

Hypertension in Pregnancy

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Abstract

Background: Hypertension affects 10% of pregnancies in the US and is the leading cause of maternal and infant mortality. Hypertension during pregnancy involves several conditions, particularly preeclampsia, a type of hypertension that differs from pregnancy, which is more de Novo or chronic hypertension. Risks to the fetus include premature birth, stunted growth, and death. Childbirth is a direct treatment for preeclampsia. Treatment of acute hypertension is necessary to prevent cerebrovascular, cardiac, and renal problems in the mother. The other two types of hypertension, chronic and transient hypertension, are usually very bad. Proper management of hypertension during pregnancy requires consideration of various factors in the cardiovascular physiology of pregnancy. The main goal is to prevent complications in the mother associated with impaired uterine blood flow and fetal blood circulation. Before prescribing an antihypertensive drug, it is important to carefully evaluate the potential risk to the fetus from the interaction of uterine drugs. This review article aims to show the investigations and treatment available in cases of preeclampsia.

Conclusion: The ultimate goal of treating high blood pressure during pregnancy is to have a healthy newborn without harming the mother's health.

Keywords: *Gestational hypertension; chronic hypertension; eclampsia; preeclampsia.*

Introduction

Pre-eclampsia is a pregnancy illness marked by high blood pressure and, in certain cases, a substantial amount of protein in the urine. The problem usually appears after 20 weeks of pregnancy. Red blood cell disintegration, a low blood platelet count, decreased liver function,

kidney failure, edema, shortness of breath due to fluid in the lungs, or vision impairments may occur in severe forms of the condition. Pre-eclampsia raises the likelihood of both the mother and the fetus having negative outcomes. If left untreated, it might lead to seizures, which is referred to as eclampsia (1).

Obesity, previous hypertension, advanced age, and diabetes mellitus are all risk factors for pre-eclampsia. It's also more common in a woman's first pregnancy and when she's expecting twins. Among other things, the underlying mechanism involves aberrant blood vessel development in the placenta. The majority of cases are diagnosed prior to delivery. Pre-eclampsia frequently persists after birth and is referred to as postpartum preeclampsia. Pre-eclampsia can sometimes start right after delivery. While high blood pressure and protein in the urine were once required to diagnose the condition, other definitions now include hypertension as well as any related organ dysfunction. After twenty weeks of pregnancy, a woman's blood pressure is considered high if it is greater than 140 mmHg systolic or 90 mmHg diastolic at two different times, more than four hours apart. During prenatal care, pre-eclampsia is frequently checked for (2).

Aspirin for people at high risk, calcium supplements in areas with poor intake, and drug treatment for previous hypertension are all recommended as preventative measures. The delivery of the baby and placenta is a successful treatment for pre-eclampsia, but full recovery can take days or weeks. The severity of pre-eclampsia and how far along in pregnancy a woman determines whether delivery is suggested. Pre-delivery blood pressure medicine, such as labetalol and methyldopa, may be administered to help the mother feel better. In people with severe eclampsia, magnesium sulfate may be given to prevent it. In both treatment and prevention, bedrest and salt intake have been found to be ineffective (3).

Pre-eclampsia affects 2–8% of all pregnancies around the world. Pre-eclampsia and other hypertensive diseases of pregnancy are among the most common causes of pregnancy-related fatalities. In 2015, they claimed the lives of 46,900 people. Pre-eclampsia normally develops after 32 weeks, however, it is linked to poorer results if it develops before. Pre-eclampsia patients have a higher risk of heart disease and stroke later in life. The word "eclampsia" comes from a Greek word that means "lightning." Hippocrates, who lived in the 5th century BC, was the first to describe the illness (4).

Causes and Risk Factors

There are several factors involved in the exact cause of preeclampsia. Experts believe that the placenta begins to nourish the fetus during pregnancy. Early in pregnancy, new blood vessels develop and change to send blood to the placenta. In women with preeclampsia, these arteries do not develop or are poorly visible. They are smaller than normal blood vessels and react differently to hormone expression, which limits the amount of blood flowing through them. Causes of these abnormal developments include: insufficient blood flow to the uterus, injury to the blood vessels, immune system problems, certain genes, and other hypertensive disorders during pregnancy, preeclampsia is one of four diseases of hypertension. . It can occur during pregnancy (5).

The other three are Gestational hypertension. Women with high blood pressure during pregnancy have high blood pressure but have little protein in their urine or other symptoms of organ damage. Some women with gestational hypertension develop preeclampsia, Chronic hypertension before pregnancy or before 20 weeks of pregnancy. But because high blood pressure is often asymptomatic, it can be difficult to tell when it started. Chronic hypertension with superimposed preeclampsia: This condition occurs in women who have been diagnosed with chronic high blood pressure before pregnancy, but then develop high blood pressure and protein in the urine or other health problems during pregnancy (6).

Preeclampsia doesn't start until there is a problem with the pregnancy. Risk factors are a History of preeclampsia. Personal or family preeclampsia significantly increases the risk of preeclampsia. The risk of preeclampsia is high during your first pregnancy, new father. Any pregnancy with a new partner increases the risk of preeclampsia in addition to a second or third pregnancy at the same age. The risk of preeclampsia is higher in very young pregnant women and in women older than 35 years. Race. Black women have a higher risk of developing preeclampsia than women of other races. Obesity. The risk of preeclampsia is higher if you are overweight and have multiple pregnancies. Preeclampsia is more common in women who have twins, triplets, or other relapses. Pregnancy gap: Children younger than two years or more than 10 years apart are at increased risk of preeclampsia. History of certain conditions: Certain medical conditions before pregnancy, such as chronic high blood pressure, migraines, type 1 or 2 diabetes, kidney disease, a tendency to form blood clots, or lupus, increase the risk of preeclampsia. In Vitro Pregnancy: Your chances of developing preeclampsia increase if your baby becomes pregnant as a result of in vitro fertilization (7).

Pathophysiology

Despite extensive research into the mechanism of pre-eclampsia, the specific etiology of the condition remains unknown. Pre-eclampsia is thought to be caused by a defective placenta, which may be removed to cure the condition in most cases. The placenta vascularizes during pregnancy to allow for the flow of water, gases, and solutes, such as nutrients and wastes, between the maternal and fetal circulations. Poor placental perfusion results from abnormal placental development. The placenta of women suffering from pre-eclampsia is aberrant, with inadequate trophoblastic invasion. This causes oxidative stress, hypoxia, and the release of chemicals that promote endothelial dysfunction, inflammation, and other reactions (8).

The clinical signs of pre-eclampsia include vasoconstriction and end-organ ischemia, as well as overall endothelial dysfunction. An imbalance of angiogenic and anti-angiogenic factors may be present in this widespread endothelial dysfunction. Women with pre-eclampsia have higher circulating and placental levels of soluble FMS-like tyrosine kinase-1 (sFlt-1) than women who are pregnant normally. sFlt-1 is an anti-angiogenic protein that inhibits the proangiogenic proteins vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). Soluble endoglin (sEng), like sFlt-1, has anti-angiogenic characteristics and has been found to be higher in women with pre-eclampsia (9).

