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Hypertensive disorders during pregnancy: current aspects of pathogenesis, screening and prevention

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Hypertensive disorders of pregnancy, including preeclampsia (PE) and gestational hypertension, are among the most common complications of the gestational period and represent one of the leading causes of maternal and perinatal morbidity and mortality worldwide. They occur in approximately 10% of pregnancies and significantly influence outcomes for both the mother and the child. Women who have experienced these complications are at increased long-term risk of developing arterial hypertension, ischemic heart disease, heart failure, and other metabolic and vascular disorders.
The article highlights current insights into the multifactorial pathogenesis of hypertensive disorders in pregnancy. Defective placentation, insufficient trophoblast invasion, impaired spiral artery remodeling, placental ischemia, angiogenic imbalance, oxidative stress, immunological alterations, and endothelial dysfunction have been identified as key mechanisms in these pathologies. Recent studies support the rationale for molecular subclassification of PE, which makes it possible to distinguish different clinical and pathogenetic phenotypes and to develop individualized preventive approaches.
Particular attention is given to biomarkers, including placental growth factor, soluble fms-like tyrosine kinase 1 receptor, and soluble endoglin, which reflect angiogenic balance and can be used to predict adverse obstetric and perinatal outcomes. Uterine artery Doppler in the I trimester is emphasized as an important method for early screening of placental disorders.
The review discusses prevention strategies supported by evidence-based medicine, recommendations of professional medical societies of various countries, including Ukraine. The most studied and safe interventions are the use of low-dose acetylsalicylic acid and calcium supplementation in women with insufficient dietary calcium intake. Promising directions of prevention and treatment, such as the use of L-arginine, vitamin D, low-molecular-weight heparins, progesterone, and statins, are also analyzed. At the same time, the absence of a universal test or a single preventive strategy able to avert all cases of PE is emphasized.
In conclusion, the contemporary concept of screening is based on the integration of clinical risk factors with biochemical and biophysical markers, enabling the identification of high-risk groups and the timely implementation of preventive measures. Future research should aim to refine prediction algorithms, optimize preventive strategies, and evaluate their long-term effectiveness and safety for both mothers and children.
Keywords: *hypertensive disorders of pregnancy, preeclampsia, gestational hypertension, pregnancy, imbalance of angiogenic and antiangiogenic factors, endothelial dysfunction, biomarkers, uterine artery Doppler, pregnancy screening, prevention of preeclampsia.*

Гіпертензивні розлади під час вагітності: сучасні аспекти патогенезу, скринінгу та профілактики

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Гіпертензивні розлади у вагітних, зокрема прееклампсія (ПЕ) та гестаційна гіпертензія, належать до найпоширеніших ускладнень гестаційного періоду і становлять одну з провідних причин материнської й перинатальної захворюваності та смертності у світі. Вони трапляються у близько 10% вагітностей і суттєво впливають на прогноз як для матері, так і для дитини. У жінок, які перенесли ці ускладнення, у майбутньому підвищується ризик розвитку артеріальної гіпертензії, ішемічної хвороби серця, серцевої недостатності та інших метаболічних і судинних порушень.
У статті висвітлено сучасні уявлення про багатофакторний патогенез гіпертензивних розладів у вагітних. Встановлено, що ключову роль у розвитку цих станів відіграють порушення плацентації, недостатня інвазія трофобласта, дефектне ремоделювання спіральних артерій, ішемія плаценти, ангіогенний дисбаланс, оксидативний стрес, імунологічні зміни та ендотеліальна дисфункція. Останні дослідження підтверджують доцільність молекулярної субкласифікації ПЕ, що дозволяє виокремлювати різні клініко-патогенетичні фенотипи й формувати індивідуалізовані підходи до профілактики. Окрему увагу приділено біомаркерам, зокрема плацентарному фактору росту, розчинному рецептору fms-подібної тирозинкінази 1 (sFlt-1) та розчинному ендогліну, які відображають стан ангіогенного балансу й можуть бути використані для прогнозування несприятливих акушерських і перинатальних наслідків. Важливу роль відіграє допплерометрія маткових артерій у I триместрі як метод раннього скринінгу порушень плацентації.
У роботі розглянуто стратегії профілактики, підтверджені даними доказової медицини, рекомендації професійних медичних товариств різних країн, зокрема й України. Найбільш дослідженими та безпечними є застосування низьких доз ацетилсаліцилової кислоти й додатковий прийом кальцію у жінок із недостатнім його харчовим споживанням. Також аналізуються перспективні напрями профілактики й лікування, зокрема із застосуванням L-аргініну, вітаміну D, низькомолекулярних гепаринів, прогестерону та статинів. Водночас підкреслюється відсутність універсального тесту або єдиної профілактичної схеми, здатної запобігти розвитку всіх випадків ПЕ.

