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Review article

Preeclampsia subtypes: Clinical aspects regarding pathogenesis, signs, and management with special attention to diuretic administration

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ABSTRACT

During normal pregnancy, blood volume increases by nearly two liters. Distinctively, the absence coupled with the extreme extent regarding the volume expansion, are likely accompanied with pathological conditions. Undoubtedly, preeclampsia, defined as the appearance of hypertension and organ deficiency, such as proteinuria during the second half of pregnancy, is not a homogenous disease. Clinically speaking, two main types of preeclampsia can be distinguished, in which a marked difference between them is vascular condition, and consequently, the blood volume.

The "classic" preeclampsia, as a two-phase disease, described in the first, latent phase, in which, placenta development is diminished. Agents from this malperfused placenta generate a maternal disease, the second phase, in which endothelial damage leads to hypertension and organ damage due to vasoconstriction and thrombotic microangiopathy. In this hypovolemia-associated condition, decreasing platelet count, signs of hemolysis, renal and liver involvement are characteristic findings; proteinuria is marked and increasing. In the terminal phase, visible edema develops due to increasing capillary transparency, augmenting end-organ damages. "Classic" preeclampsia is a severe and quickly progressing condition with placental insufficiency and consequent fetal growth restriction and oligohydramnios. The outcome of this condition often leads to fetal hypoxia, eclampsia or placental abruption. The management is limited to a diligent prolongation of pregnancy to accomplish improved neonatal pulmonary function, careful diminishing high blood pressure, and delivery induction in due time.

The other subtype, associated with relaxed vasculature and high cardiac output, is a maternal disease, in which obesity is an important risk factor since predisposes to enhanced water retention, hypertension, and a weakened endothelial dysfunction. Initially, enhanced water retention leads to lowered extremity edema, which oftentimes progresses to a generalized form and hypertension. In several cases, proteinuria appears most likely due to tissue edema. This condition already fully meets preeclampsia criteria. Laboratory alterations, including proteinuria, are modest and platelet count remains within the normal range. Fetal weight is also normal or frequently over average due to enhanced placental blood supply. It is very likely, further water retention leads to venous congestion, a parenchyma stasis, responsible for ascites, eclampsia, or placental abruption. During the management of this hypervolemia-associated preeclampsia, the administration of diuretic furosemide treatment seemingly offers promise.

Introduction

Secondary to fetal demand, blood volume increases nearly by 2 L, which refers primarily to plasma volume augmentation ("gestational hemodilution") during human pregnancy. The relaxation of resistance arteries and a parallel enhancement of water retention ensure a relative

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steady state of blood pressure throughout pregnancy.

Placental estrogens, relaxin, and progesterone stimulate endothelial nitric oxide (NO) and prostacyclin (PGI_2) production, however, other smooth muscle relaxing agents, e.g. endothelium derived hyperpolarizing factor (EDHF), and possible other gasotransmitters (carbon monoxide and dihydrogen sulfide) also contribute to vascular capacity increment [1–3].

Increasing sodium and water retention is regulated primarily by the appearance of placental renin [4]. Additionally, during early pregnancy, the relative hypovolemia stimulates the release of pituitary antidiuretic hormone (vasopressin) [5]. An important part of gestational cardiovascular adaptation is the heart volume augmentation allowing a rise of stroke volume (SV) from 70 ml to 90 ml, on average. The pulse rate also increases during pregnancy. This complex mechanism results in which cc. 5 L/min non-pregnant value of resting cardiac output (CO) elevates up to 6.4 – 6.8 L/min by the third trimester [6,7].

Central hemodynamic examinations support both the missing of gestational blood volume augmentation and water retention beyond the given vascular capacity can lead to potentially serious consequences during pregnancy [8–10].

Preeclampsia (PE) is defined as the *de novo* development of hypertension (blood pressure $\geq$ 140/90 mm Hg, four hours apart) and any sign(s) of organ deficiency, including proteinuria (daily urinary protein loss $\geq$ 0.3 g), liver function deterioration (high transaminase levels), thrombocytopenia (platelet count $\leq$ 150.000/ml), neurologic symptoms (visual sensations) and/or fetal growth restriction appearing during the second half of pregnancy [11]. This potentially catastrophic complication in pregnancy affects about 3 – 8% of pregnancies, globally. In demonstrating vast geographic differences, PE prevalence is on the increase, most predominantly in the United States [12].

