# EDUCATION & DEBATE

## Fortnightly Review

## The hypertensive disorders of pregnancy

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The hypertensive disorders of pregnancy remain an enigma. Biologically speaking, pregnancy is the time when women are the most important to the species. One feels instinctively that any condition that occurs in between 1 in 7 and 1 in 10 women during the course of their first pregnancy cannot be all bad. And yet, successive reports on confidential inquiries into maternal deaths in the United Kingdom have identified hypertension in pregnancy as the most frequently cited cause of maternal death.

I cannot cover the pathophysiology of eclampsia in this brief review. Eclampsia occurs unexpectedly in about one in 2000 maternities in the United Kingdom[1] and is therefore difficult to study systematically. More than one third of cases occur before the classic warning signs of both proteinuria and hypertension have been documented, and 44% occur post partum. Thus, the relation between eclampsia and pregnancy induced hypertension and pre-eclampsia is still controversial.

### Research problems

Research has been bedevilled by lack of consistency in diagnosis. Women with pre-existing hypertension or renal disease, or both, who do not develop pregnancy induced hypertension or pre-eclampsia have a better outcome of pregnancy than those who develop hypertension, proteinuria, and thrombocytopenia during their pregnancy. Hypertension alone, developing close to term (after 37 weeks), is usually not associated with adverse outcome and has indeed been associated with bigger babies. Definitions are thus important.

Pregnancy induced hypertension is defined as the occurrence of a blood pressure of 140/90 mm Hg or more on at least two occasions four hours or more apart after the 20th week of pregnancy in a woman known to be normotensive before this time and in whom blood pressure has returned to normal by the sixth postpartum week. When proteinuria of 500 mg/l or more is also present the condition is described as pre-eclampsia.[2] This definition of pregnancy induced hypertension, however, does not distinguish borderline essential hypertension from true pregnancy induced hypertension; therefore an increment of at least 25 mm Hg in diastolic pressure should perhaps be allowed for during pregnancy. This adjustment is logical but has not been widely adopted in studies of pathophysiology to date.

Many recent studies have focused closely on nulliparous women. With increasing parity, a diagnosis of pregnancy induced hypertension or pre-eclampsia is increasingly likely to be erroneous and underlying renal disease is more likely to be the cause.[3] Multiparous women who seem to develop pregnancy

### Summary points

- Pre-eclampsia remains the single most common cause of maternal death in the United Kingdom. Its cause is still unknown so it cannot be prevented or treated rationally

- The rise in blood pressure that occurs in late pregnancy without other symptoms may initially be compensatory for fetoplacental hypoxia and therefore physiological. This compensatory mechanism may explain the high incidence of hypertension during pregnancy

- In some women the compensation breaks down and severe multisystem disease occurs resulting in pregnancy induced hypertension and pre-eclampsia

- Lipid peroxidation and consequent endothelial damage are probably involved in pathogenesis

- Calcium excretion is reduced and intracellular free calcium concentrations increased, which could contribute to the greater pressor responsiveness

- Most of the cardiovascular changes occur during the second half of pregnancy and are hormonally driven rather than mediated by the sympathetic nervous system

- Women at risk of developing pre-eclampsia can be detected early in pregnancy by asking whether their mother developed the condition; by measuring blood pressure using a standardised method; and by checking for proteinuria

induced hypertension or pre-eclampsia are also 6-7 times more likely to become hypertensive in later life.[4] There is, however, an interesting exception to this. Isolated reports have suggested that true pregnancy induced hypertension may occur in a parous woman in her first pregnancy by a different partner, and a recent report links this to the length of sexual cohabitation before conception.[5] This suggests that during a prolonged sexual relationship women may develop an immune response against sperm, and are thus immunologically protected in later pregnancies.

One of the difficulties in studying the hypertensive diseases of pregnancy is that the hypertension and clinically evident multisystem failure are late manifestations of a disease process that was probably initiated early in pregnancy. True, they are the clincial problems that require urgent action, but they are secondary not primary problems. The site of the

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problem lies to a considerable extent in the interaction between embryo and decidua as placentation is initiated. Indeed, pre-eclampsia can occur in women with hydatidiform mole, which contains placental but no fetal tissue.[4] Placental biopsy specimens show clearly that the development of the placenta has been impaired from the start. The trophoblast fails fully to invade[6] and thus the spiral arteries dilate to only about 40% of that in normal pregnancy, which impairs the massive increase in uteroplacental perfusion in the second half of pregnancy. The failure of dilatation will thus cause, in later pregnancy, placental hypoxia, which may itself result in the systemic manifestations of the disease. This failure of dilatation is also found in women whose babies have had intrauterine growth retardation,[6] so something else is also going wrong in women with pregnancy induced hypertension.