Both sFlt-1 and sEng are elevated to some amount in all pregnant women, supporting the theory that hypertension is a typical pregnancy adaptation gone wrong. Because natural killer

cells are involved in placentation and placentation involves a degree of maternal immune tolerance for a foreign placenta, it's not surprising that the maternal immune system would react negatively to the arrival of some placentae in certain circumstances, such as a placenta that is more invasive than usual. In cases of pre-eclampsia linked with shallow implantation, initial maternal rejection of placental cytotrophoblasts may be the source of poorly modified spiral arteries, leading to downstream hypoxia and the emergence of maternal symptoms in response to elevated sFlt-1 and sEng (10).

Oxidative stress could possibly have a role in the development of pre-eclampsia. The enzyme xanthine oxidase (XO), which is found mostly in the liver, is the principal generator of reactive oxygen species (ROS). One theory is that placental hypoxia promotes increased purine catabolism in the maternal liver, which leads to increased ROS generation and releases into the maternal circulation, causing endothelial cell injury (11).

Pre-eclampsia appears to be caused by abnormalities in the maternal immune system and a lack of gestational immunological tolerance. A shift toward Th1 responses and the generation of IFN- γ is one of the most noticeable alterations in pre-eclampsia. The source of IFN- γ is unknown, although it could be uterine natural killer cells, placental dendritic cells influencing T helper cell responses, changes in the manufacture or response to regulatory chemicals, or changes in the function of regulatory T cells during pregnancy. Alterations in fetal allorecognition or inflammatory stimuli may potentially contribute to abnormal immune responses that promote pre-eclampsia. In women who develop pre-eclampsia, fetal cells such as fetal erythroblasts and cell-free fetal DNA are found in higher concentrations in the maternal blood. These observations have led to the concept that pre-eclampsia is a disease process in which more fetal material enters the maternal circulation due to a placental lesion such as hypoxia, which triggers an immunological response and endothelial damage, leading to pre-eclampsia and eclampsia (12).

The maternal-fetal conflict between the maternal organism and the fetus is one theory underlying pre-eclampsia risk. trophoblasts penetrate the mother's spiral arteries after the first trimester to change the spiral arteries and get more access to maternal nutrition. Occasionally, trophoblast invasion is impeded, resulting in insufficient modifications to the uterine spiral arteries. It is thought that the growing embryo sends biochemical signals to the mother, causing hypertension and pre-eclampsia so that the fetus can benefit from enhanced maternal nutritional circulation due to increased blood flow to the damaged placenta. Because the fetus is exclusively concerned with its own life and fitness, while the mother is concerned with this and following pregnancies, there is a conflict between maternal and fetal fitness and survival (13).

Another evolutionary theory for pre-eclampsia vulnerability is the idea of assuring mother-father pair-bonding and paternal investment in the fetus. According to researchers, pre-eclampsia is a woman's adaptation to end her investment in a fetus that may have an unavailable father, as judged by the father's frequent semen exposure to the mother. Several studies have found that women who were regularly exposed to their partners' sperm prior to conception had a lower incidence of pre-eclampsia. Additionally, subsequent pregnancies

with the same father had a lower risk of pre-eclampsia, whereas subsequent pregnancies with a different father had a higher risk (14).

The outer epithelial layer of a developing embryo comprises cytotrophoblast cells, a type of stem cell present in the trophoblast that later develops into the fetal placenta. Extravillous trophoblast cells are one form of placental cell that these cells can differentiate into. Extravillous trophoblast cells are an invasive cell type that remodels the maternal spiral arteries by replacing the epithelium and smooth muscle that line the arteries, causing arterial dilatation. This avoids maternal vasoconstriction in the spiral arteries, allowing the growing fetus to get blood and nutrients with low resistance and high blood flow (15).

Pre-eclampsia decreases extravillous trophoblast migration by aberrant expression of the chromosome 19 microRNA cluster (C19MC) in placental cell lines. MiR-520h, miR-520b, and 520c-3p are three microRNAs in this cluster that may cause aberrant spiral artery invasion. Extravillous trophoblast cells are unable to invade the maternal spiral arteries, resulting in high resistance, reduced blood flow, and nutrient deficiency in the fetus. Vitamin supplementation may reduce the risk, according to preliminary studies. Immune factors could potentially be involved (figure 1) (16).

