Hypertension in pregnancy

Cristian Poalelungi *, Iuliana Ceausu

Dr. I. Cantacuzino Clinical Hospital, Bucharest, Romania
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Abstract

Hypertension disorders of pregnancy complicate up to 6% to 10% of pregnancies and remain among the three leading causes of maternal and fetal mortality. The related complications are divided into immediate and long-term, the latter are still to be defined. There is yet no etiologic treatment knowing that our understanding of physiopathology remains elusive. In this way hypertension disorders of pregnancy require close monitoring including on the long-term, a new concept developed in recent years after it has been showed that these disorders increase especially the cardio-vascular risk.

Keywords: hypertension, pregnancy, preeclampsia, eclampsia

Introduction

Hypertension disorders of pregnancy (HDP) is a worldwide encountered health problem and, by its potential complications, increases maternal and fetal morbidity and mortality. There is a deadly triad which includes HDP, hemorrhage and sepsis - that represent the leading causes of maternal mortality, worth mentioning the fact that the last two causes are preventable.

The prevention and etiologic treatment of HDP still remain elusive. It complicates between 6% to 10% of pregnancies, the maternal mortality is estimated around 12.0/100.000 in women with HDP compared with that of 2.8/100.000 in women with normal blood pressure [1]. The 2013 guidelines of ACOG (American College of Obstetrics and Gynecology) on hypertension in pregnancy makes the difference between pregnancy-related hypertension (PHTN) and chronic hypertension (HTN). Pregnancy-related hypertension represents a spectrum of disorders that includes gestational hypertension (GH), preeclampsia (PE) with or without end organ damage and eclampsia. Among these disorders, GH affects 6%-7% of pregnancies, but it is potentially harmful by evolving into PE or chronic hypertension after delivery. PE affects between 4% to 10% of pregnancies and represents the leading cause of maternal and fetal mortality and morbidity. Risk factors are a pre-existing hypertension, especially for PE, gestational diabetes, obesity, first or multiple pregnancies, maternal age (women younger than 20, older than 35) especially correlated with the risk of developing

* Correspondence to: Cristian POALELUNGI, MD
Dr. I. Cantacuzino Clinical Hospital - Ob-Gyn
5-7 Ion Movila Street Bucharest, Romania.
e-mail: cristianpoalelungi@yahoo.com

eclampsia. Thrombophilia, a rather rare disorder, when present, complicates a third of pregnancies either with PE or in 10% of the cases small-for-gestation age infants [2]. With considerable higher risk of developing PHTN are women of African-American and Hispanic descent, medium risk in European descent population and lowest in Chinese women [3].

The aim of this article is to provide insight into the definition, classification, physiopathology, complications and treatment of the spectrum of hypertension in pregnancy.

Definition and Classification of Hypertension in Pregnancy

Hypertension in pregnancy was defined as systolic blood pressure (SBP) ≥ 140mmHg and/or diastolic blood pressure (DBP) ≥ 90mmHg.

According to Guideline Development Group, the levels of BP were defined as it follows:
- mild, if SBP between 140-149mmHg and/or DBP 90-99mmHg,
- moderate if SBP is 150-159mmHg and/or DBP 100-109mmHg and
- severe if SBP is superior or equal to 160mmHg and DBP than 110mmHg.

As already mention PHTN represents various entities:
1) Gestational hypertension - hypertension developed after 20 weeks of pregnancy, without significant proteinuria, with no prior history of high BP, usually the values of BP normalize during the 42 days following postpartum [4];
2) Preeclampsia/eclampsia – hypertension associated to an abnormal value of proteinuria after the 20th week of gestation or immediately postpartum (measurement on two occasions), the severe form of preeclampsia represents a severe high blood pressure and an end-organ dysfunction:
- oliguria inferior to 500ml/24h, creatinine superior to 135µmol/L (or 1.1mg/dl), proteinuria superior to 3g/24h, protein/creatinine ration ≥ 0.3 (mg/mg), on dipstick ≥+1, to be used whenever quantitative measurement is unavailable or
- platelet count < 100.000/microL

- liver transaminase at least twice the upper limit of the normal concentration for the local laboratory, severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
- HELLP syndrome (intravascular hemolysis, elevated livers enzymes, low platelet count)
- pulmonary edema
- cerebral or visual symptoms - e.g.: new onset and persistent headaches, not responding to usual doses of analgesics (however response to analgesics does not exclude the possibility of preeclampsia), blurred vision, scintillating scotoma
- convulsions (eclampsia) [5].

