VILNIUS UNIVERSITY
MEDICAL FACULTY

The Final Thesis

Anaesthesia Challenges in Obstetrics with the Focus on Preeclampsia

Emma Julia Schwartz,
S1830340
VI year,
5th group

Institute of Clinical Medicine, **Clinic of Anaesthesiology and Intensive Care**

Supervisor Prof. (HP) Dr. Jūratė Šipylaitė

The Head of Department/Clinic Prof. (HP) Dr. Jūratė Šipylaitė

2024

Email of the student: emma.schwartz@mf.stud.vu.lt

Table of Contents

1. Summary

Preeclampsia counts as a hypertensive disease during pregnancy. It affects 3-10% worldwide (1). It ranges from mild to severe. In addition, the disease is divided into early-onset preeclampsia, which starts before the 34th week of gestation, and late-onset preeclampsia. Late-onset preeclampsia starts after the 34th week of gestation. Preeclampsia has different impact on maternal and neonatal outcomes. The pathophysiology is still unknown, but there are some hypotheses. Risk factors include primigravida, increased maternal age, obesity, and autoimmune disease (2). Diagnostic criteria include hypertension, and changes in the laboratory results, such as increased liver enzymes or proteinuria. Moreover, a prognostic factor will be the ratio of the soluble fms- like kinase-1 and placental growth factor. Other diagnostic criteria might include Doppler ultrasound

of the uterine artery. The symptoms differ throughout the organ system; for example, abdominal pain, visual disturbances, dyspnea, nausea, and vomiting. Neuraxial anesthesia is preferred in the preeclamptic patients. The anesthesia comes with different complications. The complications of preeclampsia range from mild to severe ,and they can persist for a long time, as postpartum preeclampsia. The disease has two main complications, eclampsia and HELLP- syndrome. There is no explicit treatment, but delivery is the most sufficient treatment. The most common form of anesthesia for delivery is the neuraxial anesthesia. Preventive methods for this disease include aspirin and magnesium sulfate. It will not cure the disease, but it might prevent a severe situation. Additionally, patient education is important to recognize the disease as early as possible.

Keywords: preeclampsia, hypertension, primigravida, proteinuria, fms-like kinase-1/PIGF ratio, postpartum, neuraxial, aspirin, magnesium

2. Introduction

Preeclampsia is a hypertensive disease in pregnancy. It is defined as an ominous hypertensive disorder with end-organ involvement. It has maternal and fetal manifestations (3). It is a syndrome and can be subdivided into mild or severe (3), as well as early onset, before the 34th week of gestation, or late-onset, after the 34th week of gestation (4). The syndrome accounts for 2% of all pregnancies in Europe (4), 3-10% worldwide (1),and causes 10-15% of maternal mortalities (4), as well as 500,000 fetal deaths worldwide (5). In the United States, it is the leading cause of maternal deaths, severe maternal morbidity, maternal intensive care admissions, cesarean sections (5) and prematurity of 15% (6). It leads to 9-26% of maternal deaths in low-income countries, compared to 16% in high-income countries (7). The origin of preeclampsia is from the Greek word “Eklampsis” (8). The term “pre” is well known in the English language; it can be translated as a state “before convulsions.” Preeclampsia was also known as “EPH-Gestosis” (9). It includes edema, proteinuria, and hypertension (9). According to the American College of Obstetricians and Gynecologists (ACOG), hypertensive diseases in pregnancy can be classified as preeclampsia-eclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, and gestational hypertension (10). The progression of the syndrome is slow, it often never becomes severe, but sometimes it can progress within days (3). According to the new definition of AWMF 015/018, 2. E3 says

an ultrasound of the arteria uterinae as well as the determination of angiogenic and antiangiogenic factors, especially the sFLT1/PIGF- quotient will be helpful for the risk assessment of preeclampsia (11). It might also occur after the delivery, which is then defined as “postpartum preeclampsia” (12).

Preeclampsia can be defined as new-onset hypertension with a blood pressure of greater than 140 mmHg systolic and 90 mmHg diastolic. The first onset occurs after the 20th week of gestation, and it can be seen in proteinuria >300 mg (4), thrombocytopenia, renal insufficiency, impaired liver function tests, pulmonary edema, or visual disturbances (3), (4),4, (13). The risk factors include obesity, increased maternal age, and comorbidities (10). Preeclampsia can affect the blood supply of the placenta (6).

There are different forms of anesthesia. It includes general or regional anesthesia. The regional anesthesia consists, for example of neuraxial anesthesia. The main concerns in general and in neuraxial anesthesia are the edematous airway (14), cardiovascular dysfunction, as well as cerebrovascular system dysfunction and exaggerated coagulopathy (8). Preeclampsia could lead to eclampsia and HELLP- syndrome. The HELLP- syndrome can be found in 10-20% of the patients (4) and means hemolysis, elevated liver enzymes, and a low platelet count (1). Eclampsia has a high risk for chronic health problems including chronic hypertension, Diabetes mellitus, chronic renal failure, ischemic heart disease, cerebrovascular and peripheral vascular disease (10). An early delivery is often recommended (12), sometimes it is the only cure (9). The delivery should be after 37 weeks of gestation (9). Aspirin should be administered for the prevention of preeclampsia. It can reduce rates by 10%. The prevention should be started before the 16th week of gestation with a daily dose of 150 mg, it should be taken in the evenings and should only be given to high-risk patients (15). The goals of the thesis are to emphasize the complications regarding preeclamptic patients, to understand the prevention of the disease, as well as to have tips for practice. Moreover, the thesis shows what complications might appear in the pre-anesthetic period, anesthetic period, and post-anesthetic period.

Literature selection strategy

For the literature review, PubMed, Google Scholar, as well as the American College of Obstetricians and Gynecologists and Anesthesia Journal, were mainly used. The articles are published in a timeframe from 2011 to 2024. The focus was on the articles published in the last five years. The main language for the research was English. Complications

regarding anesthesia challenges in obstetrics, with an emphasis on preeclamptic patients, were evaluated.

3. Risk factors for preeclampsia and eclampsia

Risk factors in preeclampsia can be subdivided into general risk factors and pregnancy-related factors (4).

The general risk factors include chronic hypertension, obesity with a body mass index above 30 (3), (4), (13), pre-existing Diabetes mellitus type 1 or 2 (4), a positive family history of preeclampsia (3), (10), (13), autoimmune disease such as Systemic Lupus Erythematosus (4), (10), obstructive sleep apnea (7), and pre-existing chronic renal diseases (1), (10) or thrombophilia (10), (13). Additionally, an increased maternal age above 35 years (1), (4), (5), (10), (13), or under 18 years (16), (17) belongs to the general risk factors (4), (10), (13).

Pregnancy-related risk factors include primigravida, multiple pregnancies (4), (13), for example with triplets (13) or expecting multiples (6), previous pregnancy with intrauterine growth restriction(IUGR) (4), (7), gestational diabetes (4), (10) and assisted reproductive technologies (5), (10). The most common risk factor is primigravida (6).

The risk factors can be further subdivided into major, minor, and rare. The major risk factors consist of previous preeclampsia, chronic hypertension, pre-existing hypertension, adiposities with a body mass index above 30, diabetes, multiple gestations, and antiphospholipid syndrome (1). The minor risk factors include Systemic Lupus Erythematosus (SLE) (6), (17), previous stillbirth, pre-existing overweight with a Body Mass Index above 25, nulliparity, a previous placental abruption, assisted reproductive technology, chronic kidney disease, an advanced maternal age of 35 years or older, as well as genetic susceptibility. The rare risk factors include a positive family history of preeclampsia and Trisomy 13 (5).

Furthermore, a differentiation into high-risk factors and moderate-risk factors is possible (12). The high-risk factors include previous preeclampsia in pregnancy (11), expecting more than one baby, chronic hypertension (12), pre-existing Type 1 or 2 Diabetes mellitus or renal diseases (11), chronic hypertension, autoimmune disorders, like SLE or antiphospholipid syndrome (1), (12), (17), and the use of in vitro fertilization (7), (12). The moderate risk factors consist of a first pregnancy, obesity, a positive family history of preeclampsia, maternal age greater than 35 years (7), (11), (12) or under 18 years (17), a

previous complicated pregnancy (12), more than 10 years apart between the pregnancies (12).

