

# DSOG Guideline Bulletin: Preeclampsia and hypertension

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## Abstract

Approximately 10% of pregnancies in Denmark are complicated by hypertensive disorders of pregnancy (HDPs). The 'Preeclampsia and hypertension' guideline includes the classification, diagnosis, surveillance, and management of HDPs. This revision focuses on the diagnostic criteria for preeclampsia, preeclampsia-specific biomarkers for short-term prediction of disease, blood pressure thresholds and targets, and postpartum management. We reviewed the available literature in PubMed published since the last guideline revision in 2018, as well as the guidelines of other obstetric societies. HDPs are classified based on the timing of onset, i.e. before or after 20 weeks' gestation, and whether proteinuria (albumin-creatinine ratio (ACR)  $\geq 200$  mg/g) or other signs of organ dysfunction are present. We recommend against using the terms mild-moderate or severe preeclampsia in clinical practice. If possible, new-onset hypertension should be confirmed by home blood pressure monitoring. Women with HDPs should be monitored regularly, depending on diagnosis and clinical presentation. If blood pressure is  $\geq 140$  mmHg systolic and/or  $\geq 90$  mmHg diastolic, antihypertensive treatment with oral labetalol, nifedipine or methyldopa should be offered and titrated until reaching a target blood pressure of  $<135/85$  mmHg. Magnesium sulphate treatment is recommended in eclampsia or signs of imminent eclampsia. Delivery should be offered to women with preeclampsia at 37-38 weeks' gestation or earlier, regardless of gestational age, in preeclampsia with signs of serious, progressive disease which may include uncontrollable blood pressure, eclampsia, pulmonary oedema, progressive deterioration of biochemical parameters, or severe foetal compromise. Before operative delivery, blood pressure should be stable below 150/100 mmHg. Women with chronic or gestational hypertension should be offered induction at 38-40 weeks' gestation. Antihypertensive treatment should be continued at least one week after delivery. Lifelong yearly blood pressure monitoring is recommended to all women with HDPs.

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## Introduction

Hypertensive disorders of pregnancy (HDPs) complicate around 10% of pregnancies in Denmark, including 3-4% with preeclampsia. The aetiology behind preeclampsia is incompletely understood, although endothelial dysfunction due to placental hypoxia or systemic inflammation seems to be an important part of the aetiology (1). HDPs exist on a wide clinical spectrum from the asymptomatic woman with slightly increased blood pressure (BP) after term to early-onset, rapidly evolving preeclampsia requiring iatrogenic delivery of an extremely premature, growth restricted foetus. Although delivery is the only curative treatment of preeclampsia, controlling BP with antihypertensive agents and preventing seizures with magnesium sulphate (MgSO<sub>4</sub>) lower the risk of serious complications.

## Objectives

The objective of this paper is to describe the updated recommendations for the classification and management of HDPs in pregnancy, during delivery, and in the postpartum period.

## Methods

We searched PubMed for literature published primarily from 2018 to December 2023. The clinical guidelines of other obstetric societies including the International Society for the Study of Hypertension in Pregnancy (ISSHP) were also reviewed. Because of the scope of the guideline, it is not based on a systematic literature review. We used the OCEBM system (2) for assessing levels of evidence and strengths of clinical recommendations.

The guideline (3) was approved at the Danish Society of Obstetricians and Gynaecologists annual meeting on January 19, 2024 and was

published online (<https://www.dsog.dk/obstetrik>) on February 18, 2024.

## Results

### Classification of hypertensive disorders of pregnancy

Correct classification of HDPs is essential for optimal monitoring and care as these disorders carry different risk profiles. Hypertension is defined as stated in Table 1; HDPs are classified according to timing of onset and whether there are signs of organ dysfunction as shown in Table 2. Adjustments have been made to the diagnostic criteria for preeclampsia with this revision, mainly regarding proteinuria. While the types of organ dysfunction required for a diagnosis of preeclampsia resembles those of the ISSHP (4), the biochemical thresholds for preeclampsia are similar to those of the American College of Obstetricians and Gynecologists (ACOG) (5). Furthermore, we do not recommend classifying preeclampsia into mild or severe disease in pregnancy as women with preeclampsia regardless of severity may deteriorate rapidly and without warning (4). We have, however, chosen to define 'signs of severe disease' similar to the ACOG's 'severe features' primarily for use after delivery to inform management of future pregnancies (5).

