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REVIEW

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HYPERTENSIVE DISORDERS OF PREGNANCY
Theory of Hypoperfusion and Hyperperfusion Types of Preeclampsia

HIPERTENZIVNE BOLESTI TRUDNOĆE
Teorija hipoperfuzionog i hiperperfuzionog oblika preeklampsije

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Review

Key words: gestational hypertension, preeclampsia subtypes, management

Summary. Preeclampsia is one of the most serious complications of pregnancy. Although the etiology of preeclampsia remains obscure, examinations of central hemodynamics and recent epidemiologic data have challenged its homogenous origin. Hypertension could theoretically be secondary to elevated resistance or elevated cardiac output. Accumulating data suggest that both, organ hypoperfusion due to increased resistance of vasculature, the vascular content and also hyperperfusion due to augmented fluid retention may lead to hypertension with proteinuria in pregnancy. »Functio laesa« secondary to hypoperfusion of kidneys manifests in proteinuria in hypoperfusion type but the hypertension itself may also lead to moderate but significant proteinuria during pregnancy. Examination of central hemodynamics seems to be a useful tool for early differentiation of hypo- and hyper-perfusion types for evaluating the outcome, appropriate management and also accurate patients' recruitment for studies.

Pregled

Ključne riječi: hipertenzija trudnoće, podvrste preeklampsije, postupak

Sažetak. Preeklampsija je jedna od najozbiljnijih komplikacija trudnoće. Premda etiologija preeklampsije ostaje nepoznata, istraživanja centralne hemodinamike i svježi epidemiološki podaci su doveli u pitanje jedinstvenost njezina postanka. Hipertenzija teoretski može nastati sekundarno zbog povišenog otpora ili zbog povećanog srčanog minutnog volumena. Podatci upućuju da oboje, hipoperfuzija organa zbog povećanog krvožilnog otpora i volumena te isto tako hiperperfuzija zbog povećanog zadržavanja tekućine, mogu u trudnoći uzrokovati hipertenziju s proteinurijom. »Functio laesa« zbog hipoperfuzije bubrega očituje se kao proteinurija u hipoperfuzijskom tipu, a i sama hipertenzija može proizvesti umjerenu do značajnu proteinuriju trudnoće. Istraživanje centralne hemodinamike čini se da je koristan način za rano razlikovanje hipo- i hiper-perfuzijskog tipa da bi se prosudio ishod, odgovarajuće liječenje te pacijentice prikladne u izboru istraživanja.

Introduction

Elevated blood pressure, chronic or pregnancy-induced, complicates 6–30% of all pregnancies. The most important hypertensive gestational condition is the preeclampsia-eclampsia syndrome. Although the etiology of PE remains obscure, studies with central hemodynamics and also epidemiologic data have challenged its homogenous pathogenesis. Different pathways leading to hypertension with proteinuria during the second half of pregnancy not only may disturb the results of scientific studies but may alter our management strategies as well.

The goal of this review is to support the theory of different origination of classic symptoms of PE.

Chronic hypertension in pregnancy

Chronic hypertension is obvious if hypertension was known before conception and can be presumed if increased blood pressure is detected prior to the 20th week of gestation. Similarly, existance of elevated blood pressure over 12 weeks postpartum refers to chronic manifestation. Most patients in such cases have essential hypertension but some have underlying renal, endocrine, or vascular disease. Perinatal mortality in pregnancies with chronic uncomplicated hypertension is similar to that in normotensive pregnancies; however, the incidence of intrauterine growth restriction (IUGR) is higher. Therefore, medical supervision throughout whole gestation is essential. The use of antihypertensives in uncomplicated cases is a controversial issue. It is widely accepted that control of uncomplicated mild essential hypertension has little, if any, long-term benefit.[1] One of the main controversies concerns the effect of reduction of blood pressure on placental blood flow. In addition, control of blood pressure seems to fail to prevent the subsequent development of superimposed preeclampsia, which develops in about 20 percent of chronically hypertensive pregnant women. However, diastolic blood pressure above 100 mm Hg requires hospitalization and antihypertensive therapy should be considered. In general, if the medication used prior to pregnancy is considered safe it should be continued; if not, α-methyldopa could be the first choice. Serial examination of proteinuria, platelet count, liver and renal function, and

also fetal well-being are the usual examinations during prenatal care in such cases, regardless of known underlying disease.

