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Review Article

Comprehensive Review of Management of Hypertension in Pregnancy

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Abstract

Gestational and preexisting hypertension, eclampsia, and preeclampsia are examples of hypertensive disorders of pregnancy that complicate at least 10% of pregnancies thus contributing to maternal and perinatal mortality and morbidity. Hypertensive pregnant women also have a high risk of cardiovascular conditions in later life, which is independent of conventional cardiovascular disease risk factors. Despite the acute or long-term risks for cardiovascular diseases, very little changes have been made pertaining to recommendations for diagnosis and guidelines for treatment of hypertension in pregnancy. In this article, I will present a comprehensive review of the literature pertaining to hypertension in pregnancy. The definition and classification of hypertensive conditions in pregnancy are presented. Also presented is a detailed review of the renal and vascular physiological changes that occur during pregnancy. The management of hypertension in pregnancy is addressed, including a review of the pharmacologic therapies, and the future developments in this field.

Keywords: Hypertension; Gestational Hypertension; Pregnancy; Preeclampsia; HELLP

Introduction

Hypertension in pregnancy covers a range of conditions, sch as gestational hypertension, preeclampsia/eclampsia, chronic hypertension, and hemolysis, elevated liver enzymes and low platelets syndrome. Hypertension is the commonest disorder that occurs during pregnancy. studies have shown that high blood pressure complicates at least 1 in 10 pregnancies and affects over 240,000 American women yearly [1]. Although healthcare providers for centuries have recognized preeclampsia, not much is known about its pathogenesis or prevention. The major concern about hypertension relates to the potential complications on both the fetus and the mother. The severity of these adverse effects ranges from mild to life threatening. Most of the recommendations for the treatment of these conditions are based on observational studies and expert opinion, with no tangible evidence from randomized controlled trials. Generally, the management of hypertension in pregnancy aims at preventing cardiac and cerebrovascular complications, as well as preserving fetal and uteroplacental circulation and reducing the level of toxicity of the medication to which the fetus is exposed.

Overview of the terminology

There is no standardized definition of hypertension in pregnancy. However, the "National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy" has recommended a systolic blood pressure (SBP of value ≥ 140mmHg and/or a diastolic blood pressure (DBP) of value ≥ 90 mmHg [1]. Diagnosing hypertension in pregnancy requires two distinct measurements [2]. The severity of hypertension is defined as follows:

Non-severe hypertension: Hypertension is said to be non-severe when the values fall between 140 – 159 mmHg for SBP, and 90 – 109 mmHg for DBP. This category may sometimes be classified as "mild," or it may be subclassified as mild (140 – 149/90 – 99 mmHg), and moderate (150 – 159/100 – 109 mmHg) [3].

Severe hypertension: Systolic blood pressure is typically less than or equal to 160 mmHg while diastolic blood pressure is less than or equal to 110 mmHg [4]. Pregnant adults have lower thresholds for severe hypertension compared to non-pregnant adults. Clinical experience has shown that pregnant women usually develop hypertensive encephalopathy at low blood pressures [5]. It is worth mentioning that treatment for hypertension in pregnancy fall into two categories – the first being the management of preeclampsia/eclampsia and other acute hypertensive syndromes of pregnancy, followed by chronic hypertensive management. Acute hypertensive syndromes are typically resolved by delivery of the fetus, but close observation may be necessary in some patients, especially before 32 weeks of pregnancy. Women experiencing chronic hypertension should be thoroughly evaluated before pregnancy. Greater focus should be placed on end-organ damage, subtle signs of secondary causes of hypertension like primary hyperaldosteronism, renal artery stenosis caused by fibromuscular dysplasia, and pheochromocytoma. Focus should also be placed on medication adjustments and counseling on the risks of adverse fetal events and preeclampsia. Pregnant women with hypertensive disorders should have a comprehensive care plan, including prenatal counseling, frequent visits during gestation, appropriate and adequate intrapartum care, timely delivery, as well as postpartum follow-up. Care of hypertensive pregnant patients involves regular counseling during pregnancy with the goal of educating the woman on the risks that she and her fetus may be facing so as to help make informed decisions.