### Blood pressure measurement and whitecoat hypertension

A standardised procedure for BP measurements helps to limit physiological variation. We recommend that BP measurements are performed after five minutes' rest in a quiet room, sitting in a chair with both feet resting on the ground, shoulders relaxed, and the cuff placed at heart level. At least two measurements should be performed if BP is elevated (6,7).

White-coat hypertension is a well-described phenomenon that impacts one out of three pregnant women with hypertension (8). If possible, increased clinic BP should be confirmed by home measurements. The cutoff for hypertension at home is the same as in the clinic, i.e.  $\geq 140/90$  mmHg (9). Pregnant women with white-coat hypertension are at increased risk of hypertension and preeclampsia, and should therefore measure BP at home regularly during pregnancy, i.e. before antenatal visits (4,10).

### **Proteinuria**

Traditionally, excretion of  $\geq 300$  mg protein per day has been categorized as significant proteinuria. However, 24-hour urine collection in women with preeclampsia is obsolete. Urinary dipstick testing has been broadly used to identify proteinuria. These dipstick tests are unspecific with a high risk of false positive results.

In nephrology, proteinuria is quantified using urine albumin/creatinine ratio (UACR) which can be used in pregnancy. Urinary excretion of protein is increased during pregnancy and despite uncertainty regarding optimal cut-off levels, a threshold of UACR  $\geq 200$  mg/g was set after clinical consensus in collaboration with Danish nephrologists.

We recommend using dipstick testing for screening and that  $\geq +2$  protein requires quantitative determination with UACR (4). When significant proteinuria is identified after week 20 of pregnancy, no repeat testing is necessary.

### **Biomarkers as a diagnostic aid**

Predicting preeclampsia development and severity poses a great challenge in clinical practice. Changes in circulating angiogenic factors, i.e. soluble Fms-like tyrosine kinase (sFlt-1) and placental growth factor (PlGF), seem to occur in the presence of placental

hypoxia, which may precede preeclampsia (11). Because these changes often occur weeks before clinical debut of preeclampsia, angiogenic markers are promising for prediction, especially for ruling out the development of preeclampsia in women with signs of preterm preeclampsia (12). The optimal cut-off in clinical practice is debated. Studies indicate that incorporating PlGF into clinical practice may decrease the risk of preeclampsia with severe complications (13). We conclude that angiogenic factors can be used as an aid to predict both the development of preeclampsia and of preeclampsia with signs of severe disease.

### **Prevention of preeclampsia**

Guidance regarding the use of aspirin for preeclampsia prevention is provided in a different guideline (14). Therefore, this guideline focuses on other drugs with possible preventive effects. We found no compelling evidence that metformin, statins, or vitamin D supplementation is effective as preeclampsia prevention (15–17). In women with calcium deficiency, calcium supplementation seems to lower the risk of preeclampsia development (RR 0.49, 95% CI 0.36–0.66) (18). Although the effect may be overestimated because of publication bias, we recommend women with calcium deficiency to take oral calcium supplementation. Universal screening for calcium deficiency is not recommended.

### **Management of hypertension and preeclampsia in pregnancy**

Women with preeclampsia or BP  $\geq 150/100$  mmHg should be assessed in hospital to evaluate which cases are suitable for outpatient care. Outpatient care can be done by home monitoring or visits in obstetric clinics with comparable maternal and neonatal outcomes (19–21).

Women with preeclampsia should be offered induction at 37-38 weeks' gestation, provided the patient is well and BP is stable (<140/90 mmHg) (22). Delivery is indicated sooner, regardless of gestational age, in preeclampsia with signs of serious, progressive disease which may include uncontrollable BP, eclampsia, pulmonary oedema, progressive deterioration of biochemical parameters, or severe foetal compromise (4). The timing of delivery in preeclampsia should not solely depend on the amount of proteinuria or its increase (4). Women with chronic or gestational hypertension should be offered induction at 38-40 weeks' gestation (4,23).

