

Diagnosis and Treatment of Hypertensive Pregnancy Disorders. Guideline of DGGG (S1-Level, AWMF Registry No. 015/018, December 2013)

Diagnostik und Therapie hypertensiver Schwangerschaftserkrankungen.
Leitlinie der DGGG (S1-Level, AWMF-Registernummer 015/018, Dezember 2013)

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Key words

- preeclampsia
- hypertension
- HELLP syndrome

Schlüsselwörter

- Präeklampsie
- Hypertonie
- HELLP-Syndrom



OEGGG

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Bibliography

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Abstract



Purpose: Official guideline published and coordinated by the German Society of Gynecology and Obstetrics (DGGG). Hypertensive pregnancy disorders contribute significantly to perinatal as well as maternal morbidity and mortality worldwide. Also in Germany these diseases are a major cause for hospitalization during pregnancy, iatrogenic preterm birth and long-term cardiovascular morbidity.

Methods: This S1-guideline is the work of an interdisciplinary group of experts from a range of different professions who were commissioned by DGGG to carry out a systematic literature search of positioning injuries. Members of the participating scientific societies develop a consensus in an informal procedure. Afterwards the directorate of the scientific society approves the consensus.

Recommendations: This guideline summarizes the state-of-art for classification, risk stratification, diagnostic, treatment of hypertensive pregnancy disorders.

Zusammenfassung



Ziel: Offizielle Leitlinie, publiziert und koordiniert von der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG). Hypertensive Schwangerschaftserkrankungen verursachen weltweit einen hohen Anteil an der neonatalen und mütterlichen Morbidität und Mortalität. Auch in Deutschland tragen sie wesentlich zu Krankenhauseinweisungen während der Schwangerschaft, iatrogener Frühgeburtlichkeit und kardiovaskulärer Langzeitmorbidität bei.

Methoden: Mitglieder der beteiligten Fachgesellschaften entwickeln in einem informellen Prozess einen Konsensus. Anschließend bestätigen die Direktoren der Fachgesellschaften diesen Konsensus.

Empfehlungen: In der Leitlinie wird der aktuelle Standard für die Benennung, Früherkennung, Diagnostik, Behandlung und Nachsorge hypertensiver Schwangerschaftserkrankungen gegeben.

I Guideline Information

Guidelines Program of DGGG, OEGGG and SGGS

Information on this topic is provided at the end of the guideline.

Citation format

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Guideline documents

The editorially complete, long version and a PDF slide set suitable for PowerPoint presentation of these guidelines as well as a summary of the conflicts of interest of all the authors can be found on the homepage of AWMF:

<http://www.awmf.org/leitlinien/detail/II/015-018.html>

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See **Table 1**.

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Abbreviations

ACE	Angiotensin Converting Enzyme
ASS	acetylsalicyl acid
BMI	Body-Mass-Index
CTG	Cardiotocography
DIG	disseminated intravascular coagulation
E	eclampsia
EFCNI	European Foundation for the Care of Newborn Infants
FPR	false positive rate
HELLP	Haemolysis Elevated Liver enzymes Low Platelet count
K	Korotkoff
LR	Likelihood ratio
MoM	multiple of the median
PAPP-A	pregnancy- associated plasma protein A
PE	preeclampsia
PIGF	placental growth factor
PI	pulsatility index
RI	Resistance-Index
RR	relative risk
SSW	week of gestation
sFlt-1	soluble fms-like tyrosine kinase-1

II Using this Guideline

Purpose and objectives

Hypertensive pregnancy disorders contribute significantly to perinatal as well as maternal morbidity and mortality worldwide. Also in Germany these diseases are a major cause for hospitalization during pregnancy, iatrogenic preterm birth and long-term cardiovascular morbidity. The guideline summarizes the state-of-art for classification, risk stratification, diagnostic, treatment of hypertensive pregnancy disorders with the aim to reduce perinatal as well as maternal morbidity and mortality.

Patient care

Outpatient and inpatient care.

Target audience

This guideline is addressed to the following groups of people:

- Obstetricians
- Audience of patients:
- pregnant women

Period of validity

The validity of this guideline was confirmed by the boards/responsible persons of the participating professional associations/working groups/organizations/societies as well as by the board of the DGGG and the DGGG Guideline Commission in November 2013 and thereby approved in its entirety. This guideline is valid from December 01, 2013 to November 30, 2016. The period of validity has been estimated based on the guideline's contents. The guideline can be updated earlier if necessary; likewise, the guideline's period of validity can be extended if it continues to mirror the current state of knowledge.

III Guideline

1 Methodology

The methodology for the compilation of this guideline is prescribed by the classification assigned to the guideline. The AWMF Guidance Manual and Rules for Guideline Development (Version 1.0) sets out the rules for classifying guidelines. Guidelines are differentiated into lowest (S1), moderate (S2) and highest (S3) class. The lowest class of guideline is defined as consisting of a set of recommendations for action compiled by a representative group of experts from medical societies. In 2004 the S2 class is divided into two subclasses: S2e (evidence-based) and S2k (consensus-based). The highest class (S3) combines both approaches. This guideline is classified as: S1

The guideline, which was created in November 1999 and was already present in a previous version from 2008, was adapted according to the current literature and existing international guidelines. The contents of the guideline have been edited by the entire group of experts in three meetings in debated discussions. After editorial and content revision of the guidelines by the management of the expert group, agreement between the authors took place using written correspondence. A version was adopted which was accepted by all authors. The Guidelines Commission and Board of DGGG accepted the guideline in November 2013.