High clinical risk factors regarding PE include the following: autoimmune diseases (e.g. systemic lupus erythematosus and antiphospholipid syndrome), chronic hypertension, renal disease, type 1 and type 2 diabetes mellitus, history of PE, multifetal gestation. While moderate risk factors are as follows: maternal age $\geq$ 35 years, black race, low socioeconomic status, history of adverse pregnancy outcome or fetal growth restriction, more than ten years between pregnancies, nulliparity, and body mass index (BMI) $\geq$ 30 kg/m^2 [13]. However, in a recent survey, obesity was found as the most important predictor for PE, highlighting a distinct change in this field (14).

Hypovolemic, “classic” or placental PE

Fetal growth restriction is a hallmark regarding PE [15,16]. Growth factors are essential for normal placenta development. High levels of antiangiogenic agents, such as soluble fms-like tyrosine kinase 1 (sFlt-1), and soluble endoglin diminish the functions of placenta growth factor (PlGF) and transforming growth factor β during the first phase of placental PE. The essential etiologic role of antiangiogenic agents is shown in which the examination of PlGF/sFlt-1 ratio, especially combined with examination of serine protease corin, serves as a good diagnostic tool in the case of suspected PE (see later) [17]. In consideration of these placental abnormalities, the development of normal wide and low-pressure placenta-supplying vasculature is insufficient. Blood supply, ensured by this placenta, is not enough for normal fetal development. As a result, fetal weight gain will not achieve normal growth, and there is a distinct potential fetal hypoxia will likely develop [18].

Agents from this malperfused placenta, primarily antiangiogenic factors and, among others, several types of cytokines, fetal and placental cell debris, all entering the maternal bloodstream result in generalized endothelial cell lesions, generating two important outcomes. One is the activation of platelets and adhesion to the vascular wall. This phenomenon can lead to a serious consequence at the level of microcirculation. Discrepancies between capillary and erythrocyte diameters (5 – 10 μm and 7 – 8 μm, respectively) slows down deformable erythrocytes towards ensuring ample time for O_2 – CO_2 gas exchange. The swelling in endothelial cells and platelet adhesion can severely narrow capillary diameters. Even normal erythrocytes cannot transpass capillaries with a diameter less than 2.9 μm [19]. Distinctively, erythrocyte aggregability consistently increases by slowing down the blood flow. Additionally, erythrocyte deformability shows a decrease in PE, possibly due to altered plasma to red blood cell interactions [20]. These complex alterations lead to the development of thrombotic microangiopathy (TMA) in this subtype of PE. [21 –23].

Capillary occlusions obviously elevate systemic vascular resistance and decrease tissue blood supply. Some entrapped red blood cells suffer breakage, elevating lactate dehydrogenase enzyme levels, and can be detected as fragmentocytes in a peripheral blood smear. In the final stage, hypoxic capillaries become more transparent and a large extent of the vascular content enters to the extravasal compartment [24,25]. End-organ failures, such as anuria or eclampsia are terminal features of collapsing tissue blood supply (Fig. 1).

The other consequence in reference to endothelium damage is the development of a complex mechanism regarding vasoconstriction, resulting in hypertension. Injured endothelium cells fail to produce vasorelaxant agents (NO, EDHF, PgI_2), however, release a long-lasting, potent vasoconstrictor endothelin-1 (ET-1). Additionally, activated platelets release thromboxane A_2 (TXA_2), another vasoconstrictor. Due to contracted vasculature blood volume is considerably low in this type of PE, confirmed through classic hemodynamic examinations [26,27].

Immunologic studies highlight the etiologic role of imbalance between the maternal immune system and semi-allograft embryo in this “classic”, hypovolemic, or placental PE [28].

