Hypertension in pregnancy: classification, diagnosis and treatment.

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ABSTRACT: Hypertension in Pregnancy (HTNP) is defined as systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg in at least two different measurements during pregnancy. According to guidelines, HTNP is classified into four or more individual categories. These categories include chronic hypertension, gestational hypertension, pre-existing hypertension plus superimposed gestational hypertension with proteinuria, antenatally unclassified hypertension and preeclampsia. Although the exact causes and pathogenetic mechanisms of HTNP are not fully elucidated, the severity of the possible complications, including eclampsia and HELLP syndrome, require the maximum alertness. Physicians should consider HTNP as a crucial maternal, fetal and neonatal morbidity and mortality factor. Early detection and treatment are of major importance and should be provided in every case. In the present review the potential pathogenetic mechanisms, categories and therapeutic interventions for HTNP are discussed, according to up-to-date data.

Key Words: Hypertension, Pregnancy, Preeclampsia, HELLP syndrome.

INTRODUCTION

Hypertension in pregnancy (HTNP) represents a leading cause of maternal, fetal and neonatal morbidity and mortality worldwide. HTNP is defined as systolic blood pressure (SBP) ≥ 140mmHg or diastolic blood pressure (DBP) ≥ 90mmHg in at least two different measurements during pregnancy[1]. Hypertensive disorders in pregnancy are quite frequent. According to epidemiological studies, the prevalence of hypertension in pregnant women in Western Europe reaches a percentage of 15%[2], whereas in the USA HTNP appears in 5-7% of stated births[3]. A significant proportion of pregnant women also present heart disorders and pulmonary hypertension. As HTNP may also be combined with other disorders, such as diabetes mellitus, the contribution of more medical specialties -not only the obstetrician- is needed, in order to achieve a better and safer supervision of pregnant women.

Early diagnosis and treatment to minimize the risk of severe complications, such as eclampsia and HELLP syndrome (Haemolysis, Elevated Liver enzymes levels and Low Platelets), is of fundamental significance. Postnatal care and monitoring of mothers and neonates are also important. In cases of births characterized by a small increase in BP (less than 30 mmHg in SBP and 15mmHg in DBP), strict supervision by a specialized internist is recommended, although the risk of complications is not significant[4].

Predisposing factors for HTNP

HTNP is a multifactorial disorder. Despite insufficient knowledge related to the exact genetic and environmental mechanisms involved in its pathogenesis, many risk factors have been implicated (Table 1).

Regarding environmental factors, increased body weight and smoking are included. Increased Body Mass Index (BMI) is tightly related to the occurrence of mild hypertension and/or preeclampsia but not with severe forms of these disorders[5]. On the other hand and in contrast to previous knowledge, smoking seems

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Table 1. Risk factors for the appearance of HTNP.

Mother's age (< 16 or >35 years)
First gestation
Hereditary predisposition
Preeclampsia/eclampsia at an earlier gestation
Pre-existing-chronic hypertension
Diabetes mellitus, increased insulin intolerance
High body mass index
Increased coagulability
Renal disorders
Autoimmune diseases
Low socioeconomic level

to reduce the risk of preeclampsia through reduced expression of specific angiogenic factors, such as sFLt1 (soluble FMS-like tyrosine kinase-1) and PIGF (placental growth factor)[6]. Moreover, epidemiological studies correlate HTNP with socioeconomic data, as its prevalence is significantly higher in women with lower socioeconomic level. The absence of normal midpregnancy decrease in DBP has also been reported in these women[7].

As far as genetic and biochemical factors are concerned, low levels of renin, angiotensin II and aldosterone, along with abnormal renin - aldosterone ratio have been observed in a percentage of pregnant women with preeclampsia[8]. Polymorphisms of the synthetase of endothelial NO gene (eNOS gene)[9] and interleukin-6 gene (IL-6) have also been implicated in HTNP pathogenesis[10]. It seems that such polymorphisms in conjunction with disorders in plasma levels of antioxidant factors, such as glutathione (GSH), lead to increased oxidative stress during pregnancy and subsequent alterations in the uteroplacental flow[11].