2 Introduction

Hypertensive disorders occur in 6–8% of all pregnancies, contribute to 20–25% of perinatal mortality and are the first and second most common causes of maternal death in Europe. Preeclampsia is of particular importance (10–15% of all maternal deaths are associated with preeclampsia/eclampsia) and is responsible for at least 70 000 maternal deaths per year worldwide (for review: Lo et al. [1]). Even today, > 90% of maternal deaths from PE/E in Eu-

rope are potentially avoidable [2,3]. In Europe, the incidence of preeclampsia is approximately 2% [1,4,5].

3 Classification of hypertensive disorders in pregnancy and postpartum

The following classification, as well as the definitions, takes into account the recommendations of the American and Australian Societies and the International Society for the Study of Hypertension in Pregnancy [6–11].

3.1 Gestational hypertension (Pregnancy-induced hypertension)

Definition: Blood pressure values $\geq 140/90$ mmHg without proteinuria in a previously normotensive pregnant women occurring after the completed 20th week of pregnancy.

Cave: Mild preeclampsia develops from gestational hypertension in up to 46% of cases and severe preeclampsia develops in 9.6% [12].

3.2 Preeclampsia (Synonym: Gestosis)

Definition: Gestational hypertension and proteinuria (≥ 300 mg/24 h detected in 24-h urine or > 30 mg/mmol protein-creatinine ratio in a random urine sample occurring after the 20th completed week of pregnancy).

Cave: Clinical signs of renal impairment, hepatic involvement, pulmonary, haematological/neurological disorders or fetal growth restriction indicate the development of preeclampsia. Based on the different pathophysiology and the different risk profile for mother and child, a distinction is made between early (early-onset manifestation < 34 weeks) and later (late-onset) preeclampsia [13,14].

Preeclampsia is referred to as severe preeclampsia if at least one of the following criteria is also satisfied [8,11,15]:

- ▶ Blood pressure $\geq 160/110$ mmHg
- ▶ Renal impairment (creatinine ≥ 79.6 $\mu\text{mol/l}$ [equates to 0.9 mg/dl] or oliguria < 500 ml/24 h)
- ▶ Liver involvement (transaminase increase, persistent upper abdominal pain)
- ▶ Lung oedema
- ▶ Haematological disorders (thrombocytopenia < 100 Gpt/l, haemolysis)
- ▶ Neurological symptoms (severe headache, impaired vision)
- ▶ Fetal growth retardation (estimated fetal weight < 5 . percentile and/or pathological umbilical artery Doppler)

The degree of proteinuria is no longer a criterion for the definition of serious preeclampsia [11,15].

3.3 Eclampsia

Definition: Tonic-clonic seizures occurring during preeclampsia which cannot be attributed to any other cause.

Cave: Only associated with severe hypertension in about 50% and possible even in the absence of hypertension or proteinuria (14–34% of cases) [16,17]. 21% of women have no clinical symptoms in the week before the onset of preeclampsia [18].

3.4 HELLP syndrome

Definition: Triad of:

(H): haemolysis

(EL): elevated liver enzymes

(LP): low platelets (< 100 Gpt/l)

Cave: There is no significant proteinuria in 5–15%, no hypertension in up to 20% of cases and hypertension and proteinuria can both be absent at the same time [19].

3.5 Chronic hypertension

Definition: Hypertension $\geq 140/90$ mmHg diagnosed preconceptually or in the first half of pregnancy (before the 20th week of pregnancy) [20].

3.6 Superimposed preeclampsia

Definition: Chronic hypertension and newly emerged/worsening proteinuria after 20 weeks of pregnancy or appearance of clinical or laboratory features of severe preeclampsia (see above).

Cave: Superimposed preeclampsia develops from chronic hypertension in 17–25% (50% of these before the 34th week of pregnancy) [20].

4 Screening, prediction and prevention

A significant, single test for reliable early recognition of preeclampsia is not yet available [4,21–26]. Anamnestic details (pregnancy record), mean arterial blood pressure, biochemical markers and Doppler sonography can be used in the first or second trimester for risk assessment [27].

4.1 Screening in the first trimester

A risk assessment of maternal characteristics (age, medical history, body mass index, ethnicity), in conjunction with biophysical factors (after MoM adjusted pulsatility of the uterine artery, mean arterial blood pressure) and biochemical risk markers (e.g. pregnancy-associated plasma protein A [PAPP-A], placental growth factor [PIGF]) allows an individual risk calculation, in particular for early-onset preeclampsia.

With this combination of different methods, detection rates for early preeclampsia of 93.4 and 95.2% can be achieved with a false positive rate (FPR) of 5 or 10%.

However, this algorithm has significantly poorer detection rates of 37.8 and 71.1% for late preeclampsia [5,28].

The predictive value of the different biophysical and biochemical methods as the sole screening test is low and their use for the prediction of preeclampsia is not recommended because of the high FPR [4,5,24,28–32]. However, the high negative predictive value (> 97%) of the test method for early-onset preeclampsia or the development of intrauterine growth retardation should be emphasised [30,33,34]. Regional differences as well as socio-economic and ethnic factors can influence the results and their significance [35,36] therefore their uncritical acceptance in routine clinical practice is not recommended (especially without appropriate organizational structures and adequate counselling) [37].