Moreover, inequities in access to prenatal care and health care could be a risk factor since they do not have regular checkups, laboratory blood control, or ultrasounds. Chronic stress is also a risk factor since it can cause hypertension or stress in the body, which could further cause preeclampsia (12). Women from North America also have a higher risk of preeclampsia. Those women might get pregnant later in life, they are mostly associated with obesity, they might have pre-existing diabetes or hypertension, and in those countries, with a lack of sufficient health care systems (12).

4. Diagnostic Criteria, Symptoms and Types

Chronic hypertension can be pre-existing and is found before the 20th week of gestation. The gestational hypertension can be defined as new-onset hypertension, with a systolic blood pressure of more than 140 mmHg and a diastolic blood pressure of more than 90 mmHg, occurring after the 20th week of gestation (10).

4.1 Diagnostic criteria

Diagnostic criteria for preeclampsia include a systolic blood pressure above 140 mmHg and a diastolic blood pressure of 90 mmHg or higher (3), (7), (10), (17), (18). Otherwise, as in gestational hypertension, it appears after 20 weeks of gestation in previously healthy patients (3), (6). The onset is around the 37th week of gestation. Furthermore, it can have the onset after delivery, which is called postpartum preeclampsia. This type of preeclampsia appears during the first few days to one week postpartum (6). Moreover, the patient has proteinuria with 0.3 g or more in the urine specimen, which is a 24-hour sample, or more than 1 positive urine dipstick (3), (4) (6), (17), (18).

Symptoms of neurological complications can appear, such as eclampsia, blindness, altered mental status, stroke, clonus, severe headaches, which do not respond to medications (6), (12), (17) and visual disturbances (8), (17).

In women with preeclampsia, it can be seen as contracted plasma volume, normal or increased cardiac output, vasoconstriction, and a hyperdynamic left ventricular function. Moreover, an increased airway edema, left ventricular dysfunction in systole and diastole, a decreased glomerular filtration rate, and platelet dysfunction can be diagnosed in preeclamptic patients (8). The hyperdynamic state includes high cardiac output and low

vascular resistance (19). The hypodynamic state with high resistances causes low cardiac output and low plasma volume (16).

A systolic blood pressure of 160 mmHg or more and a diastolic blood pressure of 110 mmHg or more than at least a four-hour interval blood pressure measurement on two occasions are diagnostic criteria for severe preeclampsia (20). Additionally, proteinuria of 5 g in a 24-hour urine sample or three positive proteins are randomly found on urine tests in a four-hour interval (3), but preeclampsia can appear without proteinuria (10). Oliguria of less than 500 ml in 24 hours, new-onset cerebral and visual disturbances (6), (10), pulmonary edema, and cyanosis (7), (10), can be seen. Also, epigastric pain or pain in the right upper quadrant with nausea and vomiting (10), (12), impaired liver function test (10), thrombocytopenia under 100 000 x 10^9/L (6), (10), progressive renal insufficiency with a creatinine level more than 100 mmol/L (4), (10) and fetal growth restriction (3), (18), can be included. Severe preeclampsia can be diagnosed if one or more of the above-mentioned clinical signs can be seen (3), (10). In severe preeclampsia, a chronic placental hypoperfusion can be seen (8). To check for end-organ dysfunction, the complete blood count, especially the red blood cells and thrombocytes, should be checked (17). In addition, the liver function test and a kidney function test should be performed. A hemoglobin of more than 13 g/dL, a decreased haptoglobin count, a hematocrit of more than 38%, and a thrombocyte count of less than 100 000/µL can be seen (4), (17). The liver transaminases are more than twice increased, and the indirect bilirubin is more than 1.2 mg/dL. Lactate dehydrogenase is also a two-fold increase which, combined with the decreased haptoglobin and increased bilirubin values is a sign of hemolysis. Creatinine may present with more than 0.9 mg/dL (4), (17). Those blood values are a sign of the HELLP – syndrome. It includes hemolysis, elevated liver enzymes, and a low platelet count (21). This is a complication of preeclampsia.

Algorithms for early detection in the first trimester include a detailed anamnesis, a blood pressure measurement, Doppler ultrasound of uterine artery and evaluation of biomarkers, like PAPP-A and Placental growth factor (PIGF) (15). A more specific diagnostic tool is the soluble Fms-like tyrosine kinase-1(sFLT1) sFLT1/ PIGF ratio, which is elevated in preeclampsia (1); sFLT1 will be elevated and PIGF will be decreased (22). This can be tested at the beginning of the second trimester (18).

Additional diagnostic include the weight and height of the woman for Body Mass Index calculation (11), an ultrasound of the fetus, and amniotic fluid to check for the amount of amniotic fluid and size of the fetus (6).

4.2 Symptoms

Symptoms of preeclampsia can be divided into end-organ damages. In general, they complain about nausea and vomiting. Oliguria, proteinuria, and peripheral or generalized edema could indicate renal damage. A pulmonary problem can be seen by dyspnea and retrosternal complaints because of fluid in the lungs (23). A liver injury can be indicated by right upper quadrant pain, which is also seen in the HELLP- syndrome. Intense headaches, hyperreflexia, visual disturbances such as flickering before the eyes or visual field defects, seizures, or strokes belong to central nervous system damage. The placenta can be damaged as well. The clinical presentation includes oligohydramnios, intrauterine growth restriction, preterm delivery, intrauterine fetal death, and abruptio placentae (4), (12).

4.3 Types

Preeclamptic patients can be divided into two types based on their gestational age. The Early-onset group starts before 34 weeks of gestation (4). This group occurs in 20 % of cases. In this period, there is incomplete placentation and remodeling of the uteroplacental spiral arteries. (24) This further leads to fetal growth restriction and can cause further fetal and maternal complications. Moreover, it can lead to premature delivery, which can result in neonatal morbidity and mortality (10). Women are seen to have low cardiac output and high resistance due to vasoconstriction. This is caused by endothelial dysfunction (16). A pathological Doppler ultrasound of the uterine artery and fetal Doppler are seen. It shows resistance to the circulation of the placenta, which is due to the trophoblast invasion in the vascular system (25). Additionally, in the ultrasound, the intrauterine growth restriction can be found (15).

The Late-onset group, which begins at the 34th week of gestation (4), is more common. It can be associated with maternal comorbidities (10), (15) such as Diabetes mellitus, chronic hypertension, obesity, cardiovascular diseases, as well as advanced maternal age. The fetus has a better outcome since it can be well-grown and will have a normal body weight (10), (15). The uteroplacental dysfunction is based on placental outgrowth (15), leading to

intervillous and fetal hypoxemia (10). Women have high cardiac output and low vascular resistance (16).

Another type is postpartum preeclampsia, which has the onset an after delivery. This type will be described later.

5. Pathophysiology

The pathophysiology is not fully understood (10). Otherwise, some hypotheses exist. A failure in trophoblast cell invasion of the uterine spiral arteries occurs during placentation. This leads to a failure of spiral artery remodeling and causes a decrease in placental perfusion. An early placental hypoxia exists, and cytokines and inflammatory factors are upregulated (3). It also causes decreased blood and oxygen supply to the fetus and an intrauterine growth restriction (17). This could be an indication of the termination of pregnancy (4). Placental hypoxia leads to oxidative stress and an imbalance between proangiogenic and antiangiogenic factors (1). This will cause widespread endovascular dysfunction (10). Placental growth factor (PIGF) is a proangiogenic factor. It preserves endothelial and vascular function. The soluble fms-tyrosine kinase-1(sFLT-1) binds with the placental growth factors and has an antiangiogenic factor (9). The sFLT-1/PIGF ratio should be measured if preeclampsia is unconfirmed (10).

In patients with early- onset, this means before the 34th week of gestation, with a ratio between 38 and 85 indicating an increased risk of becoming preeclampsia in the next four weeks (26). If the ratio is higher than 85, then they seemingly develop preeclampsia (26).

