

Chapter 28 Hypertensive disorders of pregnancy and eclampsia

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Summary of Recommendations

Reducing the risk of hypertensive disorders of pregnancy

Recommend women at high risk for preeclampsia (such as previous preeclampsia from before 34-36 weeks) to take 75 mg oral aspirin daily from 12 weeks to birth of the baby. Women with SLE (systemic lupus erythematosus) or antiphospholipid antibodies or antiphospholipid syndrome are recommended low molecular weight heparin in addition (see relevant chapter).

Women with chronic hypertension

Goal: Keep blood pressure lower than 150/100 mmHg in pregnancy.

Do not use angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) in pregnancy, due to increased fetal malformation risk.

Blood Pressure Treatment of moderate and severe preeclampsia

Blood pressure $\geq 150 / 100$ mmHg is an indication for antihypertensive treatment. The purpose is to avoid maternal complications such as brain hemorrhage, hypertensive encephalopathy and seizures (Ia)¹. The goal is not to normalize blood pressure, but to obtain diastolic values around 80-100 mmHg and systolic values < 150 mmHg. High systolic pressure increases the risk of brain hemorrhage².

Eclampsia or severe preeclampsia

Loading dose with MgSO₄, followed by 24 hour maintenance dose of MgSO₄. Half the dose if threatening eclampsia as compared to maintenance dose for eclampsia.

Postpartum follow-up

Blood pressure monitoring of all women who have undergone preeclampsia. Inform women that have been diagnosed with preeclampsia that they have an increased risk of hypertension in the next pregnancy, especially if they have had severe pre-eclampsia, HELLP, eclampsia and / or delivery prior to week 34.

Search strategy

Non-systematic search and update of previous NGF guidelines. Updates are made according to the authors' experience from clinical work and research and using "Pyramide search" via The Norwegian Health Library (<http://www.helsebiblioteket.no/>) and "Up to date", "Best Practice" and NICE guidelines.

Definitions¹⁻³

Chronic hypertension

Known hypertension before pregnancy or persistent blood pressure (BP) ≥ 140 mmHg systolic and / or ≥ 90 mmHg before 20 weeks' gestation. "Superimposed" preeclampsia is diagnosed if the patient in addition develops proteinuria (without known renal disease)

Gestational Hypertension

Persistent BP ≥ 140 mmHg systolic and / or diastolic ≥ 90 mmHg occurring after 20 weeks' gestation. No proteinuria. BP normalized within 12 weeks after birth. Gestational Hypertension can develop into preeclampsia (when developing proteinuria)

Preeclampsia

- Persistent BP ≥ 140 mmHg systolic and / or diastolic ≥ 90 mmHg occurring after 20 weeks' gestation and proteinuria ≥ 0.3 g per 24 hours or total protein / creatinine ratio > 0.3 (or $\geq 1+$ proteinuria on urine dip stick test on at least two occasions)
- In very rare cases, such as in mola hydatidosa, preeclampsia can start earlier in pregnancy

Severe preeclampsia (preeclampsia and the addition of one or more of the following findings / symptoms)

- The presence of clinical symptoms: Epigastric pain, malaise, severe headache and / or other cerebral symptoms (irritability, visual disturbances, hyperreflexia), rapidly increasing edema, pulmonary edema (dyspnea, cyanosis)
- Eclampsia
- Persistent BP $\geq 160 / 110$ mmHg
- Laboratory tests: proteinuria ≥ 3 g per 24 hours, concentrated urine with oliguria (< 500 mL / 24 hours), rapidly decreasing platelet count, signs of microangiopathic hemolytic anemia (increasing LD, falling haptoglobin), elevated liver enzymes (partial or complete HELLP syndrome development)

HELLP syndrome

- Hemolysis - Elevated Liver enzymes - Low Platelets
- Hemolysis: detected as low haptoglobin in serum (< 0.2 g / l) and elevated bilirubin and / or elevated LD
- Liver affection: elevated ALT, AST and LD
- Low (by repeated measurements) platelets $< 100 \times 10^9 / L$

Eclampsia

- General seizures that occur during pregnancy, childbirth or during the first seven days after delivery, coexisting with preeclampsia or gestational hypertension (all degrees of severity) and where there is no other neurological causes for the seizures.