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Отже, сучасна концепція скринінгу ґрунтується на поєднанні клінічних факторів ризику, біохімічних і біофізичних маркерів, що дозволяє формувати групи високого ризику та своєчасно здійснювати профілактичні заходи. Подальші дослідження мають бути спрямовані на вдосконалення алгоритмів прогнозування, оптимізацію стратегій профілактики, а також на оцінку їхньої довгострокової ефективності й безпеки для матері та дитини.

Ключові слова: *гіпертензивні розлади у вагітних, прееклампсія, гестаційна гіпертензія, вагітність, дисбаланс ангіогенних та антиангіогенних факторів, ендотеліальна дисфункція, біомаркери, допплерометрія маткових артерій, скринінг вагітних, профілактика прееклампсії.*

Hypertensive disorders of pregnancy (HDP) is one of the most common cardiometabolic disorders, affecting up to 10% of women worldwide [1–10]. Following assisted reproductive technology programs, HDP complicate the course of pregnancy in more than 40% of women [11]. These conditions also impose a considerable psychological and physiological stress burden, thereby adversely influencing the overall health of both mother and child [12]. Preeclampsia (PE) and gestational hypertension represent the most frequent clinical forms of HDP, being associated with unfavorable outcomes for both mother and offspring and constituting a leading cause of maternal and neonatal morbidity and mortality [3, 4, 9, 10, 13–16].

It should be noted that women who have undergone HDP have shown an increased risk of developing cardiovascular disease in the long term [17, 18], as well as a higher prevalence of hypertensive disorders during subsequent pregnancies compared to women who did not have this complication [17, 19]. HDP is associated with an increased short-term and long-term risk of developing ischemic and non-ischemic heart failure [20]. Women with this condition have approximately twice the risk of coronary heart disease during the first 12 years after pregnancy. There may be a significant association between the timing of PE onset and long-term cardiovascular outcomes [21].

Currently, PE is classified by its severity and gestational age at diagnosis [22]. However, in recent years, increasing attention has been paid to the molecular subclassification of this pregnancy complication and the identification of subgroups of patients with different molecular patterns [22, 23]. Thus, three molecular subclasses of diseases are associated with different clinical manifestations and include “canonical preeclampsia”, “immunologic preeclampsia” and “maternal preeclampsia” [23–25]. HDP, including PE, is a heterogeneous disease with diverse clinical phenotypes reflecting different pathogenetic mechanisms that ultimately lead to endothelial dysfunction and systemic damage [26]. It is now established that vascular abnormalities are inherent to PE, they begin with placentation and continue to spread well after delivery and are likely the result of some combination of insufficient trophoblast invasion, insufficient oxygen extraction by the placental environment, a pro-inflammatory immune environment, anti-angiogenic factors, endothelial dysfunction and oxidative stress [27]. The current model of this process is characterized by defective and inadequate trophoblast invasion of the maternal decidual membrane and its artery in the early stages of placental development. Incomplete remodeling of the spiral artery leads to improper placental perfusion, placental ischemia in later pregnancy [15, 28–30]. Subsequently, a systemic maternal response occurs, including the release of antiangiogenic factors, causing generalized endothelial dysfunction and systemic inflammation [31, 32].