In late-onset patients, later than the 34th week of gestation, the ratio between 38 and 110 shows an increased risk of developing preeclampsia in the next four weeks (26). Close monitoring should be performed. A ratio of more than 110 indicates that they have a high probability of preeclampsia (26). An increase in sFLT-1 activates the vascular endothelial growth factor (VEGF) and PIGF. This decreases the maintenance of endothelial cell functions in the liver, brain, or glomeruli (5). It can also cause increased permeability in the vascular system. As a result, edema in the legs, hands, lungs, and brain is possible. A narrowing in the vascular system is possible, which causes hypertension. Also, a formation of thrombi could occur, which is mostly seen in HELLP syndrome (27). Proteinuria is another symptom that is due to increased retention of sodium in the kidneys (17).

There are two theories from 2021. The first one focuses on vascular remodeling of the spiral arteries caused by an invasion of cytotrophoblasts. This leads to the activation of the

clotting pathway. The consequences are a release of cytokines and antiangiogenic factors, vasoconstriction, endothelial dysfunction, and reduced perfusion of organs. It is a triad of placental insufficiency, vascular reactivity, and inadequate placentation. The other theory describes that maternal systemic and uterine impairment causes an abnormal placentation. Further, it causes elevated systemic vascular resistance and low cardiac output. This leads to increased left ventricular mass, hypertrophy, or diastolic dysfunction. In early-onset preeclampsia, there is higher left ventricular mass index, severe diastolic dysfunction, and increased systolic dysfunction. A reduced cardiac output and an increased systemic vascular resistance can be seen in the 20th week of gestation or later (28).

The soluble endoglin(sENG) is a cell surface coreceptor that binds and decreases levels of transforming growth factors (TGF-ß). Normally, it induces the migration and proliferation of endothelial cells. In preeclampsia, sENG mediates the downstream effects that create a vasoconstrictive state, oxidative stress, endothelial dysfunction, and microemboli that have an impact on the organ system (9).

Cardiovascular changes, pulmonary edema, and renal hypoperfusion and edema occur during preeclampsia. During preeclampsia, the women have increased venous capacity and increased blood volume due to the additional fetoplacental circulation. This leads to an increased heart rate and vascular resistance, which further leads to increased afterload (8). Pulmonary edema is often associated with increased vascular permeability, previous heart failure, and preserved ejection fraction, especially with diastolic dysfunction. The diastolic dysfunction can be seen in the left atrial volume index (LAVI). In women with preeclampsia, a left atrial volume index of 38.9 mL/m2 can be seen. An index above 34 mL/m2 indicates diastolic dysfunction (29).

The peripheral vasospasm reduced renal blood flow and decreased glomerular filtration rates activate the macula densa, which stimulates the renin-angiotensin-aldosterone system. An increase in renal sodium and water retention occurs, and causing increased extracellular volume and edema (8), (16).

The cerebral disorders could be due to cerebral vasospasm caused by cerebral ischemia, cytotoxic edema, or infarction. Another possible cause of cerebral edema is the loss of cerebral autoregulation with hyper perfusion (16).

6. Anesthesia

Anesthesia is fully involved in preeclamptic patients. The following part can be subdivided into pre-anesthetic, anesthesia, and postoperative.

6.1 Preanesthetic Period

During the pre-anesthetic period, the hemoglobin level and platelet count must be controlled. The neuraxial analgesia, which is the most common in those patients, can be performed if the platelet count is under 50,000. Thrombocytopenia can be seen in severe preeclampsia and HELLP syndrome, so it is important to understand the risk for complications (3). The fluid retention, which is common in preeclamptic patients, must be controlled because otherwise, it will cause problems during intubation (10).

The anamnesis must be performed to check for any medical issues (10), previous complications with anesthesia as with the intubation, allergies to medications, and risk factors for preeclampsia in this patient (8), and the risk has to be evaluated for prematurity and maternal and fetal complications (18). For example, a cardiac failure will mean that beta-blockers must be avoided in this case. The beta-blockers will cause maternal bradycardia and a possible heart block (10). The body mass index is also important and can be obtained during the anamnesis and physical examination. For example, hypertension and obesity can be an indication for obstructive sleep apnea (28).

The anesthesiologists needs to know the gynecological risks, such as small placenta, and premature abruption (8). Women with a previous occurrence have a higher incidence of chronic renal failure, which can lead to problems during anesthesia, for example, the excretion of the medications (28).

Intra-arterial monitoring to assess the stroke volume and arterial pressure can be helpful for fluid management.

A transesophageal echography should be performed before delivery to evaluate ventricular function, any cardiac and pleural comorbidities, and intravascular volume status (28). Additionally, the echo should be done at the 24th week of gestation to determine if a reduced cardiac output, high vascular resistance, and increased left ventricular wall thickness are present (16). An echo-guided plasma expansion can be made in the case of gestational hypertension and fetal growth restriction. It will be given nitric oxide and nifedipine (16). Moreover, a pulse wave analysis should be made. It can identify increased vascular stiffness (16). Due to the circumstances of preeclampsia, which can lead to placental insufficiency, it should always be prepared for an urgent delivery (3). For seizure prophylaxis, magnesium sulfate is given in the form of a slow bolus with 4 g intravenously in 4 hours. The blood pressure should be lower than 160 mmHg systolic to avoid a stroke or intracranial hemorrhage.

6.2 Anesthesia Period

The choice of anesthesia must be made (8). The preeclamptic patient must be evaluated to determine if there is a high risk of maternal and fetal factors (30). If it is positive, then they should undergo general anesthesia and, if possible, regional anesthesia. If there is no high risk, they can undergo regional anesthesia. In an already eclamptic patient, the intracranial pressure, bleeding, and thrombocyte count must be assessed. If the intracranial pressure is normal, no signs of bleeding, and a stable platelet count indicates regional anesthesia. Otherwise, if the intracranial pressure is increased, signs of active bleeding and thrombocyte count less than 80x10^9/L indicate general anesthesia (30).

Neuraxial analgesia is often preferred (3) because it prevents a rise in blood pressure, which can be associated with contractions during labor (10). It is beneficial because it can quickly extend to further anesthesia, and it also might increase the intervillous blood flow, reduce uterine artery resistance, and improve the placental gas exchange. Additionally, there is a decreased need for catecholamines for women, which aids in blood pressure control (31). The disadvantages include the increased risk of spinal canal hematoma, and the thrombocytopenia might be too severe for this anesthesia (10). Neuraxial anesthesia includes spinal and epidural anesthesia.

The spinal anesthesia is injected into the cerebrospinal fluid within the subarachnoid space in the spinal cord. A typical location is in the lumbar region between the lumbar vertebrae 3 and 4 (32). It is mostly used for surgeries in the regions of the lower abdomen, pelvis, and lower extremities (33). The local anesthetic drug lasts for 2 to 3 hours (34). The nerve roots in the spinal cord will be blocked, which leads to a feeling of numbness and tingling because of the profound sensation loss and loss of muscle function in the lower part. The patients will be awake. Spinal regional anesthesia has advantages because it is fast acting, effective, has less potential for trauma in the epidural space, has a reduced blunting of neuro-endocrine responses to the surgery, and there is no need for a laryngoscope. Moreover, there are no cases of neonatal depression (8). Contraindications for spinal anesthesia include comorbidities such as mitral stenosis, congenital heart diseases, pulmonary edema with systolic hypofunction, hypertrophic obstructive cardiomyopathy, and pericardial effusion (28). Other contraindications include neurological diseases, such as multiple sclerosis, and hypovolemia (33). If the patient has the HELLP- syndrome, spinal anesthesia should be started after the corticosteroid therapy (1). According to the

national guidelines, spinal anesthesia is preferred in thrombocytopenic patients with additional antiplatelet drugs and heparin (16).

The epidural anesthesia injection will be made in the epidural space at various levels of the spine, depending on the effect (35). The nerve block will cause a complete loss of sensation and muscle function. It is mostly used for analgesia during delivery (35). It also has an advantage. It relieves the pain through a catheter in a subarachnoid space in the postpartum phase. It also encourages the patient to have deeper breaths, which improves tissue oxygenation and tidal volume (8). An early onset of epidural anesthesia will decrease the blood pressure, and this will improve uteroplacental perfusion (1). It may lead to severe preeclampsia, or HELLP- syndrome, or an epidural hematoma (36). As a result of that, epidural anesthesia should be avoided in the case of a platelet count of less than 65x10^9/L (16). It also does not influence the neonatal outcome (16).

