Hypertension in pregnancy

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Hypertension (HTN) is the most commonly encountered disorder during pregnancy. High blood pressure has a negative impact on the mother and the foetus, which is why early diagnosis and proper control are mandatory to avoid complications. There are many forms of HTN disorder during pregnancy. The threshold for initiation of antihypertensive medications differs for gestational and chronic HTN during pregnancy, being lower in gestational HTN. Pre-eclampsia/eclampsia syndrome is a severe form of gestational HTN, which is only curable by delivery of the foetus. Management of HTN during pregnancy is challenging and it requires collaboration between obstetricians and cardiologists.

Hypertension

Introduction and prevalence

Hypertension (HTN) is a worldwide health problem that affects about 25-40% of individuals. It is a major cardiovascular risk factor and it is associated with many cardiovascular complications (e.g., stroke, heart failure). The prevalence of raised blood pressure is highest in Africa, where it is 46% for both sexes combined. HTN can affect people at any age; women at child-bearing age are no exception.

HTN is the most common medical disorder during pregnancy, with a prevalence of 5-10% of all pregnancies worldwide [1,2]. HTN and antihypertensive drugs have adverse effects on both the mother and the foetus.

Management of HTN during pregnancy needs expertise in the field of high-risk pregnancy and cardiovascular diseases, which is why a combined team of obstetricians and cardiologists is an important prerequisite.

Definition and forms of HTN disorders in pregnancy

Diagnosis of HTN during pregnancy is based on the standard office blood pressure (BP) measurements. Although ambulatory blood pressure monitoring (ABPM) is more accurate in diagnosing HTN and is better in predicting outcomes [3], it cannot be routinely applied because of time and money constraints. The use of automated BP measuring devices is not recommended because they tend to under-record BP and they are unreliable in pre-eclampsia [2].

Hypertension disorders in pregnancy (HDP) are classified into mild HTN (systolic BP 140-159 mmHg and/or diastolic BP 90-109 mmHg) or severe HTN (BP ≥160/110 mmHg) [1].

The nomenclature of the different forms of HDP depends on the timing of the first diagnosis of HTN and the persistence of high BP after delivery. The following forms are described in the recent European guidelines [1]:

Pre-existing hypertension

HTN diagnosis before pregnancy, early in pregnancy (before 20 weeks of gestation), or HTN continues after six weeks post-partum.

Gestational hypertension

HTN first diagnosis during pregnancy, after 20 weeks of gestation; it usually resolves within six weeks post-partum. Gestational HTN is considered a form of secondary HTN [1].

- **Pre-existing hypertension plus superimposed gestational hypertension with proteinuria**
- **Pre-eclampsia (vide infra)**
- **Antenatally unclassifiable hypertension**

This term is used when HTN is first diagnosed after 20 weeks of gestation and it is unclear if hypertension was pre-existing. Reassessment six weeks post-partum will help distinguish pre-existing from gestational hypertension.

Complications

In addition to the well-known risks of HTN, maternal risks include placental abruption and disseminated intravascular coagulation.

The foetus is at high risk of intrauterine growth retardation (25% of cases of pre-eclampsia), prematurity (27% of cases of pre-eclampsia), and intrauterine death (4% of cases of pre-eclampsia) [2].

The long-term risks of HDP and pre-eclampsia include a fourfold higher risk of chronic HTN and a twofold higher risk of stroke and ischaemic heart diseases [4].

Women who develop severe hypertension have higher rates of adverse maternal (pre-eclampsia, HELLP syndrome [haemolysis, elevated liver enzymes, and a low platelet count], and maternal length of hospital stay ≥10 days) and perinatal outcomes (perinatal death, high-level neonatal care for >48 hrs, birth weight <10th percentile, pre-eclampsia, and pre-term delivery) [5].

Investigations

Basic laboratory workup includes haemoglobin and haematocrit, urinalysis, liver enzymes, serum creatinine, and serum uric acid [1]. Hyperuricaemia in HDP is considered a marker of adverse maternal and foetal outcomes [6]. Proteinuria defines

renal affection. A dipstick test of >1+ warrants further investigations such as an albumin-creatinine ratio (ACR), that can be measured by a single spot urine sample. An ACR cut-off level of 30 mg/mmol can be used to identify proteinuria. Specific tests should be carried out whenever secondary HTN is suspected.

