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Management of Preeclampsia and Possible Proposed Medications for Combating Preeclampsia

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ABSTRACT

Apart from delivering the fetus, medication-assisted hypertension control is the most common treatment for PE. There are numerous options available and oral antihypertensives can be used in standard doses during pregnancy. Methyldopa has been shown to be safe for the fetus in the treatment of high blood pressure in pregnant women over a lengthy period of time. In terms of safety and efficacy, clonidine acts similarly to and is comparable to methyldopa. During pregnancy, β-blockers are also frequently used. Labetalol preserves uteroplacental blood flow better than other β-blockers. Calcium-channel antagonists have been used to treat chronic hypertension, moderate preeclampsia, and preeclampsia-related urgent hypertension in pregnant women. Women with elevated blood pressure during pregnancy are frequently prescribed diuretics. During pregnancy, nitroprusside is rarely used. Ketanserin is also used to treat hypertension in non-pregnant adults who aren't pregnant. Despite the fact that it is not recommended as an antihypertensive, magnesium sulfate has been used to prevent seizures in preeclamptic women for many years. Because it is impossible to say whether or not exposure to ACEI and ARB during the first trimester is safe, it's probably best to advice women who are attempting to conceive to switch to a different medicine. Several concepts for combating preeclampsia that are linked to potential RAS suppression are presented as alternate techniques to target the RAS. Management of preeclampsia and proposed medications for combating preeclampsia were investigated in this review study based on a variety of literatures.

Keywords: Management, Preeclampsia, Medications and Therapy

Introduction

Apart from delivering the fetus, medication-assisted hypertension control is the most common treatment for PE. All antihypertensive medications can cross the placenta. There are presently no randomized controlled trials that support the use of one antihypertensive drug over another. Certain medications, on the other hand, are effective at lowering blood pressure while simultaneously having a favorable pregnancy safety profile [1]. Treatment is determined on the severity and intensity of hypertension. It is also important to consider if parenteral or oral medication is preferred when choosing a drug. Antihypertensive medications were not used in women with severe gestational hypertension or severe preeclampsia, and data from several case studies showed that not using antihypertensive medications resulted in higher risks of heart failure, pulmonary edema, stroke, and mortality [2]. According to ACOG, a hypertensive emergency is severe hypertension that occurs quickly and lasts for 15 minutes or more [3]. Blood pressure readings of 160 mm Hg systolic or 105 - 110 mm Hg diastolic need to be treated right away [4]. Others have suggested that treatment should begin at a lower threshold of 155/105 if the primary goal is to prevent maternal cerebral hemorrhage, which is still the leading cause of mortality from preeclampsia [5]. The purpose of blood pressure control is to bring it down to a range of 140-160/90-100 mm Hg, which lowers the risk of cerebral hemorrhage. Lowering blood pressure below this level can be harmful to the fetus because placental perfusion is reduced [5,6]. Antihypertensive drugs for mild to moderate hypertension have insufficient data to judge the benefits and risks [7-10].

There are a variety of antihypertensives to choose from, and oral antihypertensives can be administered in standard doses during pregnancy. Antihypertensive drug clinical studies and evidence-based guidelines for pregnant women are desperately needed. Therapy can

begin if the blood pressure increases to 140 to 150/90 to 100 mm Hg [11]. The criteria for starting therapy and the targeted blood pressure targets in worldwide guidelines for the treatment of hypertension in pregnancy differ, but they are always higher than the Joint National Committee standards for the treatment of (non-obstetric) hypertension. Therapy is suggested in the United States for blood pressures of 160/105 mm Hg or greater [12] with no set treatment target; in Canada, therapy is recommended for blood pressures of 140 to 150/90 mm Hg or higher, with diastolic pressures of 80 to 90 mm Hg [13,14], and in those with comorbid conditions, 130 to 139/80 to 89 mm Hg; and in Australia, increases of 160/90 mm Hg or greater are recommended [15]. When preeclampsia is identified, antihypertensive medication is prescribed based on the gestational age and blood pressure level. Severe hypertension in pregnancy, defined as a blood pressure of 160/110 mm Hg or greater, should be treated to avoid intracerebral hemorrhage and maternal death [12,16].

Those with hypertensive encephalopathy, hemorrhage, or eclampsia need parenteral medication to drop blood pressure to 160/100 mm Hg over the next few hours [12]. Early-onset preeclampsia (<34 weeks) necessitates the use of antihypertensive medications and the prevention of both high (>160/110 mm Hg) and low (< 120/80 mm Hg) blood pressures. In some cases, controlling hypertension and keeping a careful check on things has been shown to allow for a 2-week delay in birth, which has been related to improved long-term outcomes [17]. In women with underlying renal impairment, a lower treatment threshold is permitted [18]. Because placental blood flow is likely reduced, it is critical to avoid hypotension when treating severe hypertension [11]. Therapy for acute severe hypertension in women with preeclampsia should be begun at lower dosages than usual since these patients may be intravascularly volume depleted and at increased risk for hypotension. When antihypertensive medication is used to treat preeclampsia, fetal monitoring is indicated to detect fetal distress, which could be caused by reduced placental perfusion.

In the past, a variety of antihypertensive drugs were used to treat PE with severe symptoms. There has, however, been no consensus on how to treat non-severe hypertension. Labetalol, nifedipine, and methyldopa are recommended as first-line treatments. Nifedipine, a calcium channel blocker, could be utilized as a first-line therapy, according to new studies [19-23]. In 2017, the Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists released a Committee Opinion advising that immediate-release oral nifedipine be used as a first-line drug when IV access is not available. The renin-angiotensin-aldosterone system blockers that should be avoided include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists [1]. Without significant symptoms, salt restriction, bed rest, and physical activity are not recommended for the prevention or treatment of PE [24].

Possible Proposed Medications for Combating Preeclampsia

The Use of Antihypertensive Drugs

Methyldopa is a medication that is often used to treat high blood pressure in pregnant women. It has also been proven to be safe for the fetus in the long run [1]. It is a α2-adrenergic agonist prodrug that's transformed to -methyl norepinephrine, which subsequently substitutes norepinephrine in the neurosecretory vesicles of adrenergic nerve terminals [25]. Blood pressure control is sluggish, lasting 6 to 8 hours, due to the indirect mechanism of action. It is not considered teratogenic based on limited data and a more than 40-year history of use in pregnancy. In a number of prospective trials in pregnant women, it was compared to placebo [26-28] or other antihypertensive medicines [28-31]. Treatment with methyldopa has been found to slow the progression of severe hypertension in pregnant women [32], with no negative consequences for uteroplacental or fetal hemodynamics [33] or fetal well-being [27]. In one placebo-controlled experiment (> 200 women with diastolic BP > 90 mm Hg at admission) [26], patients randomized to methyldopa had fewer mid pregnancy losses, but this tendency was not confirmed in a larger, more recent trial [27]. Central α2-agonism causes undesirable effects such as reduced peripheral sympathetic tone [25]. By acting on brainstem regions, these drugs decrease mental alertness and interrupt sleep, producing fatigue and sadness in some people.