Effects of physiological adaptation of maternal organism during pregnancy

During pregnancy, mother's organism enters a dynamic phase of interaction with many factors, leading to systemic changes. These changes are physiological and strictly controlled by autonomous hormone cycles. Due to augmented needs for oxygenation and subsequent alterations in the cardiovascular system, an increased blood flow in the uteroplacental circulation is attained in order to achieve adequate nutrition to the fetus[12,13,14,15].

As a result of the above adaptations, an increase in plasma volume occurs after the 5th week of pregnancy, reaching its peak during the 33rd week. Moreover, a 40% rise in ejection fraction is observed during that period, accompanied by a midpregnancy SBP fall. During the last trimester of pregnancy, the turgid uterus compresses inferior vena cava, therefore causing hypotensive symptoms, especially when changing body position from sitting to standing (inferior vena cava syndrome)[16].

Furthermore, vaginal delivery is associated with important changes in maternal circulation parameters. In particular, pain at birth causes a raise of about 50% in heart rate and in cardiac output (CO), along with an increase of > 20% in BP. Especially when the embryo exits the mother's uterus, SBP may reach the level of 200 mmHg through Valsalva mechanism. At the early postnatal period, venous decongestion, blood flow from the uterus to systemic circulation and redistribution of organism's water, lead to enhanced stroke volume (SV) and CO with subsequent decrease in heart rate[16]. Finally, cardiopulmonary function returns to its pre-pregnancy levels at the 12th postnatal week.

Table 2. Classification of HTNP.

1. Chronic (pre-existing) hypertension (>140/90) that either predates pregnancy or develops before 20 weeks of gestation
2. Gestational hypertension (without proteinuria)
3. Pre-existing hypertension plus superimposed gestational hypertension with proteinuria
4. Antenatally unclassified hypertension

Classification of HTNP

According to the recent guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC), [1] there are four categories of HTNP, summarized at Table 2.

Chronic (pre-existing) hypertension

Chronic hypertension is defined as BP ≥ 140/90mmHg that either predates pregnancy or develops before 20 weeks of gestation[1]. About 95% of pregnant women with chronic hypertension never develop any complications throughout pregnancy. However, in elder pregnant women (especially in those with coexisting disease predisposing to preeclampsia), a higher risk of complications is expected[4]. Chronic hypertension usually persists more than 42 days post partum[1].

Gestational hypertension

Gestational hypertension develops after 20 weeks of gestation and, in most cases, it resolves within 42 days post partum. This pregnancy-induced form of hypertension is not associated with proteinuria[1]. The development of gestational hypertension is physiological and characterized by low risk for complications. Therefore, there is no absolute indication for medical treatment in every pregnant woman with an increase in BP. However, placental disorders may co-exist with gestational hypertension, thus an extensive supervision is required in such cases, as about half of women in this category finally develop preeclampsia (PE)[16].

Pre-existing hypertension plus superimposed gestational hypertension with proteinuria

Pre-existing hypertension is associated with further worsening of BP after 20 weeks of gestation, followed by proteinuria (≥ 3g/24h)[1].

Antenatally unclassified hypertension

It is defined as hypertension with or without systemic disorders, developed after the 20th week of pregnancy, with no prior BP measurements known[1]. Under these circumstances, reassessment is necessary at or after 42 days post partum: if hypertension is resolved, it is characterized as gestational hypertension. If it is not resolved, then it is classified as pre-existing hypertension[1].

The American College of Obstetricians and Gynecologists (ACOG) also includes PE and PE with pre-existing chronic hypertension in the classification of HTNP[17].

Preeclampsia (PE)

PE is characterized by the development of hypertension and proteinuria after the 20th week of gestation[18]. The typical definition of PE includes proteinuria > 0,3g/24h accompanied with hypertension. However, in some cases, there may be no proteinuria.