Preeclampsia can affect between 1%-5% of pregnancies, usually the risk increases in women with history of chronic HPB, gestational HBP, preeclampsia, multiple pregnancies, insulin dependent diabetes. Eclampsia expresses in the form of generalized tonicoclonic seizures, usually after preeclampsia appears, but it can also develop as a first symptom. The incidence is between 1.5-3 cases/100.000 [1].

3) Chronic hypertension defined as hypertension of any etiology preceding the pregnancy or developing before the 20th week of pregnancy and still present even after 12 weeks after delivery. Its frequency lies between 1%-5% and it can worsen during pregnancy in 7% to 20% of women. Women with chronic hypertension are at risk of developing preeclampsia (17% to 25% compared to 3% the risk in the general population) [1].
4) Chronic hypertension with superimposed preeclampsia – hypertension before the 20th week of gestation accompanied by new-onset proteinuria or any other symptoms listed as end-organ associated to preeclampsia. Generally, this phenomenon develops earlier during pregnancy, it is more severe and associated to significant fetal morbidity (growth restriction).

Diagnostic methods

The recommendation is to determine the blood pressure in sitting position after a 5-minute effortless pe-

riod. If a mild or moderate hypertension is detected during the medical consultation, the possibility of 'white coat hypertension' should be eliminated. This can be detected with two methods – ambulatory pressure monitoring during the day or for 24h if the pregnant patient can tolerate the device during the night, or by auto measuring techniques – morning and evening measurement 3 times at 1-minute interval for 3 days. Regarding the detection of proteinuria, its detection should be made regardless of the blood pressure values, monthly by using de dipstick. In case of a positive result (+1) confirmation is needed by corroborating with 24h urine protein measurement.

Mechanisms of pregnancy-induced hypertension

As the main disorders related to pregnancy-induced hypertension remit after delivery, abnormalities related to placental development have been implicated. In normal pregnancies adaptive mechanism occur at cardiovascular and renal level in order to meet the fetal and maternal needs. Normally the cardiac output and circulatory volume increase between 40%-50% and in response the peripheral resistance and blood pressure decrease especially in the second and third trimesters. The glomerular filtration rate adapts in response to increase renal plasma flow by 30%-40%. Although the renin, aldosterone and angiotensin II activity increases, the vascular response to angiotensin II is reduced [6]. In pathological situation like pregnancy-induced hypertension all this adaptive mechanism fail.

The most extensive physiopathology studies have been made in the case of preeclampsia. As mentioned above, the placenta is at the central core of the disorder. Under normal conditions normal placental development require de recruitment of spiral uterine vessels (SUAs) and their transformation in large caliber ones in an early trophoblast independent phase and later in a dependent one, the overall process ends by the beginning of the second trimester. In preeclampsia all these mechanisms fail. In the first phase of SUA remodeling, placental decidualization occurs and vascular linings rearrange with the vacuolization of the endothelium and thinning of the media in the presence of matrix metalloproteinase and inflammatory cytokines secreted by the recruited leukocytes. At the cellular level a dif-

ferent range of leukocytes with the preponderance of regulatory natural killer cells that collaborate with CD4+ T lymphocytes in order to tolerate the fetal antigens and to preserve pregnancy. In preeclampsia the balance favors T 17 lymphocytes at the expense of the regulatory ones. Furthermore, de regulatory natural killer cells enhance the migration of the trophoblast cells by secreting IL-8 and interferon gamma-induce protein 10 that induce chemotaxis. During the second phase, the one dependent on trophoblast invasion, the placental cells, low in oxygen levels (pO2 around 20mmHg) migrate towards the decidua where the pressure reaches 70mmHg [7]. This phenomenon promotes the upregulation of hypoxia-inducible factor-1 α, which induces trophoblast proliferation but in the same time protects against oxidative stress. In preeclampsia there is insufficient remodeling of the SUAs and at cellular level there is an overexpression of adhesion molecules (E-cadherin) that promotes the clumping of the trophoblast cells. All these pathological changes finally lead to a hypoxic placenta that in response releases antiangiogenic molecules such as soluble endoglin, endothelium-derived vasoconstrictor (ET-1) and sFlt-1, which in animal models lead to glomerular proliferation and proteinuria [7]. Moreover, in preeclampsia pregnancies there is an overproduction of thromboxane (TXA2) promoted by lipid peroxidation and COX cascade activation at the expense of vasodilator prostacyclin (PGI2). In women with preeclampsia it has been shown that decreased methylation of TBXAS1 gene promoter leads to increased TXA2 production. It partially explains the benefic role of aspirin treatment, as it blocks COX pathway of TXA2 production [7].