Cardiovascular Physiology in Pregnancy

Hormonal changes occur during pregnancy. These changes induce major adaptations in the cardiovascular physiology of the pregnant mother [6]. Starting in the first trimester, there are hormonal surges, typically of progesterone, estrogen, and relaxin, resulting in systemic vasodilation [7-9]. The renin-angiotensin-aldosterone system (RAAS) is concurrently augmented to engender retention of water and salt, leading to an increase in the volume of plasma [10]. These events, together with an increase in the mass of ventricular walls, triggers an increase in stroke volume [11]. The increase in plasma volume leads to physiologic anemia, as the plasma volume increases at a rate faster than that at which the red blood cell mass increases [12]. The body usually attempts to compensate for the aforementioned physiologic anemia and systemic vasodilation through an increase in heart rate [10]. Tachycardia and elevated stroke volume combine to increase cardiac output during pregnancy, thus compensating for the decline in vascular resistance in order to keep the blood pressure at levels high enough for maternal and placental perfusion [11]. A meta-analysis of 39 pieces of research involving 1479 women reviewing data of cardiac output for healthy pregnancies showed that at their peaks, heart rate, stroke volumes, and cardiac output had mean increases of non-pregnant values in the range of 24%, 13%, and 31% respectively. On the other hand, systemic vascular resistance at its nadir was lower than that of non-pregnant patients by 30% [13]. Peaks for heart rate and cardiac output, plus systemic vascular resistance nadir, were timely during the third trimester, while the peak for stroke volume came early during the second trimester, trending towards pre-pregnancy values as they approached their full term [13]. However, it is important to note that due to incomplete compensation of cardiac output for systemic vasodilation perfusion [11], mean arterial blood pressure was lower than pre-pregnancy pressure, with an average nadir of 8 mmHg below the baseline during the second trimester of pregnancy [13]. It is therefore plausible that women who have been hypertensive prior to conception may not fall within the indicated range of treatment during pregnancy.

Physiology of the Kidney in Normal Pregnancy

Healthy pregnant women usually show marked glomerular hyperfiltration. Several human studies have shown a rapid rise in glomerular filtration rate and renal blood flow [14]. Increase in GFR begins in the first trimester of pregnancy and reaches the peak in the second trimester of pregnancy, where it rises above the normal levels by 40-60%. According to the study [14], the improved renal hemodynamics occurred even before changes in plasma volume and cardiac output (Figure 1). This implies that there may be different underlying mechanisms powering these physiologic alterations. It is important to note that nowhere does such a sustained improvement of function manifest in biology. The magnitude of the change has intrigued many researchers, pushing them to attempt to define the underlying mechanism so that it might be employed in the treatment of other conditions. Pregnant patients with an uncomplicated pregnancy who have an underlying renal disease usually experience an improved function which is at par with their baseline level. This physiologic change occurs for teleological reasons and is designed to accommodate the extra

waste products consequent to the enlarging fetus, placenta, and uterus. While it may appear to tail off toward the end of pregnancy, a substantive increase in renal plasma flow and glomerular filtration rate is sustained throughout the period of pregnancy. A reduction in blood urea nitrogen (BUN) accompanies the improved renal function, while glomerular filtration rate is estimated using serum creatinine tests. Low levels of nitrogen wastes in the blood are typically hallmarks of pregnancy. It is important to be cognizant of these variations from the regular non-pregnant values considering that deviation from pregnancy levels, no matter how subtle, might presage preeclampsia diagnosis.

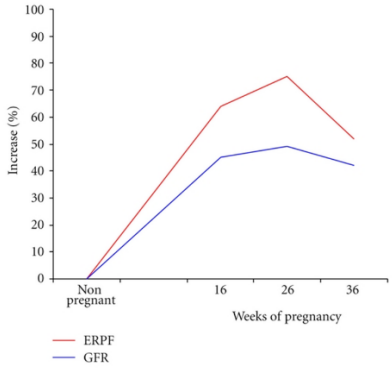

Figure 1: Changes in renal function during a state of pregnancy. There is a dramatic increase in kidney function during pregnancy. The researchers carefully documented the rapid rise in glomerular filtration rate and renal blood flow. The increments in both parameters averaged between 40% and 50%. According to Davidson, improvements in renal hemodynamics occurred before alterations in plasma volume and cardiac output [14].

