



HYPERTENSIVE DISORDERS IN PREGNANCY

Version 2.0

Hypertensive disorders in pregnancy

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Hypertensive Disorders in Pregnancy

Problem description

Hypertensive complications during pregnancy (preeclampsia, eclampsia and HELLP syndrome) are an important cause of perinatal morbidity and mortality, may cause serious maternal morbidity and are the most important cause of maternal death. Treatment protocols are necessary as serious complications are relatively rare and tend to develop acutely.

Analysis of available knowledge

This chapter is divided into sub-chapters and/or paragraphs. Please click on the sub-chapter and/or paragraph title in the left column to view its contents.

Classification

This guideline uses the definitions recommended by the International Association for the Study of Hypertension in Pregnancy (ISSHP) [1]. These recommendations are based on a consensus report of the Australian Association for the Study of Hypertension (ASSH) and a proposal of the US National High Blood Pressure Education Program.

- Pregnancy hypertension

Systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg (Korotkoff V) after a pregnancy duration of 20 weeks, measured twice, in a woman with a previously normal blood pressure. The blood pressure should have normalized three months after delivery.

- Preeclampsia

The combination of gestational hypertension and proteinuria (≥ 300 mg/24 hours). Please also refer to Laboratory tests under 2.6, Diagnostics, for proteinuria measurement. The following clinical symptoms may occur:

- ♦ Renal dysfunction: elevated creatinine levels or oliguria.
- ♦ Hepatic dysfunction: elevated transaminase levels and/or upper right abdominal or epigastric pain.
- ♦ Neurologic abnormalities: convulsions (eclampsia), serious headache, vision disorder, hyperreflexia.
- ♦ Hematologic abnormalities: thrombocytopenia, intravascular coagulation, hemolysis.

The combination of hemolysis, elevated hepatic enzyme levels and reduced platelet counts is also known as the HELLP syndrome (HELLP: Hemolysis, Elevated Liver enzymes and Low Platelets), or the ELLP syndrome if hemolysis is absent.

The current guideline defines moderate preeclampsia as a condition with diastolic blood pressures < 110 mm Hg and absence of the above clinical symptoms, and serious preeclampsia as a condition with diastolic blood pressures ≥ 110 mm Hg or the presence of the above clinical symptoms.

Occasionally, proteinuria may be absent (yet) despite serious clinical symptoms. If so, the patient should still be treated as stated under serious preeclampsia.

- Chronic hypertension

Hypertension diagnosed before the pregnancy or before a pregnancy duration of 20 weeks. Please refer to guideline 25, Chronische hypertensie (Chronic hypertension).

- Superimposed preeclampsia

Preeclampsia related symptoms as mentioned above develop after a pregnancy duration of 20 weeks in a patient with chronic hypertension.

Epidemiology

Five to 18% of nulliparous women develop pregnancy hypertension and 1-7% develop preeclampsia [2-8]. These disorders occur in nulliparous women 3x as often as in multiparous women. Numbers highly depend on definition and selection of the group studied. American studies [2, 4, 5] provide higher incidences than European studies, possibly due to inclusion of a higher percentage of women of African origin. The incidence of eclampsia is approximately 1/2000 pregnancies, with half of those occurring after childbirth [9, 10]. A Dutch low risk cohort with nulliparous women showed a hypertension in pregnancy incidence of 16%, a chronic hypertension incidence of 1.5%, and a preeclampsia incidence of 1.4% [11]. The Dutch National Obstetric Registration (hospital care) over 2002 registered 17% pregnancy hypertension and 2% preeclampsia.

Etiology

The disease's occurrence is related to the presence of trophoblasts. Immunologic, genetic and environmental factors play a part in its development. It is assumed that the disease is based on deficient building and vascularization of the placenta as well as failing normal maternal adaptation to the gravidity. Platelet activation and vascular endothelial dysfunction may occur due to as yet unknown factors, resulting in vasoconstriction and hypertension, increased vascular permeability, causing edema and proteinuria, and in some cases more extensive coagulation activation and organ damage [12].

Predisposing factors

A distinction can be drawn between factors or circumstances related to an extra large trophoblastic mass and those characterized by cardiovascular abnormalities. The first group includes multiple and molar pregnancy as well as a number of chromosomal abnormalities (triploidy in particular). The second group includes chronic hypertension, chronic vascular and renal diseases, dyslipidemia, SLE, antiphospholipid syndrome, diabetes, obesity, age > 40 years, and possibly a number of conditions characterized by thrombophilia. Nulliparous women have a 3x greater risk than multiparous women. An indication of a genetic cause is the observation that women are at greater risk of preeclampsia in their first gravidity if they have a sister or mother who has experienced preeclampsia (RR 2.2; 1.9-2.5). The partner of a man with a previous partner with preeclampsia in her first gravidity is also at greater risk in her first gravidity (RR 1.8; 1.2-2.6) [13]. Women of sub-Saharan African origin have a greater risk of preeclampsia than Caucasian women (RR 2.4; 95% CI 1.1-5.6) [14].