Epidemiology¹⁻⁴

Hypertensive pregnancy complications occurs in 8-10% of all pregnant women in Norway:

Chronic hypertension: 1-2%

Gestational Hypertension: 4-5%

Preeclampsia: 3-4%

Eclampsia: Incidence 5 / 10,000 births. Eclampsia may occur in early pregnancy (such as in mola hydatidosa), but the majority of cases seen in the latter part of pregnancy in patients with

severe preeclampsia. 40% of eclampsia events occur prior to delivery, 30% intrapartum, and 30% postpartum. Eclampsia intra- and postpartum usually occurs at term, while eclampsia antepartum occurs most often before gestational week 37.

Etiology / pathogenesis^{2,3}

Preeclampsia is a syndrome that requires the presence of placenta tissue, but where maternal predisposition also plays a significant role. For some, but not all, there is an incomplete development of the maternoplacental circulation (spiral arteries). Central to the development of maternal symptoms is an increased systemic maternal vascular inflammation with vascular (endothelial) dysfunction. A number of organs are affected in varying degrees.

Data suggest that early-onset preeclampsia (delivery <34-36 gestational weeks) and late-onset preeclampsia may have differing pathophysiologies. Early-onset preeclampsia is more often characterized by placental insufficiency. Fetal growth restriction is hence seen more often in early-onset preeclampsia.

Chronic hypertension may be primary or secondary, especially secondary to renal disease.

The cause of eclamptic seizures is not known, but one theory is that the cerebrovascular changes are the same as in hypertensive encephalopathy,⁵ including loss of auto-regulation of cerebral blood flow followed by hyper perfusion and development of cerebral edema. The mediator may involve the rapid rise in blood pressure. With advanced CT technology, cerebral affection may be seen in approximately 50% of cases. EEG is often pathological the first days after an eclamptic fit, but will usually normalize after a few weeks.

Risik factors^{2,3,6}

Increased risk of preeclampsia is seen in:

- Primiparous
- Multiple Pregnancies
- Previous undergone preeclampsia (especially if occurred <34 weeks)
- Previous undergone severe preeclampsia and / or prematurely delivery due to preeclampsia
- Age > 40 years
- Chronic hypertension
- Renal Disease
- Diabetes mellitus, also gestational diabetes mellitus
- Connective tissue diseases (especially SLE)
- Antiphospholipid syndrome (positive lupus anticoagulant and / or cardiolipin antibody and clinical history)
- High body mass index (linearly increasing risk from BMI ≥ 26)
- Family history of a mother or sister who have had preeclampsia
- Growth restricted fetus (placental failure/dysfunction)
- Thrombophilia (clinically it is not found to be efficient to screen for this)
- Notch / high PI of the uterine artery is an increased risk for preeclampsia. This ultra sound Doppler based investigation has a high negative predictive value, therefore unnecessary investigations at specialist health care can be reduced if there is a normal test. The health economic benefits of this investigation is however uncertain. Pregnant women at high risk for preeclampsia are recommended this investigation, as notch / high PI may be one factor in an overall assessment of the pregnancy
- Low concentration of PlGF (placental growth factor) and high sFlt1 (soluble Flt1) in pregnant women's blood from the second trimester predicts preeclampsia, especially early-

onset, and preeclampsia associated with growth restricted fetus. PlGF concentration has better predictive ability than most clinical factors mentioned above, but the total cost-benefit is unknown and maternal biomarkers are therefore not recommended as routine analysis today

- Combinations of risk factors provides better prediction of preeclampsia than individual factors alone. Nevertheless, the usefulness in practical clinical work currently limited, and the health economic gain is unclear

Diagnosics ^{2, 3, 7}

Clinical symptoms

In case of increasing blood pressure (with or without proteinuria), always consider clinical symptoms that can be warning signs of severe preeclampsia development, such as "feeling in bad shape", rapid weight gain / clinical edema, (strong) headache, visual disturbances, shortness of breath with chest tightness, nausea, vomiting, epigastric pain or irritability. The condition is unpredictable and can develop into a severe, life-threatening condition over a short time, from hours to days. Early-onset preeclampsia is more often associated with growth restricted fetus but also late-onset preeclampsia can have severe maternal and fetal consequences, for example in eclampsia development.