HDP such as PE share common etiological pathways with preterm labor, including dysregulated inflammation, aberrant placentation, and endothelial dysfunction. PE is also associated with fetal growth restriction (FGR), placental abruption, and stillbirth [33, 34]. PE and eclampsia belong to the “Major Obstetric Syndromes” (MOS), in which multiple pathological processes activate a common pathway, leading to the clinical recognition of these disorders [35]. MOS are obstetric complications that occur in about 15% of pregnancies, cause severe complications during the gestational period, and can lead to fetal and maternal mortality [36]. Further research is currently needed to establish an effective I trimester combined screening test for predicting the development of MOS requiring delivery at < 34 weeks [37]. Classification of obstetric syndromes depending on the presence or absence of placental lesions associated with maternal vascular malperfusion allows the use of biomarkers in early pregnancy [38]. An imbalance between the bioavailability and activity of endothelial-derived relaxing factors and endothelial-derived contractile factors plays a key role in the vascular dysfunction of PE, which is considered a complex multisystem disease of pregnancy and is increasingly recognized as a state of angiogenic imbalance characterized by altered concentrations of placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1) [15, 39]. The imbalance between PlGF and sFlt-1 seems to be one of the main causes of the well-known endothelial cell disease with decreased nitric oxide (NO) synthesis and the well-known imbalance of prostacyclin and thromboxane A2 [40]. Thus, changes in circulating angiogenic factors are associated with the diagnosis of PE and correlate with adverse perinatal outcomes. Results of an observational study among women with singleton pregnancies at risk of adverse outcomes showed a higher sFlt-1/PlGF ratio, which continued to increase until delivery. Women with a high sFlt-1/PlGF ratio delivered earlier than women with a low ratio [41]. Furthermore, these disorders are closely associated with cardiovascular morbidity and mortality in later life [42]. PlGF is an angiogenic protein synthesized in the placenta, and its concentration in the mother’s blood increases with increasing gestational age, reaching a peak at week 30 [43]. It is secreted by trophoblast cells, belongs to the angiogenic vascular endothelial growth factor (VEGF) family, and has both vasculogenic and angiogenic functions [2]. Abnormally low PlGF concentrations precede the onset of clinical PE. Soluble sFlt-1 is a circulating antiangiogenic protein that binds to the receptor-binding domains of PlGF and VEGF. Its concentrations are prematurely elevated in the serum of women with PE [43]. The sFlt-1/PlGF ratio is used to predict and diagnose PE, and maintaining a balance between these circulating factors is of great importance for preventing endothelial dysfunction [42, 44–47].

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Another marker that is widely studied as an antiangiogenic marker of PE is soluble endoglin (sEng). It is high levels of sEng and sFlt-1 that lead to endothelial dysfunction, vasoconstriction, and immune dysregulation [4].

Beyond biochemical markers, imaging techniques such as uterine artery Doppler also play an important role in early prediction of PE. The use of ultrasound as a screening/predictive tool for PE is based on the fact that defective placentation results in incomplete transformation of the spiral arteries. Uterine artery Doppler examination between 11 + 0 and 13 + 6 weeks can be performed transabdominally or transvaginally, and the mean uterine artery PI should be the Doppler index of choice for the I trimester screening [48].

The terms "screening" and "prediction" are often used interchangeably, but screening is actually a broader process. Thus, when the identification of a risk factor can lead to its prevention, "screening" is the preferred term, while "prediction" is the preferred term when there is no evidence that identifying women at risk will ultimately improve their outcome. Prediction, or calculating the risk of a disease, is an integral part of the screening process itself, but it is not equivalent to screening, as the latter also involves an intervention offered to individuals at high risk and aims to alter the natural course of the screened condition and ultimately improve outcome [49]. Regarding PE, the importance of screening and effective prevention is unquestionable, given that PE progresses rapidly, virtually without warning. Blood pressure (BP) alone is not a reliable way to stratify immediate risk for PE, as some pregnant women develop serious target organ dysfunction or uteroplacental dysfunction even with minimally elevated BP [49]. It is also proven that the duration of pregnancy decreased with increasing risk of PE in the I trimester. In the high-risk group, compared with the low-risk group, the risk of spontaneous birth was 4 times higher at gestational age from 24 to 26 weeks, 3 times higher at gestational age from 28 to 32 weeks, and 2 times higher at gestational age from 34 to 39 weeks [50].