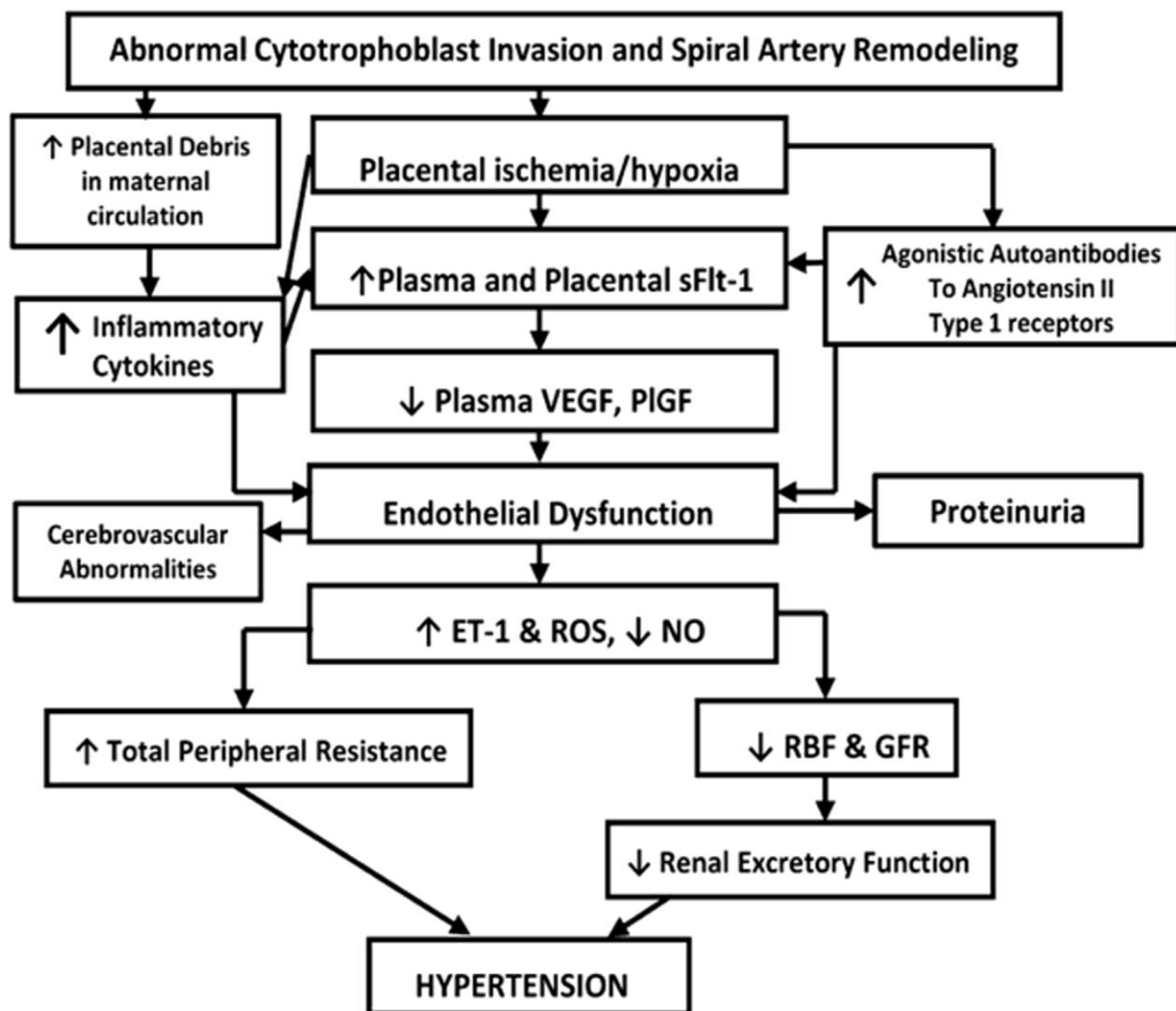


Figure 1 Pathophysiology of Hypertension during Pregnancy (17)

Classification

Sometimes there is high blood pressure before pregnancy. In some cases, blood pressure rises during pregnancy. **Pregnancy Hypertension:** In women with high blood pressure during pregnancy, high blood pressure begins after 20 weeks of gestation. There is little protein in the gut or other signs of organ damage. Some women with gestational hypertension develop preeclampsia. **Arterial hypertension:** Chronic hypertension, high blood pressure that existed before pregnancy or that occurred 20 weeks before pregnancy. But because high blood pressure is often asymptomatic, it can be difficult to determine when it started. **Chronic hypertension with superimposed preeclampsia:** This condition is seen in women with chronic high blood pressure before pregnancy who begin to experience high blood pressure and proteinuria or other problems associated with high blood pressure during pregnancy (18).

Preeclampsia occurs when high blood pressure begins after 20 weeks of pregnancy and is associated with symptoms of damage to other organs, including the kidneys, liver, blood, or brain. Untreated preeclampsia can cause serious or fatal complications for the mother and baby, including progressive syncope (eclampsia). Previously, preeclampsia was diagnosed only when a pregnant woman had high blood pressure and protein in the urine. Experts now know that you may have preeclampsia without protein in your urine (Figure 2) (19).

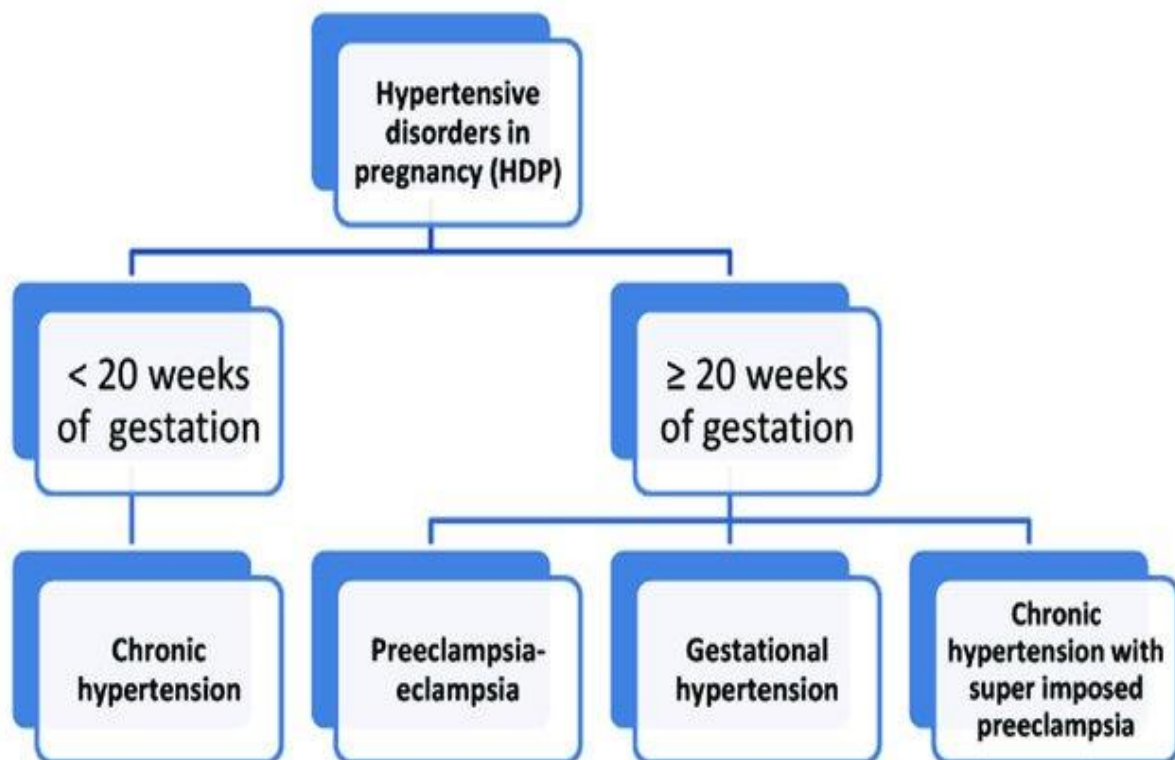


Figure 2 Classification of Hypertension in Pregnancy (20)

Signs and Symptoms

In addition to high blood pressure, other signs and symptoms of preeclampsia include too much protein in the urine (proteinuria) or additional symptoms of kidney problems, headache,

temporary loss of vision, blurred vision or sensitivity to light, visual disturbances, including abdominal pain. Usually, under the right ribs, nausea or vomiting decreased urination, decreased platelet count (thrombocytopenia), abnormal liver function, lack of fluid in the lungs, sudden weight gain, and inflammation (especially thrombocytopenia), usually accompanied by preeclampsia. However, they occur during normal pregnancy, so obesity and inflammation are not considered reliable symptoms of preeclampsia (21).

Complications

Pre-eclampsia complications can harm both the mother and the fetus. Eclampsia, the development of HELLP syndrome, hemorrhagic or ischemic stroke, liver damage and malfunction, acute renal injury, and acute respiratory distress syndrome can all aggravate pre-eclampsia (ARDS). Pre-eclampsia is also linked to a higher risk of Caesarean section, preterm labor, and placental abruption. Furthermore, due to volume expansion and fluid mobilization, some women may experience an increase in blood pressure in the first week after giving birth. Fetal problems include restricted fetal growth and the possibility of fetal or neonatal death. In the long run, a woman who has had pre-eclampsia is more likely to have it again in later pregnancies (22).