4.2 Screening and prediction in the second trimester

The measurement of the mean pulsatility index (PI) – alone or in combination with postsystolic notching – is considered the best marker for the prediction of preeclampsia with a sensitivity of up to 93% [22,23,38–40], in a low-risk group the recognition rate of the mean pulsatility index > 1.6 (95th percentile) for early-onset preeclampsia at 5% FPR was 78% and 42.8% for preeclampsia overall [22]. The detection rates for late preeclampsia are significantly lower, depending on gestational age [22]. Of clinical relevance here is also the high specificity and negative predictive value of Doppler ultrasound parameters of up to 99% [38,39,41,42]. The presentation of postsystolic notching in the uterine artery is

a reliable sign when screening for preeclampsia; however the error rate is unfortunately high because of a certain subjectivity. A further risk estimation for the development of preeclampsia and prognostic assessment of the clinical course of the disease with a pathological uterine artery Doppler in the 2nd trimester can be achieved by determining angiogenesis/antiangiogenesis factors [22, 23, 25, 42–45]. It has been shown that the serum levels of sFlt-1 (soluble fragment of the VEGF receptor 1) and PIgf already alter weeks before manifestation of the disease and that the sFlt-1/PIgf ratio has a prognostic value [43, 46–50].

4.3 Prevention

Currently the only effective way of preventing preeclampsia in women with risk factors (e.g. a history of severe preeclampsia) is to begin oral administration of low-dose acetylsalicylic acid (ASA: 75–150 mg/day) during early pregnancy (before 16 weeks) [51]. This approach significantly reduces the risk of preeclampsia before the 37th week of pregnancy, but not near term [52], as well as the risk of (severe) preeclampsia, pregnancy-induced hypertension and IUGR with pathological uterine artery Doppler results [53].

In Germany, an aspirin dosage of 100 mg/day up to 34 + 0 weeks has been established. General aspirin prophylaxis is not indicated.

5 Antenatal screening

5.1 Risk factors for the development of preeclampsia

5.1.1 Clinical history risk factors (Table 2) [39, 54–62]

Table 2 Clinical history risk factors.

	Relative risk (RR)
Antiphospholipid syndrome	~ 9
History of preeclampsia	~ 7
Body Mass Index > 30	~ 3–5
Pre-existing diabetes mellitus	~ 3.5
Family history	~ 3
Pre-existing kidney disease	~ 3
First pregnancy	~ 2.5–3
Age > 40	~ 2
Chronic hypertension	↑
► with 1 additional risk factor	1.55
► with 2 additional risk factors	3
► BP diastolic > 110 mmHg (< 20 weeks)	3.2
Autoimmune diseases	7–9.7
Ethnicity (African-American)	2

5.1.2 Pregnancy-associated risk factors

(Table 3) [39, 56, 59, 62]

Table 3 Pregnancy-associated risk factors.

	Relative risk (RR)/Likelihood ratio (LR)
Bilateral notching/increased PI/RI in the uterine artery persisting > 24. SSW	3.4–6.5
Multiple pregnancy	3
IVF/egg cell donation	↑
Gestational diabetes	
Hydrops fetalis, trisomies, molar pregnancy	

5.1.3 Recurrence risk

The recurrence risk for preeclampsia after previous preeclampsia is 11.5 to 27% [63], on average 14 to 16% [64–66], and 32% after two previous episodes of preeclampsia [66]. After previous pregnancy-induced hypertension, the risk of recurrence of the same disease in the following pregnancy is specified as 16–47% and 2–7% for preeclampsia [11, 64].

The recurrence risk for the occurrence of HELLP syndrome after a previous HELLP syndrome is 12.8% in Germany [67].

After eclampsia, there is a risk of recurrence of eclampsia of 2–16% in a subsequent pregnancy and of 22–35% for preeclampsia [68]. The risk of recurrence and the prognosis depends mainly on the gestational age of the baby (≤ 28 week of pregnancy: 38.6%; 29–32 weeks: 29.1%; 33–36 weeks: 21.9%; ≥ 37 weeks: 12.9%) and the severity of preeclampsia in the previous pregnancy (recurrence risk of 25% after severe preeclampsia, HELLP syndrome or eclampsia before 34 weeks' gestation and 55% in severe preeclampsia before the 28th week of pregnancy) as well as other accompanying factors (e.g., elevated BMI) or disorders [65].

Cave: After preeclampsia/HELLP syndrome, the risk of other hypertensive disorders occurring during pregnancy is increased.

5.2 Blood pressure measurement

Diastolic blood pressure should be recorded as Korotkoff 5 (K5 = disappearance of sound) or Korotkoff 4 (muting) if K5 is not measurable [69–71]. The measurement should be carried out manually using a cuff which is adapted to the upper arm circumference [7, 72]. The first measurement should be taken after a 2 to 3 minute rest period with the patient seated. The measurement should primarily be taken on both arms and later on the right arm if there are small differences.

24-hour blood pressure measurement is a suitable method to clarify a differential diagnosis of hypertension in pregnancy (to exclude "white coat hypertension", loss of circadian rhythm as a prognostically unfavourable sign) and to check the success of anti-hypertensive treatments [69, 70].

