The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP

Introduction

There has never been a definite consensus on the classification and diagnostic criteria for the hypertensive disorders of pregnancy. This uncertainty is likely to have led to between-centre differences in rates of adverse maternal and foetal outcomes for the various hypertensive disorders in pregnancy, particularly pre-eclampsia.

In 2000, the International Society for the Study of Hypertension in Pregnancy (ISSHP) recognised that this lack of consensus was one reason for controversies concerning counselling, management and documentation of immediate and remote pregnancy outcomes. Accordingly, the Society appointed a committee that reviewed available classifications and endorsed and published an international recommendation for how these disorders should be classified and diagnosed in pregnancy [1]. The major stumbling block remained whether or not proteinuria should be retained as a sine qua non for the diagnosis of pre-eclampsia; the Society recommended that a broad definition, at times not including proteinuria, could be applied for the clinical definition of pre-eclampsia whilst the inclusion of proteinuria would ensure more specificity around the diagnosis when reporting clinical criteria for patients enrolled in scientific research. The purpose of this document is to update ISSHP thinking on this subject.

Why is there a need for an updated statement?

In the years since this report, there have been a number of developments relevant to diagnosis, classification and management of the hypertensive disorders in pregnancy. One problem is the emerging concept that pre-eclampsia may indeed have several subtypes, the final clinical manifestation being the result of a maternal constitutive response to either abnormal placentation function or abnormal placentation [2]. Several clinical issues need be considered.

Firstly, there has been an international move away from the use of mercury sphygmomanometry, largely for occupational health and safety reasons. This has led to the widespread use of automated blood pressure devices, many of which have not been validated for use in pregnancy, or specifically in pre-eclampsia. Secondly, there has been growing recognition of the potential inaccuracies in the measurement of proteinuria and of the potential for severe maternal complications in pregnancies complicated by de novo hypertension without proteinuria [3]. Thirdly, there has been an explosion of research in general hypertension into the disorder of white coat hypertension, such that it is imperative to distinguish between this and true chronic hypertension. Fourth, the research into the cause(s) of pre-eclampsia has led to considerations that a diagnosis might move away from the traditional clinical diagnosis to one that utilises biomarkers, particularly angiogenic factors [4]. ISSHP considers that this may be a fruitful area for diagnostic criteria in the future but for now a clinical definition remains the most appropriate. Finally, a number of scholarly guidelines have been produced in recent years by the World Health Organisation (http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/index.html) and others [5–10] to assist in the management of the hypertensive disorders of pregnancy; these guidelines differ at times, including in areas such as at what level of blood pressure is therapy required to treat hypertension and when should convulsion prophylaxis be given, but there is suggestive evidence that such guidelines do make a difference to improving pregnancy outcome [9]. Many countries do not have national guidelines for the management of hypertensive pregnancies and it is hoped that this guideline might assist in drafting of local protocols.

ISSHP charged a small group of clinician researchers to provide recommendations about the appropriate classification, definitions, and management of the hypertensive disorders of pregnancy.

The revised classification for hypertensive disorders in pregnancy is as follows (Table 1):

1. Chronic hypertension.
2. Gestational hypertension.
3. Pre-eclampsia – de novo or superimposed on chronic hypertension.
4. White coat hypertension.

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Diagnostic criteria

Hypertension

Pre-eclampsia and gestational hypertension are characterised by the new onset of hypertension (>140 mmHg systolic or >90 mmHg diastolic) after 20 weeks gestation [11]; as such, it is important to have normal blood pressure documented either pre-pregnancy or at least in early pregnancy before there has been much pregnancy-related decrease in blood pressure. Otherwise, a normal first blood pressure measured between 16 and 20 weeks may result in a missed diagnosis of chronic hypertension.

When women present with hypertension in pregnancy after 20 weeks gestation and the earlier blood pressure is unknown, the woman should be managed as if she has gestational hypertension or pre-eclampsia and appropriate investigations should be done after pregnancy to determine if she has underlying chronic hypertension.

Mercury sphygmomanometry remains the gold standard for recording blood pressure in pregnancy, but ISSHP recognises that this technique is increasingly unavailable. Aneroid devices are used commonly but may be inaccurate. One detailed study found that 50% of aneroid devices had at least one reading >10 mmHg out compared to only 10% of mercury devices [12]. If an automated device is to be used, we recommend using one that has been shown to be reliable in pregnancy, such as the Omron T9P or Omron MIT Elite (HEM-7300-WE) devices [13,14]; some devices may be accurate for women with chronic or gestational hypertension in pregnancy but not for women with pre-eclampsia [15]. When such a device is not available, we recommend maintaining a mercury sphygmomanometer for the purposes of allowing calibration of any automated device that is to be used. A newer auscultatory method, utilising a liquid-crystal sphygmomanometer rather than mercury, appears to be accurate and may be a reasonable alternative to mercury sphygmomanometry or an automated device in pregnancy (Davis G, personal communication).