Eclampsia warning signs

Very many (almost 90%) have clinical symptoms (intense forehead headache, but also nausea, epigastric pain, visual disturbances, irritability or agitation) in addition to diagnosed preeclampsia prior to an eclamptic seizure.

Clinical signs (objective findings)

Preeclampsia is diagnosed by elevated blood pressure (BP) and proteinuria as described under definitions. Preeclampsia presents clinically as a maternal syndrome (hypertension, proteinuria, edema and activated coagulation) and in addition an increased risk of a fetal syndrome (fetal growth restriction, fetal hypoxia, placental abruption, intrauterine fetal death and prematurity). In late-onset preeclampsia, the maternal symptoms and signs often dominate, while both maternal and fetal signs are seen in varying degrees in early-onset preeclampsia. The fetal signs include placental insufficiency with fetal growth restriction (FGR) and fetoplacental circulation alterations.

Differential diagnosis ^{2, 3}

Differential diagnosis of severe preeclampsia and HELLP syndrome may include:

- Renal Disease
- Hepatitis (autoimmune and infectious)
- Gastroenteritis / gastritis / ulcer
- Bile disease / pancreatitis
- Worsening of SLE
- Acute fatty liver in pregnancy (AFLP)
- Hemolytic uremic syndrome (HUS)
- Thrombotic thrombocytopenic purpura (TTP), thrombocytopenia caused by autoimmunity
- Appendicitis / other causes of acute abdominal pain
- Migraine (if starts in pregnancy)
- Infections, especially in renal involvement (e.g. Hantavirus, CMV, etc)

It may be difficult to diagnose whether a patient with chronic hypertension also has developed preeclampsia (20% risk), particularly in women where proteinuria is already present prior to pregnancy due to a complicated chronic hypertension disease.

When diagnosing preeclampsia in patients with proteinuric nephropathy (before 20 weeks) and chronic hypertension, a preeclampsia diagnosis is based on other preeclampsia-like features, such as clinical symptoms, placental affection (fetal growth restriction), rapidly increasing blood pressure, transaminase elevation and activation of the hemostasis (with falling platelets etc).

Especially challenging is to distinguish "flare up" in patients with nephropathic SLE and (a worsening) preeclampsia. Consultation with referral/regional hospital obstetric clinic is recommended.

Differential diagnosis of eclampsia includes epilepsy or other diseases that can cause seizures (delirium, tumor cerebri, infections etc).

Follow-up^{2, 3, 8}

In preeclampsia the patient is referred to the Obstetric department. In mild forms of preeclampsia the patient may be followed-up as outpatient in the specialist health care with few days interval. The clinical situation may change at a short notice and admittance to the Obstetric department is required in severe preeclampsia to reduce maternal and fetal morbidity and to avoid mortality. Clinical continuity in follow-up is important, also after admission to the hospital.

Investigations when preeclampsia is diagnosed

- BP measurements: frequency depending on clinical assessment
- Proteinuria: stix, total protein / creatinine ratio or quantitation per 24 hours (rarely used nowadays, but has been the reference method)
- Blood tests: Hb, platelets, AST / ALT / LD, uric acid, creatinine
 - o In severe preeclampsia and HELLP; measure in addition albumin, INR, APTT, fibrinogen, D-Dimer, antithrombin and haptoglobin
 - o In case of suspected acute fatty liver: additionally measure plasma glucose, leukocytes, triglycerides and total cholesterol
- CTG, possibly with short-time variability
- Ultrasound: fetal biometrics (assess asymmetrical growth and fetal growth assessment), biophysical profile and Doppler examination (Umbilical artery, possibly Middle cerebral artery and ductus venosus in selected cases) (Ia)^{9, 10}

When to deliver when preeclampsia is diagnosed

Delivery is the only final "cure" for maternal symptoms in preeclampsia or the development of HELLP syndrome. In very early-onset preeclampsia (before 28-30 weeks) it is recommended to discuss delivery or expectancy with consultants at the regional women's clinic.

