Pre-eclampsia trio

Blood-pressure measurement and classification in pregnancy

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Pre-eclampsia is usually defined on the basis of new onset hypertension and albuminuria developing after 20 weeks of pregnancy. There are difficulties with measurement of these variables. Conventional sphygmomanometry remains the gold standard for blood-pressure measurement. The value of ambulatory blood-pressure measurement has yet to be established. Oedema is now omitted from all definitions of pre-eclampsia, although the finding of widespread severe oedema of sudden onset should not be ignored for clinical purposes. Definitions of pre-eclampsia based solely on hypertension and proteinuria ignore the wide clinical variability in this syndrome. Women with no proteinuria but who do have hypertension and other features such as severe headache or other symptoms, thrombocytopenia, hyperuricaemia, disordered liver function, and fetal compromise are likely to have pre-eclampsia. This notion is accepted in the new Australasian definition of pre-eclampsia and more than hinted at in the new American College of Obstetricians and Gynecologists' definition. Definitions used for clinical purposes should be as safe as practical; they are likely to include a considerable number of false positives. Most research studies are weakened if patients without the disease are included. Therefore, a separate stringent research definition of pre-eclampsia we also suggest.

Almost 100 years age, J C Briggs and H W Cook, two housemen at Johns Hopkins Hospital, described use of the Riva-Rocci sphygmomanometer to measure blood pressure in pregnancy.[1] Blood-pressure measurement is still the most commonly used screening test in antenatal care. However, pre-eclampsia is much more than pregnancy-induced hypertension.[2] The clinical presentation is extremely variable, reflecting the complexity of the underlying pathology. Thus, classification of pre-eclampsia has proved very difficult. In this review, we highlight the limitations of conventional blood-pressure measurement, assess the role of ambulatory blood-pressure monitoring (ABPM) in pregnancy, and suggest a practical approach to the classification of pre-eclampsia.

Conventional blood-pressure measurement in pregnancy

Despite widespread use, conventional blood-pressure readings are prone to inaccuracy due not only to observer and device error, but also to the inherent variability of blood pressure and to the pressor effects of attendance at the clinic (white-coat hypertension). Several authorities have made recommendations to minimise errors with regard to conventional blood-pressure measurement.[3–5] A reasonable composite protocol is that blood pressure should be measured when the woman is seated, with her feet supported or on the ground, and her arm at the level of the heart. The right arm should be used with a cuff of appropriate size. Measurements should be made with a mercury sphygmomanometer and should be recorded to the nearest 2 mm Hg. In centres where the use of mercury has been banned for clinical purposes, the mercury sphygmomanometer will have to be replaced by an electronic device that has been validated for pregnancy.

Evidence suggests that many practitioners, involved in antenatal care, fail to take even the most basic precautions to lower error. Brown and colleagues noted that 78% of obstetricians and midwives had never had their sphygmomanometer calibrated or were unaware whether it had ever been done, and only 45% of obstetricians used a large cuff when required.[6] Perry and colleagues reported that two-thirds of practitioners measured blood to the nearest 5 mm Hg and a quarter to the nearest 10 mm Hg.[7] A further area of controversy, particular to pregnancy, relates to the measurement of diastolic blood-pressure with Korotkoff phase IV (muffling) or phase V (sound disappearance). Until recently, most classifications recommended use of phase IV. Proponents of phase IV argued that, because of the unique haemodynamics of pregnancy, it more closely approximates intra-arterial blood pressure and that phase V is often very low or near zero.[3,8] These concerns have not been borne out by the evidence. Phase V seems closer to true intra-arterial blood pressure and several large studies have reported that phase V is rarely very low or zero.[9] Also, phase IV is more difficult to detect than phase V, being absent in between 17% and 57% of pregnant women.[9] Even when heard, phase IV has limited reproducibility.[10] Concerns about the safety of a change from phase IV to phase V were addressed in a prospective randomised trial of 220 pregnant women with diastolic hypertension in the second half of pregnancy.[11] The investigators reported that a change in practice would mean that one case less of severe diastolic hypertension would be recorded for every six hypertensive pregnancies but all other episodes of severe hypertension would be recorded with similar frequency. No clinically significant differences in outcome were noted when phase V was used rather than phase IV.