### **Antihypertensive treatment**

Antihypertensive treatment during pregnancy is initiated when BP  $\geq$ 140/90 mmHg, with the treatment objective (target) being a gradual reduction to <135/85 mmHg. This is in accordance with revised recommendations from ISSHP and NICE (4,24). Treatment of moderate hypertension in pregnancy reduces the risk of severe hypertension by approximately 50% (25). Additionally, the risk of preeclampsia and iatrogenic preterm delivery seems to be reduced (23).

Labetalol, methyldopa, and nifedipine are generally considered equivalent first-line treatments for moderate hypertension during pregnancy (4,5,26). In pregnancies complicated by pregestational diabetes, labetalol should not be the first choice due to an elevated risk of hypoglycemia.

There has been a general concern regarding the potential compromise of foetal growth associated with antihypertensive treatment. However, there is no evidence that antihypertensive treatment increases the risk of growth restriction (23,25).

### **Magnesium sulphate (MgSO<sub>4</sub>) treatment**

Since the Collaborative Eclampsia Trial (27) established the effectiveness of MgSO<sub>4</sub> it has been considered the drug of choice by most international obstetric societies for prophylaxis and treatment of eclampsia (4,5). Although the mode of action is only partially elucidated, it stabilizes the neuronal membrane potential and dilates vessels (28,29).

We recommend administering a bolus of 5g intravenously in 5 minutes followed by an infusion with 1g/hour. After reviewing the literature, the new Swedish guideline (26) confirmed that 24 hours is the optimal duration of the infusion period. We recommend monitoring potential toxic side effects of MgSO<sub>4</sub> during treatment by monitoring diuresis, peripheral reflexes and respiratory rate every two hours.

### **Postpartum management**

Antihypertensive medication given in pregnancy should be continued at the same dosage after delivery, unless BP <110/70 mmHg and the patient feels uncomfortable due to low BP. BP often decreases the first days after delivery only to rise and peak on days 3-6 postpartum. Tight control of BP in the immediate postpartum period may decrease the frequency of hypertension later in life (30,31). Slow tapering of antihypertensives may be initiated five to seven days postpartum when BP is stable <135/85 mmHg. In the postpartum period, Enalapril and Captopril are among first-line antihypertensive drugs, as they are considered safe to use during breastfeeding.

NSAIDs may be used for pain relief in women with preeclampsia, unless creatinine is abnormal, or platelets are low (32).

Women with HDPs should have yearly BP measurements because of their increased risk of cardiovascular disease later in life.

Women with preeclampsia with signs of severe disease should receive information

regarding prevention with low-dose aspirin in a future pregnancy.

### Conclusions

The updated guideline provides guidance regarding the diagnosis, monitoring, and management of HDPs in pregnancy and postpartum. We recommend confirming new-onset hypertension using home BP measurements, and that dipstick testing for proteinuria is

used as a screening test to determine the need for a diagnostic quantitative test (UACR). Oral antihypertensive treatment should be initiated at BP  $\geq$ 140/90 mmHg and continued until at least one week postpartum, where slow tapering of antihypertensives can be initiated when BP is stable  $<$ 135/85 mmHg. Women with HDPs should be informed of the increased risk of cardiovascular disease later in life.