Gestational duration <34 weeks

The condition is assessed from day to day. Especially in severe prematurity, a prolongation of the pregnancy is to be desired, whenever appropriate. In severe early-onset preeclampsia the risk of extremely preterm infants must be continually balanced against the maternal risk by prolonging the pregnancy⁸⁻¹¹. Available randomized trials and observational studies indicate

that expectancy may improve the neonatal outcome in preeclampsia before 34 weeks.

Conditions that are not consistent with prolonging the pregnancy is eclampsia, HELLP, or progressive or severe preeclampsia with severe clinical or pathophysiological deterioration (e.g. DIC development).

Gestational duration 34 + 0 weeks to 36 + 6 weeks

There are no available randomized studies as a basis for specific recommendations for the group of preeclamptic pregnancies between week 34 + 0 and 36 + 6, but an overall assessment of the maternal and fetal health situation must be made, similarly to the assessment of any preeclamptic pregnancy, whatever pregnancy duration.

Gestational duration ≥ 37 weeks

There are no available meta-analyses of birth induction versus expectancy in women with hypertensive disorders of pregnancy that are at or near term. The tradition in Norway has been to deliver a preeclampsia pregnancy after 37 weeks where there are mild / moderate clinical symptoms with signs of progression, but in each case, the total situation of the mother and fetus should be considered. According to a multicenter, randomized non-blinded clinical trial where women were either induced or treated with expectancy in gestational hypertension or mild preeclampsia, the induction group had better maternal outcomes without increased rates of cesarean sections. The study found no differences between the groups in neonatal outcome.¹²

Symptoms and signs that indicate the need for imminent delivery

Mother

- High blood pressure (especially where it is difficult to control) with severe subjective symptoms (see above)
- Eclampsia
- Thrombocytopenia (especially if rapid and sustained decreasing platelet number)
- Severe / increasing liver involvement
- Pulmonary edema
- Creatinine elevation
- Rapidly rising proteinuria has been considered traditionally. There is however no added value in following daily proteinuria development in pregnancies where proteinuria and preeclampsia has been diagnosed, as degree of proteinuria corresponds poorly with clinical outcome in general.

Patients should prior to delivery have their blood pressure stabilized, and consultation with the anesthesiologist can be considered. The threat to the uteroplacental circulation if lowering maternal blood pressure too much must be taken into account. The goal antepartum is not a normalization of maternal blood pressure, but diastolic values around 80-100 mmHg and systolic values <150 mmHg.

Fetus

- Pathological CTG, including pathological short-term variability (computer-assessed)¹³
 - Oligohydramnios / severe fetal growth restriction / pathological Doppler findings.
- Doppler findings are recommended to be discussed with competent colleague at own Department / optionally at hospitals with higher expertise. This applies particularly if risk for significant fetal prematurity (<28 to 30 weeks). Alarming Doppler parameters include absent or reversed flow in umbilical artery, centralization in cerebral media artery and increased PI in

ductus venosus.

Delivery mode

Caesarean section versus vaginal delivery should be considered individually; many factors are to be taken into account (gestational age, maturity of the cervix, parity, severity of preeclampsia, fetal condition and the availability of obstetric and anesthesiology resources).

Treatment

If fetal prematurity risk

Lung maturation of the fetus with corticosteroids to the mother (gestational week 23/24-34) increases survival (Ia)¹⁴.

If iv fluid is needed

Pulmonary edema may develop following much lower volume load than for other patient groups, and monitoring of the circulation must be considered.