Eclampsia

Eclampsia is defined as the occurrence of fresh convulsions in a pre-eclamptic patient that cannot be explained by other factors. It's a symptom that the underlying pre-eclamptic condition is severe, and it's linked to significant perinatal and maternal morbidity and mortality rates. Headaches, vision abnormalities, and right upper quadrant or epigastric stomach pain are all warning signs of eclampsia in someone who is currently pre-eclamptic, with a headache being the most common symptom. Brisk or hyperactive reflexes are frequent during pregnancy, but ankle clonus is a symptom of neuromuscular irritability that usually indicates severe pre-eclampsia but can occasionally occur before eclampsia. In severe pre-eclampsia, magnesium sulfate is administered to prevent seizures (23).

HELLP Syndrome

Hemolysis (microangiopathic), increased liver enzymes (liver dysfunction), and low platelets are all symptoms of HELLP syndrome (thrombocytopenia). This condition affects 10–20 percent of individuals with severe pre-eclampsia and eclampsia, and it's linked to higher maternal and fetal morbidity and mortality. HELLP syndrome occurs 50% of the time when a baby is born prematurely, 20% of the time when the baby is born late, and 30% of the time when the baby is born after birth (24).

Long term

Preeclampsia increases the risk of cardiovascular illness later in life, and a history of preeclampsia/eclampsia doubles the risk of cardiovascular mortality. Stroke, persistent hypertension, renal disease, and venous thromboembolism are among the other dangers. Age, elevated BMI, family history, and certain chronic conditions are all risk factors for preeclampsia and cardiovascular disease. Pre-eclampsia does not appear to raise the risk of

cancer. Pre-eclampsia causes a reduction in food availability to the fetus, which can lead to intrauterine growth restriction (IUGR) and low birth weight. Due to disproportionate growth, fetal undernutrition is connected to coronary heart disease later in life, according to the theory of fetal origin (25).

Pre-eclampsia can cause IUGR in the growing fetus because it causes a mismatch between maternal energy supply and fetal energy demands. According to the Barker hypothesis, infants with IUGR have poor neural development and are more likely to acquire adult diseases. Adult disorders of the fetus linked to IUGR include coronary artery disease (CAD), type 2 diabetic Mellitus (T2DM), cancer, osteoporosis, and a variety of psychiatric conditions, to name a few. Pre-eclampsia and the development of placental malfunction have also been demonstrated to run in families on the maternal side and, most likely, on the paternal side. Fetuses born to moms who were small for gestational age (SGA) were 50% more likely to develop pre-eclampsia in subsequent pregnancies, while fetuses born to both SGA parents were three times more likely (26).

Epidemiology

Pre-eclampsia affects about 2–8% of all pregnancies around the world. Pre-eclampsia has been more common in the United States since the 1990s, presumably due to an increase in the prevalence of predisposing conditions such as chronic hypertension, diabetes, and obesity. Pre-eclampsia is a prominent cause of maternal and neonatal morbidity and mortality all over the world. Hypertensive illnesses in pregnancy, which include pre-eclampsia, account for over one-tenth of all maternal deaths in Africa and Asia, and one-quarter in Latin America (27).

Women who are pregnant for the first time are more likely to develop pre-eclampsia. Pre-eclampsia is more likely to occur in subsequent pregnancies in women who have previously been diagnosed with it. Pre-eclampsia is also more likely in women who have hypertension, obesity, diabetes, autoimmune disorders like lupus, hereditary thrombophilias like Factor V Leiden, renal disease, multiple gestations (twins or multiple births), and advanced maternal age. Pre-eclampsia is more common in women who reside in high-altitude areas. Some ethnic groups are also more likely to develop pre-eclampsia (e.g. African-Americans, Sub-Saharan Africans, Latin Americans, African Caribbeans, and Filipinos). Except in those with a family history of hypertensive pregnancy, changing paternity in a subsequent pregnancy has been linked to an increased risk. Pre-eclampsia can lead to eclampsia, which is a serious condition. Eclampsia affects 0.56 per 1,000 pregnant women in developed countries and almost 10 to 30 times as many women in low-income countries as in developed countries (28).

Prognosis

High blood pressure during pregnancy has different implications depending on the disease and other circumstances. Preeclampsia does not raise a woman's risk of having chronic hypertension or other cardiac problems in general. Short-term problems, such as elevated blood pressure, usually go away within six weeks after birth in women with normal blood pressure who develop preeclampsia after the 20th week of their first pregnancy. However, some women may be more susceptible to high blood pressure or other forms of heart disease

later in life. More research is needed to assess the long-term health impacts of hypertensive problems in pregnancy, as well as to create improved ways for identifying, diagnosing, and treating women at risk. Despite the fact that high blood pressure and related diseases can be dangerous during pregnancy, the majority of women who have high blood pressure or develop preeclampsia have healthy pregnancies. Obtaining early and regular prenatal care for pregnant women is important to the identify and treat blood pressure disorders (29).

Investigations

The blood pressure of a pregnant woman is measured to determine pre-eclampsia. Diagnostic criteria: When a pregnant woman suffers the following symptoms, she is diagnosed with pre-eclampsia: Blood pressure readings of 140 mmHg systolic or 90 mmHg diastolic in an individual with previously normal blood pressure at 20 weeks of pregnancy on two separate readings taken at least four to six hours apart in an individual with previously normal blood pressure. The diagnostic criteria for essential hypertension include a rise in systolic blood pressure (SBP) of 30 mmHg or a rise in diastolic blood pressure (DBP) of 15 mmHg in a woman with essential hypertension before 20 weeks of pregnancy. A 24-hour urine sample containing 0.3 grams (300 mg) or more of protein, a SPOT urinary protein to creatinine ratio of 0.3, or a urine dipstick value of 1+ or above is considered proteinuria (dipstick reading should only be used if other quantitative methods are not available) (30).

In every pregnancy complicated by elevated blood pressure, suspicion of pre-eclampsia should be maintained even if there is no proteinuria. Proteinuria is absent in 10% of patients with other pre-eclampsia symptoms and 20% of people diagnosed with eclampsia. In the absence of proteinuria, pre-eclampsia is indicated by the presence of new-onset hypertension (high blood pressure) and one or more of the following symptoms: Kidney impairment manifests itself in oliguria, elevated creatinine levels, thrombocytopenia (platelet count 100,000/microliter), pulmonary edema, ankle edema (pitting type), and cerebral or visual problems (31).

Pre-eclampsia is a progressive condition, and these signs of organ dysfunction suggest severe pre-eclampsia. A systolic blood pressure of 160 or diastolic blood pressure of 110, as well as proteinuria of more than 5 grams in a 24-hour period, are all signs of severe pre-eclampsia. Patients with severe preeclampsia may also have stomach pain in the epigastric/right upper quadrant, headaches, and vomiting. Severe pre-eclampsia is one of the leading causes of fetal death in the womb. A rise in baseline blood pressure (BP) of 30 mmHg systolic or 15 mmHg diastolic is significant but not diagnostic, even if it does not meet the absolute requirements of 140/90 (32).