General pathology of hypertension

It is important to note that any form of hypertension in pregnancy can ultimately lead to preeclampsia. At least 35% of pregnant women with gestational hypertension experience it [15] and no less than 25% of chronic hypertensive patients [16,17]. Not much is understood about the underlying pathophysiology that upholds the superposition of, or transition to preeclampsia; but it is believed to have a link with reduced placental perfusion inducing a systemic dysfunction of the vascular endothelium [18]. The reason for this is an inefficient cytotrophoblastic invasion of the spiral arteries of the uterus [19]. This results in placental hypoxia which will induce a cascade of inflammatory conditions, altering the balance of angiogenic factors, and ultimately inducing aggregation of platelets, all manifesting as preeclampsia syndrome [19,20]. Angiogenic imbalances due to preeclampsia include reduced concentrations of placental growth factor (PIGF) and vascular endothelial growth factor (VEGF). Angiogenic imbalances is also characterized by increased concentration of the antagonist of these angiogenic factors, placental soluble fms-like tyrosine kinase 1 [21,22]. A factor in nitric oxide synthesis reduction impedes the binding of the angiogenic factors PIGF and VEGF to their receptors. Reduction of nitric oxide synthesis is vital to vascular vasodilation and remodeling, which may contribute to amelioration of placental ischemia [23]. Early-onset preeclampsia which occurs at the 34th week of gestation is believed to be caused by stress to the synctiotrophoblast resulting in poor placentation. On the other hand, late-onset preeclampsia (LOPE) which usually occurs after 34 weeks of pregnancy is secondary to outgrowth of the placenta above its own circulation [24]. Early-onset preeclampsia is associated more frequently with fetal growth restriction compared to LOPE, due to chronic placental dysfunction [11]. In the postpartum period, at least 28% of women may have de novo hypertension. Several factors may contribute to this, including administration of vasoactive agents and fluids, as well as movement of fluids from the interstitial space to the intravascular space. The fluid shift causes up to an 80% increase in the cardiac output, followed by diuresis and vasodilation, both compensatory mechanisms to ease the blood pressure [19]. Hypertension in pregnancy tends to have an increasingly relevant pathophysiology when reviewing adjunct therapies to antihypertensives specially formulated for the prevention of preeclampsia.

Chronic hypertension in pregnancy

Definition

The American College of Obstetrics and Gynecology (ACOG) defines chronic hypertension in pregnancy as blood pressure above 140 mmHg systolic and/or 90 mmHg diastolic before pregnancy [25]. Normotensive pregnant women typically experience a decrease in blood pressure right before the end of the first trimester. The decrease in blood pressure is presumably secondary to the vasodilation that is characteristic of pregnancy. Blood pressure usually reduces by 5 to 10 mmHg and stays at this level until the third trimester of pregnancy. At the third trimester, the blood pressure returns to prepregnant values. For most women with chronic hypertension, changes in blood pressure follow a similar pattern. As such, some women with hypertension may become normotensive during pregnancy. For those with persistent hypertension, their antihypertensive medications may be tapered. These alterations are usually confusing to the clinician when a pregnant woman presents for prenatal care in the second trimester once the physiological process has taken place and is now normotensive. The increased pre-pregnancy values in the third trimester may indicate gestational hypertension. In many cases, an accurate diagnosis of chronic hypertension is made only when the elevated blood pressure persists beyond 12 weeks postpartum.

Diagnosis

The diagnosis of chronic hypertension in pregnancy is based on

either a history of high blood pressure antedating pregnancy or consistent increase in blood pressure (minimum of 140/90 mmHg) at least twice more than 24 hours apart before the 20th week of gestation. Other examinations that might help an astute clinician to identify somethings akin to the presence of chronic hypertension include cardiac enlargement on electrocardiogram of chest x-ray, retinal changes due to fundoscopic examination, compromised renal function or associated renal disease, presence of underlying medical conditions that may lead to hypertension, and evidence of persistent hypertension beyond the 42nd day postpartum.