General anesthesia is usually performed for longer periods of surgery. The intravenous agents cause a loss of sensation, muscle function and are usually unconscious (37). During general anesthesia, intubation is needed. In preeclamptic patients, the risk for a failed intubation is 1:274, due to fluid retention (16). Intubation can also cause hypertension or intracranial hemorrhage (16). The hypertension can be due to the use of a laryngoscope for the intubation and the additional use of an intravenous opioid agent, such as fentanyl (30). Moreover, it can lead to left heart failure, pulmonary edema, or central edema (1). The hypertension can be treated with a small amount of nitroglycerin (3), fentanyl, alfentanil, or remifentanil (10). Remifentanil can lead to neonatal depression and should not be used as a first-line drug (28). Dexmedetomidine is often given during general anesthesia because it has a shorter and lesser incidence of delirium compared to midazolam (38). Dexmedetomidine also prolongs the recovery of the patient (28). Contraindications for general anesthesia include the possible risks and consequences of the intubation, severe coagulation disorders, HELLP- syndrome, pulmonary edema, as well as symptoms of severe cerebral edema (16).

For pharmaceutical therapy, phenylephrine can be given as a first-line vasopressor to preserve systolic function (28). Other therapeutics, including fluid restriction to less than 80 ml/h should be performed if the stroke volume cannot be measured (28).

As is already known, interstitial pulmonary edema is a symptom and complication in preeclamptic patients. This pulmonary edema leads to impaired gas exchange and further causes desaturation. This should be kept in mind for the anesthesia because the patient will need an oxygen supply (28). Mask ventilation should be performed after the given muscle

relaxants, and the use of high-flow nasal oxygen will prolong the apneic oxygenation (28). In cases of pulmonary edema, a pulmonary arterial edge catheter and an electrocardiogram should be done. The pulmonary arterial edge catheter is to measure and treat changes in blood pressure (8).

The use of uterotonic drugs includes oxytocin as a first-line medication and misoprostol as a second-line medication. The oxytocin leads to vasodilation and hypotension. Misoprostol might cause a pronounced hypertensive response (28). The patient should receive a central venous catheter in a hypovolemic state (1). Information about the volume and cardiac status will be seen in the electrocardiogram (8).

Another noninvasive method is arterial waveform analysis and impedance cardiography (8). Impedance cardiography is used to evaluate the stroke volume and contractility of the heart by measuring resistance within the thorax (39) (40). The arterial waveform analysis is used to invasively determine blood pressure by evaluating the blood pressure and the phases of ejection and filling. The increased appeal towards this method is in the continuously provided information, which leads to a faster response time in treating hypo- or hypertension (41).

6.3 Postoperative Period

In the postpartum period, attention should be paid to a postpartum uterine atony (3). It happens due to the preventive magnesium sulfate intake. Pitocin and prostaglandins can improve atony (3). The risk of postpartum hemorrhage exists and is individual (28). A risk for spinal epidural hematoma is mostly seen in patients with a platelet count under 70 x 10^9/L. In the HELLP- syndrome, the risk of bleeding is seen with a platelet count under 75x10^9/L (28). Also, the intake of uterotonic agents increased the risk of postpartum bleeding (28).

Better outcomes in the postoperative period are seen if the patients receive a peripartum magnesium sulfate infusion for spinal anesthesia.

Nonsteroidal anti-inflammatory drugs should be avoided because they have an impact on hypertensive control, renal and platelet function (28).

In the case of a cerebral hemorrhage, an MRI with a T2-weighted FLAIR sequence of the brain and a pulse-wave analysis of the middle cerebral artery should be performed (8). The patient should be transferred to the intensive care unit for close monitoring. They must be examined, for example, for reflexes and the respiratory rate, which should be less than 12

breaths per minute, or to evaluate the renal function in the form of oliguria of less than 0.5ml/kg (30).

7. Complications

The main concerns of preeclampsia are an edematous airway, dysfunction of the cerebrovascular system, and exaggerated coagulopathy, as well as cardiovascular dysfunction (8). One of the most common complications is the HELLP- syndrome. It is defined as a triad of hemolysis, elevated liver enzymes, and a low platelet count (3). The symptoms include nausea, vomiting, mental confusion, or fatigue. The syndrome can be life-threatening, develop suddenly, and cause lifelong health issues (12).

It can be differentiated into two different onset times of the disease that relate to different complications (4). Early-onset preeclampsia, before the 34th week of gestation, is associated with prematurity, fetal growth restrictions (4), low birth weight (30), and a worse maternal and fetal outcome (4). Prematurity carries a higher risk for neonatal morbidity and mortality (4). The prematurity is the main cause of cerebral palsy (42). Moreover, they have an increased risk of breathing and feeding difficulties, vision and hearing problems, developmental delays, and cerebral palsy (12). Additionally, it might lead to obesity, hypertension, insulin resistance, cardiovascular diseases, and renal dysfunctions (42).

In late-onset preeclampsia, after the 34th week of gestation, there is a higher risk of fetal hypoxemia because of the lack of placental perfusion (4).

It can also be divided into maternal and neonatal complications (28). Neonatal complications include preterm delivery, hypoxic-ischemic encephalopathy, fetal growth restrictions (28), intrauterine fetal death (11), and perinatal death (28).

The maternal complications consist of abruptio placentae, pulmonary edema, liver failure, acute renal failure, and stroke (28). The placental abruption can cause heavy bleeding (12), which further could cause a hypovolemic shock.

In general, there is a risk for long-term comorbidities for these patients (28). They have an increased risk of systolic and diastolic dysfunction, which persists for one year, in early-onset preeclampsia (28). Generally, they have an increased risk for coronary, cerebrovascular, or peripheral vascular disease, thromboembolism, stroke, post-eclampsia, white matter lesions, end-stage renal disease, and Diabetes mellitus (28). If the pregnancy is in the 20s, they might develop chronic hypertension within 10 years (28). Women in

term pregnancy with preeclampsia are seen with contracted plasma volume, vasoconstriction, normal or increased cardiac output, and a hyperdynamic left ventricular function. This further leads to complications such as increased pulmonary edema, left ventricular dysfunction in systole and diastole, and a decreased glomerular filtration rate due to an exaggerated hypercoagulable state of pregnancy (8). A dilation of the vasculature, a fall in the arterial pressure, an increased heart rate, and increased cardiac output show a reduced responsiveness to angiotensin and norepinephrine (16).

In control of hypertension with labetalol, hydrazine, and nifedipine, symptoms of tachycardia, hypotension, headaches, and abnormalities of the fetal heart rate can be noticed (7).

An anesthetic complication is a spinal epidural hematoma. This complication is most common in patients with the HELLP- syndrome, which causes an increase in bleeding.

Another complication is hypotension due to the spinal block (43). It happens because of arterial and venous vasodilation due to the sympathetic block and activation of cardioinhibitory receptors (44). The hypotension may compromise the uterine blood flow and fetal circulation, which leads to fetal hypoxia, bradycardia, or acidosis (43). If the hypotension persists for longer than two minutes, an increase in oxypurines and lipid peroxides in the umbilical vein causes an ischemia-reperfusion injury. A hypotension of more than four minutes can be associated with neurobehavioral changes in the first four to seven days of neonatal life (43). Reduced compensatory mechanisms via baroreceptors increase the risk of cardioinhibitory reflexes, such as the Bezold-Jarisch reflex, cardiac arrest, and death (43).

The most common cause of maternal death in preeclampsia is cerebral hemorrhage (8). It is associated with a diastolic blood pressure of more than 110 mmHg and a systolic pressure of more than 160 mmHg (16).

The second most common cause of maternal death in preeclampsia is pulmonary edema (8), (1).

Cerebral complications include eclamptic seizures or cerebral hemorrhage (16). Moreover, they could have cerebral ischemia or edema. Cognitive impairment with impaired memory function persists for 3-7 months (16). Eclampsia is defined as the onset of a seizure or coma with signs or symptoms of preeclampsia (12). It is combined with preeclampsia, the most common cause of death during delivery (45). The signs include headaches, vision problems, mental confusion, and altered behavior (12). It may occur before, during, or after the delivery (12). Magnesium sulfate is often given as a preventive measure for

seizures. It is also associated with complications, which include respiratory depression or cardiac arrest (7).

