**SUMMARY**

**Background:** Hypertensive disorders of pregnancy (HDP) are among the leading causes of maternal and fetal morbidity and mortality. New guidelines and findings from clinical trials must be taken into account so that the diagnosis and treatment of HDP can be optimized.

**Methods:** Current guidelines, Cochrane reviews, metaanalyses, and randomized, controlled trials were retrieved by a search in PubMed and the Cochrane Library for reports published from 2006 to March 2009. These publications were then analyzed and evaluated for their evidence levels (EL).

**Results and Conclusions:** Aside from hypertension and proteinuria, the definition of preeclampsia (PE) should also take organ dysfunction into account. Important aspects of antenatal care include the following: the early recognition of risk factors, measurement of the uterine arteries in the 1st and 2nd trimesters with Doppler ultrasonography (A diagnostic tool which is now well established), prophylactic oral administration of 100 mg of acetylsalicylic acid daily from the beginning of pregnancy, particularly in high-risk patients (EL I++), and appropriate measurement of blood pressure and urinary protein. Patients should be hospitalized whenever indicated. Therapeutic goals are adequate treatment of hypertension, as well as seizure prophylaxis with magnesium sulphate in severe preeclampsia to prevent maternal cerebrovascular complications (EL I++). If delivery is indicated, it should be performed, regardless of the gestational age (EL IV). Careful monitoring during the puerperium and a general medical review six weeks after delivery are essential. Women with preeclampsia have a significantly elevated long-term risk of developing cardiovascular diseases in later life (EL I++).

**Key words:** pregnancy, maternal mortality, obstetrics, prevention, treatment

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**Worldwide,** hypertonensive disorders of pregnancy (HDP) account for more than 50 000 maternal deaths per year. With an incidence of 12% to 18%, HDP are the second commonest cause of antenatal and postnatal deaths in industrialized countries, as well as being implicated in 20% to 25% of perinatal mortality (1, e1). Of greatest importance is preeclampsia, characterized by hypertension, proteinuria and/or organ dysfunction, which complicates between 2% and 5% of all pregnancies. (1). Severe consequences of preeclampsia include eclampsia with tonic-clonic seizures (0.03% to 0.1% of all pregnancies) (2) as well as HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count) with right upper quadrant pain as the cardinal clinical symptom (0.17% to 0.8% of all live births) (e2).

The overwhelming weight of new knowledge relating to HDP created a need for a new appraisal of the literature, with the goal of improving diagnosis and treatment.

A literature review was undertaken including Association of the Scientific Medical Societies in Germany (AWMF) guideline 015/018 (3), randomized controlled trials and meta-analyses extracted from PubMed and Cochrane reviews. This included consideration of evidence levels and covered the period 2006–03/2009.

**Clinical presentations**

**Hypertension**

The criteria for diagnosis of HDP is as follows: two readings, showing a systolic blood pressure of ≥140mm Hg and/or a diastolic blood pressure of ≥90mm Hg, taken over a period of 4 to 6 hours after 20 weeks gestation, in a woman who was normotensive prior to pregnancy (4, e3). Contrary to previous findings, the Korotkov phase V (disappearance of the blood flow murmur) is the correct means of measuring diastolic blood pressure in pregnancy. If the diastolic pressure according to this means is zero (up to 15%), then the Korotkov sound IV (the quietening of the blood flow murmur) should be used (evidence level [EL] I+) (4, e3). If “white-coat” hypertension is suspected (10% to 15%), or in cases of
One-off elevated blood pressure readings, either a 24 hour blood pressure reading should be obtained or self-monitoring undertaken at home (3). The use of the sphygmomanometer remains the gold standard for measuring blood pressure (4, e3). Oscillometric devices for measuring blood pressure has, however, been validated recently in pregnancy.

It should be noted that in 10% to 15% of cases of eclampsia and 12% to 18% of HELLP syndrome the blood pressure is normal (EL III) (e4).

Proteinuria
A urinary total protein of ≥300mg in 24 hours is considered pathological (1). Urine dipstick testing is an integral component of antenatal care. If a dipstick indicates ≥ 1+ of protein, a 24 hour collection should be assayed (1, 3). When compared with a 24 hour urine collection, the sensitivity of dipstick testing for proteinuria is only 61%, with a specificity of 97% (6). The role of the protein:creatinine ratio is controversial (7) and therefore the 24 hour urine collection remains the gold standard investigation (EL II) (3).

All pregnant women who develop de novo hypertension should have a 24 hour urine collection for protein (EL II+) (6). The severity of proteinuria does not correlate with maternal morbidity, and taken in isolation should not be considered an indication for delivery (7). In up to 34% (e5) of eclampsia and 5% to 15% of HELLP syndrome (7, e4) there may be no proteinuria.