Xerostomia (abnormally low salivation) is a common occurrence. The IQ and neurocognitive development of offspring exposed to methyldopa in utero were similar to controls at 7.5 years of age in the previously mentioned follow-up study [34]. In 5% of individuals, methyldopa has been related to an increase in liver enzymes, as well as hepatitis and hepatic necrosis [35]. Some people develop a positive antinuclear antigen or antiglobulin (Coombs) test after long-term use, which can lead to severe hemolytic anemia. In certain cases, medications from different classes are used instead.Clonidine, a selective α2-agonist, is safe and effective in the same way as methyldopa [36], but a short controlled follow-up study of 22 neonates discovered an excess of sleep disturbance in clonidine-exposed newborns, which is cause for concern [37]. It's usually prescribed as a last-resort treatment for pregnant women with resistant hypertension. During pregnancy, β-blockers are frequently used. Despite several randomized trials comparing β-blockers to placebo or other medicines [29,30,38,39], there are still unresolved issues with their use in pregnancy due to a few small studies that found a relationship with lower birth weight infants. None of the β-blockers have been shown to be teratogenic. Except for atenolol, which was started at 12 to 24 weeks of pregnancy and resulted in clinically significant fetal growth restriction and decreased placental weight compared to placebo in one small study, individual agents were not distinguishable in their perinatal effects [40,41]. This finding was confirmed by additional retrospective studies comparing atenolol to other treatments [42].

There is the potential for clinically significant differences between -blockers due to differences in lipid solubility and receptor selectivity, although this has not been investigated in pregnancy. Despite the fact that labetalol (together with oral methyldopa, nifedipine, and hydralazine) did not appear to cause neonatal heart rate effects in a systematic review of studies, oral -blockers have been related to non–clinically significant neonatal bradycardia [9,43,44]. In one out of every six babies, parenteral treatment has been observed to increase the incidence of neonatal bradycardia necessitating intervention [9]. Parenteral therapy has been shown to increase the risk of newborn bradycardia, requiring intervention in one out of every six babies [9]. A one-year postpartum follow-up study found that infants who were exposed to atenolol during pregnancy developed normally, offering more assurance [45]. β-blockers improve maternal outcomes by effectively controlling maternal blood pressure, lowering the incidence of severe hypertension, and lowering the rate of preterm admission to the hospital [9]; in a recent Cochrane analysis, they were found to be more effective in lowering blood pressure than methyldopa in ten trials [7].

Labetalol is a nonselective β-blocker that lowers blood pressure by inhibiting β- and α-adrenergic receptors. Furthermore, it can better preserve uteroplacental blood flow than other β-blockers [1]. It has a speedier onset of impact as compared to methyldopa (2 hours). It is taken intravenously to treat severe hypertension, and many individuals prefer it to hydralazine because it has less adverse effects like maternal hypotension [46]. In randomized clinical trials comparing it to either methyldopa or nifedipine, labetalol has also been shown to be safe for use during pregnancy [47,48]. When given orally to women with chronic hypertension, it appears to be as safe [27,31,49,50], and effective as methyldopa, while higher doses have been related to neonatal hypoglycemia [51]. In the CHIPS (Control of Hypertension in Pregnancy Study), however, preeclamptic women treated with methyldopa may have had better outcomes than those treated with labetalol [52]. Hepatotoxicity in the mother has also been associated to labetalol. This side effect must be distinguished from the HELLP syndrome (hemolysis, increased liver enzymes, and low platelet count). Although the majority of cases of labetalol-induced hepatotoxicity are reversible, fatalities have been reported [53].

Furthermore, deleterious consequences of β-receptor blockade are possible. Fatigue, lethargy, exercise intolerance, peripheral vasoconstriction, sleep disturbance, and bronchoconstriction are all potential side effects; however, withdrawal due to side effects is uncommon [7]. Peripherally acting α1-adrenergic antagonists are second-line hypertension medicines in non-pregnant individuals. Both prazosin and phenoxybenzamine have been used to treat hypertension caused by a suspected pheochromocytoma during pregnancy; after β-blocker has been accomplished, -blockers have been used as adjuvant medications [54,55]. These agents cannot be recommended for regular use due to a lack of experience with them in pregnancy. Calcium-channel antagonists have been used to treat chronic hypertension, moderate preeclampsia, and preeclampsia-related urgent hypertension in pregnant women [25]. Nifedipine (Adalat) and verapamil, when taken orally, do not appear to be teratogenic to fetuses [56].

Although nicardipine [57,58], isradipine [59], felodipine, Renedil [60], and verapamil [61] have been reported, most researchers have focused on nifedipine. The calcium channel blocker nifedipine has been used successfully during pregnancy. Long-acting nifedipine is preferred to short-acting nifedipine since the latter can cause a significant reduction in blood pressure, which can lead to uteroplacental perfusion loss. If an immediate treatment is needed but the patient does not have access to an IV, oral nifedipine (10 mg) can be given and repeated in 30 minutes [21]. PO nifedipine appears to be as effective as IV labetalol in the treatment of significant blood pressure rises [62]. Because of the delayed beginning to peak, oral labetalol is less effective in lowering blood pressure at first and should only be used if nifedipine is not available in a patient without IV access [62]. Long-acting nifedipine is available as 30–90 mg sustained-release tablets that can be used once a day. Every 7 to 14 days, the dosage can be increased to a maximum of 120 milligrams per day [63]. However, in some cases, immediate-release oral nifedipine may be indicated for a safe blood pressure lowering [1].

Amlodipine, a dihydropyridine calcium channel blocker routinely used to treat hypertension in non-pregnant hypertensive people, has not been extensively studied in pregnancy. Although there is only one small case series in pregnancy that we are aware of, it is frequently used and appears to be safe [64]. In pregnant women, calcium-channel blockers can cause tachycardia, palpitations, peripheral edema, migraines, and facial flushing [65]. Nifedipine appears to have little effect on uterine blood flow [66,67]. Short-acting dihydropyridine calcium antagonists are no longer recommended for the treatment of hypertension in nonpregnant patients, especially when administered sublingually, due to reports of myocardial infarction and mortality in hypertensive patients with coronary artery disease [68]. Short-acting nifedipine capsules have been connected to maternal hypotension and fetal discomfort in case reports [69,70]. Parenteral labetalol or hydralazine should be taken until the desired blood pressure target is reached if fast blood pressure control is needed. In pregnant women with severe hypertension, long-acting oral nifedipine has been demonstrated to be efficacious and safe [71], and given the danger of fetal injury from short-acting sublingual nifedipine [69,70] the long-acting formulation is suggested. Using calcium antagonists to control blood pressure in preeclampsia is complicated by the use of magnesium sulfate to prevent seizures; additive effects between nifedipine and magnesium sulfate have been reported in a few cases, resulting in neuromuscular blockade, myocardial depression, or circulatory collapse [72-74]. However, in practice, these medications are regularly used simultaneously [11,75,76], and a recent study [77] indicated that they can be given concurrently without raising risk.

Diuretics can be taken during pregnancy (with an attempt to minimize the dose) or in combination with other medicines, according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [12]. Low doses (12.5-25 mg/d) may help to avoid undesired metabolic effects such as impaired glucose tolerance and hypokalemia in women who are currently taking hydrochlorothiazide [11]. Triamterene and amiloride appear to be non-teratogenic based on a small number of case reports [11]. Spironolactone is not recommended because of antiandrogenic effects seen in animal models during fetal development, despite the fact that this hasn't been validated in a single clinical case [78]. IV labetalol or hydralazine are the first-line treatments for pregnant women with dangerously high blood pressure (160/105-110 mm Hg) [3,4]. Hydralazine is a direct vasodilator of the arterioles. Intravenous hydralazine has been routinely utilized in the treatment of severe hypertension associated with pregnancy [1]. It is most useful in the treatment of severe hypertension that requires immediate attention, or as a third-line medicine for refractory hypertension that hasn't responded to prior treatments [25]. Parenteral therapy can help manage severe hypertension promptly and can be administered orally, intramuscularly, or intravenously. Excessive vasodilation or reflex sympathetic activation can cause headaches, nausea, flushing, and palpitations, among other symptoms. In rare cases, chronic use can lead to pyridoxine-responsive polyneuropathy or immunologic reactions such drug-induced lupus-like disease.