Prevention

- Acetyl salicylic acid

Platelet activation, reduced vascular synthesis of prostacyclin (a vasodilator) and excessive production of thromboxane (a vasoconstrictor) are detectable in the early course of preeclampsia. Based on these observations it was hypothesized that acetyl salicylic acid might prevent or delay development of preeclampsia. A recent Cochrane review summarizes a large number of randomized studies [15]. Preventive usage of acetyl salicylic acid was estimated in this review to give a 15% preeclampsia reduction (from 7.8% to 6.6%) in women at higher risk of preeclampsia (32 studies, 29,331 women, RR 0.85; 95% CI 0.78-0.92; NNT 89; 95% CI 59-167). The effect size was similar in high and low risk women. A larger preeclampsia reduction was seen in studies where a daily dose of acetyl salicylic acid > 75 mg was given (13 studies, 1264 women, RR 0.34; 95% CI 0.23-0.51) compared to studies where ≤ 75 mg was given (18 studies, 28,012 women, RR 0.89; 95% CI 0.82-0.97). However, a direct comparison of varying doses is lacking. If the meta-analysis is limited to studies including > 600 women at a higher preeclampsia risk (600 women should be randomized at α 0.05 and β 0.8 to be able to show a difference of 10% versus 4%), only a small, statistically insignificant effect of acetyl salicylic acid administration before 20 weeks is seen on the occurrence of preeclampsia (9 studies, 26,994 women, RR 0.91; 95% CI 0.82-1.00), perinatal death (RR 0.89; 0.77-1.03) or a low birth weight (RR 0.97; 95% CI 0.86-1.08). The 23 studies excluded from this estimation contained less than 10% of the total number of randomized women.

A recent study comparing nulliparous women (n = 3294) randomized at 12-20 weeks to treatment with acetyl salicylic acid 100 mg or placebo did not reveal any effect on the incidence of preeclampsia (RR 1.1; 95% CI

0.6-1.8) or the incidence of pregnancy hypertension or fetal growth restriction [8]. One placebo-controlled randomized study showed a blood pressure decrease when acetyl salicylic acid 100 mg was given at bedtime [16]. By the end of the pregnancy, the systolic blood pressure was 14 mm Hg and the diastolic blood pressure 9 mm Hg lower compared to placebo when taken at bedtime. The effect of administration in the morning or at noon was similar to that of placebo. The participating women had a higher risk of pregnancy hypertension or preeclampsia, although the extent of this risk was described insufficiently. Randomization was performed before 16 weeks. Neonatal outcomes were not reported.

The conclusion is that acetyl salicylic acid may have a small preventive effect in women with a higher risk of preeclampsia, but that it does not improve perinatal outcomes.

- Calcium supplementation

A reversed relationship between calcium intake and blood pressure was observed in a number of epidemiologic studies in populations with high calcium concentrations in their food. A Cochrane review summarizes a number of randomized studies (n = 11, total number of women 6,914) of the preventive effect of calcium supplementation on the incidence of hypertension during pregnancy or preeclampsia [17, 18]. Reductions in pregnancy hypertension (RR 0.58; 95% CI 0.43-0.79) and preeclampsia (RR 0.35; 95% CI 0.2-0.6) were seen. The effect was larger in women at a higher risk of preeclampsia (RR 0.22; 95% CI 0.12-0.42) and women using food deficient of calcium (RR 0.22; 95% CI 0.16-0.54). No differences were found in caesarean section percentages, NICU admissions and perinatal death. The beneficial effect of calcium was seen in the smaller studies only. The single large study (n = 4,336) of women with a low risk and normal calcium intake did not show any differences [4]. It is likely that calcium supplementation is only useful in pregnant women with a dietary deficiency.

- Heparin

An increased prevalence of risk factors for thrombosis, such as hereditary coagulation abnormalities, presence of anticardiolipin antibodies and hyperhomocysteinemia, has been observed in women with early preeclampsia (< 34 weeks). Some treat women who have a history of early preeclampsia and established thrombophilia with fractionated low-molecular heparin during their next gravidity. Due to its uncertain preventive effect and potential risks it is advisable to use this therapy for this indication in research only [20].

- Antioxidants

One study showed a preeclampsia reduction (n = 283, RR 0.4; 95% CI 0.2-0.9) in women with an abnormal uterine artery Doppler measurement at 18-22 weeks using vitamin C 1,000 mg and 400 IU of vitamin E supplementation. However, no differences in incidence of serious preeclampsia were observed, nor differences in birth weight, pregnancy duration or perinatal outcomes [21].