They have a 3-4 times higher risk for end-stage kidney disease, a 4 times higher risk of stroke, and a 3 times higher risk of vascular dementia. The neonatal risk includes pulmonary hypertension into the teenage years and a life-long lung injury (5).

Another differential diagnosis of the headache includes postural puncture headache. This is a common resulting complication of the dural punctures performed in anesthesia, such as during a cesarean section (49).

8. HELLP –Syndrome and postpartum phase

8.1 HELLP –Syndrome

The HELLP-syndrome is a life-threatening complication and form of preeclampsia. It develops in the third trimester. 20% of patients do not have preeclampsia. HELLP stands for hemolysis, elevated liver enzymes, and a low platelet count. The pathophysiology of the syndrome has a microvascular origin. Endothelial damage and dysfunction cause it. This leads to three different mechanisms. The red blood cells might be sheared which leads to microangiopathic hemolytic anemia (MAHA) and hemolysis.

The second mechanism is the microthrombi accumulation in the liver. This causes damage to the hepatocytes and the liver enzymes are increased.

The third mechanism is platelet aggregation and agglutination, which causes a low platelet count. Risk factors include a Caucasian or European descent, an older maternal age, and a previous pregnancy with HELLP.

Signs and symptoms of HELLP-syndrome consist of fatigue, unexpected bleeding from the nose or gums, nausea, and vomiting, which is not typical for the 3rd trimester. Moreover, swelling, blurry vision, right upper quadrant pain, jaundice, cerebral edema, and hemorrhage can be noticed.

The complete blood count and liver function test should be checked for the diagnosis. Additionally, the blood group and Rh- factors, an ultrasound of the fetus and liver, and the fetal heart rate should be evaluated.

The goal is to stabilize the patients. In unstable patients, immediate delivery should be performed. In stable patients under the 34th week of gestation, dexamethasone should be given, which aids in maturing the lungs of the fetus. A reassessment of the delivery should be performed after 24 to 48 hours. If the patient is stable after the 34th week of gestation

has passed, they should receive dexamethasone, and the delivery should be performed in 24 to 48 hours.

The HELLP- syndrome could cause placental abruption as well as stroke, disseminated intravascular coagulation (DIC), and cerebral hemorrhage. In the worst-case scenario, it could lead to death (17).

8.2 Postpartum Phase

In the postpartum phase, there is a high risk for an exacerbation until seven days postpartum. Postpartum HELLP- syndrome and eclampsia can also occur (11). In the postpartum phase, a complication of gestational hypertension is postpartum preeclampsia, which might appear several weeks after delivery.

Postpartum preeclampsia can be subdivided into immediate postpartum preeclampsia and delayed postpartum preeclampsia (47). Immediate postpartum preeclampsia develops in the first two days postpartum. Delayed postpartum preeclampsia appears within 48 hours to 6 weeks; mostly it appears between the first seven to ten days. The prevalence of postpartum preeclampsia ranges from 0.3% to 27.5% (47). The risk factors of postpartum preeclampsia are similar to those of gestational preeclampsia. The risk is up 7 fold increased if patients are obese. African women have a two- to four-times higher risk of developing postpartum preeclampsia. Compared to gestational preeclampsia, it is less common in primiparous women (47).

Postpartum preeclampsia is often undiagnosed since most of the patients are discharged home earlier as the blood pressure rises. In patients with preeclampsia, the blood pressure usually drops within two days after delivery but might rise again between the 3rd and 6th days. Patients might notice neurological manifestations or the blood samples might indicate eclampsia or the HELLP syndrome (46).

Patients in the postpartum phase should have an intensive blood pressure measurement at a four-hour interval. The blood pressure should not rise above 150/100 mmHg. The reduction of hypertensive therapy in preeclamptic patients should not be reduced before the fourth day postpartum.

Moreover, they should receive magnesium sulfate intravenously to prevent seizures. This should be given for 48 hours postpartum (18).

The postpartum phase includes a long-term cardiovascular risk (28). In early-onset patients, systolic and diastolic dysfunction could exceed 1 year. Long-term risk in patients with previous preeclampsia include thromboembolism, stroke, white matter lesions,

diabetes mellitus, post-eclampsia, end-stage renal disease, cerebro- and peripheral vascular disease (3). If the maternal age is in the 20s, they might develop chronic hypertension in the next 10 years (3).

9. Treatment and Management

The only definite treatment for preeclampsia is the delivery (3).

The patient should have a regular check-up throughout the pregnancy to find out the early signs (3). To assess the arterial stroke volume and the arterial pressure intra-arterial monitoring is recommended. (28) This aids in the early detection of hypertension and changes in stroke volume. In general, management includes frequent blood gas analysis and laboratory studies, fast central-acting vasoactive medications, the estimation of intravascular volume status, and the management of hypertension (3).

Antihypertensive treatment can be divided into two phases: the initial treatment and the acute refraction of severe hypertension. The initial therapy includes hydralazine, nifedipine, and labetalol. Short-acting oral nifedipine 10- 20 mg every 4-6 hours or labetalol 200- 400 mg every 8-12 hours should be given to preeclamptic patients (46). Oral nifedipine is associated with enhanced renal blood flow compared to labetalol, which further increases the diuresis, so it should be used for volume overload (46). Nifedipine and labetalol are safe to use during pregnancy. Additionally, loop diuretics can be given to women with pulmonary edema (46). In the case of the use of loop diuretics, potassium supplementation should be added (46). The supplements should be given since loop diuretics can lead to hypokalemia (50), which further might cause cardiac arrhythmias (48).

The management of severe hypertension consists of nitroglycerin or sodium nitroprusside (3). Urapidil can also be given for the treatment of hypertension (4). Calcium channel blockers can be added for the antihypertensive treatment (7). The hypertension should be kept under 160 mmHg to prevent an intracranial hemorrhage. Magnesium sulfate and aspirin can be and should be given in preeclamptic patients to avoid eclampsia or in patients with gestational hypertension or to prevent preeclampsia (3).

Aspirin should be taken at doses of 100-150 mg and should be started before the 16^{th} week of gestation (10). Magnesium sulfate should be given in a bolus of 4g and continued with an infusion of 1g per hour. This should be given for an additional 24 hours after the last seizure (10).

The pulmonary edema should also be treated; this could be done with furosemide or nitroglycerin (4).

Nonsteroidal anti-inflammatory drugs are often given for pain relief as well as for headaches. Those drugs cause vasoconstriction, sodium, and water retention, which will cause hypertension (46). Therefore, they should be avoided or only given in very small doses, if indicated.

There are indications for hospitalization in pregnant women. Those indications include a diagnosed preeclampsia, an exacerbation of the general condition, blood pressure above 140/110 mmHg, proteinuria, rapidly increasing edema, and an increased body weight of 1 kg per week in the third trimester (4). Moreover, patients with HELLP- syndrome and eclampsia, as well as if the fetal general condition aggravates. This can be seen during the ultrasonography of the fetus or the cardiotocography (CTG) (4). It should be checked for the amniotic fluid index, expected fetal weight, and antenatal testing, in the form of a non-stress test and a biophysical profile, during the fetal ultrasound (7).

The aim of peripartum management is to control maternal blood pressure, cardiac output, and uteroplacental perfusion. Referring to this monitoring is important to detect cerebral edema, and to prevent seizures and strokes (8). In addition to magnesium sulfate, vasodilators such as dihydrazaline, methyldopa, and urapidil (16). The usage of the vasodilators aims to regulate the blood flow to the placenta and fetus in the first 20 weeks of gestation (8). Heparin, low-dose aspirin, and dipyridamole can also minimize placental ischemia. ACE inhibitors and angiotensin receptor antagonists are contraindicated (8).

In general, diuretics should be avoided, since they would shrink the intravenous compartment, which would compromise the uteroplacental blood flow (8).