Although hydralazine had a slightly greater rate of adverse events than labetalol in a meta-analysis, the evidence was insufficient to recommend one treatment over the other [46]. The hypotensive effect of hydralazine is less predictable than that of other parenteral medications. Despite reports of neonatal thrombocytopenia and lupus, hydralazine has been used in all three trimesters of pregnancy with no indication of teratogenicity [79]. Furthermore, the common side effects of hydralazine, such as headache, nausea, and vomiting, are comparable to the symptoms of preeclampsia. The consequences on uteroplacental blood flow are unknown, most likely related to changes in reflex sympathetic activation levels, and fetal discomfort could result from a sudden drop in maternal pressure [80-82]. Isosorbide dinitrate, a nitric oxide donor that operates mostly on capacitance arteries, was investigated in a limited study of pregnant women with gestational hypertension and preeclampsia [25]. Despite significant fluctuations in maternal blood pressure, cerebral perfusion pressure was unaffected, reducing the risk of ischemia and infarction when blood pressure was lowered [83].

Sodium nitroprusside is a nonselective nitric oxide donor that relaxes arteriolar and venular vascular smooth muscle. When delivered by continuous intravenous infusion, it has a near-immediate start of action and 3-minute duration of effect, making it simple to titrate. Nitroprusside metabolism produces cyanide, which is hazardous at high infusion rates; cyanide is converted to thiocyanate, which is toxic after 24 to 48 hours of infusion unless excretion is delayed owing to renal insufficiency. Only in life-threatening refractory hypertension in the days coming up to delivery is nitroprusside used during pregnancy [84]. Excessive vasodilation and cardioneurogenic (i.e. paradoxic bradycardia) syncope can occur in volume-depleted preeclamptic women [85]. The danger of fetal cyanide intoxication is unknown; in a study of 24 exposed fetuses, a review of the literature showed no link between sodium nitroprusside use and fetal death [86]. Serotonin-induced vasodilation and the subsequent release of prostacyclin and nitric oxide are mediated by S1 receptors [25]. Because of endothelial dysfunction and the loss of endothelial S1 receptors, serotonin responds only with S2 receptors during pregnancy, resulting in vasoconstriction and platelet aggregation. Ketanserin is an S2 receptor antagonist that helps non-pregnant persons with acute or chronic hypertension lowers their systolic and diastolic blood pressure. Ketanserin has not been found to be teratogenic in animals or humans, and it has been studied in small trials during pregnancy, primarily in Australia and South Africa, suggesting that it may be safe and effective in the treatment of chronic hypertension in pregnancy, preeclampsia, hemolysis elevation of liver enzymes, and low platelet syndrome [87,88].

Despite the fact that magnesium sulfate is not recommended as an antihypertensive, it has long been used to treat recurrent seizures in eclamptic women and to prevent seizures in preeclamptic women with severe symptoms. Limited double-blind, placebo-controlled trials, on the other hand, have found no significant difference in the onset of eclampsia between patients with pre-eclampsia without severe symptoms who were given magnesium sulfate and those who were given placebo [89]. "It is suggested that magnesium sulfate may not be administered universally for the prevention of eclampsia for women with preeclampsia with a systolic blood pressure of less than 160 mmHg and a diastolic blood pressure of less than 110 mmHg and no maternal symptoms," according to ACOG recommendations from 2013. In other words, the ACOG only advises magnesium sulfate for preventing eclampsia in people who have a blood pressure of 160/110 or above, or who have other severe symptoms that generally accompany seizures. Magnesium sulfate has been shown to be more successful in avoiding recurrent seizures in eclampsia than other common anticonvulsants such as phenytoin and diazepam, as well as lytic cocktails [90,91]. Magnesium sulfate's method of action in preventing seizures is uncertain; however, it is thought to be linked to its effects on the central nervous system, possibly via NMDA receptors, calcium channels, and acetylcholine. The idea that taking magnesium sulfate and nefidipine at the same time will induce serious side effects such hypotension and neuromuscular inhibition is baseless, despite the lack of evidence [77].

Although the FDA classifies angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) as class D drugs, we treat them as if they are contraindicated, especially in the second and third trimesters, due to fetal kidney injury linked to reduced perfusion [25]. Prenatal dysgenesis, oligohydramnios due

to fetal oliguria, calvarial and pulmonary hypoplasia, intrauterine growth restriction, and catastrophic newborn anuric renal failure, which is associated to Potter's syndrome (ie, bilateral renal agenesis), have all been linked to use [92,93]. ARB use during pregnancy has been associated to fetal kidney abnormalities and death, which have all been linked to renal failure [94-96]. Because it's impossible to say whether or not exposure to ACEI and ARB throughout the first trimester is safe, it's probably best to advice women who are attempting to conceive to switch to different medications. However, among people who become pregnant unintentionally while using ACEI or ARBs, the risk of birth defects increases from 3% to 7% [97]; thus, termination of the pregnancy is not recommended.

Cooper and colleagues studied a cohort of 29,507 babies who were enrolled in Tennessee Medicaid and whose mothers showed no indications of diabetes. After accounting for confounders, they discovered that 7.1 percent of newborns exposed to ACEIs in the first trimester had major congenital abnormalities, which was 2.7 times higher than infants treated to antihypertensive treatment at any point during pregnancy [97]. In addition, congenital anomalies are associated to maternal diabetes, obesity, and overweight [98-100]. The link between maternal use of ACEIs or other antihypertensive medicines in the first trimester and congenital malformations in newborns was investigated in a record linkage study utilizing the Swedish Medical Birth Register [101]. Preterm birth, placental abruption, caesarean delivery, and labor induction were all found to be more likely in women taking antihypertensive drugs. The outcomes of 91 pregnant women who took an ACE inhibitor or an ARB throughout their first trimester were studied.

Six children (10.2 percent) out of 71 born to women taking an ACEI had developmental abnormalities, including minor ventricular septal defect (1.4 percent), mild sensorineural deafness (1.4 percent), mild microcephaly (1.4 percent), hypospadias (1.4 percent), umbilical hernia (1.4 percent), and moderate congenital hypotonia (1.4 percent) [101]. The two developmental anomalies found in the 20 pregnancies that occurred while using an ARB were inguinal hernia (5%) and craniosynostosis with tower skull (5%). There was no clear evidence of an increased risk of congenital malformations in women who took ACEI or ARB during early pregnancy, according to this study [102]. Porta, et al. published the results of 615 women with type I diabetes and no retinopathy and 813 women with type I diabetes and mild to moderately severe nonproliferative retinopathy were given candesartan (32 mg/day) or placebo.