In spite of this logical and understandable mechanism regarding clinical aspects of PE, researchers consistently reported challenging findings. In 1990, Easterling and co-workers [29] reported high blood volume in preeclamptic patients. Ten years later, Xiong et al. [30] and, following some years, Scandinavian authors [31,32] reported high fetal birth weight in patients admitted with the diagnosis of PE, which excludes placental insufficiency. Moreover, opposing changes, such as increased and diminished cerebral blood perfusion was reported in preeclamptic patients [33]. These and additional mounting controversial clinical and laboratory findings challenged the homogenous etiology regarding PE.

Heterogeneous origination of PE was discussed by Ness and Roberts as recent as 1996 [34]. In 2003, while examining clinical features and central hemodynamics, two markedly distinguishable groups with hypo- and hypervolemia emerged among preeclamptic patients [35]. In the same time, van Dadelszen et al. [36] suggested to segregate patients with PE as early- or late-onset cases since the outcome of preeclamptic pregnancies is markedly dependent upon gestational age (prior to or at/later than 34 weeks) when cardinal clinical symptoms appear.

In the accumulation of relevant and convincing data allows one to state hypertension and symptoms of organ failures, such as proteinuria, can develop in pregnancy through another means, which is essentially characterized by high blood volume [37 –42].

Hypervolemic, maternal or term PE

This subtype of PE is more common than when compared with the”classic” type [43]. The important hemodynamic feature of this PE, the high blood volume, detected as CO above normal range, is experienced already in its latent phase. [10].

Increased blood volume is in accordance with increased placental perfusion and high fetal birth weight reported in preeclamptic pregnancies [30 –32]. Notably, a positive correlation between maternal CO and fetal birth weight has been demonstrated in both normal and preeclamptic pregnancies [44 –46].

According to many decades’ worth of clinical observations, the first symptom regarding this future PE is low extremity edema, which frequently evolves into a generalized form. In some cases, following

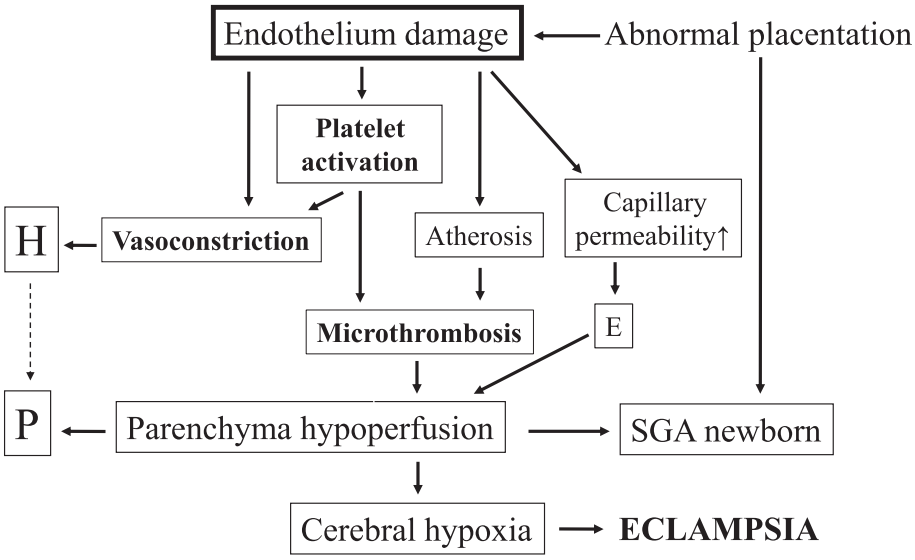

Fig. 1. Main events of hypovolemic preeclampsia development H: hypertonia, P: proteinuria, E: edema, SGA: small for gestational age.

several days or weeks, blood pressure begins to elevate. In the case of hypervolemic edema, hypertension is volume-derived; specifically, the reason for hypertension is primarily also due to the pathologically increased water retention [47].