Pregnancy-induced hypertension

The term of pregnancy-induced hypertension includes cases of *gestational hypertension* (GH, solely hypertension), *preeclampsia*: (PE, gestational hypertension with significant proteinuria), and *eclampsia*. The clinical symptoms appear during the second half of pregnancy, seldom in childbed period.

Although the outcome of *GH* with appropriate prenatal care is not worse than it is in normotensive pregnancies and blood pressure control is rarely required, it mandates close attention since nearly half of these cases develops PE. *PE* complicates 2% to 7% of all pregnancies. In many countries PE is one of the leading causes of maternal mortality and leads to about a five-fold increase in perinatal mortality.

Nowadays preeclamptic cases are distinguished as early- or late-onset types. This separation is not well-defined. In general, serious condition and outcome is characteristic in early-onset but not in late-onset cases. Denominations of early- or late-onset suggest that these subgroups are distinct only in gestational age when PE symptoms appear. However, epidemiologic studies have recently revealed that incidence of both, small-for-gestational-age (SGA) and large-for-gestational-age (LGA) newborns were elevated in cases when PE had been diagnosed.[2–4] Statistical confirmation of this old clinical notice markedly supports the theory of distinct origination of gestational hypertensive conditions because large fetus is obviously more than the absence of IUGR.

Different pathogenesis of PE is an attractive hypothesis. This is not only in accordance with wide clinical experiences, but could also explain the controversies of results of different former studies in PE, especially in central hemodynamics. Increased systemic vascular resistance (SVR) with contracted blood volume is a classical hallmark of PE.[5–7] End-organ dysfunction, placental insufficiency with oligohydramnios, IUGR (resulting SGA newborn), and fetal hypoxemia represent the characteristic outcome of this *hypoperfusion* condition.[8] On the contrary, other examiners found high cardiac output (CO) with low SVR in pre-eclamptic patients and determined PE as a hyperdynamic state.[9,10] The correlation between maternal CO and fetal birth weight in PE is well documented,[11, 12] so infants in such *hyperperfusion* cases reasonably tend to be LGA. Similar controversy has been found in brain blood flow, as both hypoperfusion and hyperperfusion may occur in PE.[13]

Occurrence of low CO with SGA newborn and also high CO with LGA newborns suggest a different pathogenesis of hypoperfusion and hyperperfusion/hyperdynamic models; however, both of them are fit for the traditional criteria for PE.

Hypoperfusion model of preeclampsia

Accumulating data suggest that the failure of maternal immune tolerance may account for hypoperfusion PE.[14] This type can be considered as a two-stage disease. Abnormal placentation (first stage) through endothelial damage is responsible for the potential of end-organ manifestations (second stage). The first stage is characterized by effects of anti-angiogenic substances such as the soluble *endoglin (sEng),*[15] *fms-like tyrosine kinas-1 (sFlt-1),*[16] and *human interferon-inducible protein 10* (*IP-10* or *CXC10*)[17] which bind and neutralize different growth factors [*vascular endothelial growth factor (VEGF)*, *placental growth factor(PlGF)*, and *transforming growth factor*-β *(TGF*-β)] required for placental and fetal angiogenesis. Agents directly from this shallowly implanted placenta and also from activated leukocytes or platelets may represent the link between abnormal placentation and endothelial inflammatory injury. Recent candidates are the anti-angiogenic agents; *free oxygen radicals* and some cytokines, first of all *tumor necrosis factor*-α,[18, 19, 20] thrombogenic content of *microparticles* released from the surface of different cells;[21] *syncytiotrophoblast microvilli;*[22] *fetal cells* and cell-free *fetal DNA*[23] circulating in a relatively huge amount in preeclamptic maternal bloodstream. Consequently, markers of endothelial injury e. g. *fibronectin,*[24] soluble *thrombomodulin,*[25] or *von Willebrand factor* [26] show elevated levels in PE.

Changes of vascular function, hemodynamics, hemorheology, and hemostasis with platelet activation, secondary basically to endothelial dysfunction and being in a close relation to each other, lead to end-organ dysfunctions in hypoperfusion PE (*Fig. 1*).