Cave: Women with "white coat hypertension" in early pregnancy may develop pregnancy-induced hypertension in up to 40% of cases and preeclampsia in 8% later in pregnancy [73].

For the outpatient care of pregnant women, self-measurement of blood pressure is recommended (at least in the morning and evening) using an upper arm monitor and a blood pressure profile should be recorded.

Cave: Automatic blood pressure monitors are suitable for this purpose, however a wrist device can measure the blood pressure systematically lower [74, 75].

5.3 Protein excretion in the urine (proteinuria)

Evidence of $\geq 1+$ protein in the urine screening test requires clarification.

A quantitative measurement of protein in urine should be performed in all patients with de novo hypertension in pregnancy [11, 76–78]. Proteinuria before 20 weeks of pregnancy is an indicator of pre-existing kidney disease [79].

The following diagnostic criteria are available:

- Protein-creatinine ratio (from random urine sample) [11, 80–83]: Values ≥ 30 mg/mmol indicate significant proteinuria (corresponding to ≥ 300 mg/day) and correlate with a proteinuria of ≥ 300 mg/day. The use of catheter urine is not necessary [84].
- Protein excretion in 24-hour urine collection (≥ 300 mg/day) [11, 72, 78, 85].

Cave: In cases of confirmed proteinuria, repeated measurements to estimate the prognosis and monitoring of preeclampsia are not useful [11, 78].

5.4 Oedema

Oedema alone is an uncharacteristic symptom that is only relevant if it increases rapidly, i.e. if significant weight gain is detected within a short period of time ($\geq 1 \text{ kg/week}$ in the III trimester) [86] or if there is pronounced facial oedema. If oedema/weight gain develops rapidly in conjunction with proteinuria, it can lead to eclampsia even without hypertension (cf. definition of preeclampsia).

6 Out-patient and clinical monitoring

6.1 Clinical chemistry and haematology

The following clinical chemistry/haematological parameters can be altered, depending on the disorder (Table 4) [6–11, 49, 87–91]:

Table 4 Clinical chemistry laboratory parameters.

Parameter	
Haemoglobin	$> 13 \text{ g/dl} = > 8.0 \text{ mmol/l}$
Haematocrit	$> 38\%$
Thrombocytes	$< 100 \text{ Gpt/l}$
	A progressive decrease in platelet counts, even within the normal range, should be monitored within a few hours (Cave: HELLP syndrome, DIC).
GPT (ALT)	Rise above the normal range
GOT (AST)	Rise above the normal range
LDH	Rise above the normal range
Bilirubin (indirect)	$> 1.2 \text{ mg/dl} = > 20.5 \mu\text{mol/l}$
Uric acid	$> 5.9 \text{ mg/dl} = 350 \mu\text{mol/l}$
Creatinine	$\geq 0.9 \text{ mg/dl} = 79.6 \mu\text{mol/l}$
Protein in urine	$\geq 300 \text{ mg/24 h}$
Haptoglobin	Drop below the normal range
Other clotting tests (e.g. rapid D-dimer increase (indicator of DIC))	Monitor
PIGF	Gestational age-specific standard value
sFlt-1/PIGF ratio	> 85

6.2 Outpatient care

With adequate cooperation between the pregnant women and excluded apparent risks for mother and child as well as guaranteed weekly medical checks, mild pregnancy-induced hypertension be treated in the outpatient clinic (including a home blood pressure protocol) [11, 92]. In addition to physical rest and the elimination of additional stress factors (possible unfitness for work or individual work prohibition), regular measurements of blood pressure, body weight and monitoring of proteinuria are priority. In addition, the well-being of the fetus (growth, Doppler, CTG) and the estimation of amniotic fluid volume should be monitored.

The pregnant mother should be referred to the hospital if a hypertensive value of 150/100 mmHg or above is measured.

The initiation of drug treatment is reserved for severe forms and should only be performed in hospital. To confirm the diagnosis of or to exclude preeclampsia, the angiogenic factors can be determined additively (PIGF, sFlt-1/PIGF ratio) [49, 87–91].

6.3 Indications for hospital referral [11, 49, 93, 94]

- ▶ Hypertension $\geq 150 \text{ mmHg}$ systolic or $\geq 100 \text{ mmHg}$ diastolic
- ▶ Apparent preeclampsia
- ▶ Proteinuria and severe weight gain in the III trimester ($\geq 1 \text{ kg/week}$)
- ▶ Impending eclampsia (Prodromal symptoms: upper abdominal pain, nausea, vomiting; CNS symptoms: visual snow, persistent headache, hyperreflexia)
- ▶ Clinical suspicion of HELLP syndrome, especially persistent upper abdominal pain
- ▶ Indicators of a threat to the fetus
 - ▶ Suspicious/pathological CTG or suspicious/pathological Doppler scan
 - ▶ IUGR
- ▶ Mild hypertension or proteinuria and further risk factors such as
 - ▶ Pre-existing maternal disorders (e.g. diabetes mellitus)
 - ▶ Multiple pregnancy
 - ▶ Early gestational age (< 34 weeks)
 - ▶ An-/Oligohydramnios
 - ▶ Pathological sFlt-1/PIGF ratio