According to Walker "Preeclampsia is the result of an initial placental trigger, which has no adverse effect on the mother and a maternal systemic reaction that produces the clinical signs and symptoms of the disorder"[19]. Many factors are implicated in the development of PE, both preconceptional and pregnancy-associated (Table 3)[20]. Abnormal placental implantation due to defects in trophoblasts (deficient trophoblastic migration and incvasion) and spiral arterioles (retention of musculoelastic media) seems to play an important role in the pathogenesis of PE, as cytotrophoblastic centers in that region are not normally developed, leading to uteroplacental hypoperfusion[16,20].

Regarding the influence of environmental factors in the pathogenesis of PE, high BMI combined with low vascular resistance is associated with late PE epi-

Table 3. Risk factors for preeclampsia (PE).

Preconceptional or chronic risk factors	Exogenous factors
Partner-related risk factors	Smoking (decreases risk)
Nulliparity, primipaternity	Stress, work-related psychosocial strain
Limited sperm exposure, teenage pregnancy, donor insemination	Inadequate diet
Partner who fathered a preeclamptic pregnancy in another woman	
Either parent the product of a pregnancy complicated by PE	
Maternal-specific risk factors	**Pregnancy-associated risk factors**
History of previous PE	Multiple pregnancy
Increasing maternal age	Urinary tract infection
Longer interval between pregnancies	Structural congenital anomalies
Family history	Hydrops fetalis
Black or Hispanic race	Chromosomal anomalies (trisomy 13, triploidy)
Patient requiring oocyte donation	Hydatidiform moles
Physical inability	
Presence of specific underlying disorders	
Chronic hypertension and renal disease	
Obesity, insulin resistance, low maternal birth weight	
Gestational diabetes, type 1 diabetes mellitus	
Activated protein C resistance (factor V Leiden), protein S deficiency	
Antiphospholipid antibodies	
Hyperhomocysteinemia	

(Kaplan N, Victor R. Hypertension with pregnancy and the pill. In Kaplan N, Victor R, eds. Kaplan's Clinical Hypertension. Philadelphia: Lippincott Williams and Wilkins, 2010: 410-29).

sodes, whereas women with low BMI usually menifest early episodes of PE[21].

It has been suggested that, following the defective placental perfusion, circulating factors, probably originated in the placenta, such as sFLt1[22] and soluble endoglin[23], are responsible for the clinical manifestations of PE, reflecting widespread endothelial dysfunction, vasoconstriction and end-organ ischemia[20]. Therefore, the pathogenesis of PE is divided into two stages: first, placental abnormalities and second, maternal systematic reaction.

The systemic features of PE can vary from mild cases with little systemic involvement, to multiorgan failure[19]. Activation of intravascular coagulation and subsequent fibrin deposition maybe responsible for much of the eventual organ damage seen in severe PE, including proteinuria and decreased GFR from the kidneys, seizures and coma from CNS, abnor-

mal liver function and local pain from the liver and consumptive coagulopathy from the blood[20]. PE may appear as a simple headache, sometimes with optical disorders due to cortical blindness, which vary from low vision to acute loss of vision. In severe cases, while PE progress to eclampsia, neurologic features of hypertensive encephalopathy and in particular seizures are also added to the above symptoms, due to both vasospasm and cerebral oedema that reflects an increase in cerebral blood flow with a failure of autoregulation[20]. Cardiopulmonary system may also participate with symptoms such as dyspnoea and angina. Upper abdominal pain is not rare, while an increase in hepatic enzymes and creatinine and/or decrease in platelet count are reported.

The severity of PE depends on different factors, such as the severity of hypertension, the early development of gestational hypertension and the presence of oliguria, proteinuria ≥ 5g/24h, thrombocytopenia (< 100000x 10^9/L), hepatic disorders, haemolysis, hyperuricemia and neurological disorders[17].

PE represents an independent risk factor for gestational hypertension, which appears as a complication of preeclampsia in about 2%-8% of pregnancies. PE develops during gestation and is characterized by mild symptoms, usually resolving within 24-48 hours after delivery. Rarely, a PE episode may persist until the 10th day post-partum. In 25% of cases, PE is associated with a low neonatal weight (< 1500g)[24,25].