Ambulatory blood-pressure monitoring

Ambulatory blood-pressure monitoring (ABPM) overcomes many of the limitations of conventional blood-pressure measurement and has become an established

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part of the clinical management of non-pregnancy hypertension. It provides objective, repeated measurements in a non-clinical environment. Because of concern that the haemodynamic changes of normal pregnancy might affect the ability of automated devices to measure blood pressure accurately, the application of ABPM has been accompanied by stringent validation of the monitoring devices. Several ABPM devices have been successfully validated specifically for use in pregnancy and used to generate normal ranges for ABPM throughout gestation.[12,13] The hope has been that ABPM will substantially enhance assessment of blood pressure in pregnancy. Clinical application of ABPM has been assessed in three main areas: white-coat hypertension; early prediction of pre-eclampsia; and prognostic assessment of hypertension in later pregnancy.

White-coat hypertension

White-coat hypertension can broadly be defined as persistently raised clinic blood pressure with normal blood pressure at other times. In the non-pregnant population, white-coat hypertension arises in up to 21% of patients with borderline hypertension.[14] The long-term risks of white-coat hypertension are between those of true hypertension and normotension.[15] Several studies have shown that white-coat hypertension is more common if the patient is female and young suggesting that it may be important in pregnancy.[16,17]

Bellomo and colleagues reported a frequency of white-coat hypertension (high office blood-pressure with normal average 24 h ambulatory blood-pressure) of 29% in 144 women with hypertension recruited in the third trimester.[18] Compared with women with white-coat hypertension, women with true hypertension were more likely to have pre-eclampsia or gestational hypertension, had significantly lower birthweights, longer hospital stay, and earlier gestation at delivery. Except for an increased caesarean-section rate, women with white-coat hypertension had similar outcomes to a normotensive control group. High office blood-pressure was defined, in this study, on the basis of two sets of three blood pressure readings taken 5 min apart. Although all women were then admitted to hospital for 24 h ABPM, no further results of conventional blood-pressure measurement were presented. Since only 12% of those women in the white-coat hypertension group were reported as having gestational hypertension it seems that most women did not have persistently raised blood pressure on conventional assessment.

However, Brown and colleagues, who studied 121 women with hypertension in the second half of pregnancy, noted that systolic and diastolic white-coat hypertension were present in only 3% and 4%, respectively.[19] White-coat hypertension was defined as average conventional blood-pressure readings (in pregnancy daycare or in hospital) of 140 mm Hg systolic or greater or of 90 mm Hg diastolic or greater with awake ambulatory average blood pressure within the normal range for ABPM-derived, gestation corrected blood pressure. The investigators concluded that use of ABPM to identify a white-coat effect in women presenting with hypertension in the second half of pregnancy is unlikely to be clinically useful. Results are awaited from an ongoing study from the same group on the possible importance of white-coat hypertension diagnosed in early pregnancy.

Early prediction of pre-eclampsia

It is well established that women who develop hypertensive complications in late pregnancy have higher average blood pressures as early as the second trimester compared with those who remain normotensive. Halligan and colleagues highlighted the potential value of ABPM when, in a study designed to provide normal reference ranges, they showed that three of four women who developed pre-eclampsia had mean nocturnal systolic blood-pressure greater than the 95th percentile between 18 and 24 weeks' gestation.[13] These findings were recorded between 13 and 21 weeks before development of clinically recognisable disease. To explore the predictive potential of ABPM further, the same group did a much larger study recruiting more than 1100 primigravid women for 24 h ABPM between 18 and 24 weeks' gestation.[20] Although much higher ambulatory blood-pressures were recorded in women who subsequently developed pre-eclampsia than in the normotensive control group, the absolute differences between the groups were small and the overlap large. The best overall predictor for pre-eclampsia was 24 h mean diastolic blood-pressure which gave a sensitivity of only 22% and a positive predictive value of only 15%. Thus ABPM in a primigravid population may not be useful clinically as an early predictor of pre-eclampsia.