Obesity (BMI $\geq$ 30 kg/m^2) is associated with increased water retention and is known as a precursor to hypertension, among non-pregnant females. Additionally, several data support the crucial role of obesity in the development of gestational hypertensive conditions. Increased weight gain during pregnancy significantly elevates the frequency of hypertension and shows a positive correlation to edema development [48]. However, it is not only augmented gestational weight gain but high pre-pregnancy weight which also is associated with the development of this type of PE [14,49]. Obesity is associated with elevated profibrinogen, and plasminogen activator inhibitor 1 levels, of which, by increasing blood viscosity, contribute to blood pressure elevation [50]. Angiotensinogen, essential for water retention, is also produced by adipocytes [51]. Moreover, insulin resistance, a distinct characteristic of obesity, will further enhance renal sodium- and water retention [52]. Several changes, associated with obesity and characteristically susceptible to hypervolemic PE are depicted in Fig. 2.

The minor increase of plasma sodium levels in hypertensive individuals is well documented. Na/K-ATPase (Na^+ pump) inhibitors, including digitalis-like cardiotonic steroid marinobufagenin (MBG), have been recognized as one of the classic agents seen in elevating blood

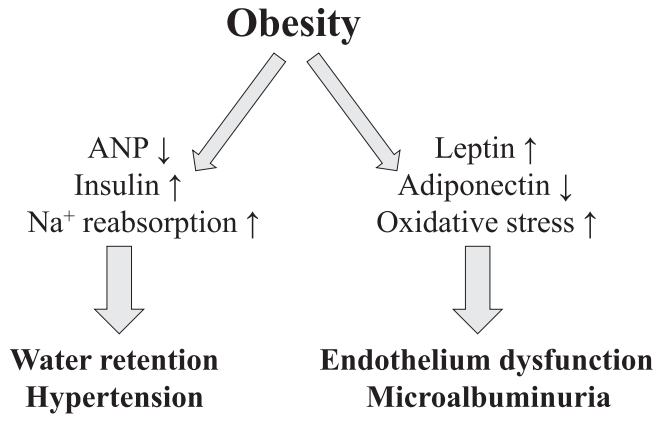

Fig. 2. Obesity-associated alterations predisposing to hypervolemic preeclampsia ANP: atrial natriuretic peptide.

pressure in response to sodium loads [53]. The potent endogen steroid MBG, also produced by the placenta, is included in the pathogenesis in reference to PE [54].

Volume overload per se can deteriorate endothelial function in nonpregnant individuals during hemodialysis [55]. A similar effect is seemingly supported by levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, which depicts incremental increase, not only in early onset, but also in late onset PE, when compared with normal pregnancy levels [56].

By increasing water retention, venous congestion of parenchyma can develop which may cause tissue hypoxia and signs of various organ dysfunctions, ranging from proteinuria to eclampsia [57]. The possible primary characteristics in the development regarding hypervolemic PE are presented in Fig. 3.

Prediction and prophylaxis of PE

Early identification of females who are considered at increased risk regarding PE may experience the opportunity to decrease an adverse perinatal outcome.

In “classic” PE, the placenta and the vessels (endothelium) are the most affected tissues in the latent phase of the disease. Therefore, the usefulness of markers regarding placental function, such as PlGF, sFlt-1, pregnancy-associated plasma protein-A (PAPP-A), and placental protein 13 and characteristics of endothelial function, such as ADMA, ET-1, and vascular cell adhesion molecule 1 for PE prediction all have been intensively studied.

On the other hand, the Doppler velocimetry assessment of flow characteristics regarding uterine artery (UtA) (pulsatility or resistance) has been considered a suitable non-invasive method for evaluating placental perfusion. Examinations for PE screening are standardized for the 11 to 13 + 6-week [58]. Abnormal UtA flow velocimetry reflects the incomplete spiral arteries remodeling and contributing placental insufficiency characteristically aligned to PE [59]. In a retrospective cohort study, measurements regarding UtA flow were performed in more than 30,000 cases. In patients with singular pregnancies, UtA flow examinations during the 9th week showed a 63.2 ~ 73.7% sensitivity and 84.2 ~ 91.3% specificity for early-onset and preterm PE, however, resulted in a lower predictive value for late-onset cases [60].