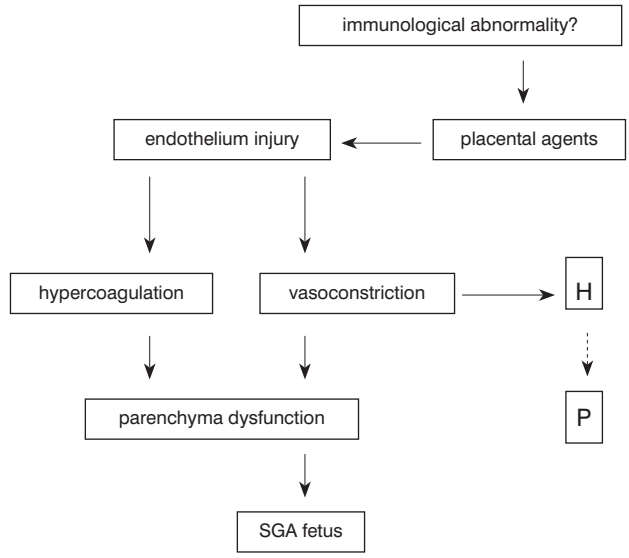

Figure 1. Development of hypertension (H), proteinuria (P), and small for gestational age (SGA) newborn in hypoperfusion model of preeclampsia.

Slika 1. Razvoj hipertenzije (H), proteinurije (P) i nedostaščeta (SGA) u hipoperfuzijskom modelu preeklampsije.

Vascular alterations

In the first and second trimester of normal pregnancy trophoblast cells invade the supporting spiral arteries. Incorporating to the vessel wall, trophoblast cells destroy the endothelial and muscular layers. These vessels become wider in diameter and unable to contract. In hypoperfusion PE this remodeling is inadequate: approximately one third to one half of spiral arteries escape from endovascular trophoblast invasion and adrenergic nerve supply of muscular layer also remains intact.[27] Inappropriate remodeling, which can also be seen in intrauterine growth retardation syndrome, could be the consequence of initial maternal rejection of trophoblast.

Beyond this special abnormality of placental vessels, patients with hypoperfusion PE suffer from general endothelial injury. Endothelial cells exhibit adjacent foam cell invasion and many vessels (e.g. placenta, glomeruli) are occluded by fibrinoid material.[28] Damaged endothelial cells produce less vasodepressive substances, e.g. *nitric oxide* (*NO*), *prostacyclin* (*PGI_2*), *endothelium-derived hyperpolarizing factor* (*EGHF*) than normal endothelium, but excrete vasoconstrictors, e.g. *entothelin-1* (*ET-1*) contributing to hypertension. In addition, vascular smooth muscle cells exhibit increased sensitivity to all vasopressors.

Hemodynamics

Generalized smooth muscle relaxation due to high endothelial production of vasodepressors is a characteristic feature of normal pregnancy. Increasing capacity of the vasculature triggers plasma volume augmentation;[29] CO increases and hematocrit falls subsequently. In hypoperfusion PE, the insufficient excretion of relaxing agents and also a high production of vasoconstrictors plasma volume and CO may even decrease while SVR and blood pressure increase. Placental/fetal blood supply, and subsequently fetal somatic development seem to be related to circulating blood volume too; neonatal birth weight shows a positive correlation to maternal CO in both normal and hypertensive pregnancies.[11,12,30]

Hemorheology

Blood perfusion of an organ can be expressed by the (simplified form) of Poisseuille-Hagen equation: *Perfusion or CO = Pressure(difference) / Resistance*. Resistance is determined by vascular diameters, and rheological properties of the blood.

In large vessels, blood viscosity depends basically on hematocrit. Because of the insufficient hemodilution in PE, hematocrit is relatively high. Blood and plasma hyperviscosity are early findings and contribute to reduced tissue (e.g. intervillous) blood flow; plasma viscosity correlates inversely with neonatal birth weight.[31]

Deformability of erythrocytes allows the cells to pass capillaries having smaller diameters than erythrocytes (3–4 μm vs. 7–8 μm). Furthermore, this phenomenon decreases whole blood viscosity because erythrocytes elongate in flow due to shear stress. Erythrocyte deformability has been found to be decreased in PE which may contribute to the decreased capillary circulation.[32,33] In slowing flow erythrocytes tend to aggregate and also to break in blocked capillaries (microthrombosis and mechanical peripheral hemolysis).