**TABLE OF SUMMARY OF EVIDENCE**

<b>Summary of evidence</b>	<b>Level of evidence</b>
Standardized blood pressure measurement affects the measured value	2b
Urine dipstick testing is non-specific for assessing proteinuria.	2a
PIGF-based diagnostics are suitable for predicting the development of preeclampsia among women suspected of preeclampsia, especially before GA 37	2a
PIGF-based diagnostics can help predict preeclampsia with signs of severe disease among pregnant women suspected of or diagnosed with preeclampsia before GA 37	2b
PIGF-based diagnostics may reduce the risk of serious complications in pregnant woman with symptoms of preterm preeclampsia without increasing the rate of neonatal complications	2b
Calcium supplementation may help prevent preeclampsia, but probably only in women with calcium deficiency.	2a
There is insufficient evidence to recommend using Metformin, vitamin D, or statins for the prevention of preeclampsia	2b
Women with well-treated hypertension (target BP < 140/90 mmHg) are less likely to develop severe hypertension, and treatment does not increase the risk of neonatal complications	1b
Women with hypertension or preeclampsia selected for outpatient follow-up can be followed at the outpatient clinic or by home monitoring with comparable maternal and neonatal outcomes.	1b
Induction of labor at GA 37+0 in women with preeclampsia without signs of severe disease, provides better maternal outcome than a wait-and-see approach without increased neonatal risks.	1b
In preeclampsia without signs of severe disease from GA 34+0-36+6, there may be maternal benefits of induction of labor, but there is an increased neonatal risk of need for admission to the neonatal unit. There appears to be no increased risk of long-term neonatal morbidity.	1b
Antihypertensive treatment reduces the risk of developing severe hypertension by around 50%.	1a
Labetalol may be more effective than Methyldopa in reducing the risk of developing severe hypertension.	1a
Methyldopa, Labetalol and Nifedipine are equivalent drugs for the treatment of moderate hypertension during pregnancy.	2b
Labetalol can mask and prolong symptoms of hypoglycemia.	2b
Magnesium sulphate (MgSO <sub>4</sub> ) is the anticonvulsant of choice for the treatment and prevention of eclampsia	1b

Preeclampsia can occur de novo postpartum	1a
The risk of postpartum hemorrhage is increased in preeclampsia	3b
NSAID treatment postpartum in hypertensive conditions is not associated with an increase of hypertension.	1b
Preeclampsia is associated with increased risk of developing cardiovascular and kidney disease later in life	1b
The following antihypertensives can be used during breastfeeding: Labetalol (Trandate), Nifedipine (Adalat), Methyldopa, Enalapril, Captopril (but not other ACE inhibitors or angiotensin II receptor antagonists), Atenolol and Metoprolol	4-5

## TABLE OF CLINICAL RECOMMENDATIONS

Recommendations	Strength
Hypertension is defined as BP $\geq 140$ mmHg systolic and/or $\geq 90$ mmHg diastolic measured on at least two occasions min. 4 hours apart. If severe hypertension (BP $\geq 160$ mmHg systolic and/or $\geq 110$ mmHg diastolic) is detected, the diagnosis of hypertension can be confirmed within minutes to ensure timely and relevant antihypertensive treatment	D
Preeclampsia is defined as hypertension accompanied by at least one of the following signs of organ dysfunction: <ul style="list-style-type: none"> <li>• significant proteinuria: albumin-creatinine ratio <math>\geq 200</math> mg/g</li> <li>• haematological complications: thrombocytopenia (<math>&lt; 100 \times 10^9/l</math>), DIC or haemolysis (haptoglobin <math>&lt; 0,3</math> g/l)</li> <li>• renal dysfunction: creatinine <math>\geq 90</math> mmol/l</li> <li>• hepatic dysfunction: ALAT <math>\geq</math> twice the upper reference range for gestational age</li> <li>• pulmonary oedema</li> <li>• neurological complications: eclampsia, altered mental status, blindness, stroke, or persistent visual scotomata</li> <li>• uteroplacental dysfunction: estimated foetal weight (EFW) <math>&lt; -22\%</math>, EFW <math>&lt; 15\%</math> with abnormal foetal Doppler flow, intrauterine foetal death, and/or placental abruption</li> </ul>	D
The following criteria for preeclampsia with signs of severe disease are considered features that require enhanced clinical attention: <ul style="list-style-type: none"> <li>• severe hypertension: BP <math>\geq 160</math> mmHg systolic and/or <math>\geq 110</math> diastolic</li> <li>• platelets <math>&lt; 100 \times 10^9/l</math></li> <li>• creatinine <math>\geq 100</math> mmol/l</li> <li>• ALAT <math>\geq</math> twice the upper reference range for gestational age</li> <li>• disseminated intravascular coagulation</li> </ul>	D