Classification
The population of hypertensive pregnant women can be subdivided into the following:

- Gestational hypertension
- Preeclampsia
- Chronic hypertension
- Superimposed preeclampsia.

Up to 22% of chronic hypertensives may develop superimposed preeclampsia with impaired prognostic (8), and up to 50% of gestational hypertensives can progress to preeclampsia (5, e6). In these patients increased antenatal care is mandatory.

Defining preeclampsia by multi organ dysfunction
In addition to the standard definition, preeclampsia can be diagnosed when, in the absence of proteinuria, one or more of the following are present:

- Deterioration of renal function: serum creatinine greater than 0.9g/L or oliguria <500mL/day
- Liver involvement: severe epigastric pain and/or elevated transaminases
- Pulmonary edema (severe preeclampsia)
- Hematological involvement: thrombocytopenia, hemolysis, disseminated intravascular coagulation (DIC)
- Neurological involvement: severe headache, persistent visual disturbance, hyperreflexia.
- Intrauterine growth restriction.

These symptoms/complications reflect the most common systemic dysfunctions of severe preeclampsia. Severe preeclampsia is diagnosed in the presence of blood pressure ≥160/110mm Hg and/or proteinuria ≥5g/24 hours (4, e3, e7).

Risk factors
Pre-existing cardiovascular, renal or autoimmune disease should have already been diagnosed preconceptually and appropriate medications for a planned pregnancy prescribed. Of utmost clinical importance is the assessment of risk factors at the antenatal booking visit.

Most pertinent are:

- HDP in previous pregnancies
- Body mass index >30
- Pre-existing diabetes
- Renal disease or chronic hypertension
- Maternal age >40 years
- Family history (9).

The relevance of inherited thrombophilia in the development of preeclampsia is unclear. Routine antenatal thrombophilia screening is not recommended. According to a recent US guideline, anti-phospholipid antibodies should be determined in patients with a previous history of severe or recurrent preeclampsia/HELLP syndrome < 34 weeks' gestation or intrauterine growth restriction (IUGR) (EL II-) (e8). A recent consensus paper recommends investigating inherited and acquired thrombophilias in these cases (EL IV) (e9).

When counselling women the risk of recurrence of preeclampsia and especially HELLP syndrome is important. An early cohort study (10) gives the absolute risk of preeclampsia recurring as 14.7% (EL II++). The recurrence risk of preeclampsia depends on the time of manifestation of preeclampsia in previous pregnancies (≤28 weeks, ≥37 weeks). Worldwide the risk for a recurrence of HELLP syndrome is between 2.1% and 19% (11). One German study gave it as 12.8% (EL III) (e10).

The most frequent pregnancy-associated risk factors for developing preeclampsia are: “bilateral notch” (diagnosed by uterine artery Doppler), multiple pregnancies and gestational diabetes mellitus.

Predictive testing
Despite the analysis of more than 100 methods, there is still no reliable and certain test for predicting HDP (9). The most useful method is uterine artery Doppler ultrasonography. If abnormal uterine flow (specifically the bilateral notch or high resistance index) is present between weeks 22 and 24, there is a 60% risk of developing preeclampsia and/or IUGR later in pregnancy. The predictive value of Doppler ultrasound is particularly high for the development of severe preeclampsia before 34 weeks and for preeclampsia with IUGR (e11). However, routine screening of all pregnant women was not recommended (e12); uterine artery Doppler is beneficial as a
test in pregnant women who are at high risk for preeclampsia (9). According to recent meta-analyses an increased pulsatility index with notching (after the 16th week) was the best predictor of preeclampsia in women with established risk factors (positive likelihood ratio: 21.0). This test should therefore be used in clinical practice (EL I-) (13).

Research is ongoing to determine the relevance of combinations of maternal risk factors, early biochemical markers (such as placental protein 13) as well as Doppler results from the first and second trimester.

Prevention
Meta-analyses and Cochrane reviews suggest no reduction in the rate of preeclampsia with the following therapies: oral magnesium, the antioxidant vitamins C and E, fish-oils and oral calcium (EL I++) (9, e13–e16). Nor is there any reduction in the risk of preeclampsia in subsequent pregnancies (EL I+++ to IV) (14, e17–e18). The oral administration of calcium supplements (at least 1g per day) may significantly reduce the risk of preeclampsia particularly in high-risk patients with poor dietary calcium intake (EL I-) (e19).