Genetic predisposition has been studied especially in family aggregation of preeclampsia. There is a susceptibility related to activing-receptor type-2 gene in Nordic an Australian population and STOX1 gene in Dutch cohort.

From a pathological approach there are several systems that are impaired especially in the case of preeclampsia, that reflect the end-organ damage. Regarding the cardiovascular system, the myocardium suffers a remodeling the consequence of sustained diastolic dysfunction that in time can lead to left ventricular hypertrophy. Furthermore, the possible development of pulmonary edema is related to a hyperkinetic left ventricle with high left pressure fillings thus volume expansion is to be made carefully. On the other hand, eclampsia

leads to sustained vasoconstriction as the endothelial dysfunction ensues and leakage into interstitial space occurs. The renal system is also implicated, from a pathological point of view there is a reduction in glomerular filtration rate and renal perfusion due to the development of glomerular endotheliosis in response to vasoconstriction. The circulatory system involves platelet dysfunction due to surface alteration, hemolysis due to endothelial disruption and coagulation changes with an increase in the factors consumption, especially VIIth, decrease antithrombin III activity promoting increased intravascular coagulation. Liver dysfunction, the mark of a severe disease, is marked by hemorrhagic foci and even hemorrhagic infarction that can transform itself into a hematoma which can lead to capsular tearing. Cerebral pathological changes are a combination of vasospasm in response to a more acute development of hypertension that develops cytotoxic edema but in the same at the capillary level the disruption leads to liquid extravation through mal-functioning cellular tight junctions and eventually to vasogenic edema [8]

Complications of pregnancy induced-hypertension

The potential complications of pregnancy induced-hypertension especially in the case of preeclampsia are divided into immediate and long term.

The immediate complications of preeclampsia represent in fact the spectrum of the severe form disease correlated with end-organ dysfunction. The most potentially harmful complications are eclampsia and the neurological disturbances and HELLP syndrome. Eclampsia occurs in the form of a grand mal seizure after the 20th week of pregnancy of 48h after delivery which can lead to status epilepticus and brain injury. It affects 1 in 400 preeclamptic women without severe criteria and 1 in 50 when there are signs of end organ damage. Grand mal seizure before the 20th week of gestation should raise the question of a molar pregnancy or other causes unrelated to pregnancy. Pathologically and radiologically the clinical manifestations are related to brain vasogenic edema which can take even the form of posterior reversible encephalopathy syndrome. Stroke associated to preeclampsia/eclampsia is incriminated in up to 36% of the cases of pregnancy related strokes [9]. The most common is the hemorrhagic stroke in the context of severe elevated blood pressure and is preceded by resistant headache. Other manifestations are various visual disturbances relates to the vasospasm in retinal vessels, some symptoms are benign and resolute – scotomata, blurred vision, others like retinal detachment, ischemia or optic nerve ischemic neuropathy can lead to permanent disability. Pulmonary edema is another fearful complication the result of cardiac dysfunction and increase vascular permeability, that can increase maternal mortality. Renal dysfunction related to preeclampsia can lead to acute kidney injury, the first cause in pregnancy, especially when associated with HELLP syndrome. The latter is one of the most serious complications related to preeclampsia and significantly increase the maternal mortality and morbidity. Itself can lead to disseminated intravascular coagulation, acute kidney and liver injury, pulmonary edema and abruption placentae.

The long term maternal risk includes cardiovascular disease in the form of coronary artery disease due to atherosclerosis, especially in patients with recurrent episodes and end-organ damage [10]. There is also the risk of developing peripartum cardiomyopathy as well as at distance after delivery, apparently for more than 5 years [11]. The mechanisms leading to the development of this complications at distance are probably related to endothelial dysfunction, proinflammatory activity and lipid peroxidation that are potentially active even after delivery. End-stage renal disease in women with preeclampsia was considered to be another fearful complication but apparently the absolute risk is small, in a 2008 study less than 1% with 20 years [12]. In a 2009 study the risk of developing subclinical hypothyroidism during pregnancy and years after was twice in nulliparous women with preeclampsia and there is a bidirectional influence as abnormal level of thyroid hormones seem to lead to endothelial damage the core pathological feature of preeclampsia [13]. The risk of developing diabetes is increased 16 to 18 fold in patients with history of gestational diabetes and preeclampsia, while the risk diminishes when there is only gestational diabetes associated [14].