<ul style="list-style-type: none"> <li>• haemolysis (haptoglobin &lt; 0,3 g/l)</li> <li>• pulmonary oedema</li> <li>• neurological complications: eclampsia, altered mental status, blindness, stroke, or persistent visual scotomata</li> </ul>	
Blood pressure measurements should be standardized: The woman rests for 5 minutes sitting in a chair with her back against the backrest, her arms on the armrests and feet on the floor without speaking, with a BP cuff of the correct size placed on her arm with no clothes in between. A minimum of two BP readings are required if BP is elevated. The average of the two final measurements is recorded.	B
If possible, in women with new-onset, non-severe hypertension without symptoms or other signs of preeclampsia the diagnosis of hypertension should be confirmed with standardized home BP measurements in order to rule out whitecoat hypertension	C
Hypertension in home BP readings is present if readings are $\geq 140$ mmHg systolic and/or $\geq 90$ mmHg diastolic	D
Urine dipstick analysis for proteinuria may be used to screen for proteinuria	B
If urine dipstick analysis shows $\geq 2+$ proteinuria, a urine sample should be sent for quantitative testing for proteinuria (albumin-creatinine ratio)	B
Significant proteinuria is present if albumin-creatinine ratio is $\geq 200$ mg/g	D
If quantitative testing is not available, $\geq 2+$ protein on urine dipstick analysis is considered significant proteinuria	D
If significant proteinuria $\geq 20$ weeks' gestation has already been noted, no further testing for proteinuria using dipstick or quantitative testing is required. Consider re-testing for proteinuria in women with known or suspected renal disease or pregestational diabetes.	D
PIGF-based diagnostics may be used as an adjunct to other clinical and paraclinical tests to predict the development of preeclampsia and progression to severe disease in women with suspected or manifest preeclampsia	B
Prevention of preeclampsia using low-dose aspirin is dealt with in the DSOG guideline "Acetylsalicylic acid in pregnancy" (2021)	-
Calcium supplementation may be considered in women with calcium deficiency and high risk of preeclampsia, e.g. early-onset preeclampsia in a previous pregnancy	B
Metformin, vitamin D, or statins are not recommended as preeclampsia prophylaxis	B
Women with well-controlled BP, no preeclampsia symptoms, and normal or slightly abnormal biochemical parameters may be monitored as outpatients. This also applies to women who, after hospital admission, meet these criteria. Significant co-morbidity should be	D



considered aggravating factors, possibly leading to more frequent outpatient visits or hospital admission	
Women with hypertension or preeclampsia can be followed as outpatients or using home monitoring, depending on local conditions	B
Foetal ultrasound for monitoring growth and Doppler flow is recommended at least every 4 weeks in women with chronic or gestational hypertension and at least every 2-3 weeks in women with preeclampsia, often at shorter intervals if the clinical condition deteriorates, or if foetal growth restriction is detected.	D
Induction is recommended at GA 37-38 weeks in women with preeclampsia	B
In women with preeclampsia and signs of serious, progressive disease, e.g. repeated episodes of severe hypertension despite treatment with 3 antihypertensive agents, progressive thrombocytopenia, progressive increase in creatinine or liver function tests, pulmonary oedema, severe neurological symptoms, eclampsia, placental abruption, or signs of severe foetal compromise, delivery is indicated as soon as possible (within hours or days) after the woman has been stabilized and relevant prophylaxis against eclampsia has been started	D
Antihypertensive treatment is usually indicated in consistently elevated blood pressure BP $\geq 140$ mmHg systolic and/or $\geq 90$ mmHg diastolic	B
Oral antihypertensive treatment is preferred for moderate hypertension to avoid sudden decreases in blood pressure	D
The aim of antihypertensive treatment is a slow reduction of BP to a target of $< 135$ mmHg systolic and $< 85$ mmHg diastolic	B
Antihypertensive treatment should be started before establishing general anaesthesia or epidural anaesthesia, and BP should be below 150/100 mmHg	D
Labetalol, nifedipine and methyldopa are considered equal first-line drugs for the treatment of moderate hypertension in pregnancy	B
Methyldopa is expensive and may be difficult to obtain which should be considered when choosing which antihypertensive agent to prescribe	D
In women with pregestational diabetes labetalol should not be the first-choice antihypertensive agent	B
Magnesium sulphate is indicated in preeclampsia with uncontrollable blood pressure, severe neurological symptoms, hyperreflexia, clonus, epigastric pain and/or HELLP syndrome	A
Eclampsia should be treated with magnesium sulphate which primarily works by preventing repeated seizures	A
Magnesium sulphate is contraindicated if the woman has a known atrioventricular block and relatively contraindicated in myasthenia gravis or impaired renal function (creatinine $> 300$ $\mu\text{mol/l}$ or eGFR 0-30 ml/min)	D