- Fish oil

Administration of fish oil is not effective for the prevention of preeclampsia (4 randomized studies, n = 1447, RR 1.0; 95% CI 0.6-1.6) [18].

- Antihypertensives

One study showed preeclampsia reduction in a group of South African women with diastolic blood pressures \geq 80 mm Hg before 20 weeks who were treated with ketanserin (a serotonin antagonist) and acetyl salicylic acid compared to acetyl salicylic acid alone (4% versus 28%, RR 0.15; 95% CI 0.04-0.7). However, no significant difference was seen in birth weight or perinatal death [22].

One study selected women with a cardiac output $>$ 7.4 l/min as measured with Doppler ultrasound at a pregnancy duration of 22-25 weeks. They were treated with a daily dose of atenolol 100 mg or placebo. The treatment group developed less preeclampsia (4% versus 18%, p = 0.04). However, birth weight in this group was a mean 440 g lower than that in the control group (p = 0.02) [23].

- Sodium limitation

A low sodium diet does not have a preventive effect on the development of pregnancy hypertension or preeclampsia [11].

Diagnosics

- Routine prenatal care

Blood pressure measurement should be an established part of prenatal care. It is measured in sitting position with the upper arm at heart level, always at the same arm (preferably the right one) and after the woman has been sitting for at least 2-3 minutes. The sound is registered more reliably when it disappears (Korotkov V) than when it becomes softer (Korotkov IV), with the former also better corresponding with the intra-arterial pressure [24]. Preferably, the blood pressure is measured twice with a reading accuracy of 2 mm Hg, to be procured by slowly depressurizing the cuff at a rate of 2 mm/heart beat. A correctly sized cuff should be used (a standard cuff for arm circumferences < 33 cm and a large cuff for wider circumferences). The cuff should encircle at least 80% of the upper arm. The equipment used should be calibrated (annually). Automatic blood pressure meters are not validated to diagnose pregnancy hypertension or determine the need to start or change a therapy. A varying difference of up to 10 mm Hg was observed between automatic and auscultatory measurements in pregnant women [25]. A significant underestimation of up to 30 mm Hg was observed using automatic measurements in women with preeclampsia [26, 27].

- Laboratory tests

Urine should be tested for protein while diagnosing pregnancy hypertension. Using a test strip should be seen as an initial quick screening test, with 1+ (corresponding with 0.3 g/l) to be considered as abnormal. However, this test is of minor diagnostic value, partly due to variations in protein excretion during the day and partly due to color assessment issues. A test strip result of 1+ or higher has a sensitivity of 55% and a specificity of 84% for the detection of proteinuria > 0.3 g/24 hours in women who have increased blood pressures [28].

Measurement of a protein (mg)/creatinine (mmol) ratio has a significantly better predictive value. Moderate proteinuria (> 0.3 g/24 hours) can be demonstrated with a sensitivity of 93% and a specificity of 92% using a cut-off value of 30 mg/mmol in women who have increased blood pressures [29].

The golden standard in identifying pregnancy hypertension is quantitative protein measurement in urine collected in 24 hours. A sample collected in 12 hours provides a similar reliability (96% sensitivity, 100% specificity compared to proteinuria > 0.3 g/24 hours in urine collected in 24 hours).

More extensive tests should be considered in case of proteinuria, subjective complaints fitting preeclampsia, or serious hypertension (systolic \geq 170, diastolic \geq 110), even without proteinuria. The primary goal of laboratory tests are identifying presence or absence of:

Hemo-concentration: hemoglobin

Renal dysfunction: creatinine, proteinuria

Hepatic enzyme abnormality: ALAT

Intravascular coagulation: platelets

Hemolysis: LDH

If indicated (HELLP syndrome, post-eclampsia state) further evaluation may be performed by testing of:

Hemostasis: APTT, PTT

Hemolysis: haptoglobin or possibly a complete blood count (fragmentocytes)

- Evaluation of the fetal condition

CTG

Ultrasound

Perinatal risk

A direct relationship between diastolic blood pressures at 24-27 weeks and perinatal complications was found in a cohort of low-risk nulliparous women: \geq 85 mm Hg likelihood ratio after a positive test (LR+) 4, \geq 90 mm Hg LR+ 7 and \geq 95 mm Hg LR+ 16. However, there was a high likelihood ratio after a negative test (LR-) (approximately 0.9), which means that a negative "test" has a moderate predictive value. Systolic pressures

were much less related to outcomes [31]. Women with maximum diastolic blood pressures ≥ 95 mm Hg had a higher maternal risk, defined as placental abruption or HELLP syndrome (RR 12; 95% CI 3-43). Preeclampsia increased both the fetal risk (RR 9; 95% CI 3-24) and the maternal risk (RR 42; 95% CI 10-178) [11]. Fetal growth retardation appears to be a problem only with preeclampsia in the preterm period. A Norwegian study found a preterm preeclampsia associated birth weight of 11-23% below the average for pregnancy duration, whereas the full term birth weights with and without preeclampsia were comparable [32]. The risk of preeclampsia for perinatal death and serious neonatal morbidity is predominantly determined by the duration of the pregnancy when the condition manifests itself, the secondary fetal growth retardation and the seriousness of the hypertension. After adjustment for these factors, the risk appears to be independent of the proteinuria level or the seriousness of the coagulation or hepatic enzyme disorder [33-37].