ISSHP recognises that in some countries there is access only to aneroid devices and until such time as a liquid crystal or automated device can be obtained in these countries aneroid devices will need to be used despite their inaccuracy. Regardless of the method used, we recommend a minimum of two BP measurements to diagnose hypertension and preferably that BP remain elevated after overnight rest in hospital or in a day assessment unit.

Chronic hypertension

Chronic hypertension refers to high blood pressure predating the pregnancy. As many women will not have had their blood pressures measured close to pregnancy, in practice we rely upon the first trimester blood pressure to define normal or high blood pressure in these women. Most cases of chronic hypertension will be due to essential hypertension, usually accompanied by a family history of hypertension and often by overweight or obesity. Other secondary causes of hypertension are less common and in this age group are usually underlying primary renal parenchymal disorders (such as reflux nephropathy or glomerulonephritis) and less commonly, fibromuscular hyperplasia of the renal arteries or primary hyperaldosteronism.

Gestational hypertension or Pre-eclampsia?

(Table 2) When de novo hypertension is present after 20 weeks gestation, the next decision is whether this represents pure gestational hypertension or pre-eclampsia. The latter is diagnosed by hypertension and the coexistence of one or more of the following new-onset conditions:

1. Proteinuria (spot urine protein/creatinine >30 mg/mmol [0.3 mg/mg] or >300 mg/day or at least 1 g/L [2 + ] on dipstick testing)
2. Other maternal organ dysfunction:
   - renal insufficiency (creatinine ≥90 umol/L; 1.02 mg/dL)
   - liver involvement (elevated transaminases – at least twice upper limit of normal ± right upper quadrant or epigastric abdominal pain)
   - neurological complications (examples include eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, persistent visual scotomata)
   - haematological complications (thrombocytopenia – platelet count below 150,000/dL, DIC, haemolysis)
3. Uteroplacental dysfunction
   - foetal growth restriction

This means that ideally all asymptomatic women with less than severe hypertension (140–159/90–109 mmHg) and no dipstick proteinuria should have the appropriate laboratory investigations done to exclude maternal organ dysfunction. Without these, it will be impossible to exclude pre-eclampsia. In some countries this approach will necessitate referral of patients (of whom some will not have pre-eclampsia) from smaller units where same-day laboratory facilities are not available. Local decision making strategies will be necessary in these areas.

Although it is probable that pre-eclampsia can be present in some cases without overt hypertension, the Society recommends maintaining new onset hypertension in the diagnosis for now.

We do not recommend diagnosing pre-eclampsia that is superimposed on chronic hypertension on the basis of a rise in blood pressure alone. For patients with underlying essential hypertension, superimposed pre-eclampsia can be diagnosed when one or more of the above features of pre-eclampsia occur in addition to the hypertension. It is harder
to diagnose pre-eclampsia superimposed upon underlying renal disease because these patients commonly have impaired GFR and/or proteinuria to begin. In these cases pre-eclampsia can generally be diagnosed when another feature such as new onset liver dysfunction, thrombocytopenia or neurological features develop. Even then uncertainty may remain and this is another area where a diagnostic test such as measurement of angiogenic or inflammatory factors in serum or urine may prove fruitful in the future.

**Proteinuria**

The gold standard for diagnosing abnormal proteinuria in pregnancy is a 24-h urinary protein ≥ 300 mg per day, though this is more a time-honoured value than one with high scientific proof [16]; ideally 24 h creatinine excretion will also be used to assess adequacy of collection as without this the estimated daily urine protein excretion is often incorrect [17]. In practice, the 24 h urine protein measurement will often be replaced with a spot urine protein/creatinine ratio, a value ≥ 30 mg per mmol (=0.26 mg/mg, usually rounded to 0.3 mg/mg) representing significant proteinuria [18–20]; this eliminates the inherent difficulties in undertaking 24-h urine collections and speeds up the process of decision-making. At present there is insufficient data to recommend using urinary albumin/creatinine ratio but this may change when more research becomes available [18,21].

