CARDIOLOGICAL PERSPECTIVE ON HYPERTENSION IN PREGNANCY

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Abstract
Hypertension is a very common and potentially devastating complication of pregnancy. Gestational hypertension and pre-eclampsia have remained one of the leading causes of both maternal and foetal morbidity and mortality. Medical treatment has not changed significantly for many years because of lack of an evidence base for the introduction of new therapies. Hypertension can be:
1.pre-existing defined as blood pressure >140/ 90 mmHg that predates pregnancy or develops before 20 weeks of gestation;
2.isolated after the 20th week (gestational hypertension);
3.associated with proteinuria (pre-eclampsia).
Finally, it can be unclassifiable hypertension.
Keywords: hypertension, pre-eclampsia, antihypertensives, ambulatory monitoring

Rezumat
Hipertensiunea arterială este o complicație frecventă a sarcinii, cu consecințe potențial dezastruoase. Hipertensiunea gestațională și preeclampsia au rămas cauze importante de morbi-mortalitate maternă și fetală. Tratamentul medicamentos nu a suferit modificări majore în ultima perioadă de timp datorită lipsei dovezilor clinice pentru terapiile mai noi. Hipertensiunea în sarcină poate fi:
1. preexistentă, cu valori ale tensiunii arteriale peste 140/ 90 mmHg determinate antenatal sau în primele 20 de săptămâni de sarcină;
2. gestațională, după săptămâna a 20-a;
3. asociată cu proteinurie (preeclampsie).
Există și forme de hipertensiune neclasificabilă.

Pregnancy is the time when women are the most important to species. Hypertension in pregnancy remain a major cause of maternal and fetal morbidity and mortality.
Blood pressure usually varies in pregnancy with a fall in blood pressure (BP) in the first and second trimester reaching systolic values that are 10-15mmHg lower than before pregnancy. This lowering is even greater in women with pre-existing hypertension, so they appear to have normal BP and then, their rise in BP in the third trimester can be misdiagnosed as preeclampsia. Normally, BP rises in the third trimester to reach the pre-pregnancy levels. After delivery the BP increases over the first postnatal days even in women whose blood pressure was normal throught pregnancy, perhaps reflecting a degree of vasomotor instability.
Studies demonstrate that women with gestational hypertension are prone to hypertension, stroke and ischemic heart disease later in life; so all women with pregnancy-induced hypertension should have regular cardiology check-up after delivery[(1-8)].
The definition of hypertension in pregnancy is based on absolute blood pressure values (systolic blood pressure>140 mmHg or diastolic blood pressure > 90 mmHg).The diagnosis of hypertension in pregnancy should be based on at least two high blood pressure readings on two separate occasions. Ambulatory BP monitoring may be superior to conventional measurements in predicting proteinuria and in general outcome of pregnancy; it may thus be

useful to perform ambulatory blood pressure monitoring, particularly in high-risk pregnant women with hypertension, or those with diabetes or renal damage. „White-coat" hypertension is a common phenomenon in young women, so ambulatory blood pressure monitoring might be useful in the initial assessment to avoid unnecessary and possibly dengerous treatment in first part of pregnancy. Technically, Korotkoff phase V (disappearance of the sounds) is recommended for the measurement of diastolic blood pressure in pregnancy and phase IV (muffling of sounds) being indicated only if Korotkoff sounds persist at very low cuff pressures. Korotkoff phase V is more reproducible and shows better correlation with true diastolic BP in pregnancy.

According to ESC-ESH Guidelines, hypertension in pregnancy comprises:
1. **Pre-existing hypertension**, which is defined as blood pressure >140/ 90 mmHg that predates pregnancy or develops before 20 weeks of gestation, usually persisting more than 42 days post partum. It may be associated with proteinuria. Undiagnosed hypertensive women may appear normotensive on first trimester because of the normal fall in BP values; then, in later pregnancy high blood pressure values are recorded and interpreted as gestational hypertension. Chronic hypertension complicates 3-5% of pregnancies and this figure is expected to rise with the trend for women to postpone childbirth after 30 years of age. The presence of pre-existing hypertension doubles the risk of pre-eclampsia and increases the risk of placental abruptio and growth restriction of fetus. When chronic hypertension is severe the risk of pre-eclampsia is as high as 46% with consequent maternal and fetal risks[(9)]. Maternal complications of hypertension include abruptio placentae, cerebral haemorrhage and superimposed pre-eclampsia. Foetal complications include prematurity, still-birth and neonatal death.