Maternal risk

Hypertensive disorders are the most common cause of directly related maternal death in The Netherlands. Direct maternal death due to these disorders was 4.3/100,000 live born children during 1996-1998 (42% of total death). The Maternal Mortality Committee of the Netherlands Society of Obstetrics and Gynaecology concluded "substandard care" in 83% of those cases [38]. Inadequate treatment of hypertension and eclampsia was present in half of the cases.

Treatment

Pregnancy termination is the only causal treatment. However, the disease may worsen in the first couple of days after delivery.

- Moderate hypertension in pregnancy (systolic blood pressure ≥ 140 and < 170 mm Hg or diastolic ≥ 90 and < 110 mm Hg)

It is important to inform the patient about the possibility of acute worsening of preeclampsia and the need to seek medical attention if preeclampsia symptoms occur.

Clinical or frequent outpatient clinical follow-up or "home care" may be the care of choice, depending on blood pressure and fetal parameters [39]. Rest is generally advised, although it is not a proven effective treatment. A Cochrane review [40] studied the effect of antihypertensive medications (40 trials, 3,797 women). Treatment reduced the risk of serious hypertension (from 19% to 9%, RR 0.52; 0.4-0.6). No effect was observed on the incidence of preeclampsia, fetal growth restriction, perinatal death, premature birth, placental abruption or caesarean section.

- Moderate preeclampsia (blood pressure as above, with proteinuria, without evident clinical symptoms as described under 2.1, Classification, Preeclampsia)

Usually, a clinical treatment is performed. It is uncertain to what degree perinatal and maternal outcomes improve by the use of antihypertensives. The Cochrane review mentioned above [40] included 4 studies of women with preeclampsia only and 14 with part of the women suffering from preeclampsia. No differences in outcomes were found between use or non-use of antihypertensives after subdivision according to the nature of the hypertensive disorder (pregnancy hypertension, chronic hypertension, preeclampsia or "mixed"). The number of assessable women was too small to draw useful conclusions. Due to this uncertainty some will decide to start antihypertensive therapy, whereas others will use the same criteria as used for hypertension in pregnancy.

- Serious preeclampsia, HELLP syndrome

Treatment of preeclampsia and HELLP syndrome are essentially identical. Treatment is performed clinically and depends highly on the pregnancy duration.

The initial treatment should consist of magnesium sulfate to prevent eclampsia [41] and/or antihypertensives to prevent cerebral hemorrhage. Target blood pressure values may be 140-160 mm Hg systolic and 90-105 mm Hg diastolic, although some advise lower values. Concomitant start of various medications, when administered intravenously in particular, is not recommended as potentiation may compromise the controllability of the antihypertensive effect. Direct intervention (caesarean section in particular) without

previous stabilization results in an increased risk of maternal morbidity and mortality. Usually, serious complications do not improve directly after delivery and may even worsen temporarily. Bleeding associated with possible coagulation abnormalities may be an additional complicating factor.

The seriousness of any laboratory test abnormalities is not a good predictor for maternal or neonatal complications [42]. If a temporizing approach is chosen, the majority of women may be expected to improve in 2-4 days after admission [43]. Worsening or failure to improve may be reasons to terminate the pregnancy. Early preterm (< 34 weeks) pregnancy termination for maternal reasons only may increase the risk of neonatal complications [44-46]. Maternal complications were rare in the studies referred to and HELLP syndrome was excluded. Thus, power was lacking to be able to evaluate maternal outcome differences between the intervention group and the temporized group.

A temporizing treatment aimed at the prevention of serious maternal complications, such as cerebral hemorrhage and eclampsia, treatment of complaints and symptoms, and control of the fetal condition were shown to be safe for the mother in a number of observational studies [33, 43, 47-49]. It should be noted however that these studies were performed in perinatologic centers. Therefore, it is highly recommended to consult with or refer to a perinatologic center in case of serious maternal morbidity (persistent disease symptoms after stabilization, platelets < 50,000, persistent high blood pressure), even after 32 weeks. It is recommended to make regional agreements concerning this matter.

Transfer to a perinatologic center after stabilization is recommended in case of a pregnancy duration < 32 weeks or an estimated fetal weight of < 1200 grams due to the high risk of worsening of the fetal condition and the need of premature delivery (please refer to Netherlands Society of Obstetrics and Gynaecology guideline 23, Verwijzing naar een perinatologisch centrum, Samenwerking tweede en derde lijn [Referral to a perinatologic center, Second and third line cooperation]).