Guidelines for the diagnosis of PE

In order to prevent unwanted outcomes, every pregnancy should be considered as a potentially dangerous one for the appearance of PE and appropriate laboratory tests should be performed. Important risk factors include proteinuria exceeding 0,3g/24h, thrombocytopenia and high levels of hepatic enzymes, creatinine, plasma proteins, lactate dehydrogenase (LDH) and uric acid[25,26]. Moreover, inversion of BP's circadian rhythm after a 24h ambulatory BP monitoring is an indication of severe PE. In general, women with the following features should be more closely evaluated and monitored[20]: first pregnancy, previous PE, ≥10 years since last baby, BMI ≥ 35, family history of PE, patient had low birth weight, DBP ≥ 80mmHg, proteinuria (≥ + on more than one occasion and ≥ 0,3g/24h), multiple pregnancy, underlying medical condition (preexisting hypertension, diabetes, renal disease, presence of antihypertensive phospholipid antibodies).

Uterine Doppler ultrasonography may reveal uteroplacental exudation. This finding in combination with the development and plasticity of the endometrium, is of great importance for the early diagnosis of PE in patients with HTNP[27]. In cases with suspected abnormal uteroplacental blood flow, pretreatment with aspirin (at a dose of 100mg/day) is recommended, independently of the final appearance or absence of PE. This therapeutic strategy seems to improve blood flow even though the exact time of initiation of antiplatelet treatment, the appropriate dosage and the specific patient groups that would benefit more are yet to be determined[28].

HELLP syndrome

HELLP syndrome is a metabolic disorder characterized by hemolysis (abnormal blood smear, LDH > 600 U/L, elevated indirect bilirubin), elevated hepatic enzymes (transaminases > 70 U/L) and thrombocytopenia (platelets < 150.000)[29]. The syndrome occurs in approximately 10% of patients with PE and is associated with significant morbidity and mortality for both mother and fetus[30]. Common presenting complaints are right upper quadrant or epigastric pain, nausea and vomiting[29]. Many patients have a history of malaise or non-specific symptoms suggesting an acute viral syndrome[30]. The syndrome shares many features with the haemolytic uremic syndrome and thrombotic thrombocytopenic purpura[20]. The presence of HELLP syndrome in pregnancy should be investigated and handled with caution, as it is frequently associated with serious complications both maternal (acute renal failure, hemorrhage) and neonatal (acute respiratory failure, hypoxic damage due to placental abruption, low birth weight, sudden neonatal death), along with disorders during delivery[16,29-31]. Corticosteroids may be used[32], however delivery is indicated if the syndrome occurs after the 34th gestational week or the fetal and/or maternal conditions deteriorate[20]. Subsequent pregnancies in patients with HELLP syndrome carry a high risk of complications such as PE, recurrent HELLP, prematurity, intrauterine growth retardation and perinatal mortality[29].

Treatment of HTNP

Ensuring a safe pregnancy and delivery should be the first priority for the attending physician. The condition of both mother and fetus must be monitored for the prevention of a premature birth, including measurement of BP, upper abdominal ultrasound and biochemical tests for the mother and uterine doppler ultrasonography and CTG (CardioTocoGraphy) for the fetus[33]. Postnatal care of the mother is also of significant importance, especially when a future pregnancy is intended[16].

Treatment strategy of HTNP is not yet globally determined and is mainly based on the experience of the attendant doctor. According to recent ESH/ESC guidelines and their latest reappraisal[34], non-pharmacological management (including close supervision and restriction of activities) should be considered for pregnant women with SBP = 140-149 mmHg or DBP = 90-95 mmHg. In the presence of gestational hypertension (with or without proteinuria) drug therapy is indicated at BP ≥ 140/90 mmHg, but in the case of preexisting hypertension without organ damage, threshold for drug therapy may be 150/95 mmHg. Levels of SBP ≥ 160-170 mmHg or DBP ≥ 110 mmHg should be considered an emergency requiring hospitalisation. In cases of mild hypertension, drug therapy could be more harmful than beneficial[26,35-37]. Moreover, a rapid decrease in BP during pregnancy may impair uteroplacental perfusion and thereby put at risk fetal development, even leading to intrauterine death. Serious complications may also appear in women with diabetes mellitus type 1 or 2. Therefore, these cases should be treated with great caution[38,39].