Prognostic assessment in late pregnancy

Approximately a quarter of women who present in late pregnancy with isolated de novo hypertension go on to develop pre-eclampsia.[21] Several studies have assessed whether ABPM can predict which patients with hypertension are liable to develop substantial complications. Compared with clinical blood-pressure readings or obstetrical daycare unit assessment, ambulatory blood-pressures correlate better with 24 h urinary protein excretion.[22] Peek and colleagues studied 109 nulliparous women with hypertension in late pregnancy and showed that ABPM diastolic blood pressure readings were more informative than diastolic blood-pressure measured in the daycare unit.[23] The relative risks of a diastolic ambulatory blood-pressure of more than 90 mm Hg for: proteinuria were 1·82 (95% CI 1·06–3·12); preterm delivery 3·75 (1·78–7·89); birthweight below the 10th centile 2·9 (1·49–5·76); admission to special care nursery 3·95 (1·71–9·13); and caesarean section 2·06 (1·24–3·44). In a much larger study of over 300 women, ABPM was again shown to be a better predictor of subsequent severe hypertension than daycare unit assessment, but in this study it was not a more useful predictor for other outcomes.[24]

Can these results be translated into clinical benefits for pregnant women with hypertension? There are several reasons why this next step may be more difficult. First, studies so far have compared ABPM with single daycare unit assessments and single conventional blood-pressure measurements in the clinic. In practice, management is likely to be based on repeated conventional measurement, particularly if the patient has pre-eclampsia. Second, although blood pressure is an important clinical feature management of women with pre-eclampsia depends not only on blood pressure but also on maternal symptomology, changes in renal and hepatic biochemistry, alterations in coagulation, and assessment of fetal wellbeing. Third, and perhaps most importantly, there have been concerns about the accuracy of some ABPM devices in women who are hypertensive during pregnancy.[25] This inaccuracy is most striking in women with established pre-eclampsia and can lead to a large underestimation of the true blood pressure. These findings have important implications not just for the application of ABPM but also for the use of

automated blood-pressure devices in women who are affected by severe pre-eclampsia.

At present, careful blood-pressure measurement with a mercury sphygmomanometer remains the gold standard. All automated blood-pressure devices need to be specifically validated for use in pregnancy and preferably in patients with pre-eclampsia. Randomised trials of ABPM compared with conventional blood-pressure measurement in hypertensive pregnant women are now urgently needed.

Defining and classifying pre-eclampsia

Oedema

Oedema is such a common feature of normal pregnancy that it is no longer part of most current definitions of pre-eclampsia. From a practical point of view, mild oedema can be ignored but sudden severe widespread oedema cannot—it is likely to be pathological and further intervention is necessary. Of course, the pathology is not necessarily pre-eclampsia; it could lie primarily in the kidney (eg, in nephrotic syndrome) or elsewhere in the circulation due to congestive cardiac failure.

Hypertension

Most would consider hypertension to be the hallmark of pre-eclampsia. Use of hypertension as a defining feature of pre-eclampsia cannot be avoided but there are difficulties with blood-pressure measurement, characterisation of a patient's blood pressure, and distinguishing a pathological from a physiological response. Also, the very notion of hypertension is an artificial one, in that whatever threshold chosen is an artefact imposed on a continuous distribution.

Can patients be characterised by their blood pressure and in particular can they be characterised by a single blood-pressure reading? All definitions of pre-eclampsia assume that this is the case and define pre-eclampsia on the basis of a single blood-pressure reading, if high enough. Two readings, 4 to 6 h apart allow the definition to be met at lower blood pressures. Single readings might be very unrepresentative of the patient's normal blood-pressure status. Perhaps the most difficult aspect of using blood pressure to define pre-eclampsia is in separating physiology from pathology. Serial studies measuring blood pressure longitudinally throughout pregnancy have shown that both diastolic and systolic blood-pressure fall in the second trimester to return to non-pregnancy values by the end of the third trimester.[26] Thus a definition of normal blood pressure should be related to gestation, an idea that has not found much favour, even though gestation-dependent changes in blood pressure have been known about for a long time. Perhaps it is believed that these gestation based blood-pressure changes are small by comparison with random variation and with measurement error.