Treatment

Treatment decision is made considering the benefits and risks both for the mother and the fetus. The

most important factor in this decision is the level of blood pressure. All types of blood pressure above 160mmHg systolic and/or 110mmHg diastolic should benefit from immediate anti-hypertensive treatment. In case of mild or moderate high blood pressure (SBP between 140-159 mmHg and/or DBP 90-109mmHg) treatment decision is made taking into account other risk factors such as cardio-vascular ones, history of cardio-vascular diseases, gestational diabetes, chronic renal diseases.

Treatment options of first intention are: methyl-dopa a central acting anti-hypertensive (inhibitor of sympathetic nervous system output at the brainstem level) used especially in pregnancy as its safety has been thoroughly documented. On the other hand, it has a slow onset of action (three to six hours) and in high doses can cause drowsiness. Labetalol in the class of the beta-blockers is extensively used as it is safe in pregnancy, the reports on fetal growth restriction and preterm birth have not been reproduced [15]. It has alpha and beta activity and it preserves the best the placental blood flow. Its use is preferred to methyldopa as it has a faster onset. Atenolol should be avoided as it has been associated to a fetal hypotrophy, pindolol and metoprolol are alternative choices to labetalol. Calcium channel blockers – nicardipine and nifedipine (sustained release tablet) are safe in pregnancy. The immediate release form of nifedipine although thought to be safe has a risk of rapid fall of blood pressure and consequently the diminution of utero-placental blood flow. Hydralazine, a vascular smooth muscle relaxant is the back-up choice in case of rapid decrease indication of blood pressure, although labetalol is preferred even in this case as its response remains more predictable. Nitroprusside in this case is advised against and is the be used at last resort at it can lead to cyanide poisoning. The drugs to be avoided in pregnancy are angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and direct renin inhibitors as they lead to fetal abnormalities, especially renal with possible oligoamnios. Thiazide diuretics can be continued in women with chronic hypertension already on this treatment, but their use is not recommended as there is the risk of volume depletion and possibly salt imbalance. Spironolactone is not safe as was proven to have anti-androgenic effects.

In the case of preeclampsia, the only curative therapy is delivery as it reduces the risk of serious complications both in mother and the fetus. If there a mild form and there is evidence of fetal growth restriction, and gestation less than 37 weeks' expectant management with betamethasone administration and close monitoring is preferred. Corticoid therapy reduces the fetal morbidity and mortality and the protocol includes the administration of 12 mg im twice, 24h. Otherwise if the gestation is superior to 37 weeks, delivery is the choice. At any time if the blood pressure is uncontrolled with signs of eclampsia, pulmonary edema, disseminated intravascular coagulation or abruption placentae occur, delivery should not be postponed. In women with HELLP syndrome, with gestation age 32-34 weeks, if both maternal and fetal vitals are stable, a 24-48 term for the administration of corticoid is acceptable before delivery. Magnesium sulphate is recommended in primary prevention when neurologic signs persist both during pregnancy and in post-partum as it reduces by 58% the risk of developing eclampsia assures both maternal and fetal neuroprotection. It is administrated under strict motoring conditions, vital signs, degree of conscience and apparition of diminished osteotendinous reflexes. Apart this if there is need to rapidly lower blood pressure labetalol 10 mg intravenously followed by 20 mg at 10 minutes' interval with progressive increase if needed up to 22mg per cycle or hydralazine 5 mg intravenously followed by 5 to 10 mg at 15 minutes' interval. Fluid therapy is to be made with caution as there is the risk of precipitating a pulmonary edema. Blood loss should be also monitored closely, and transfusion realized even if the loss is otherwise considered tolerant.

Route delivery is dictated by maternal and fetal status, gestation and presentation. Vaginal route is preferred initially, but whenever it fails, cesarean section should be performed.

Aspirin is recommended in patients with history of preeclampsia, the treatment should be started before 20-week gestation until 34 weeks. Its administration is not recommended in women with risk factors such as chronic HTA, obesity or diabetes [1]. It is now clear that low doses of aspirin are effective in secondary prevention of preeclampsia in high-risk patients, mainly those with a history of preeclampsia. Aspirin inhibits thromboxane A2 production by

platelets and so increases the prostacyclin/TXA2 ratio and reduces platelet aggregation. It also decreases production of the tissue factor thrombin. Indications for aspirin in primary prevention are a matter of debate, but recent publications suggest a strategy based on first-trimester screening of preeclampsia (with clinical parameters, biomarkers and uterine Doppler measurements) and aspirin administration to high-risk patients. Aspirin should be administered once a day in the evening at low doses ranging from 75 to 150 mg. There is good evidence showing that the efficacy of aspirin grows as the dose increases. However, aspirin crosses the placental barrier and inhibits fetal platelet aggregation [16].