Blood pressure treatment

There is no evidence of a beneficial effect in treating BP <150/100 mmHg in pregnancy. There is no maternal benefit and the treatment can cause fetal growth restriction (Ia).¹⁵ One blood pressure drug category is not found better than the other, the important thing may be to gain experience in which antihypertensives to use.

The most common used antihypertensive drugs used in pregnancy in Norway:

- Labetalol per os 100 mg x 2, augmenting to 200 mg x 3-4. Maximum plasma concentrations 1-2 hours after intake. Combination with nifedipine doses listed below is possible. A BP that is difficult to control may indicate worsening of the syndrome, and an overall assessment of indication for delivery is recommended
- Nifedipine per os 10 mg x 2, augmenting to a maximum of 40 mg x 2 / day. Effect after 45-60 minutes. Depot tablets may be appropriate: 30 mg x 1, augmenting to 30 mg x 2
- Methyldopa per os 250 mg x 2-3. May be increased to 500 mg x 3. Effect after 3-8 hours, full effect after 12 hours. This drug is not suitable if acute BP reduction is the aim. If higher doses of methyldopa is needed, it may be useful rather to choose a combination with labetalol or nifedipine due to the risk of side effects (dry mouth, constipation, depression).

Blood pressure treatment in women with chronic hypertension

Non-pregnant women using ACE inhibitor / AT-receptor antagonists or other antihypertensive drugs that should not be used in pregnancy are advised to change these drugs (see above recommended drugs) before they plan pregnancy, possibly when pregnancy is confirmed. In some cases these women with chronic hypertension may be without medication for a period in the middle of pregnancy due to physiological changes in pregnancy.

Blood pressure treatment in moderate and severe preeclampsia antepartum

BP \geq 150 / 100 mmHg⁷ is an indication for antihypertensive treatment. The purpose is to avoid maternal complications such as brain hemorrhage, hypertensive encephalopathy and seizures (Ia).¹⁶ The goal is not a normalization of the blood pressure, but achieving diastolic values around 80-100 mmHg and a systolic BP <150 mmHg. High systolic pressure increases the risk of cerebral hemorrhage.¹⁷

Blood pressure treatment in acute hypertension

Both labetalol per os and nifedipine per os are sufficiently fast-acting and can be used for gradual lowering of blood pressure (rapid lowering of blood pressure is not desirable due to the threatened uteroplacental circulation and risk of fetal intrauterine demise), possibly in combination with methyldopa. If this is not sufficient, intravenous treatment is recommended.

If oral therapy (see above for options, such as labetalol per os 200 mg, expected effect after about 30 minutes) is not tolerated because of nausea and vomiting, or there is an unstable BP and rapid rise in BP, labetalol can be administered intravenously, either intermittent or as a continuous infusion:

-Labetalol loading dose intravenously: 20 mg (4 ml of 5 mg / ml) intravenously. Effect after 5-10 minutes. If suboptimal effect after 10-15 minutes, the dose may be increased to 40-50 mg iv. Maximum dose is 200 mg.

-Labetalol continuous infusion: Mix 200 mg labetalol; 2 vials of 20 ml (5 mg / ml) in 160 ml of physiological NaCl. This gives 1mg/ml labetalol infusion. Infusion start rate is 20 ml / hour (1 mg / mL), i.e. 20 mg / hour, which can be increased with 10 to 20 ml / h about every 20-30 minutes until satisfactory BP. Maximum infusion rate is 160 ml / hour.

Intrapartum blood pressure treatment

BP increases during uterine contractions and especially during delivery of the baby, therefore women with severe preeclampsia who deliver vaginally should be closely monitored, both during delivery and postpartum.

Epidural is recommended in hypertensive women that deliver vaginally.

Postpartum blood pressure treatment

· Since the uteroplacental circulation is not a problem postpartum (as there is no longer a fetus), BP limits should be lower than before delivery, eg 140/90 mmHg

· When considering antihypertensive drugs postpartum, methyldopa should be discontinued first because of side effects. Treatment could continue with labetalol or nifedipine, or a combination

· If there is much edema postpartum, the significant quantities of liquid will be mobilized into the bloodstream and can contribute to pulmonary edema, therefore it may be appropriate to give furosemide in small doses postpartum. If symptoms of fluid overload are present, including dyspnea and possibly reduced oxygenation, this will almost always be an indication of intensive care follow-up. Patients with persistent symptoms of fluid overload should be referred to echocardiography for further diagnostics.