Administration of a corticosteroid course may halve the risk of serious neonatal morbidity or death without adverse effects on the mother [50] if birth is expected to take place before 34 weeks (please refer to Netherlands Society of Obstetrics and Gynaecology guideline 3, Dreigende vroeggeboorte [Imminent premature birth]).

Additional corticosteroids to improve the HELLP syndrome are not recommended as there is insufficient evidence that this may reduce the risk of maternal or perinatal mortality or morbidity [51].

Induction may be considered if it is decided to achieve parturition for maternal reasons. No evidence exists that pregnancy termination on the sole indication of maternal preeclampsia will improve maternal or neonatal outcomes. Yet it is not unusual to achieve birth of the child after 34-35 weeks in case of serious maternal morbidity.

- Post partum

Preeclampsia may worsen after delivery. Lower target blood pressure values than before delivery are recommended as possible adverse effects of antihypertensives on the fetus do not have to be considered any more.

Treatment specification

Treatment is symptomatic and aims at the following.

- Circulation

The selection of antihypertensives is determined by effectivity, effect rate, administration route and absence of adverse effects on the fetus. Generally, a small group of agents is used with which extensive experience has been gained. Angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin-antagonists are not recommended due to related fetal renal damage and death [52, 53]. The literature available does not provide a basis to indicate a preferred drug [54]. Clinics are recommended though to use an established treatment schedule to prevent dosage errors in acute situations. Table 1 states the medications commonly used in The Netherlands.

A very quick decrease of blood pressure should be avoided due to the risk of overtreatment and the development of hypotension. A blood pressure that is too low may adversely affect the placental circulation and lead to fetal compromise. If the effect is insufficient, it is preferred to add a second agent rather than using a very high dose of any medication [55]. Untreated women with serious preeclampsia were observed to have a reduced circulating volume and oliguria [56]. This has led some to advise plasma volume expansion in addition to vasodilative medication to prevent hypotension and improve placental circulation. Some observational studies and small randomized studies observed improvement of cardiovascular and fetal

parameters [57]. A recent randomized study investigating treatment strategies with and without plasma volume expansion showed no differences in maternal morbidity, an unfavorable tendency for children's outcome measures and higher treatment costs in the plasma volume expansion group [58]. Thus, this treatment is not recommended.

- Eclampsia prevention in preeclampsia or HELLP syndrome

Magnesium sulfate is the most effective medication to prevent eclampsia. In a recent trial over 10,000 women with preeclampsia were randomized to magnesium sulfate (loading dose 4 g followed by 1 g/hour intravenously) or placebo [41]. Administration was terminated after 24 hours and no blood levels were measured. Women were included if they had preeclampsia and there was uncertainty whether or not magnesium sulfate should be given. Over 40% of the women had serious preeclampsia and 13% were randomized post partum. Magnesium sulfate halved the risk of eclampsia occurrence (0.8% versus 1.9%; RR 0.4; 95% CI 0.3-0.6). The effect size was not affected by preeclampsia seriousness, pregnancy duration or randomization before or after delivery. Ninety one women needed to be treated to prevent one convulsion (NNT 91; 95% CI 63-143). The NNT was lower in women with serious preeclampsia (63; 95% CI 38-181) and even lower in women with imminent eclampsia (at least two symptoms of imminent eclampsia) (36; 95% CI 21-125). The NNT was higher in women with moderate preeclampsia (109; 95% CI 72-225). Maternal death was lower in the magnesium sulfate treatment group (RR 0.55; 95% CI 0.26-1.14). Serious maternal morbidity was similar in the magnesium sulfate group (3.9%) and the control group (3.6%). No differences were observed in perinatal death (12.7% versus 12.4%). Using the secondary trial analysis it is well defensible to initiate preventive therapy only in cases of serious preeclampsia or imminent eclampsia. Post partum, magnesium sulfate may be terminated earlier than after 24 hours on guidance of clinical symptoms (absence of headache and upper abdominal pain, blood pressure < 150/100 mm Hg and diuresis > 100 ml/hour [59]. Table 2 provides a dosage schedule. There is no need to measure blood levels if this scheme is followed, treatment is terminated after 24 hours and renal function is normal.

- Eclampsia

An eclamptic convulsion is almost always preceded by a period with preeclamptic complaints: headache, upper abdominal pain, restlessness, confusion, nausea and vision complaints. Sometimes, this period may be short. High blood pressure values and hyperreflexia are not reliable parameters to estimate the risk of eclampsia. Nearly half of the women with eclampsia develop convulsions post partum [10]. Most cases of post partum convulsions develop within 48 hours after delivery, but eclampsia may occur later in the puerperium up to 2 weeks after delivery) [60].