According to a recent Cochrane review, oral aspirin 75 to 150 mg per day, compared with placebo (before the 16th week), reduces the rate of preeclampsia by 17%, neonatal mortality by 14% (EL I++) (15); a meta-analysis makes this 10% and 9% respectively ( EL I++) (16). Low-dose aspirin inhibits increased thromboxane production, induced by preeclampsia, but do not appear to have a significant effect on vascular prostacyclin production.

According to the above-mentioned Cochrane review, pregnancies with pre-existing risk factors (particularly severe preeclampsia in previous pregnancies) benefit most from aspirin (15). Notwithstanding controversial studies, aspirin is not recommended after 23 weeks if a pathological Doppler flow is present (9). Aspirin is not recommended in cases of manifest preeclampsia or gestational hypertension (3).

In one recent randomized controlled trial looking at gravid women with risk factors for preeclampsia (previous preeclampsia/IUGR), the use of prophylactic low molecular weight heparin (dalteparin, weight adjusted, 4000–6000 IU/day, on or before the 16th to 36th week) lowered the incidence of preeclampsia from 23.6% to 5.5% (EL I+) (17).

Indications for inpatient review
- Hypertension (systolic ≥160, diastolic ≥100mm Hg)
- Manifest pre-eclampsia (see definitions)
- Proteinuria and profound weight gain in the 3rd trimester (≥1kg per week).
- Impending pre-eclampsia. Prodromal symptoms include severe headache/epigastric pain, neurological or visual symptoms
- Clinical suspicion of HELLP syndrome: persistent epigastric pain.
- Hypertension or proteinuria in the presence of other risk factors such as:
  - Pre-existing maternal morbidity (for example diabetes)
  - Multiple pregnancy
  - Prematurity (<34 weeks)
  - Poor maternal compliance with outpatient surveillance
- Indications of fetal compromise:
  - Suspicious / pathological CTG or
  - Suspicious Doppler sonography (specifically absent or reversed end-diastolic flow in the umbilical arteries)
  - Intrauterine growth restriction (IUGR) (<10th centile)

Indications for inpatient review
Delayed referral for specialist treatment is an area of increasing medico-legal activity. Specific indications for inpatient review/monitoring have been published recently (EL IV) (3) (Box 1)

Treatment
The initiation of medical treatment should take place in hospitals (3). Antihypertensives are indicated at a blood pressure of ≥170mm Hg systolic and/or a diastolic pressure of ≥110 mm Hg. In the case of pre-existing hypertension or other causes for superimposed hypertension (renovascular disease or diabetes for example) a threshold of ≥160/100 mm Hg is appropriate ( EL IV) (3, e7). These measures are consistent with national and international guidelines (5, e7). A clinically useful point to note is that a rise in systolic blood pressure to ≥160 mm Hg is more relevant for the development of stroke in preeclamptic women than a rise in diastolic pressure to ≥105 mm Hg. 80% of patients with stroke present...
with a diastolic blood pressure of less than 105mm Hg (e20). Of those rare patients whose stroke was primarily associated with pregnancy, 25% to 45% were in cases of preeclampsia (e21).

The aim of anti-hypertensive therapy is the prevention of maternal cerebrovascular complications. A reduction in blood pressure is of little benefit to the fetus. To the contrary, results of meta-analyses suggest that in cases of mild hypertension (<170/110 mm Hg) long-acting oral antihypertensive agents such as beta-blockers may lead to IUGR and reduced birth weights (EL I++) (18, e22).

Alpha methyl-dopa remains the first line anti-hypertensive agent for long-term control in pregnancy in Germany. There are restricted indications for Nifedipine and selective beta-1-receptor blockers (3). ACE inhibitors are contraindicated (3, e23).

According to meta-analyses and Cochrane reviews (19, e24) the previously favored acute therapy of intravenous hydralazine is associated with maternal side effects and an increased rate of fetal complications (amongst others placental abruption) (EL I++). Oral nifedipine or intravenous urapidil are therefore recommended although this constitutes an off-label use of these preparations (3). Abrupt or deep drops in blood pressure should be avoided. Target blood pressure should be 140 to 150 mm Hg systolic and not less than 90 mm Hg diastolic (EL IV) (3, e25).

Following a Cochrane review and meta-analysis the first line medication for prophylaxis and treatment of eclamptic convulsions is intravenous magnesium sulphate (EL I++) (20, e26). The application of intravenous magnesium sulphate in less severe preeclampsia is the subject of current discussion. In the MAGPIE trial the incidence of preeclampsia compared with placebo was reduced by the administration of magnesium sulphate from 1.9% to 0.8% (EL I+) (21). A comprehensive retrospective study showed no adverse effects (in particular severe hypotension) from the simultaneous administration of nifedipine and magnesium sulphate (EL III) (e27). Previously advocated plasma-expansion treatment in preeclampsia with hydroxy-ethyl starch (grounded in theoretical rheological principles) has been shown to have no management benefits (e28). Furthermore, a randomized control trial did not show any improvement in neonatal outcomes (EL I+) (22).