Seizure prophylaxis

In cases of rapid developing and severe preeclampsia, MgSO₄ seizure prophylaxis should be administered. It halves the risk of eclampsia and reduces the risk of maternal death (Magpie Trial) (Ia)^{18, 19}. Clinical evaluation as to whom should receive prophylaxis includes considering the severity and how quickly the condition worsens (threatening eclampsia). The initial dose is the same as eclampsia (see below) but the maintenance dose is halved (see eclampsia treatment). If in doubt whether there is an indication for MgSO₄, there often is a reason to administer it. It is essential to monitor a woman treated with MgSO₄. Local factors determine how this is best done (at an intensive care unit, a post-operative unit or at a obstetric/ high risk maternity ward).

Anesthesia to women with severe preeclampsia^{17, 20, 21}

- Low threshold for performing echocardiography if cardiac symptoms such as dyspnea or chest pressure
- Noninvasive systolic BP is regularly 20-30 mmHg lower than the invasive BP and this may be an argument for using artery monitoring devices during cesarean section (cs) in cases of severe preeclampsia
- At cs: spinal anesthesia is recommended if platelet count $> 75 \times 10^9 / L$. Spinal is less tissue traumatic than epidural. If an epidural catheter is in place before the woman is diagnosed with reduced platelet count, the catheter can be used also for epidural analgesia at cs. Spinal anesthesia is first choice at cs in women with rapidly increasing severity of preeclampsia and HELLP development. In women with increased risks during general anesthesia (hypertension, obesity, difficult airway intubation), these risks must be weighed against the spinal anesthesia risks (spinal hematoma) in women with HELLP and rapidly falling thrombocytes
- During anesthesia start in women with severe preeclampsia, opioids should be administered (alfentanil, remifentanil, fentanyl) before intubation to avoid potentially dangerous increase in blood pressure. Pediatrician should if possible be present during cs and should be informed of opioid use to the mother due the depressive effect on the newborn respiration
- Oxytocin must be titrated slowly (to obtain clinical effect), due to increased risk of severe cardiovascular events

Severe coagulopathy in preeclampsia / HELLP syndrome

- If signs of DIC, the degree and development should be closely monitored, as rapid delivery may be necessary. The delivery should be pre-planned, as it may be necessary to administer blood transfusion (SAG), human coagulation active plasma, platelets and fibrinogen. In some cases antithrombin concentrate may be considered
- Prior to surgery the platelets should preferably be $> 50 \times 10^9 / l$ due to the bleeding risk at lower values. In cases of vaginal delivery, platelets as low as 10 to $20 \times 10^9 / l$ may be acceptable if no clinical signs of bleeding
- Patients with severe preeclampsia / HELLP with coagulation disorders should not receive thrombosis prophylaxis with LMWH before the coagulopathy has improved and there is no clinical bleeding problem. In case of severe coagulopathy, consultation with haematologist is recommended

Corticosteroids and HELLP syndrome²²

Systemic steroids is not an established treatment for HELLP, but may be considered in special cases. In some HELLP cases, a transient improvement in blood parameters and clinical signs is seen when the standard betametasone medication is given to the mother for lung maturation of the embryo (Celestone Chronodose 12 mg im, repeated after 24 hours). Several smaller studies recommend that patients with HELLP syndrome should be treated with steroids in the form of dexamethasone (due to better effect on platelets), dosage 10 mg x 2 intravenously, but more studies are needed (Ib). Dexamethasone crosses the placenta, and possible undesirable side effects of fetal steroid exposure (beyond Celestone) must be considered. Dexamethasone to the mother is not recommended as routine treatment for the HELLP syndrome.

