomes, and Biomarkers

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Received: 22 Dec 2022 ♦ **Accepted:** 24 Jan 2023 ♦ **Published:** 31 Aug 2023

Citation: Chulkov VS, Nikolenko E, Chulkov V, Podzolko A. White-coat hypertension in pregnant women: risk factors, pregnancy outcomes, and biomarkers. Folia Med (Plovdiv) 2023;65(4):539-545. doi: 10.3897/folmed.65.e99159.

Abstract

Hypertensive disorders of pregnancy are a worldwide health problem for women. They cause complications in up to 10% of pregnancies and are associated with increased maternal and neonatal morbidity and mortality. Traditional blood pressure measurement in clinical practice is the most commonly used procedure for diagnosing and monitoring hypertension treatment, but it is prone to significant inaccuracies caused, on the one hand, by the inherent variability of blood pressure and, on the other, by errors arising from measurement technique and conditions. Some studies have demonstrated a better estimate of the prognosis for the development of cardiovascular diseases using ambulatory blood pressure monitoring. We can detect white-coat hypertension using this method, which helps to avoid overdiagnosis and overtreatment in many cases, and we can also detect masked hypertension, which helps to avoid underdiagnosis and a lack of prescribed treatment if needed. White-coat hypertension is not a benign condition – it has been shown to be associated with higher risks of developing preeclampsia, preterm birth, and small-for-gestational-age babies. In this regard, it is extremely important for clinicians to be aware of the risk factors and outcomes associated with this condition. Pregnant women should be medically monitored both during pregnancy and after delivery to detect target organ damage, cardiovascular risk factors, or a metabolic syndrome.

Keywords

hypertensive disorders during pregnancy, miRNAs, preeclampsia, pregnancy outcomes, white-coat hypertension

INTRODUCTION

White-coat hypertension (WCH) is observed in cases where a blood pressure (BP) measurement increase is recorded on an outpatient appointment with a systolic blood pressure (SBP) of ≥140 mmHg and/or a diastolic blood pressure (DBP) of ≥90 mmHg, while the blood pressure measurements at home remain consistently within the reference range.[1-4] The effect of WCH occurs quite often (in about 30% of cases) in early pregnancy, which is similar to the number of cases besides pregnancy.[5,6] The frequency of the occurrence of WCH increases with age.[7]

WCH should only be considered as a diagnosis in pregnant women before 20 weeks of gestation, according to the International Society for the Study of Hypertension in Pregnancy (ISSHP).[8] An increase in blood pressure seen only at appointments in the presence of care providers in late pregnancy is considered pregnancy-specific. This discrimination, however, is not adhered to in many studies.[9]

Using ambulatory blood pressure monitoring (ABPM), we found that white coat hypertension could be diagnosed in 30% of women diagnosed with gestational hypertension

at 20 weeks or more. The number of detected cases increases to about 70% by the third trimester of pregnancy.[6] To detect WCH, it is common to use either 24-hour ABPM or home blood pressure monitoring. A meta-analysis including 17 studies showed that the outpatient blood pressure (SBP/DBP) against the background of the effect of white coat hypertension was higher than the blood pressure measured at home by 4/3 (3-6/2-4) mmHg on average.[8] A BP of 135/85 mmHg is generally accepted as the upper reference limit for home BP measurement in healthy pregnant women, which is used in the differential diagnosis of WCH from other hypertensive disorders.[10]

White-coat hypertension and risk factors

When the factors that can influence the occurrence of WCH were investigated, it was found that nulliparous women had a much higher likelihood of developing the condition than multiparous women did. Moreover, an increase in the systolic blood pressure is more typical in the early stages of pregnancy, whereas an increase in the diastolic blood pressure is more typical in the late stages of pregnancy.[11,12] Hypertensive disorders during pregnancy (HDP), including the WCH, have also been found to be more common in pregnant women with pre-existing type 2 diabetes mellitus. According to our findings, an in-office BP of 135/85 mmHg was detected for the first time in early pregnancy in 14% of the women with pre-existing diabetes. Simultaneously, WCH was present in 84% of these women, which is 12% of the entire cohort. Chronic hypertension was detected in 14% of the cases, and normotension – in 74% of the cases. The women with WCH had a higher pre-pregnancy BMI and higher home-measured BP than normotensive individuals.[13]

Gestational diabetes, obesity, multiple pregnancy, maternal age less than 20 or older than 35 years old, and thrombophilia are also among the factors that contribute to an increased risk of developing HDP.[12] There is also an increase in the prevalence of impaired glucose tolerance and coronary artery disease among patients with WCH and hypertensive disorders compared with the normotensive group. Additionally, the highest prevalence of dyslipidemia was observed in the WCH group (41.6%), followed by the group of patients with stable hypertension (35.5%) and 19.6% in the normotensive group.[7,14]

Björklund et al.[15] found that metabolic abnormalities (insulin sensitivity, elevated fasting blood glucose, impaired glucose tolerance, and elevated serum insulin levels) and tachycardia develop over time in patients with WCH and persistent hypertension.