Magnesium sulfate is the medication of first choice to treat an eclamptic patient. The risk of convulsion recurrence with magnesium sulfate therapy is half of the risk with diazepam therapy (RR 0.5; 95% CI 0.4-0.6) and one third of the risk with phenytoin therapy (RR 0.3; 95% CI 0.2-0.5) [61]. The Collaborative Eclampsia Trial used a loading dose of 4 g and a maintenance dose of 1 g/hour intravenously. The recurrence rate in the magnesium sulfate group was approximately 10% in this study. Unknown is whether a higher dosage schedule is more effective. Administration should be performed according to an established protocol, for which table 2 may serve as a guideline. One vial of calcium gluconate or calcium levulate should be readily available to treat overdose. Treatment for more than 24 hours is rarely necessary.

In rare cases convulsions will continue to occur despite adequate treatment with magnesium sulfate. Due to the risk of respiratory depression further increases of magnesium sulfate dose are not recommended if two additional boluses of 2 g have been given and the blood level is unknown. Additional blood pressure reduction may be necessary. The patient may be sedated and intubated if necessary.

Magnesium sulfate causes vasodilation and has a blood pressure lowering effect that gradually increases over the first 1-2 hours after the start of administration. Magnesium sulfate may be combined with calcium antagonists, provided that administration or adjustments do not start at the same time. It may cause a reduction of the fetal heart beat variability and heart rate, but no decelerations. The neonate may be hypotonic at birth and therefore need respiratory support. Intravenous calcium may improve these symptoms.

One rectal dose of diazepam 10 mg may be chosen if magnesium sulfate is not available.

- Cerebral abnormalities

A vision disorder of variable seriousness, sometimes with complete blindness, may develop as a result of local edema or ischemia in the occipital cortex. Local hypodense abnormalities similar to infarction may be seen on a CT scan. However, the picture is nearly always reverses within a few days. Ophthalmologic examination is able to distinguish this problem from retinal edema, which may also cause visual field deficits. This abnormality usually resolves over 2-3 months. Hallucinations (visual or auditory) or psychiatric disorders may

occur, often as a prodrome of eclamptic convulsion.

Cerebral hemorrhage is a rare complication that may occur in relation to an eclamptic convulsion.

Differentiation between hypertension and eclampsia as the causal moment and some other cause of cerebral hemorrhage (e.g. aneurysm) resulting in convulsions and hypertension may be difficult or sometimes impossible [62]. It is particularly advisable to consult a neurologist and perform further diagnostic imaging if a patient is not responsive shortly after the convulsion or if asymmetric reflexes or neurologic deficits are present.

- Pain management in preeclamptic complaints and HELLP syndrome

Upper abdominal pain often responds well to acetaminophen, combined with codeine if necessary. If the effect is insufficient, morphine may also be given. Subcutaneous injection prolongs its effect. Intravenous administration may also be considered if necessary. Intramuscular injection is not recommended in the presence of a coagulation disorder.

- Coagulation disorder

Treatment with platelets (if the platelet count $< 50 \times 10^9/l$) and fresh plasma (ESDEP) or coagulation factors (if the APTT is prolonged) is indicated only if a caesarean section is performed or a (post partum) bleeding occurs.

- Hepatic enzyme increase

An increase in hepatic enzymes is usually associated with physical complaints. Hepatic dysfunction hardly ever occurs in HELLP syndrome. Should it occur then acute fatty liver should be considered as a diagnosis (see below).

- Hepatic hematoma

This is a rare complication occurring post partum more often than ante partum. Quickly worsening preeclampsia with severe upper abdominal pain are typical. Upper abdominal ultrasound examination or possibly a CT scan or MRI may confirm the diagnosis or make it unlikely. It is recommended to achieve parturition if hepatic hematoma occurs ante partum. The hematoma is initially treated conservatively with blood transfusion and coagulation correction. If this does not stabilize the condition, a capsular rupture is likely to have occurred. Some advise embolization of the hepatic artery and others laparotomy and hepatic tamponade with a large gauze compress [63, 64]. Lobectomy or surgical ligation of the hepatic artery is not recommended, unless it is the only way to stabilize the bleeding.

- Acute fatty liver

It is uncertain whether fatty liver is related to preeclampsia or if it is a separate disease. It is a rare disease (approximately 1:20.000). The clinical picture is characterized by quickly emerging hepatic failure with nausea, abdominal pain, jaundice, moderately elevated transaminase levels, hypoglycemia, coagulation abnormality due to coagulation factor production disorder and disseminated intravascular coagulation, elevated ammonia level, renal insufficiency and encephalopathy [65, 66]. Treatment consists of glucose infusion to correct hypoglycemia, coagulation correction and pregnancy termination. Hepatic function is usually normalized after recovery [66]. Liver transplantation may be necessary in case of complete hepatic failure.