Treatment of eclampsia

- Free airways. Make sure the patient does not fall out of bed
- Call for help; obstetrician on call and anesthesiology personnel
- Magnesium sulphate ($MgSO_4$) is the primary treatment of seizures in eclampsia. Some women will experience flushing symptoms due to vasodilation following $MgSO_4$ administration

o Diazepam 10-20 mg may be administered first, if magnesium sulphate is not available. Diazepam is administered intravenously or rectally, but has not as good seizure effect as magnesium sulphate and will also affect the baby after delivery. Start with MgSO₄ as soon as this is available.

In situations where stabilization / treatment of mother comes in conflict with a fetal indication for delivery, the mother has priority

Magnesium sulphate loading dose (17.5 to 20 mmol)

· Option A: Pre-mixed MgSO₄ bolus from pharmacy: Magnesium sulphate 0.5 mmol / ml. Injection 50ml. Administer 35 ml of this solution (= 17.5 mmol) slowly intravenously over at least 5 minutes, preferably 10 - 15 minutes

· Option B: Mix the MgSO₄ bolus solution yourself:

b1) Mix magnesium sulphate 20 mmol (2 ampoules of 10 ml of magnesium sulphate 1 mg / ml) in 20 ml NaCl 9mg / ml, which gives a total volume of 40 ml. This loading dose may be administered using a automatic pump. If administered in 15 minutes, the speed is 140 ml / h.

b2) Mix magnesium sulphate 20 mmol (2 ampoules of 10 ml of magnesium sulphate 1 mg / ml) in 100 ml glucose (1mmol / ml, 1 vial = 10 mL), is given intravenously for 5 (-15) minutes. Remember to remove 20 ml glucose before magnesium sulphate is added

Magnesium sulphate maintenance dose

· MgSO₄: 4.6 mmol / h. Maximum daily dose: 150 mmol.

· Magnesium sulphate 100 mmol (10 amp a 10 ml magnesium sulphate 1mmol / ml) in 500 ml glucose (remove 100 ml glucose before adding MgSO₄).

Infusion start 20 ml/h = 4 mmol /h. Can be increased to 30 ml /h (6 mmol / h)

If recurrent eclamptic fits

If recurrent seizures occur during MgSO₄ infusion (or after the infusion is discontinued), the loading dose of iv MgSO₄ (see above) is repeated (17.5 to 20 mmol, depending on body weight) over 5 minutes.

Control of MgSO₄ therapy

Toxic side effects of MgSO₄ can be seen clinically as abolished patellar reflex, respiratory depression and decreased urine output.

· The first two hours of MgSO₄ therapy: check patellar reflex and respiration every 10 minutes, later in 15-60 minute intervals

· Measure hourly urinary output

· If patellar reflexes are abolished: cancel magnesium infusion. Observe the respiration rate.

When the patellar reflex returns, restart the infusing with a reduced dose, if the respiration rate is normal

· If respiration rate is <16 / minute: cancel the infusion. Give O₂ on mask. Secure free airways. If pronounced respiratory depression: administer antidote (see below)

· If respiratory arrest: intubate and ventilate immediately and administer antidote (see below)

· If decreased urinary output (<25 ml / h), when it is assumed secondary to magnesium effect, without other symptoms of magnesium intoxication: reduce infusion rate to 0.5 g /h (2 mmol / hour)

· Check serum levels of magnesium when needed. Therapeutic level: 2-4 mmol / l.

· Treatment with magnesium sulphate should be continued for 24 hours after eclamptic seizures either ante- or intrapartum as well as after postpartum eclamptic seizures.

Antidote to MgSO₄ therapy

Calcium glubionate: 10 ml. Calcium-Sandoz® (9 mg calcium glubionate / ml) is to be in the room and to be given slowly intravenously if needed.