WCH is accompanied by hyperlipidemia, which, along with disorders of carbohydrate metabolism and a tendency to be overweight, links WCH to a metabolic syndrome.[7,16]

Risk factors for WCH, previously attributed to the stress response, also include female sex, smoking, and daytime systolic BP variability.[17] Vascular aging of the arteries is the dominant determinant of the 'white coat' effect. Patients with WCH have higher values of carotid-femoral pulse wave velocity, and augmentation index, which is an independent predictor of atherosclerotic lesions of carotid arteries, and an increase in the amplitude of the reflected pressure wave.[18]

Although WCH is triggered by stress-related activation of the sympathetic nervous system, the response of blood pressure to increased cardiac contraction and peripheral vasoconstriction is markedly manifested in vascular arterial aging. This is manifested by an increase in arterial stiffness and reflection of pulse waves, which increases blood pressure. WCH is associated with an increased risk of cardiovascular disease (CVD) and a higher mortality rate from CVD because vascular aging, namely an increase in arterial stiffness and a decrease in vascular wall compliance, is a recognized major risk factor for cardiovascular diseases and target organ damage, as well as the main pathophysiological factor explaining the occurrence of WCH.[19]

Diagnosis of white coat hypertension

ISSHP recommends that women with an elevated office blood pressure of ≥140/90 mmHg diagnosed before 20 weeks of gestation should be examined with ABPM, which includes frequent automatic blood pressure measurements during wakefulness and sleep for 24 hours.[1] This examination can help in the differential diagnosis of true hypertension in pregnancy from WCH.[20-22] **(Fig. 1)**.

Home blood pressure monitoring (HBPM) is an acceptable alternative when ABPM is not available. HBPM should be performed twice a day, in the morning and in the evening, and then averaged over 7 days. Mean BP ≤130/80 mmHg while awake and/or ≤115/70 mmHg during sleep is considered normal. Presence of WCH is assessed based on the data obtained. If the waking blood pressure is 130/80 mmHg or the sleeping blood pressure is 115/70 mmHg, the diagnosis is chronic hypertension.

The gold standard for ruling out masked hypertension and WCH is ABPM.[1,3,8] With the help of ABPM, the falling pattern is also evaluated, i.e. the ratio of systolic blood pressure (SBP) at night to SBP during the day.[7] The falling pattern has an important predictive value regarding the risk of later cardiovascular disease.[23] Patients with WCH are diagnosed with more variable circadian rhythm than normotensive patients, higher pulse pressure, and no dips. ABPM non-dipping status in patients with WCH is associated with decreased compliance of the vascular wall of the arteries.[24] The unfavorable falling pattern in ABPM, which is an insufficient fall in SBP at night compared to daytime, even along with normotension, should be assessed as a clinically significant independent risk factor for developing preeclampsia (PE) and cardiovascular disease in the future.[25-27]

The generally accepted upper limit of home blood pressure (135/85 mmHg) used in the differential diagnosis of WCH during pregnancy, has recently been called into ques-