6.4 Measures to be taken in hospital

6.4.1 On admission

- ▶ Diagnosis of maternal and fetal condition (hypertensive or fetal emergency?):
 - ▶ Fastest possible measurement of blood pressure on admission (repeat after adaptation phase if necessary) followed by close blood pressure measurement until stabilisation of blood pressure
 - ▶ Exclusion of prodromal symptoms (central symptoms, upper abdominal pain)
 - ▶ CTG recording (from fetal viability)
- ▶ Proteinuria diagnosis using test strips on admission and as part of quantitative protein measurement
- ▶ Laboratory according to hospital standard (see Table 4)
- ▶ Ultrasound (biometry/Doppler scan)

6.4.2 After stabilisation

- ▶ Blood pressure monitoring depending on clinical symptoms
- ▶ CTG ($1-3 \times \text{day}$)
- ▶ Laboratory monitoring daily up to $2 \times$ per week (determination of angiogenic factors (sFlt-1/PIGF ratio) for differential diagnosis/short-term prognosis if necessary)
- ▶ Monitoring of clinical symptoms, especially upper abdominal pain, headache, blurred vision, hyperreflexia, (check reflex status), impairment of consciousness, dyspnoea, increased risk of bleeding
- ▶ Hourly monitoring of urine output in pregnant women with severe clinical symptoms of preeclampsia, pulse oximetry for respiratory symptoms (for example, dyspnoea)
- ▶ Fetometry every 10–14 days and measurement of amniotic fluid volume
- ▶ Doppler scan daily/weekly
- ▶ RDS prophylaxis (24 to 34 weeks) – individualised decision
- ▶ Daily weight monitoring

7 Treatment

7.1 Basic aspects of drug treatment

Initiation of drug treatment should be the **sole responsibility of the hospital**, since inpatient observation under controlled conditions may result in the need for a blood pressure lowering drug. This continues to be problematic in terms of fetal development

Table 5 Long-term treatment with oral antihypertensives [95, 101–103] as at 12/2013.

	Drug	Dose	Notes
Suitable	Alpha-Methyldopa	250–500 mg oral (bd – qds) max. 2 g/day	First choice
Partially suitable	Nifedipine retard	20–60 mg ret. oral max. 120 mg/day	No proven teratogenic effects
	Selective β-1 receptor blocker (Metoprolol agent of choice)	Dose 25–100 mg (bd)	Increased risk of fetal growth restriction generally with β-blocker therapy
Not suitable	Diuretics		Potential impairment of uteroplacental perfusion from additional plasma volume reduction
	ACE inhibitor		No proven teratogenic effects. Contraindicated in II/III trimester: Acute renal failure in neonates, oligohydramnios
	Angiotensin AT1 antagonists		Oligohydramnios, skull hypoplasia, potentially teratogenic in analogy to ACE inhibitors and nephrotoxic for the newborn
	All other antihypertensives		Insufficient information on use in pregnancy

Cave: Dihydralazine is not recommended because of severe maternal side effects (reflex tachycardia, headache, tachyphylaxis).

and should therefore not be initiated below a persistent blood pressure of ≥ 150 mmHg systolic and/or ≥ 100 mmHg diastolic and at the latest at a value of $\geq 160/110$ mmHg [6, 11, 95]. The target blood pressure levels should be < 150 mmHg systolic and 80–100 mmHg diastolic [11].

According to current knowledge, antihypertensive treatment in severe hypertension is used to prevent maternal cerebrovascular/cardiovascular complications. The focus is on prevention of cerebral haemorrhage and supplementation with i.v. magnesium is required for effective eclampsia prophylaxis [96–100].

A benefit for fetal development and therefore improvement of the baby's prognosis by drug blood pressure reduction has not yet been proven.

Patients with infertility and chronic hypertension should be treated with drugs that are indicated in pregnancy [11, 20].

The physiological blood pressure in the first half of pregnancy has to be considered when drug treatment is used to control chronic blood pressure in pregnancy (dose reduction or discontinuation of medication if necessary).

7.2 Long-term treatment with oral antihypertensive agents

If general measures do not succeed in keeping the blood pressure at $< 150/100$ mmHg, antihypertensive drug therapy must be initiated or intensified or pre-existing medication must be resumed. Potential effects on fetal development must be considered when considering the choice of antihypertensive agent (see **Table 5**).

7.3 Treatment of severe hypertensive pregnancy disorders

7.3.1 Antihypertensive treatment

Initial antihypertensive treatment of severe hypertension (blood pressure $\geq 160/110$ mmHg) should be carried out under CTG monitoring, as a pronounced drop in blood pressure may be associated with an acute threat to the fetus. Patients should be closely monitored and regular blood pressure checks (at least once every 10–15 min) are necessary [15, 104]. The diastolic target blood pressure should not fall below 80–100 mmHg [11, 97, 104].

A severe hypertensive pregnancy disorder is present if hypertension cannot be successfully treated with oral hypertensives (s. 6.2) or a hypertensive emergency exists. A hypertensive emergency (prolonged acute severe hypertension for over 15 min with

vital hazards caused by organ damage, e.g. hypertensive encephalopathy with blurred vision, dizziness, severe headache, decreased consciousness, neurological deficits or pulmonary oedema) requires immediate drug treatment to reduce blood pressure [71, 104, 106, 107].

The medication available in Germany, nifedipine and urapidil, can both be used without preference for the initial treatment of severe hypertension [103, 108]. However, the off-label use of nifedipine and urapidil must be observed (see **Table 6**).