Further follow-up of eclampsia

- Manage blood pressure if necessary (see above)
- If the patient is not delivered prior to a eclamptic seizure: If there is a fetal delivery indication, evaluate whether the stabilization / treatment of the mother can be combined with delivery. If this is not possible, the mother must have priority. A cs is often necessary if vaginal delivery is not likely to happen soon
- Intensive monitoring after an eclamptic seizure is necessary. Usually, this should be done in an intensive unit in close collaboration between the anesthesiologist and gynecologist/obstetrician. Good laboratory services for follow-up / treatment of multiorgan affection is important. If such service is not available, the patient should be reallocated after stabilization to a hospital where such facilities exist
- Written treatment procedures are recommended and all Obstetric departments should have an "eclampsia box" easily available at all times. This box should contain the standard operation procedures for the treatment of eclampsia, forms for patient monitoring and the necessary medication and other equipment.

Complications^{2, 3, 17}

Severe complications of preeclampsia

- Eclampsia
- Cerebral haemorrhage (frequent cause of death globally)
- HELLP syndrome
- Pulmonary edema
- Renal failure
- Placental abruption
- Fetal death
- Disseminated intravascular coagulation (DIC)
- Liver rupture

These patients are often in need of many weeks of convalescence postpartum. There is increased risk of transient cognitive disturbance, mental imbalance/ depressive reactions

Severe complications of eclampsia

- Maternal and fetal death and brain damage

Clinical follow-up after hypertensive pregnancy complications and eclampsia

- Follow-up after pregnancy depends on the severity of preeclampsia in this pregnancy and the risk of preeclampsia recurrence or risk for future CVD
- It is recommended that the patient is evaluated neurologically after eclampsia, in order to consider differential diagnoses

Postpartum follow-up when in hospital

- Avoid using NSAIDs as postpartum pain regime as long as the woman has a poorly regulated hypertension, or oliguria, signs of poor kidney function, or thrombocytopenia
- Fragmin prophylaxis if low platelets: see section "Severe coagulopathy in preeclampsia / HELLP syndrome" above
- Debriefing of the clinical events with the involved doctors and midwives postpartum is

recommended. If the woman has hypertension at time of hospital discharge: appointment for BP control is made either at the maternity ward or at GP/other doctor

Postpartum control / preconceptional advices before subsequent pregnancies

- BP and urinary control after hospital discharge: timing depends on BP and other clinical variables such as any underlying illnesses, etc. The development of chronic hypertension should be assessed
- Consultation at the obstetric outpatient unit is recommended after 2-3 months following severe preeclampsia, eclampsia and HELLP, including a new review of the pregnancy, information and planning of next pregnancies. Further follow-up and assessments should be considered (for hypertension, renal function, thrombophilia, antiphospholipid syndrome)

Next pregnancy following preeclampsia

In subsequent pregnancies, these women should be followed up in collaboration with the Obstetric department from gestation week 23-24. Doppler examination of the uterine artery is recommended for groups with increased risks for preeclampsia and growth restricted fetuses.

In the next pregnancy, women with previously severe, early-onset preeclampsia, eclampsia or HELLP syndrome are at increased risk for preeclampsia again (10-40%, highest risk for the early-onset disease)

ASA prophylaxis should be considered (see below)

Later in life ²³⁻²⁶

Women with a history of preeclampsia and hypertension in pregnancy have increased risk of future cardiovascular disease (CVD). In general, the risk of future cardiovascular disease is more strongly associated with early-onset disease (and therefore early delivery) and severe forms of preeclampsia, especially where uteroplacental blood flow is affected (with growth restricted fetus or intrauterine fetal death)

These women should be given information about beneficial lifestyle and diet habits to prevent cardiovascular disease after delivery and should be followed perimenopausally for early diagnosis and treatment of CVD

Preeclampsia prophylaxis ⁷

Acetyl salicylic acid (ASA; aspirin)

Women at high risk for preeclampsia (especially women with previously severe preeclampsia, ie delivery before <34-36 weeks (Ia) ^{27,28}), but also women with chronic kidney disease or autoimmune disease (systemic lupus erythematosus and antiphospholipid syndrome):

Recommend intake of 75 mg aspirin orally daily from 12 weeks until delivery.

If SLE with phospholipid antibodies or antiphospholipid syndrome: low molecular heparin is recommended in addition (see relevant chapter).

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