Predictive tests

Many tests have been explored to predict pre-eclampsia, but no single biomarker is likely to be sufficiently predictive of the illness. Predictive tests such as placental perfusion, vascular resistance, renal dysfunction, endothelial dysfunction, and oxidative stress have all been studied. A notable test is Doppler ultrasonography of the uterine arteries to search for indications of inadequate placental perfusion. In persons who have previously had pre-

eclampsia, this test has a significant negative predictive value. Despite the fact that increased serum uric acid (hyperuricemia) is a poor predictor of pre-eclampsia, some people use it to "define" the illness. A reduction in uric acid clearance as a result of impaired renal function causes hyperuricemia (high blood uric acid levels). Anti-angiogenic proteins like soluble FMS-like tyrosine kinase-1 (sFlt-1) and angiogenic proteins like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) have shown promise for possible clinical use in diagnosing preeclampsia, though the evidence is insufficient to recommend a clinical use for these markers (33).

ASPRE, the world's largest multi-country prospective trial, recently showed impressive results in detecting pregnant women at high risk of pre-eclampsia while still in the first trimester. A combination of maternal history, mean arterial blood pressure, intra-uterine Doppler, and PlGF testing can detect more than 75 percent of women who will develop pre-eclampsia, allowing for early intervention to prevent the emergence of later symptoms, according to the study. This approach is now officially supported by the International Federation of Gynecologists and Obstetricians (FIGO) Pre-eclampsia can be predicted by looking for podocytes (specialized kidney cells) in the urine, according to new research. Studies have demonstrated that finding podocytes in the urine is a good early sign and diagnostic test for pre-eclampsia (34).

Differential diagnosis

Pre-eclampsia can imitate and be confused with conditions such as chronic hypertension, chronic renal disease, primary seizure disorders, gallbladder, and pancreatic disease, immunological or thrombotic thrombocytopenic purpura, antiphospholipid syndrome, and hemolytic-uremic syndrome. Any pregnant woman above the age of 20 weeks should be informed of the risk. Diagnosis becomes much more difficult when pre-existing disorders such as hypertension are present. High blood pressure and protein in the urine are common in pregnant women with acute fatty liver, albeit the severity of the liver damage varies. Other disorders that can cause high blood pressure include thyrotoxicosis, pheochromocytoma, and drug misuse (35).

Prevention

Preventative measures for pre-eclampsia have received a lot of attention. Preventing pre-eclampsia is difficult due to the lack of understanding of the disease's biology. The following are some of the most widely recognized recommendations (36).

Diet

Supplementing with a balanced protein and energy diet does not appear to lessen the incidence of pre-eclampsia. In addition, there is no evidence that changing one's salt intake has an effect. Antioxidant supplementation with vitamins C, D, and E had no effect on the incidence of pre-eclampsia; thus, supplementing with vitamins C, E, and D are not recommended for lowering pre-eclampsia risk. When dietary calcium consumption is insufficient, prenatal calcium supplementation of at least 1 gram per day is recommended to

avoid pre-eclampsia, especially in high-risk people. A higher selenium level has been associated with a reduced risk of pre-eclampsia. A higher cadmium level is associated with a higher risk of pre-eclampsia (37).

Aspirin

Taking aspirin has been related to a 1 to 5% reduction in pre-eclampsia and a 1 to 5% reduction in premature births in high-risk women. The World Health Organization recommends starting low-dose aspirin before 20 weeks of pregnancy for the prevention of pre-eclampsia in high-risk women. The US Preventive Services Task Force recommends starting a low-dose regimen in the 12th week for high-risk women. The advantages are reduced if you begin beyond 16 weeks. In addition to its success in identifying suspected women who would develop pre-eclampsia, ASPRE, a more recent trial, was able to show a significant reduction in the risk of early pre-eclampsia (-82%) and premature pre-eclampsia (-82%). (-62 percent). Due to high-performing screening to identify high-risk women, altered prophylactic dosage (150 mg/day), the timing of consumption (bedtime), and starting before week 16 of pregnancy, aspirin's efficacy has been achieved (38).

Physical activity

There isn't enough data to advocate either exercise or enforced bedrest as pre-eclampsia prevention methods (39).

Smoking cessation

In epidemiologic studies, the association between cigarette smoking and a lower risk of pre-eclampsia in low-risk pregnancies has been established. High-risk pregnancies (those with pregestational diabetes, chronic hypertension, previous pregnancy with pre-eclampsia, or a multifetal pregnancy) exhibited no protective effect. The reason for this mismatch is unknown; however, research suggests that the underlying condition increases the risk of pre-eclampsia to the extent where any real reduction in risk due to smoking is obscured. Smoking's bad effects on overall health and pregnancy outcomes, on the other hand, outweigh the benefits of preventing pre-eclampsia. You should stop smoking before, during, and after your pregnancy if possible (40).

Immune modulation

Because the infant and the father are genetically related, multiple studies have found that a woman's gestational immunological tolerance to the father of her child is significant. Continued exposure to the same sperm that resulted in the pregnancy, whether through vaginal or oral intercourse, appears to lower the risk of pre-eclampsia. According to one early study, "while pre-eclampsia is a disorder of first pregnancies, the preventative benefit of multiparity is lost with the change of partner." Although it is suggested that women who change partners use condoms to prevent sexually transmitted infections, the study discovered that "a certain window of sperm exposure within a stable relationship, when pregnancy is hoped for, is associated with protection against pre-eclampsia." (41).

Several further studies have since looked into the lower incidence of pre-eclampsia in women who had blood transfusions from their partners, women with lengthy histories of intercourse without barrier contraception, and women who had regular oral sex (42).

A group of Dutch reproductive biologists wanted to expand their research after discovering the importance of a woman's immunological tolerance to her baby's paternal DNA. The Dutch researchers carried out a series of tests that revealed an unexpectedly high link between a woman's oral intercourse and a lower risk of pre-eclampsia, with the protective benefits being strongest if she swallowed her partner's sperm. Males who fathered kids that resulted in miscarriage or pre-eclampsia had low amounts of key immune modifying chemicals like TGF-beta in their seminal fluid, according to a study from the University of Adelaide. The researchers discovered that "dangerous males" are more than twice as likely to have father pregnancies that result in pre-eclampsia or miscarriage. Most of the "hazardous males" appeared to be deficient in the seminal immune components required to promote immunological tolerance in their spouses, among other things (43).

With the recognition of immune intolerance as a cause of pre-eclampsia, women with recurrent pre-eclampsia, miscarriages, or in vitro fertilization failures may be given key immune factors such as TGF-beta, as well as the father's foreign proteins, orally, as a sublingual spray, or as a vaginal gel to be applied to the vaginal wall before intercourse (44).