Dihydralazine is approved for antihypertensive therapy during pregnancy; however it has significantly more maternal side-effects than urapidil (especially severe headaches, reflex tachycardia), which can complicate the differential diagnosis in relation to the progression of preeclampsia [108, 109].

According to a meta-analysis, dihydralazine is associated with a higher rate of maternal side-effects (including severe hypotension) and perinatal complications (including placental abruption) compared to nifedipine, without a definitive assessment being possible according to the authors [110, 111].

To reduce the risk of sudden severe hypotension with subsequent risk to the fetus, up to 500 ml of intravenous electrolyte solution should be infused prior to the administration of dihydralazine [11].

7.3.2 Anticonvulsive treatment

The treatment of choice for the prevention of eclampsia is the intravenous administration of magnesium sulphate which is indicated in severe preeclampsia, especially where there are central nervous system symptoms, as a significant reduction in the risk if eclampsia can be achieved with magnesium sulphate [112–116]. The effectiveness of this seizure prophylaxis is less clear for mild preeclampsia, but is under discussion after a large-scale study with > 10000 pregnancy women with mild and also with severe preeclampsia showed a halving of the eclampsia risk with magnesium sulphate (1 g/h) compared to placebo [99, 117, 118]. Magnesium sulphate is also the drug of first choice in manifest eclampsia [112–116]. Superiority over phenytoin as well as diazepam in the prevention of re-convulsions and in terms of neonatal results has also been shown [112, 114, 115, 119]. Intravenous therapy (see **Table 6**) is with a loading dose of 4–6 g of diluted magnesium sulphate administered over 15–20 min via syringe driver or short infusion and continued with a maintenance dose of 1 g/h [120].

Table 6 Acute drug treatment: Substances and doses [1, 11, 101, 102, 104, 107].

	Drug		Dosage
Antihypertensive therapy	Nifedipine	oral	initially 5 mg oral, repeat after 20 min if necessary
	Urapidil	i.v.	initially 6.25 slow i.v. (over 2 min) followed by 3–24 mg/h (via syringe driver)
	Dihydralazine	i.v.	initially 5 mg i.v. (over 2 min) followed by 2–20 mg/h (via syringe driver) or 5 mg every 20 min
With pulmonary oedema/Heart failure			
Anticonvulsive treatment	Furosemide	i.v.	10–20 mg Repeat with increased dose if necessary after 500 ml volume support
	Magnesium	i.v.	initially 4–6 g (in 50 ml) over 15–20 min (as short infusion or via syringe driver) Maintenance dose: 1 g/h

The patient should be closely monitored and the reflex state (patellar reflex), respiratory rate (should not fall below 12 breaths/min) and renal function (at least 100 ml excretion within 4 hours) generally suffice here. Calcium should be readily available for immediate intravenous injection as an antidote (1 vial = 10 ml of i.v. calcium gluconate 10% slowly over 3 min).

Alternatively, anticonvulsant therapy with diazepam or phenytoin can be given if transport is in the ambulance.

7.3.3 Volume expansion

Accompanying volume therapy has not shown any treatment advantages in previously conducted randomized trials [121, 122]. Sufficient oral volume intake should be maintained.

8 Indications for delivery

Delivery is the only causal therapy for pregnant women with preeclampsia. Prolongation of the pregnancy is primarily to prevent preterm birth and assumes an expected benefit for the baby. The decision to deliver is thus highly dependent on the gestational age and is usually indicated **after the 37th completed week of pregnancy** [11, 12, 72, 123].

8.1 Preeclampsia after the completed 34th to 37th week of pregnancy (34 + 0 to 36 + 6 weeks)

After the completed 34th week, every patient with severe preeclampsia should be delivered as soon as possible [8, 11]. This also applies in cases of severe fetal growth restriction < 5th percentile with concurrent pathological fetal or fetal-placental blood flow such as absent or reversed flow in the umbilical artery [124–132].

However, of lesser importance is the amount of amniotic fluid which, compared to IUGR, appears to have no isolated effect on pregnancy outcome in preeclampsia [133, 134]. Prolongation of pregnancy beyond the 37th week is not advisable in mild preeclampsia or pregnancy-induced hypertension [123].

In mild forms, the increased morbidity of a late preterm delivery should be considered beyond 34 weeks (34th to 37th week of pregnancy) [135, 136]. The mortality of "later preterm infants" is increased compared to full-term babies (3.5 to 5.5-fold). Postnatal late mortality (28 days – 12 months) is twice as high [137]. In contrast is the risk of intrauterine fetal death, which is 3/1000 pregnancies at the end of pregnancy (> 36 + 0 weeks).

The rate rises to 21/1000 in severe preeclampsia [138]. The IUFD rate is much lower (9/1000) in women with mild preeclampsia. The neonatal complication rate increases with the degree of fetal growth restriction (especially < 10th percentile). Women with severe preeclampsia especially have growth retarded infants

(> 12% compared to healthy women). Significant fetal weight reduction is not observed in mild preeclampsia [139].