Management

The goal of management of chronic hypertension in pregnancy is to minimize maternal risks and achieve optimal perinatal survival. The clinician can achieve this objective by adopting a rational approach that includes pre-conceptional counseling and evaluation, antenatal care, timely antepartum visits to help monitor fetal and maternal well-being, timely delivery with intrapartum monitoring, and efficient postpartum management. Management of chronic hypertension in pregnant women should begin before pregnancy, where the patient is evaluated and a complete work-up is done to assess the severity, etiology, and the presence of any underlying illnesses. Evaluation and work-up will also rule out the presence of organ damage due to prolonged hypertension. By evaluating the patient's condition, the clinician will be able to classify the condition as either high-risk hypertension or low-risk hypertension.

Gestational hypertension

Definition

According to Braunthal and Brateanu [26], gestational hypertension is one that appears de novo after a gestation period of 20 weeks in the absence of proteinuria (< 300 mg in 24 hours), and then normalizes after pregnancy. The BP readings of gestational hypertension is usually in the range of ≥140/90 mmHg on two occasions at least 4 hours apart during pregnancy after 20 weeks of gestation.

Diagnosis

The diagnosis requires that the patient have:

- High blood pressure (systolic ≥ 140 mmHg or diastolic ≥90 mmHg). The diastolic pressure in this case is measured using the fifth Korotkoff sound.
- Previously normotensive
- Absence of protein in the urine
- No preeclampsia or eclampsia.

Also referred to as transient hypertension, gestational hypertension has a retrospective diagnosis when there is no presentation of preeclampsia and if the blood pressure goes back to normal by the 12th week postpartum visit. Over fifty percent of women who have been diagnosed with gestational hypertension between the 24th and 35th week of gestation develop preeclampsia [1]. Increased surveillance is mandated in diagnosis of gestational hypertension.

Management

It is necessary to treat significant hypertension, irrespective of the assumed underlying pathology, mainly to minimize the risk of intracranial hemorrhage. Administration of antihypertensive medication may be initiated when the systolic pressure is greater than 140-170 mmHg or the diastolic pressure is greater than 90-110 mmHg. Treatment is recommended for severe hypertension when blood pressure is ≥ 170/110 mmHg. Target blood pressure becomes controversial once treatment commences, but most practitioners would aim to maintain the mean arterial pressure at < 125 mmHg. An overzealous attempt at blood pressure control may trigger placental hypoperfusion, since placental blood flow cannot be autoregulated, and this will severely compromise the fetus.

Preeclampsia

Definition

Preeclampsia is a multisystem disease of unknown etiology [27]. It is characterized by the development of proteinuria and hypertension after 20 weeks of gestation. Preeclampsia was defined as a triad of edema, hypertension, and proteinuria, but a more classic definition focuses on a gestational elevation of blood pressure and > 0.3g proteinuria every 24 hours. Many factors are associated with preeclampsia, and they include chronic hypertension, antiphospholipid syndrome, chronic renal disease, maternal age above 40 years, elevated body mass index, multiple gestation, a history of preeclampsia in previous pregnancy, pregestational diabetes mellitus, and nulliparity.

Diagnosis

In clinical practice, preeclampsia is diagnosed using the criteria of two elevated blood pressure measurements at least 6 hours apart and a 300 mg proteinuria in a 24-hour urine specimen. The 24-hour determination is considered to be accurate because urine dipsticks may be affected by factors such as maternal dehydration, variable excretion, and bacteriuria [28].

Management

Although it is a maternal disorder, preeclampsia places both the fetus and the mother at risk. The mainstay of treatment is early detection and delivery. These will minimize the risks to both the mother and fetus. The decision is easier if the pregnancy is at term: the baby will be delivered. It is important to note that delivery is not indicated for women who have a mild form of preeclampsia

until 37 to 38 weeks of gestation and should take place by 40 weeks [29,30].