Treatment

One effective treatment for preeclampsia is childbirth. As your blood pressure drops, your risk of fainting, umbilical cord injury, stroke, and excessive bleeding increases. Of course, if it is too early in your pregnancy, the birth will not be perfect for your baby. If you have been diagnosed with preeclampsia, patients will also need regular blood tests, ultrasound, and less accurate tests than expected if they have a problem-free pregnancy (45).

Drugs: Possible treatments for preeclampsia include: Drugs that lower blood pressure. These medications, called antihypertensives, are used to lower dangerously high blood pressure. A blood pressure of 140/90 millimeters of mercury (mmHg) is usually treated. There are many types of antihypertensive medications, but many are not safe to use during pregnancy. Talk to your doctor about whether you need to use antihypertensive medications in your condition to control your blood pressure. **Corticosteroids:** If you have severe preeclampsia or HELLP syndrome, corticosteroids can temporarily improve liver and platelet function and prolong pregnancy. Corticosteroids can also help your baby's lungs heal within 48 hours. This is an important step in allowing premature babies to live outside of the womb. **Anticonvulsants:** If you have severe preeclampsia, your doctor may prescribe anticonvulsants such as magnesium sulfate to prevent the first attack (46).

Rest: In general, rest is recommended for women with preeclampsia. However, research shows no benefit from this practice, which can increase the risk of blood clots and affect your financial and social life. Rest is no longer recommended for many women. **Hospitalization:** Severe eclampsia may require hospitalization. In hospitals, doctors can regularly perform stress tests and biophysical profiles to monitor the baby's health and measure the amount of

amniotic fluid. Lack of amniotic fluid indicates an inadequate blood supply to the baby. Delivery: If you are diagnosed with preeclampsia in late pregnancy, your doctor may recommend preterm delivery. The fact that the cervix begins to dilate (stretch), thin (active), or smooth (mature) can also be a factor in deciding whether to make an incision at any time (47).

In extreme cases, it is impossible to determine the age of the baby or the cervix. If you can't wait, your doctor may immediately resuscitate or order a C-section. During labor, magnesium sulfate can be given intravenously to prevent seizures. If you need postpartum pain, ask your doctor what to take. NSAIDs such as ibuprofen (Advil, Motrin IB, etc.) and naproxen sodium (Aleve) can increase blood pressure. After giving birth, the other symptoms of high blood pressure and preeclampsia may take some time to go away (48).

Prevention

Researchers continue to find ways to prevent preeclampsia, but no specific strategy has yet been developed. To reduce the risk, reduce salt, change activity, reduce calories, and eat garlic and fish oil. It has been shown that increasing the intake of vitamins C and E is not beneficial. Other studies have reported a link between vitamin D deficiency and an increased risk of preeclampsia. However, some studies have shown a link between vitamin D supplementation and a reduction in the risk of preeclampsia, while others have failed. However, in some cases, the risk of preeclampsia may be reduced (49).

Low-dose aspirin: If you experience some risk factors, such as a history of preeclampsia, multiple pregnancies, chronic hypertension, kidney disease, diabetes, or autoimmune disease, your doctor may recommend a daily low-dose aspirin (81 mg). Twelve years. Weeks pregnant, calcium supplements: In some communities, women with calcium deficiency before pregnancy and those who do not get enough calcium from their diet during pregnancy may benefit from calcium supplements to prevent preeclampsia. However, women in the United States or other developed countries are unlikely to experience calcium deficiency, suggesting that calcium supplements may benefit them. You mustn't take any medications, vitamins, or supplements without first checking with your doctor. Before you get pregnant, especially if you have preeclampsia, it's best to stay as healthy as possible. Lose weight if necessary and make sure other conditions, like diabetes, are managed properly. If you are pregnant, take care of yourself and your baby with daily prenatal care. If preeclampsia is identified early, you and your doctor can work together to prevent complications and make better decisions for you and your child (50).

There is currently no specific way to prevent hypertension. Some factors that cause high blood pressure can be controlled and some cannot. Follow your doctor's instructions for diet and exercise. Other ways to prevent high blood pressure during pregnancy include: Use salt as needed, drinking at least 8 glasses of water a day, increasing the amount of protein you eat, and limiting the number of fried foods, but reducing it, and getting enough rest. Exercise regularly, increase your legs several times a day, avoid alcohol, avoid caffeinated beverages, and your doctor may prescribe medications and supplements (51).

Discussion

Hypertension during pregnancy is defined as a blood pressure of 140/90 mm Hg. Korotkoff Class V (disappearance) is used in place of Korotkoff Phase IV to determine DBP. In the case of outpatient treatment, blood pressure should be measured by sitting quietly after a short rest. In hospitalized patients, the effect of inferior vena cava compression by an enlarged uterus lying on their side is eliminated, which prevents the return of veins and causes a decrease in blood pressure. Regardless of the posture, special care should be taken to keep the patient's hands at heart level. Wrap your arms around your heart to significantly lower your blood pressure. During pregnancy, low blood pressure is achieved by using the right arm while the patient is lying on his left side. This blood pressure test can only show changes in the hydrostatic pressure that is caused by placing the right hand on the heart. Therefore, an increase in blood pressure from dorsal to dorsal side may only represent a postural event and not a positive effect on rollover tests, which were considered preeclampsia. The National High Blood Pressure Education Program (NHBPEP) Working Group recently released another report that looks at the classification of high blood pressure during pregnancy. The term "temporary hypertension" has been replaced by "pregnancy hypertension", which is used only during pregnancy in a group of women who develop hypertension after 20 weeks of pregnancy without proteinuria (52).

Conclusion

The main goal of treating high blood pressure during pregnancy is to give birth to a healthy baby without jeopardizing the health of the mother. Early diagnosis and close monitoring of the mother and foetation are required. Without proteinuria, hypertension is generally healthy and easy to control. Antihypertensive drugs should be used with caution and the risk to the fetus from uterine infections should be carefully assessed. Severe preeclampsia is an emergency delivery and can have fatal consequences for the fetus and mother. Ideally, these women should be hospitalized and treated with rest, antihypertensive drugs, and magnesium sulfate to prevent seizures. Direct treatment of preeclampsia at birth: For milder forms farther away, it is desirable to correct the prognosis of the baby by postponing birth.