0 to 8 weeks after their last menstrual cycle, 42 women on candesartan and 45 women on placebo became pregnant and quit taking the medicine. Despite the fact that no woman remained on candesartan after eight weeks of pregnancy, the average length of time women were exposed to it is unknown [103]. There was no difference in pregnancy outcomes between the two groups, and there was no increase in the rate of neonatal deformity. Two stillbirths and two "sick infants" occurred in the candesartan group, while one stillbirth, eight "sick babies," and one ventricular septal defect occurred in the placebo group [103]. Li et al. also looked at 465,754 pregnant women in Northern California and their live-born children. The study did not include women who were taking an ARB while pregnant. Women who had been diagnosed with hypertension but had not taken any antihypertensive drugs while pregnant and those who had neither a diagnosis of hypertension nor a record of any antihypertensive drug prescriptions served as controls. The offspring of women who used either ACEIs or other antihypertensive medicines during the first trimester of pregnancy, or who had hypertension but did not take antihypertensive drugs, had a similar elevated risk of congenital cardiac defects [104].

During late pregnancy (119–133 days of gestation—term is 147 days), captopril (2.8–3.5 mg/kg) reduced maternal blood pressure for 2 hours in pregnant sheep. On the other hand, fetal blood pressure was reduced for up to two days [105]. The pressor response was generated by an intravenous bolus of ATI blocker (167–426 ng/kg). Once the Ewe's blood pressure had stabilized, captopril was given to her again. All ewes and fetuses had decreased basal blood pressure 10 minutes after receiving captopril injection. Stillbirth was a significant risk, and 7 of the 8 ewes had stillborn lambs. Captopril (3.3 mg) caused a 37 percent stillbirth rate in late gestational-age rabbits (24–28 days gestation—term is 31 days), compared to 6 percent in saline control rabbits [105]. Harewood et al. looked into whether reduced maternal blood pressure was associated to fetal deaths and discovered that fetal mortality was most likely due to the direct action of enalapril (7.5 mg/day) on the fetal RAS rather than placental ischemia. There were no prenatal abnormalities found during the postmortem assessment of the dead fetuses [106]. Reduced uteroplacental blood flow, low birth weight, fetal hypotension, preterm delivery, and fetal death have all been linked to ACEI usage in the second and third trimesters in animal studies. Reduced fetal renal function and urine production, which can lead to oligohydramnios with fetal anuria, neonatal hypotension, renal failure, and hypocalvaria, are the most commonly observed adverse effects of ACEIs or ARBs taken in the second or third trimester [93,107-109]. Prenatal exposure to ACEIs or ARBs during the first trimester, according to previous studies, is unlikely to produce fetal malformations. On the other hand, fetal exposure to ACEIs or ARBs during the second or third trimester has been associated to fetal malformations. ACEIs and ARBs should be avoided by women who are pregnant or may become pregnant.

Alternative Therapies

Suppression of the RAS would potentially be useful in the treatment of preeclampsia; however, due to the side effects associated with RAS suppressing medications, this class of drugs is not recommended for the treatment of preeclamptic women [110]. As an alternative to targeting the RAS, some options for treating preeclampsia that are connected to potential RAS suppression are presented.

Rest and Physical Activity

Preeclampsia is a disorder that occurs when the volume of plasma in the mother's blood becomes too low during pregnancy [111]. Exercise is thought to decrease placental perfusion, whereas bed rest is thought to increase placental perfusion in pregnant women, a condition that may be associated to the onset of preeclampsia [112]. Spontaneous miscarriage, early labor, fetal development retardation, edema, persistent hypertension, and preeclampsia have all been treated with bed rest during pregnancy [110]. The effects of bed rest in the treatment of preeclampsia, on the other hand, are still debated [113]. Deep vein thrombosis and pulmonary embolism, to name a few, are risks of rest [114]. The WHO does not recommend home rest or strict bed rest to avoid preeclampsia or improve pregnancy outcomes in women who already have it [115]. Exercise has an effect on the renin-angiotensin system. In those with heart failure, physical activity has been proven to lower oxidative stress, increase nitric oxide (NO), and decrease ANG II levels [116]. Physical activity, whether occupational or recreational, has been associated to a lower incidence of preeclampsia in epidemiological studies [117]. However, because there is just a small amount of evidence in the literature [117-119], it is impossible to say whether interventional physical activity improves the course of preeclampsia [110].

Antioxidants

It has been claimed that oxidative stress raises the risk of essential hypertension and preeclampsia through reducing NO bioavailability [120,121]. In animal studies, ATII increases vascular superoxide production, which reduces the physiological impact of endothelium-derived NO [122]. Endothelium-dependent forearm vasodilation is reduced in humans when ANG II is blocked, although vitamin C improves endothelial dysfunction [123]. Certain researchers have looked at the effects of antioxidant supplementation with vitamins C and E on the risk of preeclampsia. Pregnant women between the ages of 9 and 16 weeks of pregnancy, or 14 and 22 weeks of pregnancy, were given a daily vitamin C and 400 IU vitamin E medication or a placebo until they gave birth [110]. Vitamin C and E supplementation from 9 to 16 weeks of pregnancy or from 14 to 22 weeks of pregnancy till delivery had no influence on the rate of preeclampsia [121,124]. Previous study has connected low maternal serum 25-hydroxy vitamin D (25(OH)D levels to a higher risk of preeclampsia, and vitamin D treatment has been proven to lower that risk [125]. People with 25(OH)D insufficiency (15.0 to 29.9 ng/mL) and deficit ((<15.0 ng/mL) exhibited higher circulating ANG II levels than people with normal 25(OH) D levels (≥30.0 ng/mL) [110]. Furthermore, when compared to those with adequate vitamin D levels (145 mL/min/1.73 m2), those with vitamin D deficiency (115 mL/min/1.73 m2) had considerably slower renal plasma flow responses to injected ATII [126].

Anticoagulation Therapies

Preeclampsia causes thrombocytopenia, disseminated intravascular coagulation, and platelet aggregation [110]. Abnormal placental development can potentially lead to placental ischemia. In vitro, aspirin suppresses AT1R and VEGF expression in HMVECs mediated by ANG II [127]. Preeclampsia can be prevented by taking antiplatelet medicines every day, especially low-dose aspirin, as early as the second trimester. Although no detrimental effects have been identified, there is a lack of long-term evidence [128,129]. CLASP demonstrated that low-dose aspirin did not diminish the incidence of proteinuric preeclampsia in 9364 women who were randomly administered 60 mg aspirin or a placebo daily [130]. Furthermore, Kyle et al. discovered that starting low-dose aspirin (60 mg/day) at 28 weeks of pregnancy did not prevent preeclampsia in ATII-sensitive women [131]. In 2014, the US Preventive Services Task Force (USPSTF) recommended that women who are at high risk for preeclampsia after 12 weeks of pregnancy take low-dose aspirin (81 mg/day) as a preventive drug [128].