- Renal dysfunction

Preeclampsia may be associated with significant protein loss in urine, resulting in a lowering of plasma albumin. Protein loss may cause significant edema and sometimes also ascites or pulmonary edema. In serious cases symptomatic treatment may consist of limited fluid intake (as recommended with nephrotic syndrome).

Oliguria often occurs and has no consequences provided serum creatinine remains normal, and does not need treatment. Additional fluid intake or forced drinking usually leads to increased edema. If creatinine

elevation occurs, it is often related to HELLP syndrome, placental abruption or preexistent renal dysfunction [67].

It always resolves post partum, although temporary dialysis is necessary in some cases. Diuretics are recommended only in case of overfilling. The fluid balance and electrolytes should be monitored carefully. Usually, the creatinine level decreases quickly, but correction of proteinuria may take up to one year in some cases. Renal function recovers nearly always without residual dysfunction, unless renal dysfunction already existed before the pregnancy.

- Low salt diet

There are no randomized studies of the effect of salt limitation on the treatment of preeclampsia and it is unclear whether salt limitation has any therapeutic effect.

- Fetal condition

A real risk of fetal compromise exists in case of serious maternal disease. After maternal stabilization a temporizing treatment makes no sense if signs of fetal compromise are present, unless pregnancy duration or estimated fetal weight provide a basis for a non-intervention decision.

Follow-up

Organ-function disorders usually resolve without residual dysfunction (unless abnormalities existed before the disease developed). Recovery may take some time though. Correction of increased blood pressure may take up to six months and resolution of proteinuria may take even longer sometimes. Women having experienced serious preeclampsia may have concentration problems, memory problems, vision disorder or fatigue for a long time. Improvement of those complaints may take a year. The disease period often leaves an ineradicable impression upon the woman and her family, even if (in hindsight) the medical problems appear to be not as bad as expected. An active patient association (the HELLP Syndrome Foundation, P.O. Box 636, 3800 AP Amersfoort, The Netherlands) aims at organizing fellow-patient contact and providing information about the disease. Standard hereditary coagulation deficiency or antiphospholipid antibody tests lack therapeutic consequences and is therefore only recommended within a research framework. Women who have experienced pregnancy hypertension or preeclampsia have a higher risk of hypertension at an older age (RR 1.5; 95% CI 1.1-2.1 and RR 2.6; 95% CI 1.7-3.7) [68] as well as a higher risk of cardiovascular death, particularly in case of preterm delivery (RR 8.1; 95% CI 4-15) [69].

Recurrence risk

Women with early preeclampsia (< 34 weeks) and without underlying disease (such as hypertension, renal disease, SLE) have a risk of pregnancy hypertension at a next gravidity of approximately 25%. The risk of serious morbidity (HELLP syndrome among others) is 2-6% [70-72] and dependent of the pregnancy duration at delivery in the index pregnancy. However, there is a significant risk of fetal growth restriction. Its seriousness is affected particularly by the degree of growth restriction in the first gravidity. On average the birth in a next gravidity takes place one month later and the baby is 1,300-1,400 g heavier [70]. This is independent of whether or not a blood pressure increase occurs in this gravidity. Women developing preeclampsia in a second or later gravidity have a recurrence risk that is 2 x as high [70]. A Norwegian study estimated the risk of preeclampsia in a next pregnancy using data of the Norwegian birth registry over 1967-1992 [73]. The risk was 1% if no preeclampsia occurred in the first gravidity and the birth weight was \geq 3000 grams, 1.5% if the birth weight was \geq 2000 and < 3000 grams, and 3% if the birth weight was < 2000 grams. Those risks were 9, 16 and 24% respectively if preeclampsia did occur in the index pregnancy

Minimum care needed

1. Medication to treat systolic blood pressures \geq 170 mm Hg and/or diastolic blood pressures \geq 110 mm Hg is strongly recommended. In cases of preeclampsia lower cut-off values are often used (evidence level C-D).

2. Magnesium sulfate is the most effective drug to prevent eclampsia and further convulsions after eclampsia (evidence level A2).
3. Before transportation of or surgery on patients with serious preeclampsia is performed it is strongly recommended to stabilize such patients by means of administration of magnesium sulfate to prevent eclampsia and/or treatment of blood pressure to prevent cerebral hemorrhage (evidence level C).
4. Fetal monitoring is recommended by means of cardiotocography in case of acute changes in the clinical picture and/or medication adjustments, unless a non-intervention policy is used based on pregnancy duration and estimated fetal weight (evidence level C).
5. A corticosteroid course reduces the risk of neonatal complications if delivery takes place < 34 weeks and does not adversely affect preeclampsia (evidence level A2).
6. Plasma volume expansion does not improve maternal or neonatal outcomes (evidence level A2).
7. It is advisable to refer patients with early preeclampsia (< 32 weeks) or serious disease symptoms due to preeclampsia to a perinatologic center or to consult the regional center about the treatment (evidence level D).
8. It is recommended to perform treatment of eclampsia and serious preeclampsia in accordance with an established (institutional) protocol (evidence level D).
9. It is advisable to inform a pregnant woman that she should consult her obstetric care provider if she experiences physical complaints as described for preeclampsia (evidence level D).
10. Preeclampsia should be considered as a highly varying clinical syndrome with clinical parameters being more important than laboratory parameters to estimate its seriousness (evidence level C).
11. Medication to treat moderate pregnancy hypertension (diastolic blood pressure < 110 mm Hg and systolic blood pressure < 170 mm Hg) does not improve perinatal outcomes (evidence level A).