In collapsing microcirculation hypertension could be beneficial for maintaining organ (e.g. placental) perfusion.[34]

Hypercoagulation and platelet activation

It is well known for some decades that platelets and also intravascular coagulation cascade are activated in PE. Damaged endothelial cells produce more adhesive substances (e.g. *fibronectin*, *vascular cell adhesion molecule-1*, *E-selectin*) and possess less antithrombotic capacity (e.g. weak *thrombomodulin* effects) than normal endothelial cells.[24, 25, 35] Activated platelets not only release the vasoconstrictor *thromboxane A_2* (TXA_2), but also increase the expression of adhesive agents.[36] Platelets this way enhance the endothelium–leukocyte contact and trigger leukocyte arrest and transendothelial migration.[37] Damaged erythrocytes show an enhanced aggregability as well.[33] In the most severe cases generalized microthrombosis develops finally. Therefore, altered hemostasis may contribute to the collapse of microcirculation and subsequent multiorgan hypoperfusion and dysfunction.

In this compound process platelets play a pivotal role. Platelets are activated in different actions and conditions such as immune answer, blood coagulation, or defense against infection. The most potent platelet-activating agents are collagen, ADP, TXA_2, and thrombin. Appearance of fetal cells (or debris) in maternal circulation initiates immune responses in which platelets are important signaling cells and also influence leukocyte functions.[37,38] Further platelet activation is caused by the impairment of endothelium as it exposes the subendothelial collagen to vessel content. ADP escapes from damaged erythrocytes and TXA_2 is released from activated platelets. Thrombin concentration is also increased in PE.

The relationship between PE and infection was posed by the PE model based on low-dose endotoxin infusion in pregnant rats.[39] Since then several studies found correlation between PE and different forms of infection.[40] The link between PE and different inflammations may be the further enhance of platelet activation, since platelets are involved in anti-infection reactions too by producing bactericide agents (*thrombocidin I* and *II*), and also by the internalization of bacteria and viruses.[37]

Hyperperfusion model of pre-eclampsia

Pathophysiology of hyperperfusion model of PE was outlined first on the basic findings of high CO and low SVR in preeclamptic patients.[9,10] According to Poisseuille-Hagen equation hypertension can be a result of

not only elevated vascular resistance but also high CO. It has been proposed that hyperdynamic condition is associated with extreme vasodilatation, elevated CO, and increased capillary leak. The leakage accounts for the characteristic visible and pulmonary or cerebral edema. Vasodilatation of the glomerular afferent arteriole, which exposes capillaries to increased flow and systemic pressure, could mediate the development of hypertension and proteinuria. This theory is supported by renal artery blood flow velocimetry examinations. Renal autoregulation is altered in PE, leaving glomeruli unprotected from increased blood pressure.[41] In accordance, the hypertension and the proteinuria correlate with a severity of glomerular lesion. In general, relaxed terminal arterioles and capillary beds could be damaged by hypertensive overflow exposure: mesangial and subendothelial deposits with focal segmental hyalinosis and sclerosis are usual findings in hypertension.[42] These alterations might also be related to hyperperfusion lesion in pregnancy *(Fig. 2)*.

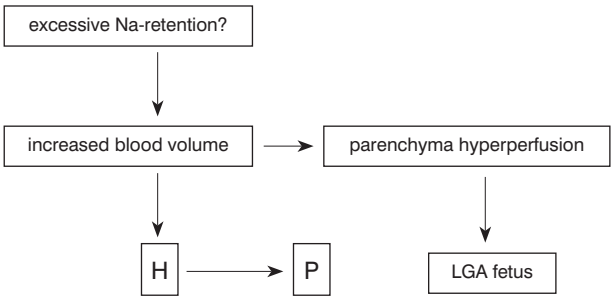

Figure 2. Possible development of hypertension (H), proteinuria (P), and large for gestational age (LGA) newborn in hyperperfusion model of preeclampsia.

Slika 2. Mogući razvoj hipertenzije (H), proteinurije (P) i velikog djeteta u hiperperfuzijskom modelu preeklampsije.