COMT and 2ME

In pregnant mice deficient in COMT, the absence of 2ME, a natural metabolite of estradiol that is high throughout the third trimester of normal human pregnancy, caused a preeclampsia-like phenotype [132,133]. COMT is a catabolic enzyme that degrades a wide range of bioactive chemicals, such as catecholamines and catecholestrogens [110]. COMT transforms 17-hydroxyestradiol to 2ME as a rate-limiting step in estrogen degradation, using 17-hydroxyestradiol as a substrate. The concentration of maternal 2ME in the blood grows fast during a normal pregnancy; however, levels of COMT and 2ME are substantially lower in women with severe preeclampsia [132-134]. Hydralazine is well-known for its use in preeclampsia treatment. On the other hand, hydralazine reduces placental COMT activity [135], thus clinicians should use it with caution. In Comt(-/-) pregnant mice, 2ME has been shown to ameliorate all preeclampsia-like symptoms without producing toxicity, as well as diminish placental hypoxia, HIF-1 expression, and enhanced sFLT-1 expression [132]. Furthermore, 2ME may prevent vasospasm in pregnant women by acting as a direct vasodilator [136]. 2ME inhibits the AT1 receptor in vascular smooth muscle cells [137]. 2ME also inhibits HIF-1α, which helps to reduce preeclampsia's restricted trophoblast invasion. 2ME (Panzem), an anticancer drug that inhibits HIF-1α [138-140], is now being investigated in phase II clinical studies. As a result, 2ME is now a drug that may be used orally. 2ME could be utilized to treat preeclampsia if it is proved to be safe in pregnant women [110].

Nutritional intervention, on the other hand, can aid in the better functioning of the COMT-2ME system during pregnancy. Because homocysteine is converted to S-adenosyl homocysteine (SAH), a potent COMT inhibitor, high homocysteine levels may be associated to an increased risk of preeclampsia. Folic acid functions by remethylating homocysteine and changing it to methionine [136,137,141,142]. Supplementing with folic acid throughout the second trimester has been associated to a lower risk of preeclampsia [137]. COMT can be reduced by a variety of endogenous and exogenous substances, including as polychlorinated biphenols (PCBs), dioxins, mercury, and SAH.

As a result, from an epidemiological approach, avoiding exposure to such ambient COMT suppressors would be relevant to the design of any antipreeclampsia medication [110].

Conclusion

The goal of blood pressure regulation is to lower it down to a range of 140-160/90-100 mm Hg rather than "normal." Various antihypertensive medicines have previously been used to treat PE with severe symptoms. Methyldopa is a medication that is often used to treat high blood pressure in pregnant women. Blood pressure regulation is delayed due to the indirect mechanism of action, with no negative impacts on uteroplacental or fetal hemodynamics or fetal welfare. Clonidine, a selective α2-agonist, is largely used as a third-line treatment for pregnant women with refractory hypertension. There is the potential for clinically significant differences between β-blockers due to differences in lipid solubility and receptor selectivity, although this has not been investigated in pregnancy. By efficiently managing maternal blood pressure, lowering the incidence of severe hypertension, and lowering the rate of preterm admission to the hospital, β-blockers improve maternal outcomes.

Many patients prefer labetalol to hydralazine for treating severe hypertension because of the reduced risk of maternal hypotension and other negative effects. Nifedipine, a calcium channel blocker, has been successfully used during pregnancy. During pregnancy, diuretics can be used as needed. Intravenous hydralazine has been routinely utilized in the treatment of severe hypertension associated with pregnancy. Nitroprusside is only used in the days coming up to delivery in cases of life-threatening refractory hypertension. Many patients prefer labetalol to hydralazine for treating severe hypertension because of the reduced risk of maternal hypotension and other negative effects. Nifedipine, a calcium channel blocker, has been successfully used during pregnancy. During pregnancy, diuretics can be used as needed. Intravenous hydralazine has been routinely utilized in the treatment of severe hypertension associated with pregnancy. Nitroprusside is only used in the days coming up to delivery in cases of life-threatening refractory hypertension. On the other hand, fetal exposure to ACEIs or ARBs during the second or third trimester has been associated to fetal malformations. Several ideas to treat preeclampsia that are connected with probable RAS inhibition are presented, including the use of rest and physical activity, antioxidants, anticoagulant therapy, and avoiding exposure to COMT and 2ME suppressors, among others.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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This study did not receive any funding.

Authors' Contributions

LM had participated in the design of the study, data analyses, and manuscript preparation; and the authors could have read and approved the final manuscript.

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References

1. Odigboegwu O, Pan L, Chatterjee P (2018) Use of Antihypertensive Drugs During Preeclampsia. Front Cardiovasc Med 5: 50.
2. Magee L, Abalos E, von Dadelszen P, Sibai B, Easterling T, et al. (2011) How to manage hypertension in pregnancy effectively. Br J Clin Pharmacol 72: 394-401.
3. (2011) ACOG. Committee Opinion no. 514: Emergent therapy for acute-onset, severe hypertension with preeclampsia or eclampsia. Obstet Gynecol 118: 1465-1468.
4. (2022) ACOG. Diagnosis and Management of Preeclampsia and Eclampsia #33. American Congress of Obstetricians and Gynecologists.
5. Martin J, Thigpen B, Moore R, Rose C, Cushman J, et al. (2005) Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. Obstet Gynecol 105: 246-254.
6. Creasy R, Resnik R, Iams J, Lockwood C, Moore T (2008) Creasy & Resnik's Maternal Fetal-Medicine: Principles and Practice. Vol. Sixth Edition. Philadelphia, USA: Elsevier Saunders, pp. 673.
7. Abalos E, Duley L, Steyn D, Henderson-Smart D (2007) Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 1: CD002252.
8. Von Dadelszen P, Magee L (2005) Antihypertensive medications in management of gestational hypertensionpreeclampsia. Clin Obstet Gynecol 48: 441-459.
9. Magee L, Ornstein M, von Dadelszen P (1999) Fortnightly review: management of hypertension in pregnancy. BMJ 318: 1332-1336.
10. Von Dadelszen P, Ornstein M, Bull S, Logan A, Koren G, et al. (2000) Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. Lancet 355: 87-92.
11. Magee L (2001) Drugs in pregnancy. Antihypertensives. Best Pract Res Clin Obstet Gynaecol 15: 827-845.

12. (2000) Report of the National High Blood Pressure Education Program Working Group. High blood pressure in pregnancy. Am J Obstet Gynecol 183: S1-22.

13. Helewa M, Burrows R, Smith J, Williams K, Brain P, et al. (1997) Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. CMAJ 157: 715-725.

14. Magee L (2008) Diagnosis, evaluation, and management of thehypertensive disorders of pregnancy. J Obstet Gynaecol Can 30: S1.

15. Brown M, Hague W, Higgins J, Lowe S, McCowan L, et al. (2000) The detection, investigation and management of hypertension in pregnancy: full consensus statement. Aust N Z J Obstet Gynaecol 40: 139-155.

16. Rey E, LeLorier J, Burgess E, Lange I, Leduc L (1997) Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. CMAJ 157: 1245-1254.

17. Withagen M, Wallenburg H, Steegers E, Hop W, Visser W (2005) Morbidity and development in childhood of infants born after temporising treatment of early onset pre-eclampsia. BJOG 112: 910-914.

18. Sibai B (2002) Chronic hypertension in pregnancy. Obstet Gynecol 100: 369-377.

19. Duley L, Henderson-Smart D, Meher S (2006) Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev 3: CD001449.

20. Vermillion S, Scardo J, Newman R, Chauhan S (1999) A randomized, doubleblind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. Am J Obstet Gynecol 181: 858-861.

21. Raheem I, Saaid R, Omar S, Tan P (2012) Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG 119: 78-85.

22. Shekhar S, Sharma C, Thakur S, Verma S (2013) Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy: a randomized controlled trial. Obstet Gynecol 122: 1057-1063.

23. Rezaei Z, Sharbaf F, Pourmojieb M, Youefzadeh-Fard Y, Motevalian M, et al. (2011) Comparison of the efficacy of nifedipine and hydralazine in hypertensive crisis in pregnancy. Acta Med Iran 49: 701-706.