Eclampsia

Definition

Eclampsia is basically the convulsive form of preeclampsia and presents in 0.5% of patients who have mild preeclampsia, as well as in 2 – 3% of patients with severe preeclampsia [31-37]. Stroke is the most feared complication of eclampsia and the most prominent cause of maternal death [38]. A 1995 French population-based study identified 31 cases of stroke in pregnancy. It is important to note that eclampsia accounted for almost half of both non-hemorrhagic and hemorrhagic strokes [39]. Martin and colleagues in a recent study examined 24 women who had suffered strokes in an eclampsia and preeclampsia setting [40]. The results from the study showed that their systolic blood pressures were > 155 mmHg right before their cerebrovascular accidents. Only five patients attained a diastolic pressure of 105 mmHg and were therefore not eligible for treatment according to guidelines by ACOG and NHBPEP [1].

Diagnosis

Eclampsia patients usually present with generalized tonic-clonic seizures. The evaluation for this condition is based on the diagnosis of preeclampsia as it is a fatal complication of this disease process. Preeclampsia diagnosis is centered on blood pressure as new-onset hypertension may develop after 20 weeks of gestation. Patients whose systolic blood pressure is ≥ 140 mmHg and/or diastolic blood pressure is ≥ 90 mmHg are diagnosed of new-onset hypertension. Patients may also have any of the following: renal dysfunction, proteinuria, liver dysfunction, thrombocytopenia, central nervous system symptoms, and pulmonary edema [41].

Management

Magnesium sulfate is the first line medication because it is effective in preventing recurrent seizures compared to diazepam or phenytoin [42]. If the patient has been treated with a dose of magnesium sulfate and is receiving a continuous infusion, an additional 2g should be administered intravenously. On the other hand, a 6-g loading dose may be given intravenously over 15 to 20 minutes, followed by an hourly maintenance infusion of 2g.

Care for respiratory system include:

- Head-down tilt to drain bronchial secretion
- Keep the upper respiratory tract clear by mucus aspiration through a plastic airway
- Oxygen administration during and after fits

HELLP syndrome

HELLP syndrome presents in 10 – 20% of severe eclampsia and preeclampsia pregnancies [43]. Weinstein and colleagues first described the syndrome in 1982 [44] as being featured by hemolysis, low platelets, and elevated liver enzymes. HELLP syndrome is associated with significant morbidity and mortality. HELLP syndrome has a prevalence of 0.5% to 0.9%. over 70% of cases occur in the third trimester of pregnancy, while the remainder occurs within 48 hours of delivery [44]. Women with HELLP syndrome have a 0-24% mortality rate with a 37% perinatal death rate [45]. The liver damage in HELLP syndrome is triggered by an ischemic perfusion injury. Failure of the spiral arteries to remodel due to inadequate trophoblast invasion result in placental ischemia. This activates the endothelium, accompanied by a high release of antiangiogenic factors to cause proteinuria and hypertension. It may result in multiorgan microvascular injury, which is the underlying cause of liver damage in HELLP syndrome. Also, the abnormal fetal oxidation of fatty acids and release of metabolic intermediates into the maternal circulation causes vascular and liver dysfunction. This happens when there is a defect in mitochondrial fatty acid oxidation.

Diagnosis

HELLP syndrome is diagnosed by two classifications: Mississippi and Tennessee. The Mississippi classification evaluates the severity of the condition through the lowest measured platelet count along with lactate dehydrogenase test (LDH) and aspartate aminotransferase test (AST). Class I is severer and has a high risk of morbidity and mortality. It is characterized by a platelet count below 50,000/microL. Class II is characterized by a platelet count of 50,000 to 100,000/microL. While class III HELLP syndrome is characterized by a platelet count of 100,000 to 150,000/microL [46,47].

Management

It is recommended that patients be hospitalized for regular monitoring of laboratory values. During hospitalization, the patients should receive treatments meant for severe pre-eclampsia. Magnesium sulfate should be given for seizure prophylaxis along with labetalol, hydralazine, or nifedipine. Maternal-fetal observation should be done during each step of management since immediate delivery is recommended for HELLP patients except those whose condition has stabilized between 24 to 34 weeks of gestation. Corticosteroids are recommended for this group of patients (2 doses of 12 mg betamethasone administered intramuscularly every 12 hours or 4 doses 12 mg dexamethasone administered intravenously every 12 hours). Platelets, plasma, and red cell transfusion may be also beneficial for some patients.