2. **Gestational hypertension** (complicating 6-7% of pregnancies[(10)]) means pregnancy-induced hypertension without proteinuria. Pre-eclampsia is gestational hypertension associated with significant proteinuria (>300 mg/l or >500 mg/24h or dipstick ++ or more). Hypertension develops after 20 weeks of gestation and usually resolves within 42 days post partum. Pre-eclampsia was classically defined as a mixture of hypertension, proteinuria and edema; now edema is no longer in the diagnostic criteria because is present in more than half of normal pregnancies and lacks specificity. Pre-eclampsia is one of the most frequently causes of maternal death; the risks to the fetus are: premature delivery (pre-eclampsia is a common cause of prematurity) and impared growth. Pre-eclampsia may also manifest with few maternal signs, as isolated intrauterine growth restriction[(11)].
Eclampsia is defined as grand mal seizure associated with pre-eclampsia. Often, eclampsia occurs unexpectedly sometimes before the warning signs of hypertension and proteinuria. Risk factors for developing pre-eclampsia includes nulliparity, previous pre-eclampsia, diabetes, chronic hypertension, increased body mass index, thrombophilia (both inherited and acquired), diabetes, large placentas (hydatidiform mole, placentas with multiple gestations).
The pathophysiology of pre-eclampsia has two stages: reduced placental perfusion (due to abnormalities of implantation and vascular remodeling) and the maternal syndrome (decreased blood flow to organs resulting in hemorrhage, hemoconcentration and necrosis). Pre-eclampsia extends well beyond isolated hypertension and a rise in urinary albumin excretion. Recent findings implicated angiogenic factors in the pathophysiology of pre-eclampsia. Hyperuricemia correlate well with maternal morbidity, but there is a even stronger association of high level of uric acid with small birth weight infants and fetal mortality. The subset of women with elevated serum uric acid represents a group at increased risk for adverse outcomes. A rise in uric acid can lead to an inhibition of fetal angiogenesis in the third trimester, which has the result of a small infant and a reduction in nephron number[(12-16)].

3. Pre-existing hypertension plus superimposed gestational hypertension with proteinuria. Pre-existing hypertension is associated frequently with further worsening of blood pressure and a protein excretion rate >3 g/day in 24-hour urine collection after 20 weeks of gestation.
4. Antenatally unclassifiable hypertension. Hypertension based on blood pressure measurements after 20 weeks of gestation with no history of previous values. Re-assessment is necessary post partum. If BP values are normalised, the condition should be re-classified as gestational hypertension with or without proteinuria. If hypertension is not resolved, the condition should be reclassified as pre-existing hypertension.

To improve the care of pregnant women we have to remember some very important points:
- ask about genetics: „did your mother have hypertension in her pregnancy(ies)?"
- correct measurement of blood pressure early in pregnancy (it can identify women with pre-existing hypertension or borderline BP values and can be a useful baseline to assess the future BP rise). In cases of doubt, please refer patient for ambulatory blood pressure monitoring.
- testing for proteinuria.

Is important to have some basic laboratory investigations:
- hematocrit because hemoconcentration supports the diagnostic of gestational hypertension/ pre-eclampsia
- platelet count because low levels supports consumption in small vessels
- clotting time
- liver tests (AST, ALT). Transaminase increases in the HELLP syndrome (haemolysis, elevated liver enzymes, low platelets. Headache, visual disturbance and pulmonary oedema may also occur)
- LDH because elevated levels supports the diagnostic of hemolysis
- Serum creatinine and uric acid. Creatinine is reduced in a normal pregnancy, so normal values may indicate a level of renal impairement/ failure
- Dipstick test for proteinuria and if positive proteinuria on 24-hour urine collection
- Blood film- in severe pre-eclampsia microangiopatic haemolytic anemia can intervine

Management of hypertension in pregnancy[17,18]

1. Pre-pregnancy
Women with chronic hypertension needs a carefull assessment of BP control, exclusion of secondary hypertension, and informations about the increased risk of pre-eclampsia and drug effect on fetus. From the many drugs used to treat hypertension a special mention is to be made about angiotensin converting enzyme (ACE) inhibitors (e.g. captopril, enalapril) and angiotensin receptor blockers (ARBs) which are fetotoxic (oligohydramnios, intrauterine growth restriction, pulmonary hypoplasia, fetal renal tubular dysplasia[19]) and so prohibited in pregnancy. Women with history of pre-eclampsia in previous pregnancies needs prophylactic treatment with low-dose aspirin.
2. Antenatal management
Very important are correct blood pressure measurement (ambulatory monitoring is useful when white coat hypertension is present or suspected) and proteinuria screening. Close surveillance is mandatory in women at increased risk. Increased placental vascular resistence assessed by doppler ultrasound examination of the uterine arteries (20-24 weeks of gestational age) identifies a high-risk subgroup. Women with preexisting hypertension or pre-eclampsia needs frequent fetal ultrasound examination to assess fetal growth (risk of intrauterine growth restriction) and umbilical and uterine artery flow.

Non-pharmacologic management (supervision, limitation of activities, normal diet without salt restriction) should be considered for pregnant women with systolic blood pressure of 140–149 mmHg and/or diastolic blood pressure of 90–95 mmHg. Treatment usually begins with bed rest. We need to fiind no evidence of serious disease such as proteinuria, hyperuricemia and renal impairment.