24. (2013) ACOG. Hypertension in Pregnancy: Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 122: 1122–1131.

25. Podymow T, August P (2011) Antihypertensive drugs in pregnancy. Semin Nephrol 31: 70-85.

26. Redman C (1976) Fetal outcome in trial of antihypertensive treatment in pregnancy. Lancet 2: 753-756.

27. Sibai B, Mabie W, Shamsa F, Villar M, Anderson G (1990) A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy. Am J Obstet Gynecol 162: 960-967.

28. Leather H, Humphreys D, Baker P, Chadd M (1968) A controlled trial of hypotensive agents in hypertension in pregnancy. Lancet 2: 488-490.

29. Fidler J, Smith V, Fayers P, De Swiet M (1983) Randomised controlled comparative study of methyldopa and oxprenolol in treatment of hypertension in pregnancy. Br Med J (Clin Res Ed) 286: 1927-1930.

30. Gallery E, Ross M, Gyory A (1985) Antihypertensive treatment in pregnancy: analysis of different responses to oxprenolol and methyldopa. Br Med J (Clin Res Ed) 291: 563-566.

31. Plouin P, Breart G, Maillard F, Papiernik E, Relier J (1988) Comparison of antihypertensive efficacy and perinatal safety of labetalol and methyldopa in the treatment of hypertension in pregnancy: a randomized controlled trial. Br J Obstet Gynaecol 95: 868-876.

32. Redman C, Beilin L, Bonnar J (1977) Treatment of hypertension in pregnancy with methyldopa: blood pressure control and side effects. Br J Obstet Gynaecol 84: 419-426.

33. Montan S, Anandakumar C, Arulkumaran S, Ingemarsson I, Ratnam S (1993) Effects of methyldopa on uteroplacental and fetal hemodynamics in pregnancy-induced hypertension. Am J Obstet Gynecol 168: 152-156.

34. Cockburn J, Moar V, Ounsted M, Redman C (1982) Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet 1: 647-649.

35. Schweitzer I, Peters R (1974) Acute submassive hepatic necrosis due to methyldopa. A case demonstrating possible initiation of chronic liver disease. Gastroenterology 66: 1203-1211.

36. Horvath J, Phippard A, Korda A, Henderson-Smart D, Child A, et al. (1985) Clonidine hydrochloride—a safe and effective antihypertensive agent in pregnancy. Obstet Gynecol 66: 634-638.

37. Huisjes H, Hadders-Algra M, Touwen B (1986) Is clonidine a behavioural teratogen in the human? Early Hum Dev 14: 43-48.

38. Rubin P, Butters L, Clark D, Reynolds B, Sumner D, et al. (1983) Placebo-controlled trial of atenolol in treatment of pregnancy-associated hypertension. Lancet 1: 431-434.

39. Paran E, Holzberg G, Mazor M, Zmora E, Insler V (1995) Beta-adrenergic blocking agents in the treatment of pregnancy-induced hypertension. Int J Clin Pharmacol Ther 33: 119-123.

40. Magee L, Duley L (2000) Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 4: CD002863.

41. Butters L, Kennedy S, Rubin P (1990) Atenolol in essential hypertension during pregnancy. BMJ 301: 587-589.

42. Lip G, Beevers M, Churchill D, Shaffer L, Beevers D (1997) Effect of atenolol on birth weight. Am J Cardiol 79: 1436-1438.

43. Magee L, Elran E, Bull S, Logan A, Koren G (2000) Risks and benefits of beta-receptor blockers for pregnancy hypertension: overview of the randomized trials. Eur J Obstet Gynecol Reprod Biol 88: 15-26.

44. Waterman E, Magee L, Lim K, Skoll A, Rurak D, et al. (2004) Do commonly used oral antihypertensives alter fetal or neonatal heart rate characteristics? A systematic review. Hypertens Pregnancy 23: 155-169.

45. Reynolds B, Butters L, Evans J, Adams T, Rubin P (1984) First year of life after the use of atenolol in pregnancy associated hypertension. Arch Dis Child 59: 1061-1063.

46. Magee L, Cham C, Waterman E, Ohlsson A, von Dadelszen P (2003) Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ 327: 955-960.

47. Peacock W, Hilleman D, Levy P, Rhoney D, Varon J (2012) A systematic review of nicardipine vs labetalol for the management of hypertensive crises. Am J Emerg Med 30: 981-993.

48. Molvi S, Mir S, Rana V, Jabeen F, Malik A (2012) Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. Arch Gynecol Obstet 285: 1553-1562.

49. Pickles C, Symonds E, Pipkin F (1989) The fetal outcome in a randomized double-blind controlled trial of labetalol versus placebo in pregnancy-induced hypertension. Br J Obstet Gynaecol 96: 38-43.

50. Sibai B, Gonzalez A, Mabie W, Moretti M (1987) A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. Obstet Gynecol 70: 323-327.

51. Munshi U, Deorari A, Paul V, Singh M (1992) Effects of maternal labetalol on the newborn infant. Indian Pediatr 29: 1507-1512.

52. Magee L, von Dadelszen P, Singer J, Lee T, Rey E, et al. (2016) Do labetalol and methyldopa have different effects on pregnancy outcome? Analysis of data from the Control of Hypertension In Pregnancy Study (CHIPS) trial. BJOG 123: 1143-1151.

53. Clark J, Zimmerman H, Tanner L (1990) Labetalol hepatotoxicity. Ann Intern Med 113: 210-213.

54. Freier D, Thompson N (1993) Pheochromocytoma and pregnancy: the epitome of high risk. Surgery 114: 1148-1152.

55. Grodski S, Jung C, Kertes P, Davies M, Banting S (2006) Phaeochromocytoma in pregnancy. Intern Med J 36: 604-606.

56. Magee L, Schick B, Donnenfeld A, Sage S, Conover B, et al. (1996) The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. Am J Obstet Gynecol 174: 823-828.

57. Bartels P, Hanff L, Mathot R, Steegers E, Vulto A, et al. (2007) Nicardipine in pre-eclamptic patients: placental transfer and disposition in breast milk. BJOG 114: 230-233.

58. Jannet D, Carbonne B, Sebban E, Milliez J. Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial. Obstet Gynecol 84: 354-359.

59. Wide-Swensson D, Ingemarsson I, Lunell N, Forman A, Skajaa K, et al. (1995) Calcium channel blockade (isradipine) in treatment of hypertension in pregnancy: a randomized placebo-controlled study. Am J Obstet Gynecol 173: 872-878.

60. Casele H, Windley K, Prieto J, Gratton R, Laifer S (1997) Felodipine use in pregnancy. Report of three cases. J Reprod Med 42: 378-381.

61. Belfort M, Anthony J, Buccimazza A, Davey D (1990) Hemodynamic changes associated with intravenous infusion of the calcium antagonist verapamil in the treatment of severe gestational proteinuric hypertension. Obstet Gynecol 75: 970-974.

62. Tuffnell D, Jankowitcz D, Lindow S, Lyons G, Mason G, et al. (2005) Outcomes of severe preeclampsia/eclampsia in Yorkshire 1999/2003, Yorkshire Obstetric Critical Care Group. BJOG 112: 875-880.