Doppler ultrasound of the uterine arteries (performed after 20 weeks of gestation) can detect those at a higher risk of gestational hypertension, pre-eclampsia, and intrauterine growth retardation [7].

Pre-eclampsia/eclampsia syndrome

Definition

Gestational hypertension with significant proteinuria (>0.3 g/24 hrs or ≥30 mg/mmol ACR). As proteinuria may be a late manifestation of pre-eclampsia, it should be suspected when de novo HTN is associated with symptoms (e.g., headache, visual disturbances, abdominal pain, or abnormal laboratory tests). Eclampsia is a severe form of pre-eclampsia associated with generalised tonic-clonic seizures [2]. In a few cases, pre-eclampsia may develop in the early post-partum period.

Risk factors

Women at increased risk of developing pre-eclampsia are primigravida, those with multiple pregnancy, morbid obesity (body mass index [BMI] >35 kg/m^2), diabetes mellitus, renal disease or autoimmune diseases (i.e., systemic lupus erythematosus, antiphospholipid syndrome). Chronic pre-existing hypertension, a history of pre-eclampsia in a previous pregnancy or familial history of pre-eclampsia are also considered risk factors for developing pre-eclampsia [8].

Pathophysiology

This is still unclear, but many theories propose a placental vascular insufficiency due to endothelial dysfunction, vasoconstriction and micro-thrombosis. Oxidative stress of the syncytiotrophoblast (the epithelial covering of the placental villi in contact with maternal blood) is one of the explanations. When stressed, the syncytiotrophoblast releases many factors, including pro-inflammatory cytokines, anti-angiogenic agents, exosomes and cell-free foetal DNA, into the maternal circulation. These disrupt maternal endothelial function resulting in a systemic inflammatory response and cause hypertension and other manifestations of the disease (haematologic, cardiac, neurologic, pulmonary, renal, and hepatic dysfunction) [9]. Genetics may also play a role.

Complications

Maternal complications include multiple organ failure. Maternal mortality is estimated to be 9% in the United States of America (USA), which is why the USA preventive task force recommended measuring the BP at every prenatal visit [10]. Foetal growth restriction

occurs due to placental insufficiency and is a common cause of premature delivery [8].

Pre-eclampsia accompanied by haemolysis, elevated liver enzymes and low platelets is called HELLP syndrome. HELLP is a life-threatening condition which may be fatal if not detected and treated early. The global mortality rate of HELLP syndrome has been reported to be as high as 25% [11].

Treatment

Currently, there is no sure way to prevent hypertension and there is no clear role for lifestyle modifications in reducing HDP [2].

The aim of prescribing antihypertensive medications is to decrease progression to severe HTN and to prolong pregnancy till foetal maturity [12].

Hospitalisation is needed for patients with severe HTN.

Antihypertensive drugs

The threshold for initiation of antihypertensive medications is ≥150/95 mmHg for patients with pre-existing HTN and >140/90 mmHg for patients with gestational HTN (with or without proteinuria) and patients with subclinical hypertension-mediated organ damage (HMOD) [1]. The target BP should be <140/90 for all hypertensive pregnant women. Because of the physiological drop of BP in the second trimester, some women become able to withdraw their antihypertensive medication [2].

Both maternal hypertension and maternal antihypertensive use during pregnancy were associated with increased risk of congenital heart diseases (CHDs) such as pulmonary valve stenosis, secundum atrial septal defect, ventricular septal defect and coarctation of the aorta. Hypertensive mothers who reported antihypertensive use had higher risk of these CHDs than untreated mothers [13]. That is why the pregnancy and lactation labelling rule (PLLR) system must be checked before prescribing any drugs to pregnant women.

Drugs for mild HTN

Beta-blockers

Beta-blockers (BB) are first-line medication during pregnancy and lactation. Labetalol is one of the commonest drugs used in HDP. It can be used parenterally in cases of severe HTN. BB may cause foetal bradycardia or intrauterine growth retardation; thus, proper monitoring of the foetus is essential. Atenolol is better avoided during pregnancy [2].