The comparative benefit of different treatment strategies in women with chronic hypertension without other aggravating factors and in women with PE is not well studied. Non-pharmacological measures, such as low salt diet, limitation of activities and bed rest in the left lateral position, although advised, have not been proven effective enough in the treatment of hypertension during pregnancy[40].

Drug therapy

No consensus on treatment strategy (drugs, initiation and duration of therapy) for severe hypertension during pregnancy is available. In clinical practice, widely accepted limits for initiation of treatment are SBP ≥ 150 mmHg and DBP > 95 mmHg. This threshold should be lower (140/90 mmHg) in women with known hypertension or coexistent hypoclinical organic damage[1]. An increase of SBP ≥ 170 or DBP ≥ 110 mmHg represents an urgent situation and requires hospital treatment for the pregnant woman[1]. According to several researchers, target of therapy is SBP < 125mmHg and DBP = 90-100 mmHg[33,41].

Drug treatment depends on the severity of hypertension and the urgency of the situation. In cases of non-severe hypertension, peros administration of a-methyldopa is the first choice. In several studies, a-methyldopa has been proven safe for the fetus and neonate. However, in 15% of the mothers taking a-methyldopa side effects such as mouth dryness, drowsiness and depression, may appear[36,42,43].

Selective b-blockers (atenolol, metoprolol, labetalol) and calcium ion channels antagonists (nifedipine sustained release, nitrendipine) are second-line drugs. Concerns for the teratogenicity of these drugs are not confirmed by the latest studies[44]. However, when prescribing atenolol, the doctor should be cautious because this drug seems to be related to intrauterine growth retardation, especially when it is used during the first and second trimester of the pregnancy[33,45]. Overall, b-blockers should be used exclusively during the third trimester in order to reduce the possibility of fetal growth disorders, except for those cases where BP is not controlled by the use of other antihypertensive agents, such as a-methyldopa or hydralazine[17].

Hydralazine is administered either peros, in cases of chronic hypertension, or parenterally, in cases of acute hypertensive crisis[46]. As hydralazine may cause side effects like headache, palpitations and dizziness, especially when administered as monotherapy, the co-administration of a-methyldopa or b-blockers is recommended[47]. In a meta-analysis of clinical studies, fetal side effects of hydralazine, such as placental abruption, heart rate disorders and low APGAR score have been reported. However, these data are not efficient enough to exclude the use of hydralazine in clinical practice[48]. On the contrary, a recent Canadian study showed that hydralazine along with labetalol are the most commonly used, parenterally administrated, antihypertensive drugs for the management of severe HTNP[49].

Intravenous infusion of sodium nitroprusside is useful in hypertensive crises, but prolonged administration should be avoided (fetal cyanide poisoning). Intravenous reduction of BP in these cases should not be greater than 25% of the initial value during the first hours, gradually reaching the level of 160/100 mmHg[50].

Magnesium sulphate remains the drug of choice for the treatment of preeclampsia and prevention of eclamptic convulsions[51]. Furthermore, it exerts neuroprotective properties to the fetus[52], although fetal toxic effects have been also reported when the drug is given in high doses[53]. Alternative antihypertensive agents may provide additional benefit in the management of hypertension in preeclamptic patients. For example, in PE with pulmonary oedema, nitroglycerine is preferred. Diuretics are contraindicated because plasma volume is reduced in PE. Only furosemide may be used, under strict control of water-electrolyte balance[1].

ACE inhibitors and angiotensin II antagonists are strictly prohibited as they have been associated with serious fetal side effects, such as abortion, intrauterine growth restriction and death, and neonatal renal failure[1,54,55]. No current clinical trials regarding the use of renin receptor blockers like aliskiren are available.