Patients with uncomplicated preeclampsia should be monitored two times a week until the 37th week of gestation in the absence of complications (5). In general, women should lose weight if overweight, control their blood pressure, avoid caffeine, get healthy food, get enough sleep, and have a regular exercise routine (6). In patients with a delivery in the 34th week of gestation, antenatal steroids should be directly administered for lung maturation (7).

The eclamptic patients should receive airway management as well as anticonvulsive treatment such as magnesium sulfate (17). Furthermore, mother and fetus should be closely monitored in this situation. A delivery is recommended when the seizure is stopped and the mother is stable.

10. Prevention and tips for practice

Preeclampsia or its complications, such as HELLP or eclampsia, can be prevented. For this reason, magnesium sulfate and aspirin are mostly administered.

Magnesium sulfate is used as the first choice (7) in seizure prophylaxis (3) because it is anticonvulsive and vasodilative. It also reduces the rates of cerebral palsy and motor dysfunction in infants (16). Its function is to reduce the irritabilities in the central nervous system by decreasing the activity at the neuromuscular junction (3). Moreover, it can be used for the relaxation of the uterine and smooth muscles. Magnesium sulfate should be given at the beginning with a loading dose of 4 to 6 g over 20 to 30 minutes. It should be continued with a magnesium sulfate infusion of 1-2 g/ hour until 12 to 24 hours after the prophylaxis (3). The prophylaxis of magnesium should be given for symptoms of visual scotomata, ongoing or recurrent severe headache, oliguria, nausea or vomiting, epigastric pain, severe hypertension, and progressive deterioration in the blood tests. The laboratory tests of increased creatinine and liver transaminase, as well as a decreased platelet count, point out an indication for prophylactic magnesium (10). A therapeutic dose for seizure prophylaxis should be 6 to 8 mg/dL (3). This should be carefully given since a dose of 10 mg/dL could cause deep tendon reflex loss. This can be seen in an electrocardiogram when the PQ interval is prolonged and the QRS complex is widened. A dose of 15 to 20 mg/dL can cause respiratory arrest, and even 20 to 25 mg/dL can lead to death (3). Magnesium sulfate can lead to toxicity in patients with a decrease in renal function and oliguria because it will be excreted via the renal system (3). Those patients should be closely monitored (26) by checking the deep tendon reflexes, respiratory rate (3), electrocardiogram monitoring (8), and neurological status (3). The urine output will show a magnesium level of 30 ml/h. If the patient has an overdose of magnesium sulfate, they should receive 10 mL of calcium gluconate 10% over 10 minutes (8).

Another therapeutic prevention is aspirin. Aspirin belongs to the family of Nonsteroidal Anti-inflammatory drugs. It inactivates cyclooxygenase 1(COX1) and 2 (COX2), which suppresses the production of prostaglandins and thromboxane. It causes an antithrombotic effect by the inhibition of platelet aggregation. Aspirin is an analgesic, antipyretic, and anti-inflammatory drug (42). Low doses of aspirin should be given in the first stage of hypertension with a blood pressure of 130/80 mmHg (13). High blood pressure can lead to seizures, stroke, premature rupture of the placenta, low birth weight, premature delivery, and maternal organ damage of the liver and kidneys (5). A study included 1020 pregnant women with first-stage hypertension and compared a group with low-dose aspirin to those

with the placebo. The result showed that women with the placebo had a 39.1% preeclampsia prevalence compared to those with aspirin, who had a prevalence of 23.8%. This shows that aspirin can be a preventive measure of preeclampsia (13). In general, it reduces the risk for preeclampsia by 62% and reduces the small gestational age in neonates born before the 37th week of gestation by 20% (42). It prolongs the pregnancy and might shift the onset of preeclampsia. Aspirin is safe in pregnancy; otherwise, it is associated with an increased risk for hemorrhage and postpartum hemorrhage in patients with a low risk for preeclampsia. It should be given to women with multiple risk factors (51). However, it has no positive effects on chronic hypertension because of the preexisting endothelial dysfunction (42). Aspirin should be given at a dose of 150 mg and given in the evenings, and it should be only administered to high-risk patients. The start should be before the 16th week of gestation because it might reduce the risk of placental abruption. The placentation is completed by the 16th to 18th week of gestation. If aspirin is started from the 13th week to the 26th week, there is an increased risk of placental abruption (42). For the prediction of the severity of cardiorespiratory dysfunction in patients with preeclampsia, a Point of care ultrasonography (POCUS) is performed by evaluation of lung ultrasonography to identify interstitial pulmonary edema. In this case, the interlobular septa become edematous, which will be seen in the ultrasonography as a “common tail” or “B-lines” (28). The optic nerve sheath diameter (OSND) can predict if there is an increase in intracranial pressure and/or increased disease severity. This will be seen if the OSND is more than 20 mmHg. The incidence of abnormalities is approximately 59%, with a higher number of cardiac abnormalities instead of interstitial pulmonary edema (28). A systolic blood pressure of more than 160 mmHg systolic must be treated to prevent intracranial hemorrhages (8).

In patients with gestational hypertension and fetal growth restriction, an echo-guided plasma expansion can be performed. The patient will be treated with nitric oxide and antihypertensive therapy, like nifedipine. This leads to the improvement of the mother and fetus. (16)

11. Conclusion and tips for practice

All in all, it can be concluded that preeclampsia is associated with different challenges for anesthesiologists, gynecologists, and pediatricians. It also involves a complex interplay of genetic, immunologic, and acquired factors (9). Preeclampsia is a multisystem disorder,

that occurs in 2-5% of all pregnancies (16). It has a significant impact on maternal and fetal morbidity, as well as mortality (16). There is no definitive cure, but the most preventive and helpful treatment is the delivery of the fetus and placenta (5). Preeclampsia also provides long-term consequences, such as increased risk for cardiovascular diseases, dementia, and chronic hypertension (5). Moreover, in early-onset preeclampsia, systematic changes, including vasoconstriction, low cardiac output, and low filling pressure, can be noticed (16). Since the only cure is delivery, it can lead to preterm deliveries, which might cause low birth weight or an early placental abruption (6). Preeclamptic patients may also notice signs of blurry vision, chest pain, headache, or nosebleeds. These symptoms can indicate the HELLP syndrome. This is a complication of preeclampsia because it might damage the liver and the red blood cells and interfere with the blood clotting cascade (6). If the HELLP- syndrome remains untreated, it can further cause a heart attack, kidney disease, stroke, or another preeclampsia in the future (6). One of the main diagnostic factors is the sFLT1/PIGF ratio, since preeclamptic patients have a maternal angiogenic factor imbalance (5). The imbalance of those factors has an impact on vascular function. If an angiogenic factor disbalance is present, there is an increased risk for the patient to develop preeclampsia (5). Neuraxial anesthesia is preferred in preeclamptic patients if they do not have any coagulation disorders (8). Spinal anesthesia, in general provides more hemodynamic stability. Moreover, this form of anesthesia causes fewer spinal epidural hematomas (16). On the other side, spinal anesthesia can be associated with hypotension since it leads to an increased arterial wall tone (8). This hypotension can easily be treated and is usually just transient (8). Preeclampsia should also be treated symptomatically. If the blood pressure is over 160 mmHg systolic and it is not treated, it may cause cerebral hemorrhage (16). The treatment plan should be based on the individual patient's presentation (36). One of the preventive methods includes the education of the patients regarding hypertensive diseases during pregnancy (17). They should also be informed about the symptoms and signs. Those might include increased blood pressure, unrelieved headaches, abdominal pain, and confusion (17). The patient should be also informed that the best lying position is the lateral side on the left, and they should rest more frequently during the day. Additionally, the fetal movements should be counted and written down. The movements should be counted for one hour when sitting or lying on the left side, and they should always be measured at the same time of the day (17). A differential diagnosis of preeclampsia should be kept in mind. Those differential diagnoses may include chronic hypertension, Lupus erythematosus, chronic liver or renal diseases, gestational

hypertension, epilepsy, or antiphospholipid antibody syndrome (7). Moreover, pheochromocytoma or thrombotic microangiopathies can be part of the differential diagnosis (7).