Breastfeeding is not contraindicated, even in women with preeclampsia. Lactation is possible even in patients treated with labetalol, metoprolol but the fetus should be monitored for signs of beta blockade. Diuretics should be avoided, ACE inhibitors as enalapril can be used as second choices. Methyldopa is excreted in human milk but not in significant doses. Concerning the contraception in the first 6 months estroprogestative are not recommended as they can increase the risk of venous and arterial events.

Conclusion

Hypertension in pregnancy is among the most common health problems and causes significant mortality and morbidity. Although described long time ago, its pathological mechanisms are yet to be completely discovered thus the difficulty in its management. The take home message is to identify and monitor closely the pregnancies at risk and to continue this process even after delivery as complications can develop event at distance.

References

1. Claire Mounier-Vehier, Jacques Amar, Jean-Marc Boivin, Thierry Denolle, Jean Pierre Fauvel et al. Hypertension and pregnancy. Expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology. Presse Med. 2016 Jul-Aug;45 (7-8 Pt 1):682-99. doi: 10.1016/j.lpm.2016.05.012. Epub 2016 Jul 9
2. Clark EA, Silver RM, Branch DW. Do antiphospholipid antibodies cause preeclampsia and HELLP syndrome? Curr Rheumatol Rep. 2007 Jun;9(3):219-25.
3. David A. Savitz, Valery A. Danilack, Stephanie M. Engel, Beth Elston, and Heather S. Lipkind. Descriptive Epidemiology of Chronic Hypertension, Gestational Hypertension, and Preeclampsia in New York State, 1995–2004.Matern Child Health J. 2014 May; 18(4): 829–838. doi: 10.1007/s10995-013-1307-9.
4. Antza C, Cifkova R, Kotsis V. Hypertensive complications of pregnancy: A clinical overview. Metabolism. 2017Nov21. doi: 10.1016/j.metabol.2017.11.011.
5. American College of Obstetrics and Gynecologists, Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122:1122
6. Joey P. Granger Barbara T. Alexander William A. Bennett Raouf A. Khalil. Pathophysiology of pregnancy-induced hypertension. American Journal of Hypertension, Volume 14, Issue S3, 1 June 2001, Pages 178S–185S,
7. Ruxandra I. Sava. Keith L. March. Carl J. Pepine. Hypertension in pregnancy: Taking cues from pathophysiology for clinical practice. https://doi.org/10.1002/clc.22892
8. Malik R, Kumar V. Hypertension in Pregnancy. Adv Exp Med Biol. 2017;956:375-393. doi: 10.1007/5584_2016_150.
9. www.uptodate.com
10. Kessous R, Shoham-Vardi I, Pariente G, Sergienko R, Sheiner E. Long-term maternal atherosclerotic morbidity in women with pre-eclampsia.Heart. 2015 Mar;101(6):442-6. doi: 10.1136/heartjnl-2014-306571. Epub 2015 Jan 6.
11. Behrens I, Basit S., Lykke JA, Ranthe MF, Wohlfahrt J, Bundgaard H, Melbye M, Boyd HA. Association Between Hypertensive Disorders of Pregnancy and Later Risk of Cardiomyopathy.JAMA. 2016 Mar 8;315(10):1026-33. doi: 10.1001/jama.2016.1869.
12. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. N Engk J Med. 2008;359 (8):800
13. Lykke JA, Langhoff-Ross J, Sibai SM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension. 2009 Jun;53 (6) :944-51. Epub 2009 May 11
14. Fitton CA, Steiner MFC, Aucott L, Pell JP, Mackay DF, Fleming M, McLay JS. In-utero exposure to antihypertensive medication and neonatal and child health outcomes: a systematic review. J Hypertens. 2017;35 (11):2123.
15. A. Atallah, E. Lecarpentier, F. Goffinet, M. Doret-Dion et al. Aspirin for Prevention of Preeclampsia Drugs (2017) 77:1819–1831. DOI 10.1007/s40265-017-0823-0.