During the peripartum period, the appropriate drug therapy should be decided according to drug's concentration in breast milk. A-methyldopa, metoprolol, labetalol and ACE inhibitors are completely safe, although the latter may impair renal function of the newborn[33,56,57].

Administration of possibly dangerous agents (ACE inhibitors, angiotensin II antagonists, atenolol) should be discontinued before conception in women treated for hypertension. If high BP levels persist, safer antihypertensive agents, such as a-methyldopa and labetalol, should be used[17].

CONCLUSION

HTNP represents an important factor of maternal, fetal and neonatal morbidity and mortality worldwide. The exact environmental and genetic factors contributing to the pathogenesis of the different forms of HTNP are not fully elucidated. Early diagnosis and treatment is of invaluable importance and may prevent serious obstetrical complications. Proper collaboration between the obstetrician-gynaecologist, the internist and other specialists will help towards this direction.

Uterine doppler ultrasonography is particularly useful for the monitoring of the intrauterine growth disorders. Drug treatment must be individualized, according to both the available guidelines and the distinctiveness of each case. Generally, drug therapy is recommended in cases of severe hypertension, with a-methyldopa being the drug of choice. In women presenting with severe symptoms, especially in the case of life-threatening eclampsia or HELLP syndrome, caesarean delivery is recommended, independently of fetal viability. Finally, intensive postnatal monitoring of the mother is of significant importance.

Υπερτασική νόσος στην κύηση: ταξινόμηση, διάγνωση και αντιμετώπιση.

Νίκη Κατσίκη, Δημήτριος Γοδόσης, Σπυρίδων Κωμαΐτης, Απόστολος Χατζητόλιος

Τμήμα Αγγειακών Παθήσεων και Υπέρτασης, Α΄ Προπαιδευτική Παθολογική Κλινική, Νοσοκομείο ΑΧΕΠΑ, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης

ΠΕΡΙΛΗΨΗ: Η υπερτασική νόσος της κύησης (ΥΝΚ) ορίζεται ως η παρουσία συστολικής αρτηριακής πίεσης ≥ 140mmHg ή διαστολικής ≥ 90mmHg σε δύο τουλάχιστον διαφορετικές μετρήσεις κατά της διάρκεια της εγκυμοσύνης. Έχουν καθιερωθεί διάφορες μορφές ΥΝΚ, ανάλογα με τις εκάστοτε κατευθυντήριες οδηγίες. Στις κατηγορίες αυτές περιλαμβάνονται η χρόνια (προϋπάρχουσα) υπέρταση, η υπέρταση της κύησης, η χρόνια υπέρταση με συνοδό υπέρταση κύησης, η μη ταξινομούμενη υπέρταση και η προεκλαμψία. Παρά το γεγονός ότι τα ακριβή αίτια και οι παθογενετικοί μηχανισμοί της ΥΝΚ παραμένουν σε μεγάλο βαθμό αδιευκρίνιστα, η βαρύτητα των επιπλοκών, στις οποίες περιλαμβάνονται η εκλαμψία και το σύνδρομο HELLP, απαιτούν τη μέγιστη επαγρύπνηση. Ο κλινικός ιατρός οφείλει να αντιμετωπίζει την ΥΝΚ σαν έναν βασικό παράγοντα νοσηρότητας και θνησιμότητας τόσο για την εγκυμονούσα, όσο και για το έμβρυο και το νεογνό. Η έγκαιρη διάγνωση και θεραπευτική παρέμβαση είναι πρωταρχικής σημασίας και πρέπει να εφαρμόζονται σε κάθε περίπτωση. Στην παρούσα ανασκόπηση περιγράφονται οι πιθανοί παθογενετικοί μηχανισμοί που εμπλέκονται στην εμφάνιση της ΥΚΝ, οι διάφορες μορφές της και οι σύγχρονες διαθέσιμες θεραπευτικές επιλογές.

Λέξεις Κλειδιά: Υπέρταση, Κύηση, Προεκλαμψία, Σύνδρομο HELLP.

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