Management of hypertension in pregnancy

Pharmacological therapy

Various agents have long been used to combat high blood pressure. These include hydralazine, methyldopa, calcium channel blockers, prostacyclin, diazoxide, ketanserin urapidil, isosorbide, prazosin, and magnesium sulfate [48]. Medications most used in recent times include intravenous labetalol, intravenous hydralazine, and calcium channel blockers [49]. Hydralazine may be less recommended, as studies have shown that intake of calcium channel blockers by pregnant women reduced the likelihood of persistent high blood pressure when compared to treatment with hydralazine. The studies included a meta-analysis of 35 studies involving 3573 women [48] and another meta-analysis with 21 trials involving 893 women [50]. Another review pointed out that hydralazine had the potential of contributing to adverse maternal hypotension, placental abruption, cesarean sections, oliguria, and as well as adverse effects on fetal heart rate [50]. Some researchers have attempted a comparison between oral nifedipine and IV labetalol, but a 2016 meta-analysis involving 7 studies found a significant reduction in maternal side effects in subjects receiving nifedipine treatment (confidence interval 0.35-0.94; relative risk 0.57). Control of persistent hypertension, neonatal or fetal outcomes, and maternal morbidity and mortality had no significant difference statistically. This explains why all three agents have received recommendations by international guidelines [51,52]. Severe hypertension in pregnancy devoid of end-organ complications is considered a medical "urgency." The patient's blood pressure must be lowered to no more than 160/110 mmHg. The blood pressure must be reduced by less than 25% within the first hours of treatment, while it decreases more gradually in the following hours. Reducing the blood pressure forcefully may increase the fetus' risk for under perfusion, due to the fact the fetoplacental unit is incapable of autoregulating the flow of blood. On the other hand, severe hypertension with attendant end-organ complications including acute kidney injury or pulmonary edema is considered an "emergency" an indication that decrease in blood pressure must be done fast [50]. There is not much evidence to recommend any blood pressure target in preeclampsia individuals, or in women with renal or cerebrovascular complications. The point at which therapy should be introduced has been a subject of controversy. Quite a number of guidelines recommend that therapy be started by 150/100 mmHg. Other guidelines recommend treatment for blood pressure above 160/110 mmHg [51,53,54]. Failure to initiate intensive treatment for systolic blood pressure was associated with mortality due to aortic dissection and cerebral hemorrhage [55]. However, clinicians show outward concern over the risk of placental under perfusion, especially when the levels are below 110/80. In preeclampsia due to pulmonary edema, the European Society of Cardiology recommends the intravenous infusion of nitroglycerin [56]. The reduction of blood pressure should occur at a rate approximately 30 mmHg with a timeline of 3-5 minutes followed by a slower rate until the target blood pressure is achieved. Postpartum care of preeclampsia patients includes monitoring of clinical conditions and blood pressure. There is need to continue previous medications when blood pressure is elevated and gradually withdrawn when the blood pressure normalizes. Discontinue blood pressure medications if BP is less than 110/70 mmHg or if the patient exhibits symptoms [57].

Adjunct management measures of severe hypertension in preeclampsia

Magnesium sulfate is recommended for seizure prophylaxis in preeclampsia patients with severe features (hypertension and neurological disorders or hypertension and proteinuria) [51]. This recommendation was established by a randomized placebo-controlled trial, the Magpie Trial, in which 10,000 women received either a magnesium sulfate therapy or a placebo after being diagnosed of a blood pressure of >140/90 mmHg and proteinuria measuring 30 mg/dL. Patients who were given magnesium sulfate had their risk of preeclampsia reduced by 58%. Maternal mortality also improved in this group [58]. This result was confirmed in a study that showed that pregnant preeclampsia patients had a lower incidence of seizure after a magnesium sulfate therapy compared to those who were given nimodipine [59]. Nimodipine is a calcium channel blocker. It is worth mentioning that recipients of magnesium therapy were more likely to require hydralazine for control of blood pressure [59]. The use of magnesium sulfate for seizure prophylaxis in preeclampsia patients without severe features is controversial and based on the number required to treat in order to prevent a seizure [51,52]. As such, there may be differences in recommendations for the use of magnesium sulfate as seizure prophylaxis depending on clinical scenario and resource setting [46,48,52]. Several studies have reported exaggerated hypotension upon combination of magnesium sulfate and nifedipine [55-57]. On the other hand, a retrospective case-control study did not point to the fact that nifedipine increased the risk of neuromuscular weakness and other magnesium-based side effects [58]. The ACOG therefore recommends simultaneous administration when indicated (ACOG task force 2013).