In clinical practice, recent tests for prediction of PE are primarily confined to the use of sFlt-1/PlGF ratio with a cut-off at 38, of which, in the case of suspected PE, depicts a good negative, yet a modest positive predictive value [61]. Broadening the examined parameters involved in

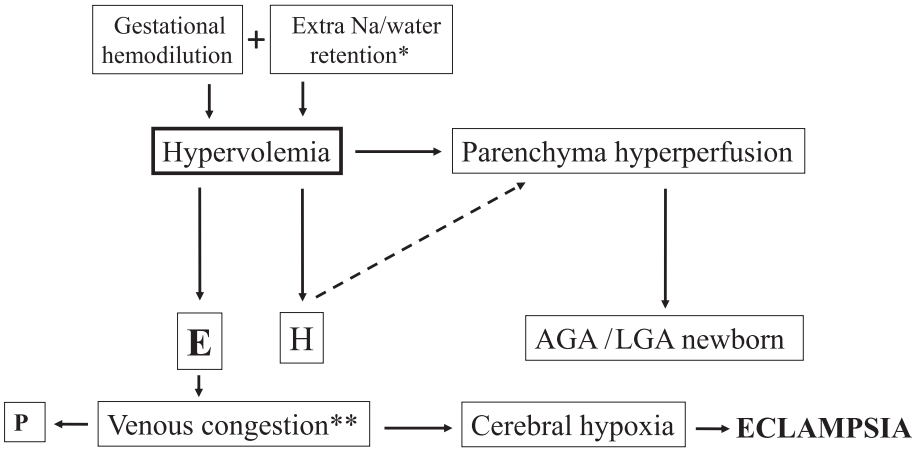

Fig. 3. Main events of hypervolemic preeclampsia development *high risk factor: obesity, **needs further confirmation H: hypertonia, P: proteinuria, E: edema, AGA: appropriate for gestational age, LGA: large for gestational age.

placental or vascular function may improve the efficacy of PE prediction. Serra B. et al. [62] recently developed a first trimester multivariate Gaussian distribution model for screening regarding early onset preeclampsia. Examined parameters included maternal age, BMI, mean arterial pressure, UtA pulsatile index, serum PAPP-A, PlGF and the crown-rump length of the embryo. However, this model resulted in a very good 94% detection rate, a simpler and less expensive method will one day soon be appreciated in daily practice.

Identification of novel potential biomarkers may likely improve PE prediction.

Promising biomarkers include placental messenger RNAs, placental and endothelial micro RNAs and cell-free RNA [63,64]. Evaluation of changes in maternal plasma proteome represents another new method deemed beneficial in predicting early onset PE and helps to distinguish PE phenotypes [65].

It has been widely accepted, in cases of increased probability of PE development, administration of aspirin is suggested to prevent or at least to decrease the severity of the disease. Aspirin inhibits platelet aggregation by altering the balance between the platelet inhibitor PGI_2 and platelet aggregator and vasoconstrictor TXA_2 through an irreversible inhibition of the platelet cyclooxygenase enzyme. Consequently, TXA_2 synthesis declines in platelets. In a *meta*-analysis including nearly 19,000 participants, the administration of aspirin was associated with a reduction in the risk of preterm PE (relative risk, 0.62; 95% confidence interval, 0.45–0.87). The reduction for preterm PE was confined to the subgroup in which aspirin administration was initiated prior to 17 weeks and the aspirin dose was more than100 mg/day. A similar effect for term PE was not detected [66].

In the prediction of hypervolemic, maternal PE, an evaluation of several clinical and laboratory markers (systolic blood pressure, serum/blood urea nitrogen, creatinine, calcium, and potassium levels, platelet- and white blood cell counts and urinary protein loss) determined during early second trimester can offer beneficial information [67].

According to prophylaxis, a salt-restricted diet may decrease the effect of MBG, supporting the antihypertensive therapy [68]. In the case of low calcium intake, Ca supplementation was found to reduce the incidence and serious complications of PE but fails to decrease recurrent PE [69]. Noteworthy, effects of Ca supplementation may be different in different PE subtypes. A mild diuretic, e.g. phytotherapy, in gestational edema among obese patients is a questionable issue.

Management of PE

An effective examination of maternal CO in PE is seemingly the key method for improved management since it allows a principal segregation of hypo- or hypervolemic types, which obviously need different managements [42,70,71].