Conflict of Interest

There is nothing to disclose

References

- 1) Eiland E, Nzerue C, Faulkner M (2012). "Preeclampsia 2012". *Journal of Pregnancy*. 2012: 586578. doi:10.1155/2012/586578. PMC 3403177. PMID 22848831.
- 2) Al-Jameil N, Aziz Khan F, Fareed Khan M, Tabassum H (February 2014). "A brief overview of preeclampsia". *Journal of Clinical Medicine Research*. 6 (1): 1–7. doi:10.4021/jocmr1682w. PMC 3881982. PMID 24400024.
- 3) American College of Obstetricians Gynecologists; Task Force on Hypertension in Pregnancy (November 2013). "Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in

- Pregnancy" (PDF). *Obstetrics and Gynecology*. 122 (5): 1122–31. doi:10.1097/01.AOG.0000437382.03963.88. PMC 1126958. PMID 24150027. Archived (PDF) from the original on 2016-01-06. Retrieved 2015-02-17.
- 4) WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia (PDF). 2011. ISBN 978-92-4-154833-5. Archived (PDF) from the original on 2015-05-13.
 - 5) Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG (May 2014). "Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force". *Annals of Internal Medicine*. 160 (10): 695–703. doi:10.7326/M13-2844. PMID 24711050. S2CID 33835367.
 - 6) Arulkumaran N, Lightstone L (December 2013). "Severe pre-eclampsia and hypertensive crises". *Best Practice & Research. Clinical Obstetrics & Gynaecology*. 27 (6): 877–84. doi:10.1016/j.bpobgyn.2013.07.003. PMID 23962474.
 - 7) Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. (GBD 2015 Mortality and Causes of Death Collaborators) (October 2016). "Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015". *Lancet*. 388 (10053): 1459–1544. doi:10.1016/s0140-6736(16)31012-1. PMC 5388903. PMID 27733281.
 - 8) Hypertension in pregnancy. ACOG. 2013. p. 2. ISBN 9781934984284. Archived from the original on 2016-11-18. Retrieved 2016-11-17.
 - 9) Martin N (2018-08-14). "Trusted Health Sites Spread Myths About a Deadly Pregnancy Complication". ProPublica. Lost Mothers. ProPublica. Archived from the original on 2021-05-15. Retrieved 2021-05-28. From the Mayo Clinic to Harvard, sources don't always get the facts right about preeclampsia. Reached by ProPublica, some are making needed corrections.
 - 10) Martin N, Montagne R (2017-05-12). "The Last Person You'd Expect to Die in Childbirth". ProPublica. Lost Mothers. ProPublica. Archived from the original on 2019-06-21. Retrieved 2021-05-28. The death of Lauren Bloomstein, a neonatal nurse, in the hospital where she worked illustrates a profound disparity: The health care system focuses on babies but often ignores their mothers.
 - 11) Lambert G, Brichant JF, Hartstein G, Bonhomme V, Dewandre PY (2014). "Preeclampsia: an update". *Acta Anaesthesiologica Belgica*. 65 (4): 137–49. PMID 25622379.
 - 12) Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R (August 2010). "Pre-eclampsia". *Lancet*. 376 (9741): 631–44. doi:10.1016/S0140-6736(10)60279-6. PMID 20598363. S2CID 208792631.
 - 13) Bibbins-Domingo K, Grossman DC, Curry SJ, Barry MJ, Davidson KW, Doubeni CA, et al. (April 2017). "Screening for Preeclampsia: US Preventive Services Task Force Recommendation Statement". *JAMA*. 317 (16): 1661–1667. doi:10.1001/jama.2017.3439. PMID 28444286. S2CID 205091250.
 - 14) Mohler ER (2006). *Advanced Therapy in Hypertension and Vascular Disease*. PMPH-USA. pp. 407–408. ISBN 9781550093186. Archived from the original on 2015-10-05.

- 15) Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B (November 2009). "Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the south coast air basin of California" (PDF). *Environmental Health Perspectives*. 117 (11): 1773–9. doi:10.1289/ehp.0800334. PMC 2801174. PMID 20049131. Archived from the original (PDF) on 2009-07-19. Retrieved 2009-07-05.
- 16) Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC (April 2014). "Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis". *BMJ*. 348: g2301. doi:10.1136/bmj.g2301. PMC 3988319. PMID 24735917.
- 17) Mustafa R, Ahmed S, Gupta A, Venuto RC (2012). "A comprehensive review of hypertension in pregnancy". *Journal of Pregnancy*. 2012: 105918. doi:10.1155/2012/105918. PMC 3366228. PMID 22685661.
- 18) Innes KE, Byers TE (November 1999). "Preeclampsia and breast cancer risk". *Epidemiology*. 10 (6): 722–32. doi:10.1097/00001648-199911000-00013. JSTOR 3703514. PMID 10535787.
- 19) Chen DB, Wang W (May 2013). "Human placental microRNAs and preeclampsia". *Biology of Reproduction*. 88 (5): 130. doi:10.1095/biolreprod.113.107805. PMC 4013914. PMID 23575145.
- 20) Ouyang Y, Mouillet JF, Coyne CB, Sadovsky Y (February 2014). "Review: placenta-specific microRNAs in exosomes - good things come in nano-packages". *Placenta*. 35 (Suppl): S69-73. doi:10.1016/j.placenta.2013.11.002. PMC 3944048. PMID 24280233.
- 21) Xie L, Mouillet JF, Chu T, Parks WT, Sadovsky E, Knöfler M, Sadovsky Y (December 2014). "C19MC microRNAs regulate the migration of human trophoblasts". *Endocrinology*. 155 (12): 4975–85. doi:10.1210/en.2014-1501. PMC 4239420. PMID 25211593.
- 22) Skjaerven R, Vatten LJ, Wilcox AJ, Rønning T, Irgens LM, Lie RT (July 2005). "Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort". *BMJ*. 331 (7521): 877. doi:10.1136/bmj.38555.462685.8F. PMC 1255793. PMID 16169871.
- 23) Ehret G (July 2018). "Genes for Preeclampsia: An Opportunity for Blood Pressure Genomics". *Hypertension*. 71 (2): 285–286. doi:10.1161/HYPERTENSIONAHA.118.10840. PMC 6397719. PMID 29967038.
- 24) Phipps EA, Thadhani R, Benzing T, Karumanchi SA (May 2019). "Pre-eclampsia: pathogenesis, novel diagnostics and therapies". *Nature Reviews Nephrology*. 15 (5): 275–289. doi:10.1038/s41581-019-0119-6. PMC 6472952. PMID 30792480.
- 25) McGinnis R, Steinthorsdottir V, Williams N (June 2017). "Variants in the fetal genome near FLT1 are associated with risk of preeclampsia" (PDF). *Nature Genetics*. 49 (8): 1255–1260. doi:10.1038/ng.3895. PMID 28628106. S2CID 205354725.
- 26) Steinthorsdottir V, McGinnis R, Williams NO (November 2020). "Genetic predisposition to hypertension is associated with preeclampsia in European and Central Asian women". *Nature Communications*. 11 (1): 5976. doi:10.1038/s41467-020-19733-6. PMC 7688949. PMID 33239696.