Therefore, given that a state of angiogenic imbalance is central to the pathogenesis of PE, this knowledge is increasingly influencing the use of angiogenic biomarkers to improve the prognosis, diagnosis, and treatment of the disease [39]. The Fetal Medicine Foundation (FMF) algorithm takes into account risk factors such as BP, placental biomarkers: pregnancy-associated plasma protein (PAPP) A and PlGF; uterine artery Doppler [51]. Therefore, women should be screened for clinical risk markers of PE at the time of enrollment. A repeat screening is recommended at 11–14 weeks using a combination of clinical risk factors, BP, uterine artery pulsatility index, and PlGF, even if patients already have "high risk" clinical factors [49]. Interpretation of PlGF-based test results may help clinicians improve pregnancy outcomes, as increasing evidence points to a role for sFlt-1/PlGF in predicting adverse pregnancy and perinatal events [39].

In addition, calculating PE risk using online calculators [51, 52] involves taking into account maternal cardiometabolic risk factors that affect early placentation, as well as maternal vascular adaptation to pregnancy (e.g., chronic hypertension, diabetes, obesity, kidney disease, and autoimmune diseases prior to pregnancy) [15, 28, 29].

Management of pregnant women in Ukraine, in accordance with the unified clinical protocol, involves referring patients for examination in accordance with the gestational age and existing risk factors. It is important for women to be explained in an accessible form the essence of the problems associated with the development of HDP [53]. The effectiveness of screening is significantly increased when maternal characteristics are combined with biochemical and biophysical markers. As a result, it is important to identify pregnant women at high risk, ideally using predictive algorithms [54]. New and potential risk factors can be used to quantify the risk of PE. These include family history (age of the pregnant woman 40 years or older, PE in the mother/sister, early onset of cardiovascular disease in the family); ethnic group (African American / South Asian, mixed marriage). According to the history, risk factors are PE in a previous pregnancy, antiphospholipid syndrome, hypertension (diastolic BP ≥ 90 mmHg), kidney disease or proteinuria; diabetes mellitus, low birth weight and/or preterm birth, hereditary thrombophilias, elevated triglycerides, cocaine and methamphetamine use, and previous miscarriage before 10 weeks with the same partner and body mass index (BMI) ≥ 35 kg/m^2. Risk factors during the current pregnancy are multiple pregnancy, bleeding in early pregnancy, first pregnancy, interval between pregnancies of more than 10 years or less than 2 years, systolic BP of 130 mmHg or diastolic BP of 80 mmHg or more, use of assisted reproductive technologies, new partner, short duration of sexual intercourse, gestational trophoblastic disease, excessive weight gain during pregnancy, infections during pregnancy (urinary tract infections, periodontal disease). Biochemical and clinical risk markers in the I trimester are microalbuminuria and abnormal levels of screening markers PAPP, human chorionic gonadotropin (hCG), PlGF < 12 pg/mL). In the II and III trimesters – gestational hypertension, abnormal levels of the II trimester screening markers (alpha-fetoprotein, hCG, InhA, estriol), abnormal uterine artery blood flow velocity, FGR, as well as an increase in the sFlt-1/PlGF ratio > 85 (20 + 0 – 33 + 6 weeks). The clinical significance of the above risk factors for PE is currently being discussed. Practical recommendations, if the patient has one or more of them, have not yet been developed [53].

It should also be noted that no single test or set of tests in the I or II trimester can reliably predict the development of all cases of PE [55].

According to the results of the examination, a pregnant woman in the risk group should be informed that low doses of acetylsalicylic acid from the early stages may be useful for the prevention of PE. According to the standard of medical care, the risk group for the disease includes women who have at least one high-risk factor (type 1 or 2 diabetes mellitus, chronic arterial hypertension, hypertensive disorders during the previous pregnancy(s), chronic kidney disease, autoimmune diseases (systemic lupus erythematosus, antiphospholipid syndrome), multiple pregnancy) or two moderate-risk factors (first pregnancy, age of the pregnant woman 40 years and older, interval between pregnancies more than 10 years, BMI 35 kg/m^2 or more at the first visit to the antenatal clinic, family history of PE) [56].