Tips for practice include close monitoring of hypertensive pregnant women. Moreover, aspirin and magnesium sulfate can be given after the 16th week of gestation for seizure prophylaxis. Diuretics should be avoided because they shrink the intravenous compartment, and this would compromise the uteroplacental blood flow. Hypertensive treatment can be given in the form of hydralazine, nifedipine, and labetalol. Nonsteroidal anti-inflammatory drugs should be given carefully, they might cause hypertension due to vasoconstriction. The choice of anesthesia is individual, but neuraxial anesthesia is preferred since general anesthesia often leads to further hypertension due to the medications. The only definite treatment is the delivery. The patients should be closely monitored after the delivery for hypertension and possible postpartum preeclampsia, this is often missed.

Literature review

1. **Wallenborn, J.** *Notfallsituationen in der geburtshilflichen Anästhesie.* Leipzig : Aktuellen Wissen für Anästhesisten Refresher Course, Main 2014.

2. **Gynecologists, American College of Obstetrician and.** American College of Obstetrician and Gynecologists. *American College of Obstetrician and Gynecologists.* [Online] June 2020. [Zitat vom: 20. December 2023 .] https://journals.lww.com/greenjournal/abstract/2020/06000/gestational_hypertension_and_preeclampsia__acog.46.aspx.

3. **Ronald D. Miller, Manuel C. Pardo Jr.** *Basics of Anesthesia.* Philadelphia : Elsevier/Saunders., 2011. 616-089.5..

4. **Amboss.** ***Amboss.*** **[Online] Amboss Medical knowledge, 29. January 2024. [Zitat vom: 3. February 2024.] https://next.amboss.com/us/article/VO0GrT?q=hypertensive%20disorders%20of%20pregnancy.**

5. Sarosh Rana, Elizabeth Lemoine, Joey P. Granger, S. Ananth Karumanchi. American Heart Association. ***American Heart Association.*** **[Online] 29. March 2019. [Zitat vom: 8.**

January 2024.] https://www.ahajournals.org/doi/pdf/10.1161/CIRCRESAHA.118.313276.

6. Professionals, Cleveland Clinic medical. Cleveland Clinic. *Cleveland Clinic.* [Online] 14. October 2021. [Zitat vom: 21. January 2024.] https://my.clevelandclinic.org/health/diseases/17952-preeclampsia.

7. Karrar, Shahd A. und Hong., Peter L. National Library of Medicine. *National Library of Medicine.* [Online] 13. February 2023. [Zitat vom: 24. January 2024.] https://www.ncbi.nlm.nih.gov/books/NBK570611/.

8. Sharma, Jayavelan Ramkumar and Nidhi. hilarispublisher. *hilarispublisher.* [Online] 3. October 2018. [Zitat vom: 11. November 2023.] https://www.hilarispublisher.com/open-access/anesthetic-considerations-in-preeclampsia.pdf.

9. Christopher W. Ives MD a, Rachel Sinkey MD b c, Indranee Rajapreyar MD d, Alan T.N. Tita MD, PhD b c, Suzanne Oparil MD d. Science Direct. *Science Direct.* [Online] 6. October 2020. [Zitat vom: 14. January 2024.] https://www.sciencedirect.com/science/article/pii/S0735109720362987?via%3Dihub.

10. Russel, Robin. National Library of Medicine. *National Library of Medicine.* [Online] June 2020. [Cited: January 16, 2024 .] https://pubmed.ncbi.nlm.nih.gov/32049882/.

11. Wagner, Dr. med. Konstantin. *Präeklampsie.* [Video] s.l. : Richtig Wissen, 2017.

12. Staff, Mayo Clinic. Mayo Clinic . *Mayo Clinic* . [Online] 15. April 2022. [Zitat vom: 23. january 2024.] https://www.mayoclinic.org/diseases-conditions/preeclampsia/symptoms-causes/syc-20355745.

13. Association, American Heart. American Heart Association. *American Heart Association.* [Online] 25. May 2018. [Zitat vom: 3. january 2024.] https://www.heart.org/en/news/2018/07/19/low-dose-aspirin-could-help-pregnant-women-with-high-blood-pressure-avoid-a-dangerous-condition.

14. Andrew N. Chalupka, Lisa Leffert. orphananethesia. *orphananethesia.* [Online] July 2019. [Zitat vom: 21. January 2024.] https://www.orphananesthesia.eu/de/erkrankungen/handlungsempfehlungen/präeklampsie/919-preeclampsia-

2/file.html#:~:text=Neuraxial%20(spinal%2C%20epidural%2C%20or,potentially%20high%2Drisk%20general%20anaesthetic.

15. D. Surbek, M. Hodel, M. Baumann, O. Lapaire. sggg. *sggg.* [Online] [Zitat vom: 18. January 2024.] https://www.sggg.ch/fileadmin/user_upload/PDF/67_Diagnostik_Praeeklampsie.pdf.

16. Gogarten, Wiebke. National Library of Medicine. *National Library of Medicine.* [Online] 22. June 2009. [Zitat vom: 19. January 2024.] https://pubmed.ncbi.nlm.nih.gov/19318931/.

17. Evdokia Dimitriadis, Daniel L. Rolnik, Wei Zhou, Guadalupe Estrada-Gutierrez, Kaori Koga, Rossana P. V. Francisco, Clare Whitehead, Jon Hyett, Fabricio da Silva Costa, Kypros Nicolaides & Ellen Menkhorst. Nature Reviews Disease Primers. *Nature Reviews Disease Primers.* [Online] 16. February 2023. [Zitat vom: 18. December 2023.] https://www.nature.com/articles/s41572-023-00417-6.

18. Horizonte, MD. *Präeklampsie, HELLP Syndrom - Markus Schmidt - Repetitorium Gynäkologie Online Kurs.* [Video] 2021.

19. Ruth Bedson, MBBS FRCA Anna Riccoboni, MBChB FRCA. BJA Education. *BJA Education.* [Online] April 2014. [Zitat vom: 20. December 2023 .] https://www.bjaed.org/article/S1743-1816(17)30109-9/fulltext#.

20. Gynecologists, American College of Obstetricians and. American College of Obstetricians and Gynecologists. *American College of Obstetricians and Gynecologists.* [Online] April 2023. [Zitat vom: 22. January 2024 .] https://www.acog.org/womens-health/faqs/preeclampsia-and-high-blood-pressure-during-pregnancy.

21. Werner Rath, Panagiotis Tsikouras, and Patrick Stelzl. National Library of Medicine. *National Library of Medicine.* [Online] . May 2020. [Zitat vom: 22. February 2024 .] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7234826/#:~:text=HELLP%20syndrome%20is%20a%20laboratory,diseases%2C%20making%20early%20diagnosis%20difficult.

22. Harald Zeisler, M.D., Elisa Llurba, M.D., Ph.D., Frederic Chantraine, M.D., Ph.D., Manu Vatish, M.B., Ch.B., D.Phil., Anne Cathrine Staff, M.D., Ph.D., Maria Sennström, M.D., Ph.D., Matts Olovsson, M.D., Ph.D., Shaun P. Brennecke, M.B., B.S., D.Phil., Hol.