In this hyperperfusion model of PE placental blood perfusion is increased and newborns' weights tend to be LGA. In accordance, it has been demonstrated that birth weight progressively increases with increasing blood pressure until the hypertensive range is reached; this effect is probably mediated by increased uteroplacental blood perfusion.[43]

Vasodilatation is considered as the trigger for blood volume augmentation in pregnancy.[29] The disturbance of this mechanism, e.g. a higher production of vasodepressor substances or increased sodium retention[44] might explain the overflow of the vasculature and subsequent hypertension, edema, and endothelial lesion in hyperperfusion PE. It is not elucidated whether increased transparency is the only symptom of endothelial dysfunction in hyperperfusion PE. However, *fibronectin* levels of maternal serum, a marker of endothelial injury, exhibit a negative correlation to neonatal birth weights.[45]

Patients in this group are characteristically obese, necessarily edematous, and possess an increased gestational weight gain.[46] Obesity is known to be associated with gestational hypertension or preeclampsia;[47] gestational edema is associated with higher fetal weight.[48] Proteinuria is seldom serious and may even improve with blood pressure control. Hematocrit level and blood viscosity increase with gaining extravasal fluid accumulation.

Management principles in different types of preeclampsia

Management strategies will obviously differ for hypo- or hyperperfusion PE, therefore, an early differentiation is mandatory. Examination of maternal central hemodynamics seems to be a useful tool because high stroke volume (SV) or CO excludes hypoperfusion background; in general, a CO of 8 l/min or more excludes hypoperfusion model.[46] For hemodynamic examination echocardiography and bioimpedance cardiography are non-invasive methods; the invasive examination by thermodilution with Swan-Ganz catheter is justified rather in serious but stable cases when immature fetal lung requires pregnancy prolongation.

It seems that poor outcome is more common in *hypoperfusion* type PE. Delivery is indicated after 34 weeks' gestation in severe PE and also earlier if serious complication (e.g. imminent eclampsia, severe fetal growth restriction, non-reassuring fetal tests, or HELLP syndrome) develops. Hypoperfusion PE can be predicted in the midtrimester by determination of the ratio of PlGF / sEng or sFLt-1/ PlGF ratios.[49,50]

For the expectant management in moderate hypoperfusion PE, deliberate intravenous volume expansion with vasodilators (e.g. hydralazine, nifedipine) may be beneficial.[51] However, antihypertensives fail to improve the outcome.[52] Calcium dobesilate augments basal and reactive NO production of the endothelium, improves blood rheology, and decreases the blood pressure this way.[53] Antihypertensive treatment (α-methyldopa, nifedipin, labetalol) is indicated in severe PE when systolic blood pressure is at least 160 mmHg or diastolic value is at least 110 mmHg. Use of magnesium sulfate is associated with eclampsia preventing effect too in contrast to any other anticonvulsive or antihypertensive agent.[54] Corticosteroid administration for accelerating fetal lung maturation should always be considered before 34 weeks' gestation.[55]

Patients with *hyperperfusion* PE require rather hypertension control with an agent that has no vasodilator activity (e.g. cardio-selective β-blockers).[9] In the absence of hemoconcentration, use of diuretics seems to be justified. Serious complication is rare;[45] however placental abruption is frequently associated with preeclamptic edema.

Eclampsia. Cerebral perfusion.

Eclampsia appears approximately in 5 percent of preeclamptic pregnancies. Maternal and perinatal mortality

ranges from 0.5% to 14% and from 10% to 28%, respectively. Eclampsia is considered as brain dysfunction secondary to hypoxia which is the part of generalized organ dysfunction in serious PE. Examination of cerebral blood flow in pre-eclamptic women may give information about events during eclampsia.

Results of blood velocity examinations in middle cerebral (also retinal and ophthalmic) arteries by transcranial Doppler ultrasonography in preeclamptic patients are also controversial. Cerebral vasoconstriction with increased perfusion pressure is a common finding.[55,56] In this hypoperfusion condition the brain underperfusion may account for eclampsia. Microthrombosis was already found in women died due to eclampsia more than a century ago.[57] In addition, postmortem examinations suggest also the involvement of coagulation and rheological factors in the development of eclampsia.

Alternatively, a significant number of women with severe PE have cerebral overperfusion. In this group the uncontrolled perfusion pressure may cause vascular damage leading to hypertensive encephalopathy and overperfusion injury.[13, 58]

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