Weight reduction is not recommended during pregnancy in obese women. The majority of women in this category have good maternal and neonatal outcomes; there is no evidence that pharmacological treatment is improving neonatal outcome. There are generally not sufficient data regarding medical treatment in pregnancy; women with child-bearing potential are usually excluded from clinical trials, so there are no data available for most of antihypertensive drugs. Consequently the recomandation is to treat only cases with sufficient BP elevation to pose a potential risk to mother and fetus. Treating mild blood pressure elevations can increase the risk of growth restriction of fetus. Some small studies have suggested that treatment in mild hypertension may prevent pre-eclampsia[20,21]. Calcium supplementation of at least 1g daily halved the risk of pre-eclampsia in high-risk patients[22,23].

Low-dose aspirin can be used prophylactically in women with a history of pre-eclampsia. Pre-eclampsia is characterised by diminished production of prostacyclin and prostaglandin E and increased production of thromboxane compared to normal pregnancy. It was hypothesed that low-dose aspirin would reduce platelet-derived production of thromboxane, with no direct influence on synthesis of prostacyclin and prostaglandin E; the effect will be the restoration of normal vascular tone. Women at high-risk of developing pre-eclampsia can be treated with low-dose aspirin (100mg) daily; this dose is safe (with documented no increase in bleeding and abruptio placentae)[24].

Management of low-risk hypertension (BP 140–160/90–110, normal physical examination, ECG and ultrasound, and no proteinuria) rely on frequent supervision because the patient may become high risk through development of severe hypertension or pre-eclampsia. The blood pressure tends to fall during pregnancy so it may be possible to discontinue drug treatment (if initiated). Delivery is indicated when pre-eclampsia develops or fetal growth slows/ stops.

Management of high-risk patients (severely elevated BP values, end-organ involvement, poor obstetric history, co-morbidity from renal impairment, diabetes or collagen vascular disease) rely on individual assessment and frequent clinical, biochemical and ultrasound examination. Unfortunatelly, there are no placebo controlled trials of pharmacological regimes for the treatment of severe hypertension in pregnancy. Antihypertensive therapy is indicated for mother (end-organ protection) and foetus (prolongation of the pregnancy).

Treating chronic hypertension is mandatory if severe; continuing administration of attihypertensive drugs in mild-moderate hypertension is controversial. Lowering mother BP values can reduce uteroplacental perfusion and impair the normal growth of fetus. The problems is related with the studies done on this topic which are usually too small to demostrate net benefit.

Antihypertensive drugs used in pregnancy are:

- **Methyldopa** which is the only drug to have a proper trial to demonstrate clearly his safety profile (25). Methyldopa was used extensively in pregnancy and is the agent of first choice in the majority of cases. This treatment is now nearly abandoned for use in general population with hypertension because of side effects (orthostatic hypotension, fatigue). The dose is 0.75-4 g per day in three divided doses.
- None of the **beta-blockers** have been associated with teratogenicity. Labetalol has the advantage of vasodilatation. The dose is 100 mg twice daily up to 2400 mg per day. When given only late in pregnancy atenolol and metoprolol have not been associated with any serious adverse reactions. Atenolol has been linked to low weight for gestational age.

- **Nifedipine** is safe but should not be given sublingually or intravenously because rapid and excessive BP reduction may sometimes cause myocardial infarction and foetal distress.
- **Clonidine** can be used in the third trimester; usual dose is 0.1–0.3 mg per day in divided doses up to 1 mg per day
- The use of **diuretics** is controversial because they can induce pre-eclampsia by reducing plasma volume and potentiating the response to other antihypertensives. Furosemide can be used in pregnancy complicated by cardiac failure

It appears reasonable to recommend drug treatment when systolic blood pressure is >150 mmHg and/or diastolic blood pressure is >95 mmHg. A lower threshold (140/90 mmHg) is indicated in women with hypertension with subclinical organ damage or symptoms at any time during pregnancy. Systolic blood pressure >170 mmHg or a diastolic blood pressure >110 mmHg should be considered an emergency and require hospitalization. Emergency treatment can be done by intravenous nitroglycerine (largely available in Romania, starting 5 μg/ min to a maximum of 100μg/ min, is the drug of choice in pre-eclampsia with pulmonary edema), sodium nitroprusside (drug of choice but not often available in Romania- dosage 0.5-5 μg/ kg/ min by intravenous continuous infusion; prolonged administration carries an increased risk of fetal cyanide poisoning), intravenous labetalol (rarely used), oral methyldopa or nifedipine. Intravenous hydralazine should no longer be considered because its use is associated with perinatal adverse effects. ACE inhibitors and angiotensin receptor antagonists are prohibited in pregnancy. Diuretic therapy is indicated only in cases of pre-eclampsia and oliguria. Magnesium sulfate i.v. is effective in the prevention of eclampsia and the treatment of seizures. Induction of delivery is indicated in gestational hypertension with proteinuria, visual disturbances, coagulation abnormalities or fetal distress.

3. Is important also the **management of hypertension in post partum period.** Gestational hypertension usually resolves. Brest-feeding must be encouraged and atenolol, metoprolol and diuretics should be avoided.

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