Preventing preeclampsia

Some adjunct therapies are administered to minimize one's risk of developing preeclampsia. Aspirin has been used as a preventive therapy for preeclampsia since 1979 [60]. The mechanism of action of aspirin involves reversing platelet aggregation triggered by imbalance of prostacyclin/thromboxane A2 ratio [20]. At least 30 trials have validated the efficacy of aspirin in preeclampsia prevention: with the most recent being the Aspirin for Evidence-Based Preeclampsia Prevention trial [60]. In the study, 150 mg of aspirin and placebo were administered to two groups of 798 women at risk for preeclampsia. Only 1.6% of the

women on aspirin had preterm preeclampsia compared to 4.3% of the ones who were given placebo (OR, 0.38; 95% CI, 0.20-0.74, p = 0.004) [60]. In another study, a 2017 meta-analysis of over 45 randomized studies involving a total of 20,909 pregnant women showed that aspirin had dose dependent effects and these effects correlated with the trimester (gestational age) at which the aspirin was initiated. aspirin was more effective against preeclampsia when initiated at less than 16 weeks of pregnancy at high doses. It was also effective at preventing fetal growth restriction and severe preeclampsia. However, the chances of preventing fetal growth restriction, severe preeclampsia or preeclampsia were almost zero when aspirin was initiated after 16 weeks. Also, the dose effect was nonexistent when initiated in the late phase of the gestational period [61]. As such, the European, American and British professional societies recommend aspirin for women who have a high risk for preeclampsia (for instance, women with a history of chronic hypertension, diabetes, preeclampsia, renal disease, and autoimmune disease) [46,49,62]. Epidemiological studies conducted in the 1950s showed a link between calcium supplementation or intake of calcium-rich diets with reduced rates of preeclampsia and eclampsia [63,64]. Some randomized controlled trials have confirmed this observation. A meta-analysis of 27 studies involving 18,064 women found that supplementation with calcium at high dose (≥1 g/day) drastically reduced the rates of hypertension, preeclampsia, and preterm birth [65]. The World Health Organization (WHO) recommends that people deficient in calcium should supplement with 1.5-2g of oral calcium [66]. Research is currently ongoing on the role of statins in the treatment and prevention of preeclampsia. Studies involving preclinical animal models suggests that the benefits of statins are attributed to their pleiotropic anti-inflammatory, antioxidant, and antithrombotic effects, alleviating endothelial dysfunction which is believed to be at the root preeclampsia pathogenesis. Emphasis is placed on its effects on tyrosine kinase-1 expression and nitric oxide synthesis [67]. A case series on the effect of pravastatin on preeclamptic women demonstrated that pravastatin ameliorated endothelial dysfunction and reduction in antiangiogenic biomarkers. This was discovered during analysis of their placentas. The researchers also discovered that the patient's proteinuria, uric acid levels and blood pressure were stabilized [68].

α-adrenergic agonists

Methyldopa has a long track record in pregnancy. An extensive follow-up study on infants birthed by women who had been treated with methyldopa during pregnancy did not find any underlying cognitive or general health problems [69]. This impressive safety record explains why methyldopa has been recommended by the National High Blood Pressure Education Program (NHBPEP) working group [1]. Methyldopa has a central effect. It decreases sympathetic tone, and thus may exert a couple of side effects, such as impaired sleep patterns and sedation. Methyldopa may also elevate liver enzymes which can distort diagnosis of HELLP syndrome. Methyldopa, while relatively safe, is not necessarily a BP lowering agent and its many side effects can limit its use. However, methyldopa can be taken together with other antihypertensives to attain target blood pressure levels.