When neither 24 h nor P/Cr measures of proteinuria are available, dipstick testing still provides reasonable assessment of proteinuria, particularly when values are greater than 1 g per litre i.e. 2+ [20,22]. As discussed in the Society’s accompanying document [23], it is the presence or absence of proteinuria that is important, the degree of proteinuria providing very little additional risk stratification such that it is not included in considerations of the severity of pre-eclampsia [3,20,24,25]. The one situation where the degree of proteinuria impacts management is when nephrotic syndrome intervenes as a result of pre-eclampsia, thus necessitating prophylaxis against thrombo-embolism. When the spot urine protein/creatinine ratio is above 230 mg/mmol then it is probable that nephrotic range proteinuria exists [26]; where possible this can be confirmed in such cases by 24 h urine protein measurement.

**HELLP**

The combination of haemolysis, elevated liver enzymes and thrombocytopenia is often referred to as the HELLP syndrome. For clinicians familiar with the management of pre-eclampsia, this constellation of abnormalities signifies a more serious part of the spectrum of this disorder and is still considered within the overall context of managing pre-eclampsia, not an isolated and separate disorder. ISSHP endorses this approach so as to reduce confusion amongst those less familiar with the multisystem complications that might occur in pre-eclampsia. In other words, women with features of HELLP syndrome should be considered to have pre-eclampsia so that all the features of pre-eclampsia will be sought and addressed. A more detailed discussion of the HELLP syndrome is part of the accompanying ISSHP document [23].

**Foetal growth**

Controversy remains as to whether foetal growth restriction in the context of new onset gestational hypertension, without any other maternal feature of pre-eclampsia, should be considered to define pre-eclampsia. The authors’ view was that this should apply, given that pre-eclampsia is most commonly of itself a primary placental disorder.

**Gestational hypertension**

Gestational hypertension is defined as the de novo development of high blood pressure after 20 weeks gestation, without any of the abnormalities that define pre-eclampsia, as discussed above. This condition is usually benign. However, it can progress to pre-eclampsia in about 25% of cases, more so when the hypertension presents before 32 weeks [27].

**Gestational proteinuria**

In recent years, gestational proteinuria has been recognised as a real entity. It is unclear exactly how many pregnancies are affected by this condition, defined as the new onset of proteinuria in pregnancy without other obvious features of pre-eclampsia or primary renal disease. Women with gestational proteinuria have blood levels of placental growth factor that are intermediate between those of normal pregnancies and pre-eclampsia, prompting consideration that these women have an early and mild form of pre-eclampsia [28]. The recommended approach to management of these women is to consider three possible outcomes:

- No features of pre-eclampsia develop throughout pregnancy and proteinuria disappears postpartum;
- This proteinuria turns out to be the first feature of pre-eclampsia which is defined when subsequently the blood pressure rises or other features of pre-eclampsia develop (as above);
• The proteinuria persists postpartum and ultimately signifies a primary renal disease which has coincidentally developed in the pregnancy, an unusual event.

Monitoring of these women more frequently than usual is therefore recommended for the remainder of their pregnancy, as well as assessment of proteinuria about three months post partum.

White-coat hypertension

(Fig. 1) In the general population it is now recognised that up to one in four patients with elevated clinic or office blood pressure have white coat hypertension [29]. This diagnosis can be eliminated partly by having clinic or office blood pressures recorded by a nurse, rather than a doctor, preferably using repeated blood pressure readings [30]. Ideally, the diagnosis is confirmed by demonstrating normal BP using 24 h ambulatory BP monitoring (ABPM) in the first half of pregnancy but ISSHP acknowledges that this is not always practical on national or international scales, with some countries having no access to this service at all. Where a diagnosis of white coat hypertension is confirmed, pregnant women can be managed with regular home blood pressure assessments and antihypertensives can be avoided, at least up to blood pressure levels of 160–170/110 mmHg. There are limited studies on the outcome of these pregnancies but it appears that up to half will develop true gestational hypertension or pre-eclampsia [31]; it is possible that the risk of pre-eclampsia is twice that of the normal pregnant population, though this needs to be confirmed. The important messages around white coat hypertension are as follows:

• it is reasonable to withhold antihypertensive therapy in this group,

• blood pressure should continue to be monitored regularly at home,

• Increased surveillance is required throughout pregnancy to detect the emergence of pre-eclampsia.

• In areas where home blood pressure assessments are not available, maternal blood pressure should be checked regularly, preferably weekly, by a health care worker; this is probably best done by someone other than a doctor to reduce the likelihood of a white-coat effect.