In the absence of opportunity regarding a hemodynamic examination, clinical signs may help in differentiating PE subgroups. The gestational week, when cardinal symptoms of PE are manifested, accurately differentiating various PE subgroups may prove daunting. As prenatal care appointments are usually organized at 3–4 weeks, PE can be diagnosed as late onset, however, hypertension and proteinuria will have likely have already developed several weeks ago. In contrast, fetal growth restriction, in the absence of congenital fetal anomalies, refers to “classic”, hypovolemic PE [72]. On the other hand, high pre-gestational BMI and high gestational weight gain with generalized edema and normal or high estimated fetal weight are referred to as a hypervolemic type.

Management of “classic”, hypovolemic PE

Since precise pathogenesis and development of the first phase regarding”classic” PE remains obscure, the management, in general, is limited to close observation, including blood pressure, laboratory markers, and fetal well-being, promotion of fetal pulmonary maturation, and delivery induction in preventing the most severest complications.

The prescribed antihypertensive treatment in PE remains a controversial issue. Extremely high, uncontrolled hypertension and serious complications regarding PE, including eclampsia, pulmonary edema or placental detachment are also associated with high blood pressure, requiring urgency (intravenous or sublingual) antihypertensive treatment. In the case of imminent eclampsia, intravenous $MgSO_4$ medication is prescribed, which also effective in lowering levels of blood pressure. However, large scale and sudden drop in blood pressure could be harmful to the fetus.

From an alternative perspective, accepting vascular resistance originates primarily from capillary clogging, increasing blood pressure and for a brief interlude can compensate for increasing vascular resistance. The basic correlation between hemodynamic parameters is expressed by the Poiseuille-Hagen equation. According to its simplified form: perfusion of an organ = pressure difference (in and out)/vascular resistance. Stated more simply: perfusion = pressure/resistance. Moreover, since blood pressure depressor drugs cross through the placenta, fetal blood pressure is also decreased, deteriorating further fetal condition. Maternal and fetal tachycardia, secondary to blood pressure decrease, might rather a compensatory sign than when compared with potential side effects regarding blood pressure depressors. Not surprisingly, a decrease of mean arterial pressure by 10 mm Hg results in a decrease of fetal birth weight by 176 g, on average, according to a metaregression analysis with a high case number [73].

Careful antihypertensive medication is indicated once blood pressure

persists at 160 mm Hg systolic or 110 mm Hg diastolic pressure, or above [13]. In hypovolemic PE, when hypertension is caused due to vasoconstriction, vasodilator agents (e.g. nifedipine) are the most logical choice, however, methyldopa and labetalol show similar affectivity in unselected cases [74]. Additionally, calcium dobesilate (CAD) may have favorable effects on microcirculation by promoting NO synthesis, improving diminished erythrocyte deformability, reducing platelet aggregation, and decreasing vascular permeability [75]. In a double-blind study, CAD had positive effects on factors of microcirculation and significantly decreased blood pressure in gestational hypertension [76]. CAD and other agents, such as pravastatin, metformin, and ezomeprazole, primarily through decreasing sflt-1 production, may favorable influence the outcome of placental PE, however, further studies are necessary for the clinical application [77].

In promoting fetal pulmonary maturation, corticosteroid (betamathasone or dexamethasone) administration is recommended prior to gestational week 34.

In general, following gestational week 34, delivery induction serves a better outcome, however, individual evaluation, including fetal well-being, proves essential in each serious preeclamptic case.

Management of maternal, hypervolemic PE

In hypervolemic PE, organ perfusion is excellent at the beginning of the disease, manifesting in increased placental perfusion and normal/high fetal weight [20–22,41].

Maternal co-morbidities are strongly associated with hypertensive disease in pregnancy [78]. Therefore, effective management of predisposing diseases can result in a favorable effect in emerging PE.

Ones vasculature is relaxed, vasodilator blood pressure depressors fail to improve cardiovascular function. Instead, agents with negative effects on CO, alpha- and beta blocker (labetalol) or centrally acting alpha-methyldopa can be a far better choice if and ones blood pressure decrease manifests.