Some individuals could respond differently and have higher blood pressure than non-pregnant women at the end of the third trimester, without pre-eclampsia; this is known as gestational[3] or transient[5] hypertension, a condition which in the absence of other features of pre-eclampsia is associated with fetal growth enhancement rather than fetal growth restriction.[27] Nevertheless women who are going to develop the full syndrome of pre-eclampsia usually become hypertensive before they develop proteinuria, and therefore new onset hypertension without other features of pre-eclampsia (pregnancy-induced hypertension) is often thought of as a prodromal phase before development of the complete syndrome. Clinicians must remember, however, that hypertension could be due to pathological processes other than pre-eclampsia. For example, phaeochromocytoma can mimic all features of pre-eclampsia.

Proteinuria

If hypertension is the hallmark of pre-eclampsia, then most would believe that it is proteinuria which distinguishes the hypertension of other causes (sinister or innocent) from the hypertension of pre-eclampsia. But, because of the variability of pre-eclampsia it is possible to have severe disease with all the other features of pre-eclampsia but without proteinuria.

For clinical purposes, proteinuria is usually screened for by using a dipstick technique, which indirectly tests for the presence of protein; + albuminuria being taken as positive. But it is the amount of protein secreted in the urine over a 24 h period that is the gold standard. The concentration of protein in the urine varies a lot throughout the day partly in relation to urine concentration, which can be allowed for by measuring the urine protein/creatinine ratio, rather than the protein concentration itself.[28]

There are potentially as many errors estimating proteinuria by the use of dipsticks as there are in blood-pressure measurement. Formal methodological studies have shown that pupil midwives, trained midwives, and trained laboratory staff differ in their assessment of albuminuria using dipsticks, the worst performers being pupil midwives.[29] Also dipsticks themselves do not accurately predict the presence of significant quantities of proteinuria. There are high false positive and false negative rates with a + reading if a protein concentration of 300 mg/L is judged significant. There would be fewer false positives and not many more false negatives if ++ proteinuria was used as an index of significant proteinuria. Nevertheless in the interests of patient safety it is likely that + proteinuria, a spot concentration of 500 mg/L or total excretion of 300 mg per 24 h will continue as the definitions of substantial proteinuria with regard to pre-eclampsia.

Proteinuria like hypertension and oedema might also be due to other conditions like kidney disease or urinary tract infection.

Current classifications of pregnancy hypertension

Three definitions are commonly cited.[3,30,31] In general these definitions are advocated for epidemiological purposes—ie, to describe the incidence and prevalence of hypertension in pregnancy in populations rather than to guide clinical management or to stringently characterise patients with pre-eclampsia for research purposes (panel).

Davey and MacGillivray's definition[3] of pregnancy hypertension, is detailed and also considers several different forms of hypertension that could arise in pregnancy. With regard to gestational proteinuric hypertension and pre-eclampsia, the definition stipulates normotension before 20 weeks' gestation, and hypertension and proteinuria developing after 20 weeks. Hypertension is diagnosed by a single diastolic blood-pressure of 110 mm Hg or greater (phase IV) or consecutive readings of 90 mm Hg or greater on more than one occasion at least 4 h apart. Proteinuria is defined as a 24 h excretion of 300 mg or more, two clean-catch urine specimens at least 4 h apart with: 2+proteinuria by dipstick; 1+proteinuria if specific gravity less than 1030; and protein/creatinine index of 300 or more.

Redman and Jefferies[32] sought blood-pressure characteristics that would maximise the chance of

The American College of Obstetricians and Gynecologists'[30] definition revised by a National Institutes of Health working group in 1990, and very recently updated[31] classifies hypertension in pregnancy as: chronic hypertension; pre-eclampsia-eclampsia; pre-eclampsia superimposed on chronic hypertension; and gestational hypertension.

Definitions

Pre-eclampsia
Diagnosed on the basis of hypertension with proteinuria

Hypertension—blood pressure >140 mm Hg systolic or 90 mm Hg diastolic occurring after 20 weeks in a woman who was normotensive before 20 weeks' gestation.

Hypertension should be confirmed by two separate measurements

Proteinuria—300 mg/L protein in a random specimen or an excretion of 300 mg per 24 h.

In the absence of proteinuria, pre-eclampsia is "highly suspected" when increased blood pressure is accompanied by evidence of other systemic features of the condition.

Chronic hypertension—blood pressure ⩾140/90 before the 20th week of pregnancy or if only diagnosed during pregnancy, persisting 6 weeks after delivery.