Prediction and prevention of pre-eclampsia

Many clinical, ultrasonographic, and laboratory parameters have been explored during early pregnancy as tools for predicting who will later develop pre-eclampsia; these include, amongst others [32–36]:

• uterine artery doppler studies,

• measurement of angiogenic factors (such as soluble Endoglin, sFlt-1 and sFlt-1/Placental Growth Factor ratio)

• ADAM-12, plasma PAPP-A, PP 13, homocysteine, ADMA, uric acid and leptin,

• Urinary albumin or calcium

Maternal characteristics that are associated with an increased likelihood of pre-eclampsia include:

• previous pre-eclampsia, particularly when more serious or early onset before 34 weeks

• pre-existing medical conditions (including chronic hypertension, underlying renal disease, or pre-gestational diabetes mellitus),

• underlying antiphospholipid antibody syndrome,

• multiple pregnancy;

Office or Clinic BP ≥140/90 mmHg before 20 weeks gestation

24 hr ABPM

Awake BP < 130 /80 mmHg AND
Sleep BP < 115/70 mmHg

Diagnose White-coat hypertension
• Risk of GH is 50%
• Risk of PE is 8%

Monitor for remainder of pregnancy with HBPM
Validate the device against Hg sphygmomanometry

Diagnose hypertension if HBPM ≥ 135/85 mmHg after 20 weeks

Diagnose chronic hypertension
• Risk of PE is 25%

Monitor with HBPM if a white-coat effect apparent on ABPM

Fig. 1. Clinical application of ABPM in early pregnancy to diagnose and manage white-coat hypertension. Hypertension is diagnosed if either average systolic or diastolic BP is elevated, awake or sleep. ABPM = ambulatory blood pressure monitoring; GH = gestational hypertension; PE = pre-eclampsia; HBPM = home blood pressure monitoring. From reference [55].
Other factors less strongly associated with pre-eclampsia include but are not limited to:

- primiparity (although pre-eclampsia may occur in subsequent pregnancies even in the absence of pre-eclampsia in the first),
- primipaternity – both changed paternity [37] and an interval greater than 5 years have been associated with an increased risk for pre-eclampsia [38],
- short duration of sexual relationship (<6 months) prior to the pregnancy [39],
- obesity,
- African American race,
- advanced maternal age,
- family history of pre-eclampsia [40,41].

Thrombophilias have no clear association with near term pre-eclampsia but Factor V Leiden may be a risk factor for the rarer case of very early onset pre-eclampsia, particularly when associated with severe foetal growth restriction [42].

At present, there is no clinically useful prediction model for the development of pre-eclampsia.

As well as predicting the development of pre-eclampsia there are recent studies aiming to predict clinical outcomes for women when they initially present with early features of pre-eclampsia. Measurement of angiogenic factors may play a role in this regard in the future but is still at a research stage [43].

A clinical predictive model, the PIERS model, can predict the likelihood of a composite severe adverse maternal outcome using the following variables gathered from 6–48 h after admission with pre-eclampsia [44,45]:

- gestational age,
- chest pain or dyspnoea,
- oxygen saturation,
- platelet count,
- serum creatinine,
- AST.

In practice, pulse oximetry is probably used infrequently and defaults to an oxygen saturation of 97% in the risk model when oximetry is not available (https://piers.cfr.ca/PIERSCalculatorH.aspx).

Prevention

No treatment to date can reliably prevent pre-eclampsia in all women; even the analyses of studies of large numbers of women using aspirin or calcium for prevention of pre-eclampsia remain open to differing interpretations.

On balance, we believe that for women considered to be at increased risk for pre-eclampsia on the basis of clinical factors mentioned above, both low dose aspirin and calcium (particularly in the setting of low calcium intake) are recommended for the prevention of pre-eclampsia [46–48]. Aspirin should be given at a dose between 75 and 150 mg per day, started preferably before 16 weeks, possibly taken at night, and continued until delivery; about 70 women need to be treated to prevent one case of pre-eclampsia, particularly severe pre-eclampsia. Calcium at a dose of at least 1 g/d has been shown to reduce the likelihood of pre-eclampsia in women with low calcium intake.

Supplemental Vitamin C and E are not recommended and may in fact be associated with worse pregnancy outcomes [49].

Management

ISSHP endorses the following key management points:

1. Women with an initial diagnosis of pre-eclampsia should be admitted to hospital in all cases; following assessment in hospital, some women with pre-eclampsia may be managed in specialised outpatient settings, such as day assessment units or antepartum home care programs in hospitals with appropriate expertise.