Diuretics (thiazides or loop diuretics) are frequently applied agents to decrease hypertension, by reducing CO, in non-pregnant patients. Thiazides promote diuresis by inhibiting the N/Cl co-transporter located in the nephron of kidney. Thiazides decline Na reabsorption which increases urinary fluid loss, which in turn decreases extracellular fluid and plasma volume. Possible side effects of the thiazide diuretics include - hyponatraemia, hypomagnesia, nausea, dizziness and headache. Chronic therapy may be associated with hyperuricaemia and gout.

Furosemide is a type of loop diuretics, which functions in decreasing the reabsorption of sodium produced by the kidneys. Furosemide inhibits the luminal Na-K-Cl co-transporter in the loop of Henle by binding to the chloride transport channel. In this regard, increased levels of Na, Cl, and K remain in the urine. Furosemide administration is associated with hypokalaemia, while long-term administration can lead imbalance of other electrolytes, rarely hyperglycaemia, hyperuricaemia, thiamine deficiency and also transient hearing loss.

During pregnancy, diuretics can increase also fetal urination, detected as polyhydramnios.

In consideration of PE with contracted blood volume, a further decrease of CO by diuretics can prove harmful. Therefore, guidelines for managing gestational hypertension or PE, without distinguishing hypo- or hypervolemic cases, do not recommend the use of diuretics. Therefore, studies with diuretics during pregnancy are limited primarily to prophylaxis or the postpartum period of PE.

Collins et al. [79] in 1985 reported nine studies with nearly 7,000 females regarding the continuous administration of thiazid diuretics during pregnancy to prevent PE. This review failed to elicit reliable evidence regarding the beneficial effects of diuretics on PE prevention, since the results of studies showed stunningly diverse results. In another study, twenty-one pregnant women, who showed elevated CO (considered as pre-hypertensive condition) received a daily administration of 20 mg furosemide, initiated between the thirteen and thirty-second weeks. An improvement of hyperdynamic circulation was achieved as SV and CO significantly decreased, but did not lower blood pressure in the control examination three weeks later [80]. In a randomized placebo controlled study, preeclamptic patients received 20 mg of furosemide during the postnatal period. Five days administration promoted patient recovery, decreased blood pressure and, in this regard, antihypertensive demand [81]. Ascarelly et al. [82] randomly administrated 40 mg of furosemide or placebo for five days during postpartum period in two hundred sixty-four patients with severe, mild or superimposed PE. A decrease in blood pressure and less antihypertensive therapy was required during hospitalization and at discharge in severe preeclamptic patients than when compared with the other two groups.

It is noteworthy to state, there were no diuretic-related adverse effects recorded in either of these studies. Similarly, Sibai et al. [83] demonstrated that a reduced plasma volume in patients treated with diuretics was not associated with an adverse pregnancy outcome.

In consideration of hypertension, increased gestational weight gain, remarkable levels of edema, and even proteinuria, which all can be explained by water retention beyond the given vascular capacity in hypervolemic PE, the use of diuretics seems to be fully justified.

The first report referencing administration of diuretics in preeclamptic pregnancies was published in 2017 [84]. The daily administration of 40 mg furosemide resulted in a parallel decrease of CO and both systolic and diastolic blood pressure in fourteen patients with PE experiencing high CO. Results of this simple study need confirmation but suggests the potential benefits regarding furosemide in selected PE cases and underlines the etiological role of excessive water retention in the development of a PE subgroup.

Additionally, non-pharmacological methods can improve the effectiveness in antihypertensive management during pregnancy [85].

According to pregnancy termination, in early late hypervolemic PE (gestational weeks: 34–37), planned delivery is associated with improved maternal yet with less favorable neonatal outcome, compared with expectant management [86].

Currently, the clinical relevance of this novel PE consideration implies the following. Considering CO or clinical features, the separation of PE cases as either placental or maternal type, is indicated. In the case of placental type, a vasodilator is the preferable drug to a careful decrease of blood pressure, if it is deemed beneficial. In maternal PE, diuretic therapy is a worthy consideration following delivery. In an adipose patient afflicted with generalized gestational edema, with or without hypertension, diuretic management is recommended. On the other hand, in following up regarding the issue of new guidelines of PE management is highly suggested.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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