In preeclampsia with signs of severe disease or clinical suspicion of overhydration (oedema), recommendations are as follows: <ul style="list-style-type: none"> <li>• maintain a neutral peripartum fluid balance (0-balance), and a negative postpartum balance &gt;1000 ml/day</li> <li>• fluid intake should be limited to &lt;80 ml/hour (&lt;2 l/24 hours). Continue this fluid restriction until diuresis is sufficient in eu-volemic patients</li> </ul>	D
Oliguria is common in the immediate postpartum period. If urine output is <40 ml/h for 6-8 consecutive hours or 0 ml/h for 2 consecutive hours a fluid bolus and/or diuretic treatment is considered (furosemide 5-80 mg intravenously), depending on the clinical situation. Hypovolemia should be excluded. If oliguria is not resolved with this treatment, consider involving an anaesthesiologist	D
Excess blood loss is initially replaced with crystalloid fluids 1:1. In women with preeclampsia with signs of severe disease or clinical suspicion of overhydration, no more than 1000 ml of crystalloid should be administered; in preeclampsia without these signs, up to 2000 ml of crystalloids may be given	D
Oral antihypertensive treatment should be continued in the postpartum period	B
Postpartum tapering of antihypertensive medication should be postponed until one week postpartum at the earliest (depending on the clinical situation), and only when BP is stable <135/85 mmHg	B
De novo hypertension postpartum (BP > 140/90 mmHg) should be treated with antihypertensive medication. In case treatment is needed for longer periods of time, i.e. in women with chronic hypertension, first choice could be ACE inhibitors e.g. Enalapril or Captopril (these two drugs are approved for use while breastfeeding). ACE inhibitors may be given when creatinine is stable (not necessarily within normal range) postpartum	B
Debut of preeclampsia postpartum is treated in the same way as antenatal preeclampsia	B
Women with preeclampsia are monitored by biochemical parameters every 4-6 hours in the acute stage. After clinical and biochemical improvement, less frequent monitoring is indicated. Biochemical parameters may be repeated before discharge from hospital to determine whether further follow-up is needed.	D
In women with HDPs NSAIDs may be used as pain medication postpartum, unless creatinine is > 90. In women with preeclampsia and thrombocytopenia, NSAIDs should be used with caution.	B
Prophylaxis against postpartum haemorrhage including synthetic oxytocin infusion is recommended in preeclampsia with signs of severe disease	B
LMWH should be considered in women with preeclampsia with signs of severe disease until the patient is fully mobilized (typically 6 days or	-

more), unless the patient continues to be at high risk of bleeding and/or she has thrombocytopenia, depending on her other risk factors for thrombosis. Please refer to clinical guidance by DSTH/DSOG.	
<p>Clinical guidance by DSTH regarding evaluation for thrombophilia recommends as follows:</p> <ul style="list-style-type: none"> <li>• antiphospholipid antibodies should be taken in women with placenta-mediated pregnancy complications</li> <li>• in women with placenta-mediated pregnancy complications, there is no evidence to support evaluation for hereditary thrombophilia</li> </ul>	-
Women with gestational hypertension or preeclampsia should be informed that their risk of chronic hypertension, cardiovascular disease, and renal disease is elevated later in life, and should be informed to consult their general practitioner for follow-up.	D

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