The New England Journal of Medicine. ***The New England Journal of Medicine.*** **[Online] 7. January 2016. [Zitat vom: 7. February 2024.] https://www.nejm.org/doi/full/10.1056/nejmoa1414838.**

23. Staff, Mayo Clinic. Mayo Clinic . ***Mayo Clinic.*** **[Online] 15. April 2022. [Zitat vom: 11. January 2024 .] https://www.mayoclinic.org/diseases-conditions/preeclampsia/symptoms-causes/syc-20355745.**

24. R. Nirupama, S. Divyashree , P. Janhavi , S.P. Muthukumar , P.V. Ravindra. Science Direct. ***Science Direct.*** **[Online] February 2021. [Zitat vom: 22. December 2023.] https://www.sciencedirect.com/science/article/abs/pii/S2468784720303457?via%3Dihub.**

25. José Geraldo Lopes Ramos, Nelson Sass , Sérgio Hofmeister Martins Costa. Thieme. ***Thieme.*** **[Online] 2017. [Zitat vom: 17. January 2024.] https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0037-1604471#N1100E.**

26. Wünsche, Dr. Falko. Medizin Zentrum Dortmund. ***Medizin Zentrum Dortmund.*** **[Online] MVZ Dr Eberhard & Partner. [Zitat vom: 11. January 2024.] https://www.medizin-zentrum-dortmund.de/de/laboratoriumsmedizin/untersuchungsprogramm/untersuchung/3414/.**

27. Khalid, Farhan, Mahendraker, Neetu und Tonismae., Tiffany. National Library of Medicine. ***National Library of Medicine.*** **[Online] 29. July 2023. [Zitat vom: 21. January 2024.] https://www.ncbi.nlm.nih.gov/books/NBK560615/.**

28. van Dyk D, Dyer RA, Fernandes NL. National Library of Medicine. ***National Library of Medicine.*** **[Online] December 2021. [Zitat vom: 18. January 2023.] https://pubmed.ncbi.nlm.nih.gov/34776105/.**

29. Nivedita Jha, MBBS, MS Ajay Kumar Jha, MD, DM. American Journal of Obstetrics and Gynecology. ***American Journal of Obstetrics and Gynecology.*** **[Online] 24. August 2022. [Zitat vom: 15. December 2023.] https://www.ajog.org/article/S0002-9378(22)00674-3/fulltext.**

30. Wenk, D. Bremerich · T. Annecke · D. Chappell · R. Hanß · L. Kaufner · F. Kehl · P. Kranke · T. Girard · W. Gogarten · S. Greve · S. Neuhaus · D. Schlembach · L. Schlösser · T. Standl · S. Treskatsch · T. Volk · J. Wallenborn · S. Weber · M. ***Die geburtshilfliche Analgesie und Anästhesie.*** **s.l. : Aktiv Druck & Verlag Gmbh, Juli 2020.**

31. Guo L, Qin R, Ren X, Han C, Xue W, He L, Ma L, Pan H, Ma S, Chen Y, Ni X. National Library of Medicine. *National Library of Medicine.* [Online] 18. February 2022. [Zitat vom: 21. January 2024.] https://pubmed.ncbi.nlm.nih.gov/35190176/.

32. MD, Swarup Sri Varaday und Raghavendra, Meda. Medscape. *Medscape.* [Online] 27. August 2018. [Zitat vom: 11. December 2023.] https://emedicine.medscape.com/article/2000841-overview#?form=fpf.

33. Olawin AM, M Das J. National Library of Medicine. *National Library of Medicine.* [Online] 27. June 2022. [Zitat vom: 30. January 2024 .] https://www.ncbi.nlm.nih.gov/books/NBK537299/#:~:text=Spinal%20anesthesia%20is%20a%20neuraxial%20technique%20where%20local%20anesthetic%20is,the%20brain%20and%20spinal%20cord.

34. NHS. nhsfife. *nhsfife.* [Online] [Zitat vom: 8. December 2023.] https://www.nhsfife.org/services/patients-carers-and-visitors/preparing-for-surgery/general-information-about-your-anaesthetic/spinal-anaesthetic/#:~:text=A%20local%20anaesthetic%20drug%20is,you%20are%20having%20it%20for.

35. direct, Health. Health direct. *Health direct.* [Online] September 2023. [Zitat vom: 11. December 2023 .] https://www.healthdirect.gov.au/surgery/epidural-anaesthetic#:~:text=will%20I%20recover%3F-,What%20is%20an%20epidural%20anaesthetic%3F,certain%20areas%20of%20your%20body.

36. Cheng, C., Liao, A. H., Chen, C. Y., Lin, Y. C., & Kang, Y. N. National Library of Medicine. *National Library of Medicine.* [Online] 11. March 2021. [Zitat vom: 12. January 2024.] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7970950/.

37. Staff, Mayo Clinic. Mayo Clinic. *Mayo Clinic.* [Online] 16. February 2023. [Zitat vom: 11. January 2024 .] https://www.mayoclinic.org/tests-procedures/anesthesia/about/pac-20384568#:~:text=Overview,intravenous%20medicines%20and%20inhaled%20gasses.

38. (DIVI), Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI) Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin. AWMF. *AWMF.* [Online] 2020. [Zitat vom: 11. January 2024.]

https://register.awmf.org/assets/guidelines/001-012l_S3_Analgesie-Sedierung-Delirmanagement-in-der-Intensivmedizin-DAS_2021-08.pdf.

39. Giorgio Cattaneo Prof. Dr.-Ing., Dr.-Ing Johannes Port. University of Stuttgart. ***University of Stuttgart.*** **[Online] [Zitat vom: 30. January 2024.] https://www.bmt.uni-stuttgart.de/en/research/impedance-cardiography/.**

40. Gmbh, Medizinische Messtechnik. Medis Medizinische Messtechnik Gmbh. ***Medis Medizinische Messtechnik Gmbh.*** **[Online] Medis Medizinische Messtechnik Gmbh. [Zitat vom: 18. January 2024.] https://www.medis.company/en/methods/impedance-cardiography.**

41. Stephen A. Esper MD, MBA (Assistant Professor of Anesthesiology) , Michael R. Pinsky MD, CM, Dr hc (Professor of Critical Care Medicine, Bioengineering, Cardiovascular Diseases and Anesthesiology). Science Direct. ***Science Direct.*** **[Online] December 2014. [Zitat vom: 11. Feburary 2024.] https://www.sciencedirect.com/science/article/pii/S1521689614000718.**

42. Daniel L. Rolnik PhD, Kypros H. Nicolaides MD , Liona C. Poon MD. Science Direct. ***Sciende Direct.*** **[Online] February 2022. [Zitat vom: 9. January 2024.] https://www.sciencedirect.com/science/article/pii/S0002937820308735?via%3Dihub.**

43. Šklebar, I., Bujas, T., & Habek, D. National Library of Medicine. ***National Library of Medicine.*** **[Online] June 2019. [Zitat vom: 18. December 2023 .] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6813480/.**

44. Ferré, F., Martin, C., Bosch, L., Kurrek, M., Lairez, O., & Minville, V. National Library of Medicine. ***National Library of Medicine.*** **[Online] 3. June 2020. [Zitat vom: 12. December 2023.] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7276328/.**

45. M., Laskowska. National Library of Medicine. ***Nationla Library of Medicine*** **. [Online] 7. July 2023 . [Zitat vom: 11. December 2023.] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10334845/.**

46. Baha M. Sibai, MD. American Journal of Obstetrics and Gynecology. ***American Journal of Obstetrics and Gynecology.*** **[Online] 16. September 2011. [Zitat vom: 15. January 2024.] https://www.ajog.org/article/S0002-9378(11)01155-0/fulltext.**

47. Alisse Hauspurg, MD Arun Jeyabalan, MD. American Journal of Obstetrics and Gynecology. ***American Journal of Obstetrics and Gynecology.*** **[Online] 6. July 2021. [Zitat vom: 13. December 2023.] https://www.ajog.org/article/S0002-9378(20)31201-1/fulltext.**

48. Inger L. Meek, Mart A.F.J. van de Laar, and Harald E. Vonkeman*. National Library of Medicine. ***National Library of Medicine.*** **[Online] 7. July 2010. [Zitat vom: 11. January 2024.] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4036661/#:~:text=In%20these%20situations%20NSAID%20use,and%20cardiac%20output%20%5B51%5D.**

49. Albert R. Moore, MD1, Paul M. Wieczorek, MD2 und Jose C. A. Carvalho, MD, PhD3. JAMA Network. ***JAMA Network.*** **[Online] 16. September 2019. [Zitat vom: 11. December 2023 .] https://jamanetwork.com/journals/jamaneurology/article-abstract/2751252.**

50. Saeed Khaled Alzghari PharmD, MBA, MS, BCPS, ... Sidhartha D. Ray PhD, FACN, in. Science Direct. ***Science Direct.*** **[Online] 2020. [Zitat vom: 22. January 2024 .] https://www.sciencedirect.com/topics/veterinary-science-and-veterinary-medicine/diuretic.**

51. Gynecologists, American College of Obstetricians and. American College of Obstetricians and Gynecologists. ***American College of Obstetricians and Gynecologists.*** **[Online] 2023. [Zitat vom: 11. December 2023.] https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/07/low-dose-aspirin-use-during-pregnancy.**