In preeclampsia fluid restriction of 80 to 100 mL per hour is mandatory (due to the risk of pulmonary edema).

**Special considerations for HELLP syndrome**

According to the current literature the treatment and indications for delivery in HELLP syndrome are the same as in severe preeclampsia (3). In addition to the routine application of betamethasone for fetal lung maturation (indicated <34 weeks) there is evidence from randomized controlled trials, that glucocorticoids which do not cross the placenta (such as prednisolone or dexamethazone) induce clinical and biochemical remission of HELLP syndrome and prolong pregnancy (EL I+) (11). A Cochrane review of the evidence, however, suggests there are, as yet, insufficient data to be certain (e29).

**Obstetric interventions and indications for delivery**

To date delivery is the only definite curative treatment of preeclampsia (3). In cases of mild, therapeutically well-controlled preeclampsia without evidence of IUGR or suspicious Doppler findings, an induction of labour at completed 37 weeks could be considered. In severe preeclampsia/HELLP syndrome immediate delivery is required ≥34 weeks. Birth should only take place once the maternal condition has been stabilized (3). Patients between 24 and 33+6 weeks should be managed expectantly in a tertiary perinatal center in order to reduce neonatal morbidity and mortality. There should be an assessment of the severity and dynamics of the disease, of the fetal organ’s maturity and condition as well as stabilization of the mother.

**BOX 2**

**Indications for immediate delivery**

- Fetal indications, e.g., hypoxia (CTG), reversed end diastolic flow
- Maternal indications (apply also for HELLP syndrome):
  - After an eclamptic fit
  - Severe therapy-refractory hypertension
  - Therapy-refractory renal failure
  - Pulmonary edema
  - Signs of disseminated intravascular coagulation (DIC) (progressive thrombocytopenia, rapid increase in d-dimer)
  - Persistent, severe epigastric pain
  - Impending eclampsia: manifest neurological signs/symptoms
  - Other maternal/fetal complications, e.g., placental abruption, suspicion of intracerebral hemorrhage, liver hematoma/rupture.
There should be facility for emergency caesarean section around the clock (EL IV) (3).

In order to avoid maternal and fetal complications, absolute indications for delivery regardless of gestational age are necessary (Box 2) (EL IV) (3, 23). The results of 11 observational studies looking at severe preeclampsia showed a prolongation of pregnancy in 48.5% to 62.7% of cases of an average duration of 10.4 days. The rate of severe maternal complications was 25.1% to 28.4% (23). In severe preeclampsia the decision to continue a pregnancy before the 24th week is at the clinician’s individual discretion, but should be undertaken only after an exhaustive discussion with the woman. It is worth remembering that the rate of maternal complications is as high as 65% and the average perinatal mortality is, on average, 82% (24).

Mode of delivery
If the condition of mother and fetus is stable a vaginal birth with close medical supervision could be considered. In severe preeclampsia—dependent on the urgency of delivery and favorability of the cervix—induction of labour is an option (success rate in pregnancies remote from term on average 54%) (e30). In all other cases caesarean section is indicated (Box 2).

Puerperium
The rate of post-partum HELLP syndrome lies between 7% and 30% (11). Postpartum eclampsia occurs in as many as 28% of cases (2). Close maternal medical observation is recommended for at least 48 hours after birth. If blood pressure is difficult to manage, consultation of an experienced internist is required. Target blood pressure on discharge should be less than 150/100 mm Hg (3). Weaning is not necessary in most cases. Follow-up after the puerperium should be with a specialist or general practitioner and aimed at the timely detection of hypertension, renal disease, or cardiovascular complications.

Long-term prognosis
Women with severe preeclampsia have a significantly increased risk of developing cardiovascular disease in later life. According to a recent meta-analysis (EL I+) (25) the following relative risks (RR) are given:

- Hypertension—RR 3.7 (average follow up 14 years)
- Ischaemic heart disease—RR 2.16 (11.7 years)
- Stroke—RR 1.81 (10.4 years)
- Maternal death—RR 1.49 (14.5 years).

Referral of affected mothers to their general practitioners for lifestyle changes, risk assessment and screening for cardiovascular diseases, would be a valuable goal for future screening programs. The implications of severe maternal preeclampsia for the future health of the infant is the subject of current, intensive research.

Conflict of interest statement
The authors declare no conflicts of interest according to the guidelines of the International Committee of Medical Journal Editors.

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