Another major problem in studying the pathogenesis of the disease is that there is no naturally occurring experimental model in animals. So called sheep toxaemia (twin lamb disease) is a disorder of carbohydrate metabolism. Pregnant animals can be made hypertensive, but that is not the same thing. We are therefore confined in early pregnancy to studies of blood samples and trophoblast obtained at chorion villus sampling and to studies using such monitoring techniques as Doppler ultrasonography that are safe during repeated use.

## Causes of hypertensive disorders in pregnancy

Women have a genetic predisposition to develop pre-eclampsia,[7] although the wide variation in presentation of the condition means that the mode of inheritance is uncertain. Exclusion mapping found no evidence for linkage to the HLA region and indicated that the "pre-eclampsia gene" was most likely to lie on chromosome 1, 3, 9, or 18.[8] In 1993 Ward et al described a mutation in the angiotensinogen gene (chromosome 1), which seemed to be associated with an increased tendency to pre-eclampsia.[9] Given the changes in the renin-angiotensin system in pre-eclampsia this generated considerable interest. At present, however, the observed effect seems to be specific to certain populations.[10]

### LIPID PEROXIDATION

The possible role of lipid peroxidation in pregnancy induced hypertension and pre-eclampsia is increasingly being investigated.[11] Free oxygen radicals in the body cause various types of damage, including lipid peroxidation and subsequent endothelial cell injury, and damage to proteins and nucleic acids. Lipid peroxides can also be produced enzymatically. In pregnancies with established pre-eclampsia general lipid peroxidation is increased.[11] Indeed, one recent cross sectional study found a strong correlation between concentrations of the products of lipid peroxidation and the mean arterial pressure, although not with fetal outcome.[12] Cells and tissues are usually protected from the effects of lipid peroxidation by several naturally occurring antioxidants. Combined serum measurements of antioxidant activity suggest that the normal rise during pregnancy is diminished in women with pre-eclampsia. Some antioxidant activities are significantly reduced in pre-eclampsia but not in pregnancy induced hypertension.[11]

A balance between peroxide generating and peroxide removing mechanisms may control cyclo-oxygenase activity, and thus the rate of generation of prostaglandins. Prostacyclin is an extremely potent vasodilator and antiaggregatory agent synthesised in the vascular endothelium. Its actions are usually delicately balanced by those of thromboxane, a potent locally acting vasoconstrictor and proaggregatory

agent. Peroxides inhibit prostacyclin synthase but do not influence thromboxane synthase.[13] Early in a normal pregnancy the excretion of a major metabolite of prostacyclin, 6-ketoprostaglandin $F_{1\alpha}$, increases massively, but it does not in women who subsequently develop pregnancy induced hypertension or pre-eclampsia.[14] The overall effect is a clear diminution in the vasodilator effect. Inhibition of prostacyclin synthesis causes the formation of foam cells, the accumulation of cholesteryl esters, and atherogenesis. Acute atherosis, including the presence of foam cells, is a feature of placental bed biopsy specimens from women who have had pre-eclampsia.[15] Thus an event or events giving rise to increased free oxygen radical activity might explain two of the well documented changes in pre-eclampsia. What is not clear is how early in gestation this occurs, and whether it can reasonably be viewed as a primary factor or is secondary to something else.

### ENDOTHELIAL DYSFUNCTION

The case for generalised endothelial dysfunction in pre-eclampsia has been elegantly reviewed.[16] It could certainly account for such phenomena as platelet activation and the increased circulating concentrations of fibronectin and factor VIII antigen. Disruption of endothelial integrity would also be associated with a general loss of vasodilator capacity, which could account for the enhanced pressor response to angiotensin II and noradrenaline, first described more than 25 years ago in pre-eclamptic women and repeatedly confirmed since. Another endothelially derived vasodilator is nitric oxide, which was originally described in this context as endothelially derived relaxation factor. Superoxide easily breaks down nitric oxide,[13] so the balance between oxygen and nitric oxide is likely to be one of the control mechanisms of vascular tone.