8.2 Preeclampsia after the completed 24th to 34th week of pregnancy (24 + 0 to 33 + 6 weeks)

Patient care should take place in a **perinatal centre**. A **primary conservative approach** is recommended because there are hardly any serious effects on the mother, but clear benefits for the child can be expected under continuous monitoring [140–142]. A fundamentally similar approach appears justifiable for HELLP syndrome [143, 144]. Severe fetal growth restriction < 5th percentile alone does not constitute a clear indication for delivery in cases of severe preeclampsia before the 34th week as long there are no highly pathological Doppler results [127, 132, 145].

The assessment of the risk and the potential benefit of watchful waiting approach must be continuously reassessed, taking into account all maternal and fetal changes. In addition to the considerable importance of gestational age, the question of completed RDS prophylaxis plays an important role in making an individual decision.

In addition to fetal indications are the following maternal indications for delivery. In each individual case, the value of completing RDS prophylaxis should be weighed against the urgency of ending the pregnancy for a maternal indication [6, 11, 146].

- Refractory severe hypertension
- Refractory renal failure
- Cardiac decompensation
- Acute lung oedema
- Disseminated intravascular coagulation
- Persistent severe upper abdominal pain
- Newly developing serious central nervous system symptoms
- Eclampsia

8.3 Preeclampsia ≤ 24th week

Significant maternal and perinatal morbidity and mortality are to be expected [147–149]. The decision to continue the pregnancy should be made individually. The focus is on the avoidance of maternal complications.

8.4 Method of delivery

Vaginal delivery can be tried if the maternal and fetal conditions are stable as there is no increased risk to the baby with optimum monitoring. The severity and the dynamics of the disease and the chances of success of a vaginal birth (e.g. cervical ripening) should be considered when deciding on the method of delivery [151, 152].

9 Postnatal care

Cave: Postpartum HELLP syndrome (7–30%) and postpartum eclampsia (up to 28%) [68, 153].

- ▶ Continuation of intensified monitoring up to 48 hours postpartum
- ▶ In severe preeclampsia: magnesium sulphate i.v. up to 48 hours postpartum
- ▶ Blood pressure monitoring postpartum until normalisation of blood pressure; guidance on self-monitoring of blood pressure [154]
- ▶ Target blood pressure on discharge < 150/100 mmHg
- ▶ Tapered dose reduction or alteration of antihypertensive treatment

9.1 Drug treatment

- ▶ In pregnancy-associated hypertension, tapered dose reduction of antihypertensive drug treatment is usually possible within 3 days to 6 weeks postpartum in most cases.
- ▶ If blood pressure has not normalized up to 6 weeks postpartum: diagnosis and treatment as recommended by the German Hypertension Society [155, 156].

Continuation of ongoing treatment or conversion to oral medication if necessary (metoprolol, nifedipine, alpha-methyldopa) [103, 156].

9.2 Breast feeding

Discontinuation of breast feeding because of an antihypertensive drug treatment is usually not necessary with the large selection of antihypertensives which are compatible with breast feeding [103].

9.3 Counselling

A final discussion with the patient about the disease, the individual course and other consequences is essential, in the presence of her partner if possible, with the offer of meeting again, e.g. before planning/occurrence of another pregnancy [157, 158]. Referral should be made to self-help groups, e.g. Arbeitsgemeinschaft Gestose-Frauen e.V. (Women's Gestosis Working Group, www.gestose-frauen.de), Bundesverband der Frühgeborenen e.V. (Federation of Premature Babies e.V., <http://www.fruehgeborene.de>) and European Foundation for the Care of Newborn Infants (EFCNI: www.efcni.org; www.enemenemini.eu/de/Home). Use of oral contraception is possible after preeclampsia/HELLP syndrome [159].

10 Care after preeclampsia

10.1 Further diagnostics after the postpartum period

- ▶ Measurement of serum creatinine and proteinuria, including microalbuminuria, proteinuria ideally from a 24 h urine collection
- ▶ Evaluation of possible kidney damage 3 months postpartum [160–163]
- ▶ Referral to a nephrologist if there is persistent proteinuria and/or increased serum creatinine
- ▶ In severe preeclampsia – clarification of antiphospholipid syndrome/systemic lupus erythematosus [164]

10.2 Follow-up of infants

Monitoring and follow-up is based on the general guidelines. This particularly applies to growth-retarded infants and premature births. An additional examination of sensory integration disorders should be planned the first year of life and also for full-term

infants or for infants born after 34 weeks. Another additional examination is recommended in the third year of life, preferably in a socio-paediatric centre.

10.3 Future life – planning further pregnancies

- ▶ Point out to the patient the increased risk of cardiovascular disease for both mother and child [165–183]
- ▶ Inform the patient about the risk of recurrence after preeclampsia/HELLP syndrome (see above) [65, 67, 184–188]
- ▶ Diagnosis and treatment where appropriate of cardiovascular risk factors (nicotine, blood lipids, diabetes, metabolic syndrome, lifestyle changes) [167, 170, 174, 176]
- ▶ Consultation (internist, gynaecologist) before planned pregnancy (including prevention) [162, 189, 190]

11 Special features of HELLP syndrome

11.1 Diagnosis

The diagnosis is made by laboratory tests with evidence of the triad of haemolysis, elevated liver enzymes and thrombocytopenia [191]:

(H): haemolysis (Haptoglobin ↓)

(EL): elevated liver enzymes (Transaminases ↑ [GOT, GPT])

(LP): low platelets (Thrombocyte count ↓ [< 100 G/l])

The following clinical symptoms can occur simultaneously [164, 192]:

- ▶ Right-sided upper abdominal pain/epigastric pain: > 90%
- ▶ Hypertension: 80%
- ▶ Proteinuria: up to 15%
- ▶ Both proteinuria and hypertension may be missing in HELPP syndrome (HELLP syndrome without preeclampsia)
- ▶ Possible neurological symptoms

11.1.1 Laboratory parameters

Clinical chemistry tests should initially be repeated at 6–8 hourly intervals, especially when they are only discrete at the start of the disorder or are not completely altered in terms of the classic triad [164, 193].