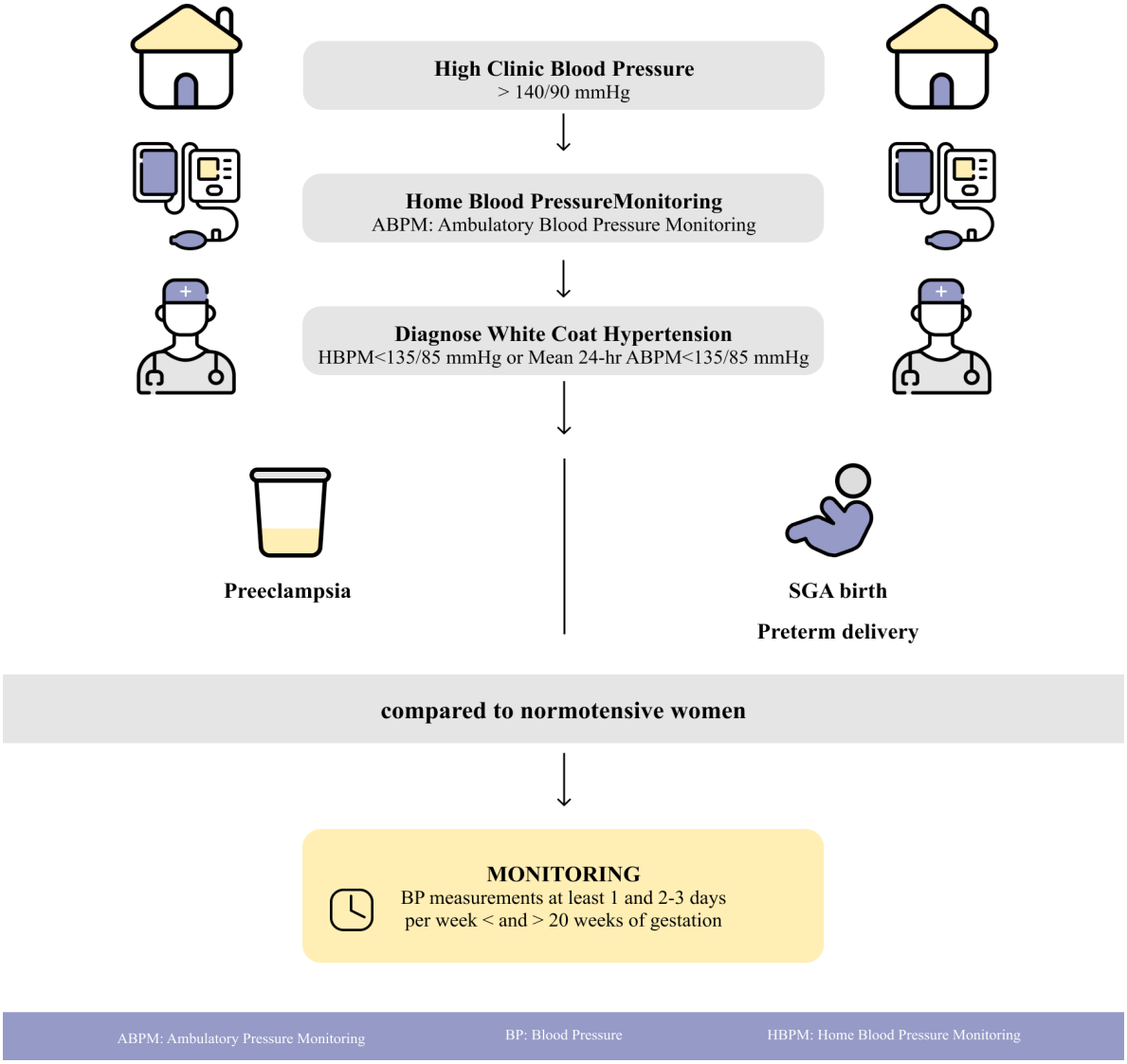

Figure 1. White coat hypertension diagnostic criteria and monitoring during pregnancy.

tion.[28] Normal office values of blood pressure during the day in pregnant women are recognized as blood pressure values less than 130/77 mmHg at ≤22 weeks, 133/81 mmHg at 26–30 weeks, and 135/86 mmHg at 30 weeks. In late pregnancy, the upper reference limit is 140/91 mmHg for office blood pressure and 123/78 mmHg for home BP. The average difference between office BP and home BP in healthy pregnant women is 10 mmHg.[10,29] Daily fluctuations in blood pressure during pregnancy amount to a nighttime decrease in SBP and DBP by 12%-14% and 18%-19%, respectively. The nighttime decrease in blood pressure weakens before the onset of nephropathy against the background of gestational arterial hypertension.[10]

According to the findings of a Japanese study of pregnant women, an increase in blood pressure of 10 mmHg according to ABPM increases the risk of giving birth to small-for-gestational-age newborns by 1.74 times.[30]

White-coat hypertension and pregnancy outcomes

Women diagnosed with WCH in early pregnancy are twice more likely to develop HDP compared to normotensive women.[13,23] According to various data, based on ABP monitoring in early pregnancy, 40% of women subsequently develop gestational hypertension.[6,31] Women who have WCH before 20 weeks of pregnancy are five times more likely than normotensive women to develop PE.[10,26,32] However, the risk of developing PE was not significantly higher compared to normotensive women when WCH was diagnosed at any stage of pregnancy.[8] According to the results of a retrospective cohort study, it was confirmed that WCH diagnosed in the first trimester of pregnancy is a risk factor for developing PE and gestational hypertension in late pregnancy.[33]