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Colophon

© 2005 Netherlands Society of Obstetrics and Gynecology This guideline, developed by the Netherlands Society of Obstetrics and Gynecology's Quality Committee under the ultimate responsibility of the Board of the Netherlands Society of Obstetrics and Gynecology, was established at the 583rd general meeting held on May 20, 2005, in Noordwijkerhout, The Netherlands. The guideline was drawn up by dr. H. Wolf on behalf of the Otterlo Obstetric Working Party.

Netherlands Society of Obstetrics and Gynecology guidelines describe the minimum of care to be provided by a gynecologist in average situations. They are of an advisory nature. Gynecologists may arguededly deviate from a guideline when concrete circumstances make such deviation necessary. This may be the case, among other things, when a gynecologist has to meet the objective and/or subjective needs of a specific patient.

Policy at an institutional level may incidentally prevent a guideline to be (completely) applicable locally. This guideline expires five years after its date at the latest. Date: May 2004.

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Tables

Table 1 Antihypertensives

Medication	Type	Advised dosage	Action	Half-life	Adverse effects	Lactation	Details
Methyldopa	α_2 receptor agonist	2-3 x 250-1000 mg	After 3-4 hrs, max. after 4-6 hrs	20 hours	Sedation (usually temporarily), headache, depression	Yes	Not in case of hepatic disease
Nifedipine	Calcium antagonist	2 x 10-40 mg retard 1 x 30-90 mg oros	After ½-1 hour After 2-4 hours	Retard 6-11 hours, oros 24 hours	Headache, nausea, flushing	Yes	Preferably not as capsules due to the risk of hypotension; possible interaction with MgSO ₄ - not to be raised concomitantly
Labetalol	α_1 and β receptor antagonist	i.v. 10-30 mg/hr orally 3 x 50-200 mg	i.v. immediately, orally after 1-4 hrs	4-6 hours (shorter during gravidity)	Flushing, nausea, vomiting	Yes	In case of high i.v. dosage: neonatal bradycardia and hypotension, especially early preterm
Ketanserin	Serotonin antagonist with weak α_1 receptor blockade	Start with a 5 mg bolus and 4 mg/hr, raise with a 5 mg bolus and additional 2 mg/hr infusion up to max. 14	i.v. after 1-3 min, orally after 1 hr	13-18 hours	Rare: dry mouth, headache, dizziness	No?	ECG before administration due to risk of Q-T wave prolongation

		mg/hr					
Dihydralazine	Peripheral vasodilation	Start with 5 mg in 30 min, then 1 mg/hr, raise if necessary after 30 min in steps of 1 mg/hr	i.v. after 5-10 min, orally after 1 hr	4-5 hours	Tachycardia, headache, nausea	Yes	Not effective if dissolved in glucose; beware of hypotension/hypovolemia; with special doctor's statement only

Table 2
Magnesium sulfate

Dosage [41, 60]

Solution: 20% magnesium sulfate, intravenous administration with infusion pump

	<i>Dosage</i>	<i>Time</i>
Loading dosage	4-6 g = 20-30 ml	In 10-30 min.
Maintenance dosage	1 g = 5 ml	In 60 min.
Extra in case of repeat convulsion (maximum 2 x)	2 g = 10 ml	In 5 min.

- In rare cases convulsions will continue to occur despite adequate treatment with magnesium sulfate. Due to the risk of respiratory depression, further increases of the magnesium sulfate dose are not recommended if two additional boluses of 2 g have been given and the blood level is unknown. Additional blood pressure reduction may be necessary. If necessary, lorazepam 4 mg i.v. may be given slowly or the patient may be further sedated and intubated.
- In principle, administration of magnesium sulfate can be terminated after 24 hours.
- In case of overdosage: 10 ml calcium levulate or calcium gluconate (= 1 g) intravenously in 5 minutes.
- Blood level monitoring is not needed if the patient is treated according to the standard schedule and her urine production is adequate.

Blood levels

Recommended value: 2-3 mmol/l

In case of intoxication:

4-5 mmol/l = disappearance of patellar reflex

Approx. 6.5 mmol/l = respiratory depression

Approx. 13 mmol/l = cardiac arrest

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