Pre-eclampsia superimposed on chronic hypertension is regarded as highly likely in women with hypertension alone who develop new proteinuria, or in women with pre-existing hypertension and proteinuria who have sudden increases in blood pressure or proteinuria, thrombocytopenia, or increases in hepatocellular enzymes.[31]

Gestational hypertension—development of hypertension without other signs of pre-eclampsia.

Oedema—removal of oedema as a defining sign was an important change in this amended classification.

identifying women with other features of pre-eclampsia such as a high proportion of primigravidae and the development of proteinuria. The definition was therefore based on a diastolic blood-pressure below 90 mm Hg before 20 weeks and a subsequent rise of at least 25 mm Hg to a maximum reading of at least 90 mm Hg. In many ways, this is the most practical definition because it allows a diagnosis to be made in the absence of proteinuria and does not rely on oedema; limitations are the need to know the blood pressure in the first half of pregnancy and the inability to diagnose pre-eclampsia superadded on pre-existing hypertension.

A way forward

The variable nature of pre-eclampsia mirrors the complexity of the pathophysiology of the condition. It is possible that pre-eclampsia is not a single entity, but only a final common pathway by which the woman reacts to pathological pregnancy. Any definition will to some extent be arbitrary, and may be supported by consensus, but not by a precise relation to pathology. It is therefore not surprising that an agreed classification has proved so elusive. In these circumstances, why do we seek to define pre-eclampsia? Clinicians seek to define pre-eclampsia to identify a group of women that have pregnancies at higher than average risk either to the women themselves or to their fetuses. By contrast, researchers seek to define pre-eclampsia so that workers can be as certain as possible that they are studying pre-eclampsia and not some other disease. Unlike the clinical definition, it does not matter if some who have the disease are omitted. What matters is that those who do not have the disease are excluded.

Clinical definition

Given the current high expectations for the outcome of pregnancy, the definition should be as all encompassing as practical, even if it has a high false-positive rate—ie, women will be included where the excess risk is small, if there is any at all. For such a group a practical definition for pregnancy-induced hypertension would be: new hypertension with blood pressure of 140 mm Hg systolic or greater or 90 mm Hg diastolic or greater (phase V) arising after 20 weeks. This group does not necessarily have pre-eclampsia but is at risk of developing pre-eclampsia and must receive closer monitoring. The development of pre-eclampsia will usually depend on the appearance of new proteinuria (+ albuminuria on at least two occasions not in labour, urine protein concentration 500 mg/L, urine protein excretion 300 mg per 24 h) but other features such as fetal compromise symptoms, eclampsia, hyperuricaemia, thrombocytopenia, or other manifestations of HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome could also be used to define the appearance of pre-eclampsia. A very similar approach has recently been advocated by the Australasian Society for the Study of Hypertension in Pregnancy.[33] In essence it is not necessary to define the change from pregnancy-induced hypertension to pre-eclampsia for clinical management once the patients have already been selected as high risk. That is because their management will depend on the appearance of other features of pre-eclampsia, not an arbitrary definition of the condition. For the same reason it is not necessary for clinical purposes to define pre-eclampsia superadded on pre-existing hypertension. For clinical purposes, all women who present before 20 weeks' gestation with hypertension (⩾140/90 mm Hg) or who have lower blood pressures taking antihypertensive drugs are at increased risk and need to be monitored for the development of other features of pre-eclampsia.

Research definition

Since women with recurrent pre-eclampsia often have other underlying conditions such as renal disease or hypertension, the disease should be defined only in primigravidae. Blood pressure should be measured before 20 weeks' gestation, be less than 140/90 mm Hg (Korotkoff phase IV), and rise after 20 weeks' gestation to 90 mm Hg diastolic or more on two occasions at least 4 h apart, or to 100 mm Hg diastolic or greater on one occasion. There should be proteinuria greater than 300 mg per 24 h developing de novo after 20 weeks' gestation. By 3 months after delivery, blood pressure should be recorded as normal, less than (140/90 mm Hg) and there should be no proteinuria. The above suggestions do not preclude study of patients who are multigravid or who have other diseases. But such patients should be analysed separately from those who have the more narrowly defined form of the condition.

In conclusion, granted the lack of precision in definition of pre-eclampsia, any definition that is used clinically should be as loose as practical for patient safety, whereas research definitions should be stringent.

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