2. Clinical assessment of women with pre-eclampsia should include measurement of pulse oximetry where possible.

3. Maternal blood tests should be performed at least twice weekly (and again in response to a change in clinical status) in most women with pre-eclampsia, including haemoglobin, platelet count, liver enzymes, electrolytes, creatinine, and uric acid.

a. There has been controversy about the utility of uric acid and whether or not it should be retained in the tests performed. Evidence suggests that amongst hypertensive pregnant women, including women with gestational hypertension alone, elevated gestation corrected uric acid remains a valuable test to alert clinicians to the possibility of foetal growth restriction [50,51]. However, uric acid should not be used to determine the timing of delivery.

4. Whilst controversy remains around the BP level at which to institute antihypertensive therapy, there is general agreement that blood pressures above 160–170/110 mmHg require urgent treatment, with lowering of systolic and diastolic blood pressure below 160–170/110 mmHg over a few hours; blood pressures at these levels are thought to be surrogate markers for the risk of stroke, as well as a reflection of increased severity of the overall condition of pre-eclampsia. A number of different anti-hypertensives can be used to control BP in pregnancy. In the acute setting short acting oral nifedipine or intravenous labetalol or hydralazine is commonly used. In the day to day management oral methyldopa, nifedipine, oxprenolol, and hydralazine remain commonly used medications. ACE inhibitors and A2 receptor blockers should be avoided.

5. There is no current agreement as to what level BP should be maintained when antihypertensives are instituted for non-urgent indications in pregnancy. ISSHP believes that existing data do not permit definitive statements to be made. The Canadian guidelines recommend 130–155/90–105 mmHg in the absence of co-morbid conditions [10], and the NICE guidelines recommend keeping BP below 150 mmHg systolic and between 80
Specific indications for delivery of women with pre-eclampsia.

1. Inability to control maternal blood pressure or if pre-eclampsia develops, in which case the indications are as above.
2. Women with chronic hypertension, gestational hypertension or white-coat hypertension should be delivered no later than 40 weeks and earlier if there is inability to control maternal blood pressure or if pre-eclampsia develops, in which case the indications are as above.

Table 3
Specific indications for delivery of women with pre-eclampsia.

a. Women with pre-eclampsia at \( \geq 37 \) weeks gestation should be delivered
b. Women with pre-eclampsia between 34 and 37 weeks can be managed with an expectant conservative approach, as below.
c. Women with pre-eclampsia at <34 weeks gestation should be managed with a conservative (expectant) approach at a centre with Maternal and Foetal Medicine expertise, delivery being necessary when one or more of the following indications emerge:
   i. Inability to control maternal blood pressure despite antihypertensives.
   ii. When available, maternal pulse oximetry <90%, or pulmonary oedema unresponsive to initial diuretics
   iii. Progressive deterioration in liver function, GFR, haemolysis or platelet count
   iv. ongoing neurological symptoms, as described above, or eclampsia
   v. Placental abruption
   vi. Reversed end-diastolic flow in the umbilical artery Doppler velocimetry, a non reassuring CTG, or stillbirth.

Of note, neither the serum uric acid nor the level of proteinuria should be used as an indication for delivery.

Women with chronic hypertension, gestational hypertension or white-coat hypertension should be delivered no later than 40 weeks and earlier if there is inability to control maternal blood pressure or if pre-eclampsia develops, in which case the indications are as above.
Of note, neither the serum uric acid nor the level of proteinuria should be used as an indication for delivery.

What do other guidelines say?

ISSHP acknowledges the expertise and rigorous approach that has been undertaken in the development of several key guidelines including:

- NICE (5)
- SOMANZ [3]
- Canadian [8]
- ACOG (ACOG. Practice guideline WQ 24)

The key areas in which these guidelines differ are:

1. (1) the requirement for proteinuria in the diagnosis of pre-eclampsia (NICE)
2. (2) the level at which routine antihypertensive treatment of blood pressure is mandatory and the target BP thereafter
3. (3) when magnesium sulphate should be administered

Adopting the management recommendations of any of these guidelines is entirely justified and appropriate. Importantly, ISSHP recommends that each unit has a specific policy as to which management guidelines are to be followed so that there is uniform practice within each unit. In addition, each unit should strive to record and evaluate their maternal and foetal outcomes to ensure that their policies and guidelines remain appropriate.

Ethics statement

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Competing interests

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