63. Smith P, Anthony J, Johanson R (2000) Nifedipine in pregnancy. BJOG 107: 299-307.

64. Ahn H, Nava-Ocampo A, Han J, Choi J, Chung J, et al. (2007) Exposure to amlodipine in the first trimester of pregnancy and during breastfeeding. Hypertens Pregnancy 26:179-187.

65. Papatsonis D, Lok C, Bos J, Geijn H, Dekker G (2001) Calcium channel blockers in the management of preterm labor and hypertension in pregnancy. Eur J Obstet Gynecol Reprod Biol 97: 122-140.

66. Lindow S, Davies N, Davey D, Smith J (1988) The effect of sublingual nifedipine on uteroplacental blood flow in hypertensive pregnancy. Br J Obstet Gynaecol 95: 1276-1281.

67. Rizzo G, Arduini D, Mancuso S, Romanini C (1987) Effects of nifedipine on umbilical artery velocity waveforms in healthy human fetuses. Gynecol Obstet Invest 24: 151-154.

68. Furberg C, Psaty B, Meyer J Nifedipine (1995) Doserelated increase in mortality in patients with coronary heart disease. Circulation 92: 1326-1331.

69. Impey L (1993) Severe hypotension and fetal distress following sublingual administration of nifedipine to a patient with severe pregnancy induced hypertension at 33 weeks. Br J Obstet Gynaecol 100: 959-961.

70. Puzey M, Ackovic K, Lindow S, Gonin R (1991) The effect of nifedipine on fetal umbilical artery Doppler waveforms in pregnancies complicated by hypertension. S Afr Med J 79: 192-194.

71. Brown M, Buddle M, Farrell T, Davis G (2002) Efficacy and safety of nifedipine tablets for the acute treatment of severe hypertension in pregnancy. Am J Obstet Gynecol 187: 1046-1050.

72. Ales K (1990) Magnesium plus nifedipine. Am J Obstet Gynecol 162: 288.

73. Waisman G, Mayorga L, Camera M, Vignolo C, Martinotti A (1988) Magnesium plus nifedipine: potentiation of hypotensive effect in preeclampsia? Am J Obstet Gynecol 159: 308-309.

74. Ben-Ami M, Giladi Y, Shalev E (1994) The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. Br J Obstet Gynaecol 101: 262-263.

75. Altman D, Carroli G, Duley L, Farrell B, Moodley J, et al. (2002) Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 359: 1877-1890.

76. Scardo J, Vermillion S, Hogg B, Newman R (1996) Hemodynamic effects of oral nifedipine in preeclamptic hypertensive emergencies. Am J Obstet Gynecol 175: 336-340.

77. Magee L, Miremadi S, Li J, Cheng C, Ensom M, et al. (2005) Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. Am J Obstet Gynecol 193: 153-163.

78. Groves T, Corenblum B (1995) Spironolactone therapy during human pregnancy. Am J Obstet Gynecol 172: 1655-1656.

79. Widerlov E, Karlman I, Storsater J (1980) Hydralazine-induced neonatal thrombocytopenia. N Engl J Med 303: 1235.

80. Mabie W, Gonzalez A, Sibai B, Amon E (1987) A comparative trial of labetalol and hydralazine in the acute management of severe hypertension complicating pregnancy. Obstet Gynecol 70: 328-333.

81. Fenakel K, Fenakel G, Appelman Z, Lurie S, Katz Z, et al. (1991) Nifedipine in the treatment of severe preeclampsia. Obstet Gynecol 77: 331-337.

82. Vink G, Moodley J, Philpott R (1980) Effect of dihydralazine on the fetus in the treatment of maternal hypertension. Obstet Gynecol 55: 519-522.

83. Nevo O, Thaler I, Shik V, Vortman T, Soustiel J(2003) The effect of isosorbide dinitrate, a donor of nitric oxide, on maternal cerebral blood flow in gestational hypertension and preeclampsia. Am J Obstet Gynecol 188: 1360-1365.

84. Shoemaker C, Meyers M (1984) Sodium nitroprusside for control of severe hypertensive disease of pregnancy: a case report and discussion of potential toxicity. Am J Obstet Gynecol 149: 171-173.

85. Wasserstrum N (1991) Nitroprusside in preeclampsia. Circulatory distress and paradoxical bradycardia. Hypertension 18: 79-84.

86. Sass N, Itamoto C, Silva M, Torloni M, Atallah A (2007) Does sodium nitroprusside kill babies? A systematic review. Sao Paulo Med J 125: 108-111.

87. Bolte A, van Geijn H, Dekker G (2001) Pharmacological treatment of severe hypertension in pregnancy and the role of serotonin(2)-receptor blockers. Eur J Obstet Gynecol Reprod Biol 95: 22-36.

88. Steyn D, Odendaal H (2000) Serotonin antagonism and serotonin antagonists in pregnancy: role of ketanserin. Obstet Gynecol Surv 55: 582-589.

89. Sibai B (2004) Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. Am J Obstet Gynecol 190: 1520-1526.

90. Duley L, Henderson-Smart D (2003) Magnesium sulphate versus phenytoin for eclampsia. Cochrane Database Syst Rev 4: CD000128.

91. Duley L, Gulmezoglu A (2001) Magnesium sulphate versus lytic cocktail for eclampsia. Cochrane Database Syst Rev 1: CD002960.

92. Pryde P, Sedman A, Nugent C, Barr M (1993) Angiotensin-converting enzyme inhibitor fetopathy. J Am Soc Nephrol 3: 1575-1582.

93. Buttar H (1997) An overview of the influence of ACE inhibitors on fetal-placental circulation and perinatal development. Mol Cell Biochem 176: 61-71.

94. Briggs G, Nageotte M (2001) Fatal fetal outcome with the combined use of valsartan and atenolol. Ann Pharmacother 35: 859-861.

95. Lambot M, Vermeylen D, Noel J (2001) Angiotensin-IIreceptor inhibitors in pregnancy. Lancet 357: 1619-1620.

96. Saji H, Yamanaka M, Hagiwara A, Ijiri R (2001) Losartan and fetal toxic effects. Lancet 357: 363.

97. Cooper W, Hernandez-Diaz S, Arbogast P, Dudley J, Dyer S, et al. (2006) Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 354: 2443-2451.

98. Stothard K, Tennant P, Bell R, Rankin J (2009) Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA 301: 636-650.

99. Racusin D, Stevens B, Campbell G, Aagaard K (2012) Obesity and the risk and detection of fetal malformations. Semin Perinatol 36: 213-221.

100. Sheffield J, Butler-Koster E, Casey B, McIntire D, Leveno K (2002) Maternal diabetes mellitus and infant malformations. Obstet Gynecol 100: 925-930.

101. Lennestål R, Otterblad Olausson P, Källén B (2009) Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. Eur J Clin Pharmacol 65: 615-625.

102. Karthikeyan V, Ferner R, Baghdadi S, Lane D, Lip G, et al. (2011) Are angiotensin-converting enzyme inhibitors and angiotensin receptor blockers safe in pregnancy: a report of ninety-one pregnancies. J Hypertens 29: 396-399.

103. Porta M, Hainer J, Jansson S, Malm A, Bilous R, et al. (2011) Exposure to candesartan during the first trimester of pregnancy in type 1 diabetes: experience from the placebo-controlled DIabetic REtinopathy Candesartan Trials. Diabetologia 54: 1298–1303.

104. Li D, Yang C, Andrade S, Tavares V, Ferber J (2011) Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ 343: d5931.