Alpha methyldopa

This is an α2-adrenergic agonist that has central nervous system (CNS) and peripheral nervous system effects. It is one of the safest drugs during pregnancy; been used for more than 40 years, with no serious side effects on the mother or the foetus, although it

has been largely displaced by labetalol as the first-line agent of choice for most patients. The recommended daily dose of methyldopa is 0.5–3.0 g in 2–4 doses. Side-effects include sleepiness, dry mouth, general malaise, haemolytic anaemia, and hepatopathy [14].

Calcium channel blockers

Calcium channel blockers (CCBs) are among the recommended antihypertensive drugs during pregnancy. Both dihydropyridines and non-dihydropyridines are allowed [2].

Diuretics

The use of diuretics during pregnancy carries a potential risk of oligohydramnios. Unless there is a compelling indication for the use of diuretics (e.g., heart failure), their use is not recommended. Diuretic therapy is better avoided in pre-eclampsia because the plasma volume is contracted [2]. Only loop diuretics are allowed, while thiazide and potassium-sparing diuretics are contraindicated during pregnancy.

Renin-angiotensin-aldosterone system inhibitors

Renin-angiotensin-aldosterone system (RAAS) inhibitors include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), renin inhibitors, non-selective (spironolactone) and selective (eplerenone) aldosterone antagonists.

Recent studies suggest that exposure early in pregnancy during the period of organogenesis does not confer an increase in the risk of malformations [15]. However, animal and human data suggest that RAAS inhibitor use during the second and third trimesters is associated with a higher risk of complications, including renal dysplasia, pulmonary hypoplasia, and growth restriction [16].

The guidelines recommend against the use of RAAS inhibitor drugs during pregnancy and lactation (Class III recommendations). Beta-blockers are used as an alternative to ACEIs and ARBs in younger hypertensive women planning pregnancy [1].

Drugs for severe HTN

HDP emergency is defined as BP ≥170/110 mmHg. It necessitates immediate hospital admission and parenteral antihypertensive medications [2]. Intravenous labetalol and nicardipine as well as oral methyldopa and CCB can be used. Hydralazine is now only used when other drugs fail to control HTN, because of its increased perinatal adverse effects [17].

Treatment of pre-eclampsia/eclampsia syndrome

- Women at a risk of developing pre-eclampsia should be advised to take 100–150 mg of aspirin daily from weeks 12–36 gestation [18]. Aspirin can decrease the risk of pre-eclampsia by 12% and the risk of premature delivery by 14% [19].
- Women with a diagnosis of pre-eclampsia should be admitted and offered antihypertensive medications, if not previously given. Intravenous labetalol and

nicardipine are usually used to lower the BP but foetal bradycardia is a concern. In case of pulmonary oedema, nitroglycerine infusion is recommended. The consensus is to reduce BP to levels lower than 160/105 mmHg.
- Intravenous magnesium sulfate is the treatment of choice in patients with eclampsia fits.
- Delivery of the placenta (and the foetus, of course!) is the only cure for pre-eclampsia; yet, in asymptomatic patients, delivery can be delayed to the 37th week of gestation.

Timing and mode of delivery

Vaginal delivery is preferred unless there are obstetric or medical contraindications.

Delivery at 37 weeks is recommended in uncomplicated patients. Women with pre-eclampsia with visual or haemostatic disorders or HELLP syndrome should be delivered as soon as possible [2].

Management of HTN post-partum

When HTN persists after delivery, antihypertensive drugs should be continued. Almost all drugs are secreted in milk, but in varying amounts [20]. Because of the lack of evidence, most physicians use the same rules applied for drugs during pregnancy in the breastfeeding period. Methyldopa should be avoided because of the risk of post-partum depression.

Conclusion

HDP is a heterogenous disease that increases the risk of maternal and foetal morbidity and mortality. Early detection and management are warranted by routine measurement of BP at the regular antenatal care visits. Obstetricians and cardiologists should share in the management of HDP.

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