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Daily low-dose aspirin use during pregnancy is now considered safe and has a low risk of serious maternal or fetal complications, or both, associated with the drug. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine support the criteria for the US Preventive Services Task Force recommendations for the prevention of PE. However, in the absence of high-risk factors for PE, current evidence does not support the use of low-dose aspirin prophylactically to prevent early pregnancy loss, FGR, stillbirth, or preterm birth [48, 57]. Aspirin is a nonselective nonsteroidal anti-inflammatory drug that irreversibly inhibits cyclooxygenase enzymes involved in the conversion of arachidonic acid to prostaglandins and thromboxane. It inhibits the production of thromboxane A2 by platelet aggregation, thereby increasing the prostacyclin/thromboxane A2 ratio and decreasing platelet aggregation [54].

As evidence for the prevention of PE with aspirin accumulates, a recent study examined its efficacy at doses of 150 mg, which is higher than previously recommended. However, there is ongoing debate about the dose of the drug that should be used during pregnancy and when to start therapy. Recommendations for its prophylactic use in pregnant women vary somewhat, for example, depending on the country [54, 58]. Specific doses of aspirin and prevention of PE have been studied in 23 randomized trials (32,370 women). Women randomly assigned to 150 mg of aspirin had a 62% reduction in the risk of PE (0.38). All doses of aspirin had a maximum reduction in the risk of PE at any gestational age of 30% [59].

The strategy of screening and prevention of PE is well accepted by a large number of women of different ethnic backgrounds. It should be noted that low-dose aspirin is considered a safe intervention during pregnancy. However, there are studies that show that the implementation of such a strategy is not associated with a significant reduction in the incidence of PE, but at the prevention stage, low-dose aspirin is effective in reducing its incidence by 41% among women at high risk [37]. In Ukraine, in accordance with the standard of medical care, the recommended dose of acetylsalicylic acid is 100–150 mg per day every evening, starting from 12 to 36 weeks of pregnancy. Its administration requires an increase in the dose of folic acid to 800 mcg (0.8 mg) per day [56]. Oral calcium is recommended as an additional preventive measure for women with insufficient dietary intake [49, 60–64]. A systematic Cochrane review has shown that calcium supplementation before and during pregnancy may reduce the risk of PE in women or pregnancy loss at any stage of gestation [65]. A recent meta-analysis of 26 randomized controlled trials (total number of participants 20,038) showed that calcium supplementation reduced the risk of PE by 49% and the risk of gestational hypertension by 30% compared with placebo. In addition, there was a trend towards a lower incidence of preterm birth, induction of labor, low birth weight, perinatal mortality, and maternal mortality in the calcium-supplemented group [66]. Therefore, in population groups with insufficient dietary calcium intake (less than 600 mg per day), to reduce the risk of PE, pregnant women from 16 weeks and until delivery are recommended to take its preparations daily at a dose of 1.5–2 g in terms of elemental calcium (during meals) [56].