105. Broughton Pipkin F, Symonds E, Turner S (1982) The effect of captopril (SQ14,225) upon mother and fetus in the chronically cannulated ewe and in the pregnant rabbit. J Physiol 323: 415-422.

106. Harewood W, Phippard A, Duggin G, Horvath J, Tiller D (1994) Fetotoxicity of angiotensin-converting enzyme inhibition in primate pregnancy: a prospective, placebo-controlled study in baboons (*Papio hamadryas*). Am J Obstet Gynecol 171: 633-642.

107. Barr M (1994) Teratogen update: angiotensin-converting enzyme inhibitors. Teratology, pp. 399-409.

108. Barr M, Cohen M (1991) ACE inhibitor fetopathy and hypocalvaria: the kidney-skull connection. Teratology 44: 485-495.

109. Rosa F, Bosco L, Graham C, Milstien J, Dreis M, et al. (1989) Neonatal anuria with maternal angiotensin-converting enzyme inhibition. Obstet Gynecol 74: 371-374.

110. Ueki N, Takeda S, Koya D, Kanasaki K (2015) The relevance of the Renin-Angiotensin system in the development of drugs to combat preeclampsia. Int J Endocrinol 2015: 572713.

111. (1961) COPE I. Plasma and blood volume changes in pregnancies complicated by pre-eclampsia. J Obstet Gynaecol Br Commonw 68: 413-416.

112. Mathews D, Shuttleworth T, Hamilton E (1978) Modern trends in management of non-albuminuric hypertension in late pregnancy. Br Med J 26: 623-625.

113. Meher S, Abalos E, Carroli G (2005) Bed rest with or without hospitalisation for hypertension during pregnancy. Cochrane Database Syst Rev 19: CD003514.

114. Colman-Brochu S (2004) Deep vein thrombosis in pregnancy. MCN Am J Matern Child Nurs 29: 186-192.

115. (2011) World Health Organization. WHO Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia. Geneva, Switzerland: World Health Organization.

116. Zucker I, Schultz H, Patel K, Wang H (2015) Modulation of angiotensin II signaling following exercise training in heart failure. Am J Physiol Heart Circ Physiol 308: H781–91.

117. Weissgerber T, Wolfe L, Davies G (2004) The role of regular physical activity in preeclampsia prevention. Med Sci Sports Exerc 36: 2024-2031.

118. Avery M, Leon A, Kopher R (1997) Effects of a partially home-based exercise program for women with gestational diabetes. Obstet Gynecol 89: 10-15.

119. Yeo S, Steele N, Chang M, Leclaire S, Ronis D, et al. (2000) Effect of exercise on blood pressure in pregnant women with a high risk of gestational hypertensive disorders. J Reprod Med 45(4): 293-298. Erratum in: J Reprod Med 45: 607.

120. Zalba G, San José G, Moreno M, Fortuño M, Fortuño A, et al. (2001) Oxidative stress in arterial hypertension: role of NAD(P)H oxidase. Hypertension 38: 1395-1399.

121. Rumbold A, Crowther C, Haslam R, Dekker G, Robinson J (2006) ACTS Study Group. Vitamins C and E and the risks of preeclampsia and perinatal complications. N Engl J Med 354: 1796-1806.

122. Rajagopalan S, Kurz S, Munzel T, Tarpey M, Freeman B, et al. (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest 97: 1916-1923.

123. Hirooka Y, Eshima K, Setoguchi S, Kishi T, Egashira K, et al. (2003) Vitamin C improves attenuated angiotensin II-induced endothelium-dependent vasodilation in human forearm vessels. Hypertens Res 26: 953-959.

124. Roberts J, Myatt L, Spong C, Thom E, Hauth J, et al. (2010) Vitamins C and E to prevent complications of pregnancy-associated hypertension. N Engl J Med 362: 1282-1291.

125. Hyppönen E, Cavadino A, Williams D, Fraser A, Vereczkey A, et al. (2013) Vitamin D and pre-eclampsia: original data, systematic review and meta-analysis. Ann Nutr Metab 63: 331-340.

126. Forman J, Williams J, Fisher N (2010) Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. Hypertension 55: 1283-1288.

127. Mitra S, Wang X, Khaidakov M, Ding Z, Ayyadevera S, et al. (2012) Aspirin downregulates angiotensin type 1 receptor transcription implications in capillary formation from endothelial cells. J Cardiovasc Pharmacol 60: 187-192.

128. Henderson J, Whitlock E, O'Connor E, Senger C, Thompson J, et al. (2014) Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 160: 695–703.

129. Askie L, Duley L, Henderson-Smart D, Stewart L (2007) PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet 369: 1791-1798.

130. Beroyz G, Casale R, Farreiros A, Palermo M, Margulies M, et al. (1994) CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. Lancet 343: 619-629.

131. Kyle P, Buckley D, Kissane J, de Swiet M, Redman C (1995) The angiotensin sensitivity test and low-dose aspirin are ineffective methods to predict and prevent hypertensive disorders in nulliparous pregnancy. Am J Obstet Gynecol 173: 865-872.

132. Kanasaki K, Palmsten K, Sugimoto H, Ahmad S, Hamano Y, et al. (2008) Deficiency in catechol-O-methyltransferase and 2-methoxyoestradiol is associated with pre-eclampsia. Nature 453: 1117-1121.

133. Berg D, Sonsalla R, Kuss E (1983) Concentrations of 2-methoxyoestrogens in human serum measured by a heterologous immunoassay with an 125I-labelled ligand. Acta Endocrinol (Copenh) 103: 282-288.

134. Barnea E, MacLusky N, DeCherney A, Naftolin F (1988) Catechol-o-methyl transferase activity in the human term placenta. Am J Perinatol 5: 121-127.

135. Barnea E, Fakih H, Oelsner G, Walner S, DeCherney A, et al. (1986) Effect of antihypertensive drugs on catechol-O-methyltransferase and monoamine oxidase activity in human term placental explants. Gynecol Obstet Invest 21: 124-130.

136. Miller A (2003) The methionine-homocysteine cycle and its effects on cognitive diseases. Altern Med Rev 8: 7-19.

137. Wen S, Chen X, Rodger M, White R, Yang Q, et al. (2008) Folic acid supplementation in early second trimester and the risk of preeclampsia. Am J Obstet Gynecol 198: e1–7.

138. Lakhani N, Sarkar M, Venitz J, Figg W (2003) 2-Methoxyestradiol, a promising anticancer agent. Pharmacotherapy 23: 165-172.

139. Sweeney C, Liu G, Yiannoutsos C, Kolesar J, Horvath D, et al. (2005) A phase II multicenter, randomized, double-blind, safety trial assessing the pharmacokinetics, pharmacodynamics, and efficacy of oral 2-methoxyestradiol capsules in hormone-refractory prostate cancer. Clin Cancer Res 11: 6625-6633.

140. Tevaarwerk A, Holen K, Alberti D, Sidor C, Arnott J, et al. (2009) Phase I trial of 2-methoxyestradiol NanoCrystal dispersion in advanced solid malignancies. Clin Cancer Res 15: 1460-1465.

141. Mantovani E, Filippini F, Bortolus R, Franchi M (2014) Folic acid supplementation and preterm birth: results from observational studies. Biomed Res Int, pp. 481914.

142. Li Z, Ye R, Zhang L, Li H, Liu J, et al. (2013) Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. Hypertension 61: 873-879.

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