The mode of action of clonidine is similar to methyldopa. However, it has a more potent effect in lowering blood pressure. It is important to note that clonidine may affect fetal growth, especially if maternal heart rate is reduced after initiation of therapy [70]. It may trigger a rebound hypertension and has a not-so-strong safety record. Clonidine should be used when the patient has low tolerance to methyldopa.

Beta blockers

The tolerance level for beta blocker in pregnancy is high. Labetalol is widely used for treatment of hypertension in pregnancy. Labetalol is a non-selective beta blocker with antagonistic effect on alpha-1 and beta receptors. Side effects of Labetalol include decreased tolerance to exercise, fatigue, and bronchospasm in patients with a reactive airway condition. Several prospective trials have compared labetalol to methyldopa. It is important to note that neither medication exerted any negative fetal or maternal outcomes [71,72]. Labetalol is available in intravenous and oral forms, implying that it may be used both for inpatient and outpatient management. Atenolol has minimal side effects on systolic blood pressure in women with preeclampsia. It also has an adverse effect on intrauterine growth [73]. It is important that atenolol be avoided in pregnancy considering that there are other more effective medications.

Non-pharmacological therapy

Weight loss, reduced salt intake and other lifestyle interventions are extremely beneficial in non-pregnant hypertensive individuals. However, prospective, randomized trials have not established any evidence that engaging in an exercise program may prevent preeclampsia in at-risk pregnant individuals [1,74] although it has shown some benefits in animal studies [75]. There is no evidence that partaking in any weight loss program can prevent preeclampsia in pregnancy [76] even though obesity constitutes a risk for preeclampsia and hypertension [77]. The Institute of Medicine recommended that women with a body mass index of 25-29.9 (overweight) prior to pregnancy should gain no more than 15-25 lbs. during pregnancy, compared to individuals with normal weight (BMI 18.5-24.9) who may gain 25-35 lbs. [78]. The new recommendations states that obese women whose BMI is greater than 30 should gain no more than 11-20 lbs. Bed rest is recommended, as studies have proven that it lowers blood pressure, reduces premature labor, and promotes diuresis [79,80].

Recommendations for future studies

There is evidence that hypertension in pregnancy increases the risk for both and acute and chronic cardiovascular disease. On the other hand, current recommendations for the management of hypertension in pregnancy have remained unchanged for many years, due to a deficit in research on the benefits of normal blood pressure in pregnancy. Several studies are ongoing (ClinicalTrials.gov – NCT01192412, NCT01351428, NCT00293735, NCT00194974, NCT01361425) with the aim of providing information on preferred therapeutic targets in pregnant women with hypertension [62]. While the research are underway, it is important that women with chronic hypertension take their anti-hypertensive medications during the period of pregnancy, while also monitoring dose adjustments and blood pressure [81]. It is recommended that patients with a history of hypertension in pregnancy be referred to cardiology or primary care. This will facilitate the control and monitoring of risk factors [63]. Affected women may have to undergo routine screening for serum creatinine, urinalysis, and blood urea nitrogen (all being parameters for renal disease). Future research should investigate the probable link between aggressive blood pressure control during hypertension in pregnancy and renal & cardiovascular disease outcomes in the affected women.

Conclusion

Hypertension in pregnancy is a prevalent complication of pregnancy. It is associated with fetal and maternal morbidity and mortality. The main objective in the management of hypertension in pregnancy is striking a balance between the benefits enjoyed by the pregnant individual due to improved control of blood pressure, and the fetal risks due to intrauterine toxicity from medications as well as a uteroplacental hypoperfusion. Delivery is the standard of care for severe forms of hypertension in pregnancy. A pre-pregnancy evaluation is recommended for women with chronic hypertension. The woman must be carefully observed during pregnancy. Research is ongoing on the effective management of hypertension in pregnancy and the maternal implications that may influence future guidelines.

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