Insufficiency and deficiency of vitamin D in the mother are increasingly recognized as a public health problem and are associated with adverse consequences for the mother and fetus [67–71]. An updated Cochrane review found that vitamin D supplementation compared with placebo for the prevention of PE (8 studies, 2,313 women) demonstrated very uncertain evidence [72]. However, a systematic review and meta-analysis from 2024 to 2025 suggest a potential association between vitamin D intake and a reduced risk of PE in pregnant women. The pooled analysis demonstrated a significant reduction in the risk of PE among those receiving vitamin D supplementation (hazard ratio 0.61; 95% confidence interval (CI) [0.50–0.75], $p < 0.001$), suggesting a potential protective effect. Vitamin D supplementation during pregnancy significantly reduces the risk of both PE and preterm birth, although its effect on neonatal outcomes remains unclear. These findings highlight the potential value of vitamin D supplementation in prenatal care to improve maternal outcomes. Therefore, future research should focus on improving our understanding of the mechanisms linking vitamin D deficiency to PE, and on clarifying the precise conditions and requirements for the effective use of vitamin D supplementation during pregnancy [73, 74]. According to the recommendations of the National Institute for Health and Care Excellence (NICE) for the prevention of hypertensive disorders during pregnancy, NO donors, progesterone (Pr), diuretics and low molecular weight heparin (LMWH), as well as magnesium, folic acid, antioxidants (vitamins C and E), fish oil, etc., are not recommended [17]. However, recent multicenter studies have shown promise in the use of pravastatin and prophylactic drugs such as metformin, LMWH, NO donors, and L-arginine, which may be effective for selected patients with specific risk profiles (morbid obesity, placental thrombosis, etc.) [40]. Therefore, it is systematic review studies that contribute to making better decisions about their results [75]. One such systematic literature review included studies conducted over a long period of time and indicated a current interest in the use of L-arginine in reproductive medicine, both among women and in experimental studies [16]. Taking L-arginine during pregnancy may have a positive effect on fetal growth, maternal BP, and the prevention of PE [76]. As a precursor for the synthesis of NO, polyamines, and other biologically important molecules, arginine plays a key role in pregnancy and fetal development. These mechanisms may be crucial for fertilization, implantation, embryonic development, and placental angiogenesis. In addition, NO is a relaxing factor important for the regulation of placental-fetal blood flow. Experimental studies have shown that arginine deficiency in the placenta of women with PE reduces NO and increases superoxide formation, leading to NO deficiency and excessive peroxynitrite formation [77]. Moderate to high-quality evidence suggests a beneficial effect of prenatal oral L-arginine in women with a history of adverse pregnancy outcomes. Therefore, its use can be at least moderately recommended for women with a history of adverse pregnancy outcomes and high risk of PE, or with PE, gestational or mild chronic hypertension [78]. Results of a systematic review and meta-analysis showed

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that L-arginine supplementation during pregnancy reduces the incidence of PE in women at high risk of it. However, it does not significantly improve maternal and neonatal outcomes [79].

Hormonal effects on angiogenic balance and BP have been demonstrated in the treatment of PE. Administration of Pr drugs has been shown to improve PE-like symptoms in rat models. This raises the possibility that the previously described increase in hormone levels in this disease is compensatory, but probably insufficient [80]. Endogenous Pr is known to support pregnancy and has anti-inflammatory properties that may modulate the inflammatory response associated with pathogenesis PE [34]. One potential trigger for the development of PE is an imbalance between T-helper 1 and T-helper 2 (Th1/Th2), caused by Pr deficiency, an increase in cytolytic natural killer (NK) cells and inflammatory cytokines, which in turn leads to endothelial dysfunction, fetal growth retardation and hypertension. Pr signals the synthesis of Pr-induced blocking factor (PIBF), which has anti-inflammatory effects and may contribute to the regulation of the balance of inflammation during pregnancy. Blockade of this factor causes hypertension, inflammation and signs of endothelial dysfunction [81]. PIBF secreted by maternal lymphocytes provides the immunological effect of Pr during pregnancy, and its reduced levels play an important immunological role in the occurrence of PE [82]. In addition to its anti-inflammatory effects, Pr has a regulatory role in the adaptation of the maternal cardiovascular system during pregnancy. This adaptation of maternal vessels to pregnancy is critical for expanding the capacity of blood flow through the uteroplacental unit to meet the needs of the developing fetus, and the failure of the maternal vascular system to adapt appropriately can lead to pregnancy-related complications such as PE [83]. To date, the results of a systematic review and meta-analysis of randomized controlled trials have established that vaginal Pr when used in the I trimester of pregnancy can prevent PE and hypertensive diseases during pregnancy. It should be noted that when the drug is started in the II or III trimester, it does not have such an effect [84].