- 27) Maynard S, Venkatesha S, Thadhani R (May 2005). "Soluble Fms-like Tyrosine Kinase 1 and Endothelial Dysfunction in the Pathogenesis of Preeclampsia". *Pediatric Research*. 57 (5 Part 2): 1R–7R. doi:10.1203/01.PDR.0000159567.85157.B7. PMID 15817508.
- 28) Chen CP (March 2009). "Placental abnormalities and preeclampsia in trisomy 13 pregnancies". *Taiwanese Journal of Obstetrics and Gynecology*. 48 (1): 3–8. doi:10.1016/S1028-4559(09)60028-0. PMID 19346185.
- 29) Zadora J, Singh M, Herse F (September 2017). "Disturbed Placental Imprinting in Preeclampsia Leads to Altered Expression of DLX5, a Human-Specific Early Trophoblast Marker". *Circulation*. 136 (19): 1824–1839. doi:10.1161/CIRCULATIONAHA.117.028110. PMC 5671803. PMID 28904069.
- 30) Bounds KR, Chiasson VL, Pan LJ, Gupta S, Chatterjee P (September 2017). "MicroRNAs: New Players in the Pathobiology of Preeclampsia". *Frontiers in Cardiovascular Medicine*. 4: 60. doi:10.3389/fcvm.2017.00060. PMC 5622156. PMID 28993808.
- 31) Cunningham FG, Leveno KJ, Bloom S, Gilstrap L, eds. (2010). *Williams obstetrics* (23rd ed.). New York: McGraw-Hill Medical. ISBN 978-0-07-149701-5.
- 32) Bartsch E, Medcalf KE, Park AL, Ray JG (April 2016). "Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies". *BMJ*. 353: i1753. doi:10.1136/bmj.i1753. PMC 4837230. PMID 27094586.
- 33) Garg AX, Nevis IF, McArthur E, Sontrop JM, Koval JJ, Lam NN, et al. (January 2015). "Gestational hypertension and preeclampsia in living kidney donors". *The New England Journal of Medicine*. 372 (2): 124–33. doi:10.1056/NEJMoa1408932. PMC 4362716. PMID 25397608.
- 34) van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, Bisschop PH (2011). "Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review". *Human Reproduction Update (Review)*. 17 (5): 605–19. doi:10.1093/humupd/dmr024. PMID 21622978.
- 35) Vissenberg R, van den Boogaard E, van Wely M, van der Post JA, Fliers E, Bisschop PH, Goddijn M (July 2012). "Treatment of thyroid disorders before conception and in early pregnancy: a systematic review". *Human Reproduction Update (Review)*. 18 (4): 360–73. doi:10.1093/humupd/dms007. PMID 22431565.
- 36) Drife JO, Magowan B (2004). *Clinical obstetrics and gynecology*. Edinburgh, New York: Saunders. pp. 367–70. ISBN 978-0-7020-1775-9.
- 37) McMaster-Fay RA (2008). "Pre-eclampsia: a disease of oxidative stress resulting from the catabolism of DNA (primarily fetal) to uric acid by xanthine oxidase in the maternal liver; a hypothesis". *Bioscience Hypotheses*. 1: 35–43. doi:10.1016/j.bihy.2008.01.002.
- 38) Laresgoiti-Servitje E, Gómez-López N, Olson DM (April 2010). "An immunological insight into the origins of pre-eclampsia". *Human Reproduction Update*. 16 (5): 510–24. doi:10.1093/humupd/dmq007. PMID 20388637.

- 39) Redman CW, Sargent IL (June 2005). "Latest advances in understanding preeclampsia". *Science*. 308 (5728): 1592–4. Bibcode:2005Sci...308.1592R. doi:10.1126/science.1111726. PMID 15947178. S2CID 21889468.
- 40) Davis JA, Gallup GG (2006). "Preeclampsia and other pregnancy complications as an adaptive response to unfamiliar semen". In Platek SM, Shackelford TK (eds.). *Female Infidelity and Paternal Uncertainty. Evolutionary Perspectives on Male Anti-Cuckoldry Tactics*. Cambridge University Press. pp. 191–204. doi:10.1017/CBO9780511617812.010. ISBN 9780511617812.
- 41) Fu ZM, Ma ZZ, Liu GJ, Wang LL, Guo Y (January 2018). "Vitamins supplementation affects the onset of preeclampsia". *Journal of the Formosan Medical Association = Taiwan Yi Zhi*. 117 (1): 6–13. doi:10.1016/j.jfma.2017.08.005. PMID 28877853.
- 42) Matthiesen L, Berg G, Ernerudh J, Ekerfelt C, Jonsson Y, Sharma S (2005). "Immunology of preeclampsia". *Chemical Immunology and Allergy*. 89: 49–61. doi:10.1159/000087912. ISBN 978-3-8055-7970-4. PMID 16129952.
- 43) Longo DL (2012). *Harrison's principles of internal medicine*. New York: McGraw-Hill. pp. 55–61. ISBN 978-0-07-174889-6.
- 44) Rolnik DL, Wright D, Poon LC, Syngelaki A, O'Gorman N, de Paco Matallana C, et al. (October 2017). "ASPRE trial: performance of screening for preterm preeclampsia". *Ultrasound in Obstetrics & Gynecology*. 50 (4): 492–495. doi:10.1002/uog.18816. PMID 28741785. S2CID 24728853.
- 45) Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. (May 2019). "The International Federation of Gynecology and Obstetrics (FIGO) initiative on preeclampsia: A pragmatic guide for first-trimester screening and prevention". *International Journal of Gynaecology and Obstetrics*. 145 (Suppl 1): 1–33. doi:10.1002/ijgo.12802. PMC 6944283. PMID 31111484.
- 46) Craici IM, Wagner SJ, Bailey KR, Fitz-Gibbon PD, Wood-Wentz CM, Turner ST, et al. (June 2013). "Podocyturia predates proteinuria and clinical features of preeclampsia: longitudinal prospective study". *Hypertension*. 61 (6): 1289–96. doi:10.1161/HYPERTENSIONAHA.113.01115. PMC 3713793. PMID 23529165.
- 47) "Pre-eclampsia predicted using test during pregnancy". *BBC News*. 2011-11-12. Archived from the original on 2011-11-18. Retrieved 2011-11-22.
- 48) Brown CM, Garovic VD (October 2011). "Mechanisms and management of hypertension in pregnant women". *Current Hypertension Reports*. 13 (5): 338–46. doi:10.1007/s11906-011-0214-y. PMC 3746761. PMID 21656283.
- 49) "Pre-eclampsia-Eclampsia". *Diagnosis and management of pre-eclampsia and eclampsia*. Armenian Medical Network. 2003. Retrieved 2005-11-23.
- 50) Ota E, Hori H, Mori R, Tobe-Gai R, Farrar D (June 2015). "Antenatal dietary education and supplementation to increase energy and protein intake". *The Cochrane Database of Systematic Reviews* (6): CD000032. doi:10.1002/14651858.CD000032.pub3. PMID 26031211.
- 51) Duley L, Henderson-Smart D, Meher S (October 2005). "Altered dietary salt for preventing pre-eclampsia, and its complications". *The Cochrane Database of Systematic Reviews* (4): CD005548. doi:10.1002/14651858.CD005548. PMID 16235411.

52) Rumbold AR, Crowther CA, Haslam RR, Dekker GA, Robinson JS (April 2006).
"Vitamins C and E and the risks of preeclampsia and perinatal complications" (PDF).
The New England Journal of Medicine. 354 (17): 1796–806.
doi:10.1056/NEJMoa054186. hdl:2440/23161. PMID 16641396.