Evidence of haemolysis is best performed by determining haptoglobin (decreased in 95–97% of patients, the most sensitive parameters of haemolysis) [164, 193–199].

Further haemolysis parameters [164]:

- ▶ Detection of fragmentocytes in a peripheral blood smear (54–86%)
- ▶ Total bilirubin raised (47–62%)

LDH is not a haemolysis-specific parameter in HELLP syndrome [164, 192, 196, 197]; however it correlates with the severity of the disease [200].

An increase in C-reactive protein is detected in up to 62% of cases of HELLP syndrome and is not a result of infection [199, 201–205].

11.1.2 Pain symptoms

Right-sided upper abdominal pain/epigastric pain may occur with HELLP syndrome, even before laboratory evidence of HELLP syndrome. Pain may also be retrosternal. If right upper quadrant abdominal pain or retrosternal pain occurs after the 18th week, HELLP syndrome must be excluded in the differential diagnosis or confirmed.

11.1.3 Clinical course

Fluctuating in spurts, with possible remissions in up to 46% of cases or exacerbation within hours [143], in particular the development of coagulopathy (DIG) occurs more often than with preeclampsia (no heparin administration, haemostasis correction with fresh frozen plasma if necessary) [153, 164, 193].

11.1.4 Indications for delivery

Fetal indications for delivery The indications for delivery of a fetal perspective correspond with the general indications for delivery (see, Chap. 8) using the recognised diagnostic methods (Doppler sonography, biometrics, CTG, fetal heart rate variability) taking into account the gestational age.

Maternal indications for delivery The indications for delivery from a maternal perspective are based on the maternal condition. With the aim of reducing neonatal morbidity and mortality, a conservative approach – preferably in a **perinatal centre** [206] – is recommended at a gestational age of below 34 weeks, at least until clinical stabilization [19, 141, 143, 164, 206–210]. The indications for immediate ending of a pregnancy are based on the maternal and fetal indications of severe preeclampsia. A pregnancy should be ended especially if there is associated, severe or treatment-refractory preeclampsia, disseminated intravascular coagulation (DIC), severe renal insufficiency, congestive heart failure or pulmonary oedema [19, 143, 164, 206, 208].

Logistical requirements for prolongation of a pregnancy are the intensive monitoring of mother and child, the availability of frequent laboratory controls, the possibility of immediate ending of the pregnancy by Caesarean section and close interdisciplinary cooperation with neonatology and anaesthesiology. The therapeutic approach to stabilize the maternal situation is generally based on the criteria described for severe preeclampsia [193, 208, 210].

If HELLP syndrome is confirmed, pregnancy should be ended after 34 weeks of pregnancy. A vaginal delivery can be tried if the maternal and fetal conditions are stable. There is currently insufficient clinical experience for induction of labour (e.g. with prostaglandins) in HELLP syndrome. It should be noted that when HELLP syndrome occurs, the cervix is often unripe and the duration and success of labour induction are therefore unforeseeable [193, 208, 210].

Induction of labour is generally possible if all the above criteria are taken into account.

11.1.5 Special features of treatment

Glucocorticoids are increasingly used as part of the prolongation of pregnancy according to the following treatment regimens [206, 211–214]:

- ▶ Methylprednisolone (Urbason®) 32 mg/day i.v. (or increased dose if necessary)
- ▶ Dexamethasone 2–3 × 10 mg/day i.v.

Cave: Methylprednisolone does not readily cross the placenta, therefore additional lung ripening therapy is necessary (e.g., betamethasone) [197, 215–217].

In the majority of studies, glucocorticoids used ante- or postpartum resulted in clinical and biochemical remission of differing durations (the majority of studies used dexamethasone) [164, 211, 213, 214, 219–232].

In contrast, a placebo-controlled double-blind study found that glucocorticoids had no effect [233]. According to a Cochrane analysis, there is currently insufficient data available regarding a benefit for the fetal/maternal outcome and the uncritical use of corticosteroids is not recommended [234].

11.1.6 Follow-up after HELLP syndrome

HELLP syndrome is not a contraindication for further pregnancies [159, 164, 189]. Use of oral contraception is possible. The recurrence risk is increased compared to women after uncomplicated pregnancies and is between 2 and 19% [67, 159, 164, 187, 188, 235, 236]. Early HELLP syndrome (< 32 weeks) appears to be accompanied by an increased risk of a recurrence of early HELLP

syndrome [235]. According to a Germany-wide study, the risk of HELLP syndrome after HELLP syndrome is 12.8%; the risk of other hypertensive disorders during the pregnancy is 30.4% [67]. In subsequent pregnancies, the administration of low-dose aspirin is indicated (100 mg/day) from early pregnancy. Patients should be monitored according to the criteria of a high-risk pregnancy after HELLP syndrome.

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