LMWH is a class of anticoagulant drugs and is increasingly being used in the modulation of inflammation, anticancer therapy, and obstetric complications [85]. LMWH has been evaluated for the prevention of various placenta-mediated pregnancy complications, including severe PE and recurrent miscarriage. The study demonstrates significant cardiovascular abnormalities in pregnant women at high risk for PE and suggests that LMWH improves maternal vascular function [86]. A systematic review showed that LMWH was associated with a significant reduction in the risk of PE and other placental-mediated complications in women at high risk and when treatment was initiated before 16 weeks of gestation. Combination therapy with low-dose aspirin was associated with a significant reduction in the risk of PE compared with low-dose aspirin alone [87]. A subsequent systematic review and meta-analysis found that in women at high risk of PE without thrombophilia, the combination of LMWH and low-dose aspirin is effective in preventing both PE and preterm birth and FGR [88]. However, there have been publications about conflicting results of clinical trials evaluating LMWH for the prevention of PE [89]. Thus, a randomized controlled trial conducted in 5 top-tier centers in 3 countries showed that the use of enoxaparin in addition to standard therapy does not reduce the risk of recurrence of PE and the birth of babies with low weight for gestational age during subsequent pregnancies [90]. Prophylactic LMWH therapy initiated before 14 weeks of gestation, with aspirin use during pregnancy, is not associated with an improvement in the angiogenic profile, which may be a molecular explanation for the lack of clinical benefit reported in studies [91].

Given that there is no effective treatment for PE other than delivery, therapeutic perspectives on oxidative stress and NO / endothelial NO synthase (eNOS) dysfunction should be considered. For example, multicenter, randomized, double-blind clinical trials based on vitamin C and E supplementation in early pregnancy have not shown significant improvement or reduction in adverse maternal or perinatal outcomes in high-risk women [92, 93]. However, a recent meta-analysis of the use of oral antioxidant therapy in the prevention and/or treatment of PE demonstrated its positive effect on the prevention of PE and FGR. A total of 32 studies were selected for analysis (22 of which focused on the analysis of methods for the prevention of PE and 10 on its treatment) and included 11,198 participants [94].

High-certainty evidence suggests that dietary and/or physical activity interventions have little or no effect on the risk of PE (15 studies, 5,330 women; relative risk (RR) 0.95; 95% CI [0.77–1.16]) [95, 96]. However, moderate-certainty evidence suggests that dietary and/or physical activity interventions probably prevent hypertension during pregnancy (11 studies, 5,162 women; RR 0.70; 95% CI [0.51–0.96]) [95, 96]. In addition, salt restriction during pregnancy is not recommended solely to prevent gestational hypertension or PE. Regarding rest, exercise, and work, women with chronic hypertension or those at risk of HDP should be given the same advice as healthy pregnant women [17].

Given the evidence that treatment can reduce maternal and perinatal morbidity and mortality, as well as the well-established accuracy of BP measurements, the US Preventive Services Task Force found sufficient evidence that screening for PE leads to significant benefits for the mother and child [97].

Therefore, there is currently no doubt that further research is needed to develop a more individualized preventive approach for individual women with individual risk profiles, and especially with regard to the timing of intervention, dose, and long-term safety [40].

CONCLUSIONS

HDP, particularly PE, remain a major cause of maternal and perinatal morbidity and mortality worldwide. Contemporary evidence highlights the multifactorial nature of their pathogenesis, with central roles played by defective placentation, angiogenic imbalance, endothelial dysfunction, oxidative stress, and immunologic dysregulation. Recent advances in molecular subclassification and

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the study of angiogenic biomarkers such as PlGF, sFlt-1, and sEng provide new opportunities for improving diagnosis, prognosis, and risk stratification.

Screening strategies that combine maternal characteristics with biochemical and biophysical markers show the greatest promise, while low-dose aspirin and calcium supplementation remain the most evidence-based preventive interventions. Novel therapeutic approaches, including L-arginine, LMWH, vitamin D, and pravastatin, show potential but require further validation in large randomized controlled trials. Despite these advances, no single test or intervention can yet reliably predict or prevent all cases of PE. Future research should focus on refining individualized risk assessment, optimizing preventive strategies, and clarifying the long-term cardiovascular and metabolic implications for both mother and offspring.

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