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HDP are a worldwide health problem for women and their infants.[34-37] When WCH was detected at any stage of pregnancy, it increased the risk of premature birth and births of small-for-gestational-age infants by 2-3 times, according to most studies.[8,32] Simultaneously, these results may have limitations, given the recommendations of the International Society for the Study of Hypertension in Pregnant Women to include only women under 20 weeks of pregnancy in the diagnosis of WCH. Therefore, when managing women throughout pregnancy, it is necessary to diagnose WCH in a timely manner before the 20th week of pregnancy.[8]

Generally, WCH diagnosed during pregnancy tends to have a better prognosis than gestational hypertension: the risk for PE, a birth of small-for-gestational-age newborns, and preterm birth is significantly lower in women with WCH than that of women with gestational hypertension.[26,29] Delivery in women with WCH occurs about 1 week later compared with women with chronic hypertension.[32]

Based on these findings, it is possible to conclude that WCH is associated with worse perinatal and maternal outcomes when compared to normotensive subjects, but better outcomes when compared to gestational hypertension and chronic hypertension, and thus occupies an intermediate risk for developing complications.[38-40]

The role of miRNAs in the development of white-coat hypertension

Recently, microribonucleic acids (microRNAs) have been targeted as potential biomarkers.[41] MicroRNAs are not prone to rapid degradation, therefore, they can be measured both in tissues and in biological fluids. According to the update of the miRNAs database from 2018, 2654 mature miRNAs were discovered in humans.[42,43]

A study identified 9 microRNAs with reduced expression and 7 miRNAs with increased expression in the placenta of patients with developed severe PE compared to the control group of healthy pregnant women.[44] Overexpression of microRNA-21 is positively correlated with elevated blood pressure. The direct target of microRNA-21 is mitochondrially encoded cytochrome B (mt-CytB), the stimulation of which increases the production of reactive oxygen species. As is well known, an increase in oxygen causes vascular wall remodeling due to the development of endothelial dysfunction, inflammation, and cell migration[45] Moreover, miRNA-21 overexpression can trigger the development of the atherosclerotic process by targeting the endothelial nitric oxide synthase (eNOS).[46]

The analysis of published data has shown the association of many types of microRNAs with the pathogenesis of various types of hypertensive disorders. This is explained by their pleiotropic properties, the ability to regulate the expression of numerous target genes, and their participation in complex regulatory networks. However, only 2 miRNA types, miRNA-21 and miRNA-130a, were expressed in essential hypertension and pulmonary arterial hypertension. Here, miRNA-21 demonstrates a particularly high degree of expression.[47] Additionally, there is a direct correlation between increased expression of miRNA-21 levels and the development of white coat hypertension.[48] Simultaneously, the role of microRNA-21 in the proliferation and apoptosis of vascular smooth muscle cells and cardiomyocytes and participation in the functions of cardiac fibroblasts is already well known.

Dysregulation of microRNA-21 expression can initiate the proliferative status of smooth muscle and endothelial cells of the pulmonary artery in the early phase of hypoxic exposure. Elevated levels of miRNA-21 and B-type natriuretic peptide have also been diagnosed in patients with pregnancy-induced hypertension.[49]

The role of the increased miRNA-21 expression in the development of left ventricular concentric remodeling with an increase in the thickness of the interventricular septum according to echocardiography and a decrease in the number of functioning nephrons against the background of an increase in blood pressure was demonstrated by the study's findings. Simultaneously, a feature of developing myocardial remodeling is the predominance of precisely hypertrophic changes in the myocardium over fibrosis. However, specific mechanisms of microRNA-21 involvement in the pathogenesis of myocardial remodeling require further research.[50]

CONCLUSIONS

White-coat hypertension, previously thought to be a simple sympathetic nervous system response to stress, has much deeper roots. The genetic link between the development of WCH and increased expression of miRNA-21, so-called marker that increases in various forms of hypertension, has been established. Furthermore, increased arterial stiffness has been shown to play a pathogenetic role in the development of WCH.

WCH is accompanied by metabolic disorders manifested by hyperlipidemia, impaired carbohydrate metabolism, and a tendency to be overweight. Based on clinical and laboratory characteristics, WCH belongs to the spectrum of BP disorders with an intermediate risk between normotensive and persistent hypertensive disorder.

The WCH diagnosed during pregnancy is not a benign condition; it is associated with an increased risk of developing PE and gestational hypertension, and with several adverse perinatal outcomes, such as an increase in the number of preterm births and births of small-for-gestational-age newborns. Therefore, clinicians need to be aware of the risk factors and outcomes associated with WCH. Patients with WCH should be closely monitored and controlled. They should be carefully evaluated for target organ damage, cardiovascular risk factors, and metabolic syndrome. Additionally, ABPM and HBPM should be widely used at the stage of diagnosis and control of WCH, to perform some preventive measures to prevent the development of target

organ damage subsequently.

According to the recommendations of the European Society of Hypertension and the Guidelines of the European Society of Cardiology, for WCH without additional cardiovascular risk factors, the therapeutic approach may be limited to effective lifestyle changes, such as regular aerobic physical activity, weight loss, salt restriction, and smoking cessation. This should be accompanied by a close clinical and laboratory follow-up in pregnant women with WCH, including regular home BP measurements throughout pregnancy and periodic performance of ABPM.

The International Society for the Study of Hypertension in Pregnancy does not suggest a surveillance of pregnancy with WCH for perinatal outcomes: it does not consider monitoring for small-for-gestational-age newborns or preterm birth in the absence of PE. Simultaneously, some authors insist on monitoring the abovementioned adverse perinatal outcomes and assessing the state of the fetus in WCH.

Currently, there is not enough information on the potential benefit of a strategy to prevent the development of PE in WCH, namely, the prescription of low-dose aspirin to pregnant women with this diagnosis. In patients with stable WCH at high or very high cardiovascular risk, because of the presence of multiple risk factors, type 2 diabetes mellitus, renal dysfunction, any confirmed markers of target organ damage, and cardiovascular diseases, medical treatment may be considered in addition to appropriate lifestyle modification measures.

WCH with identified signs of vascular aging should be under strict control. Pharmacological therapy may be indicated for patients with WCH and increased pulse wave reflection. In this regard, the measurement of indicators of vascular aging in patients with WCH is important to identify a high-risk subgroup. Additionally, in the future, uterine arteries Doppler velocimetry and the study of some serum biomarkers to assess the likelihood of developing HDP and their complications should be considered.

Acknowledgements

The authors have no support to report.

Funding

The authors have no funding to report.

Competing Interests

The authors have declared that no competing interests exist.

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Гипертензия белого халата у беременных: факторы риска, исходы беременности и биомаркеры

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Дата получения: 22 декабря 2022 ♦ **Дата приемки:** 24 января 2023 ♦ **Дата публикации:** 31 августа 2023

Образец цитирования: Chulkov VS, Nikolenko E, Chulkov V, Podzolko A. White-coat hypertension in pregnant women: risk fac-tors, pregnancy outcomes, and biomarkers. Folia Med (Plovdiv) 2023;65(4):539-545. doi: 10.3897/folmed.65.e99159.

Резюме

Гипертензивные расстройства беременных представляют собой глобальную проблему для здоровья женщин. Они вызывают осложнения до 10% беременностей и ассоциируются с высокими материнской и перинатальной заболеваемостью и смертностью. Традиционное измерение артериального давления в клинической практике является наиболее часто используемой процедурой диагностики и контроля лечения артериальной гипертензии, однако оно подвержено значительным неточностям, обусловленным, с одной стороны, присущей вариабельностью артериального давления, а с другой – погрешностями, возникающими из-за методики измерения и условий. Некоторые исследования продемонстрировали лучшую оценку прогноза развития сердечно-сосудистых заболеваний при использовании амбулаторного мониторирования артериального давления. С помощью этого метода мы можем выявить гипертензию белого халата, что во многих случаях помогает избежать гипердиагностики и чрезмерного лечения, а также выявить маскированную гипертензию, что помогает избежать гиподиагностики и отсутствия назначенного лечения в случае необходимости. Гипертензия белого халата не является доброкачественным заболеванием — было показано, что она связана с более высоким риском развития преэклампсии, преждевременных родов и рождения детей с малым весом для гестационного возраста. В связи с этим крайне важно, чтобы клиницисты знали о факторах риска и исходах, связанных с этим состоянием. Беременные женщины должны находиться под медицинским наблюдением как во время беременности, так и после родов для выявления поражения органов-мишеней, сердечно-сосудистых факторов риска или метаболического синдрома.

Ключевые слова

гипертензивные расстройства при беременности, микроРНК, преэклампсия, исходы беременности, гипертензия белого халата