### MEMBRANE FLUIDITY

Changes in the cell membrane that affect the functioning of receptors may also be important in pregnancy induced hypertension and pre-eclampsia. In studies using platelets as models of vascular smooth muscle, the density of binding sites for angiotensin II was lower in women during a normal pregnancy than in those who were not pregnant but was unchanged in women with established disease.[17] Intriguingly, a prospective study showed that although primigravidas who remained normotensive showed a very rapid fall in binding site density during the first few weeks of pregnancy, nulliparous women who developed pregnancy induced hypertension never showed such a fall.[18] Membrane fluidity is altered in established pregnancy induced hypertension and pre-eclampsia[19]; plasma concentrations of (n-3) polyunsaturated fatty acids are lower in established disease than in normal pregnancy, which might contribute to the change. In a large scale prospective study, however, the changes in essential fatty acid concentrations occurred late rather than early and were therefore presumably secondary (M D M Al, personal communication).

### CALCIUM

Lipid peroxidation in cell membranes increases their permeability to calcium.[20] Prospective studies have shown a slow rise in platelet intracellular free calcium concentration with gestation in normotensive primigravidas, the concentration being significantly raised by the third trimester in women with pre-eclampsia.[21] This may contribute to the efficacy of calcium channel blockers in the treatment of hypertension in pregnancy.

The rise in intracellular free calcium concentration in hypertensive pregnant women is interesting in another context. In established pregnancy induced hypertension and pre-eclampsia urinary calcium

excretion (usually expressed in relation to urinary creatinine concentration) falls in direct proportion to the severity of the condition.[22] What is less clear is whether this is an early or late change. Some groups have identified a fall in the ratio of urinary calcium to creatine concentration in the second trimester as being a predictor of pregnancy induced hypertension and pre-eclampsia while others have failed to do so.[23] The mechanism for the presumed calcium retention has not been identified.

CARDIOVASCULAR SYSTEM

Limited prospective data suggest an initial hyper-activation in the cardiovascular system which subsequently falls below that in normal pregnancy in women who show intrauterine growth retardation or develop pre-eclampsia, or both.[24] In established pre-eclampsia before treatment the cardiac index (cardiac output in relation to body surface area) is reduced by some 22% while systemic vascular resistance is noticeably raised.[25] Interestingly, Easterling et al described cases of apparent pre-eclampsia occurring before 28 weeks' gestation in which more than half of the women had a raised cardiac output and low systemic vascular resistance.[26] Although the women were said not to have chronic hypertension, they were, however, substantially heavier and may have had underlying hypertensive tendencies.

The raised systemic vascular resistance of established pre-eclampsia is not sympathetically mediated. More than 40 years ago, ganglion blockade with tetraethylammonium chloride was shown to be less effective in women with pre-eclampsia than in normotensive pregnant women.[27] Logically therefore treatment should be with direct vasodilators and not with agents that reduce the activity of the sympathetic nervous system. A recent brief survey reviews current treatment.[28]

Plasma volume is contracted in established disease,[29] but not all hypertensive pregnant women develop oedema in the upper parts of the body. This so called dry pre-eclampsia is said to have a worse outcome.[4] The contraction in volume is associated with veno-constriction. A prospective study found, however, that early vasodilatation was similar in women who subsequently became hypertensive and in normotensive women, but it was greatly enhanced during the six weeks before the onset of hypertension, when it fell sharply.[30] These data suggest an initial response that is subsequently overwhelmed.

**Are pregnancy induced hypertension and pre-eclampsia the same disease?**

Whether pregnancy induced hypertension and pre-eclampsia are early and late manifestations of the same disease, presenting at different stages of gestation in different women, or whether they are distinct entities is still contentious. Clinical experience suggests that many women who develop pregnancy induced hypertension in the second trimester will show steadily worsening hypertension, accompanied by the development of proteinuria, thrombocytopenia, and failing renal and hepatic function that defines pre-eclampsia. If the disease starts later, or delivery is expedited, however, pre-eclampsia may never supervene. The fact that late onset pregnancy induced hypertension is not associated with a worse outcome for the fetus than normotension,[31] taken together with the high incidence of the condition, suggests that it begins as a physiological response to an underlying problem, presumably of fetoplacental perfusion. Various pressor agents, such as angiotensin II, stimulate the synthesis of vasodilators such as nitric oxide[32] and prostacyclin, especially in the uterus.[33] The pregnant uterus

contains an autonomous renin-angiotensin system, and in pregnancy induced hypertension angiotensin II is released into the venous circulation from it and is present in higher concentrations in the peripheral circulation.[33] One hypothesis is therefore that impaired uteroplacental blood flow in pregnancy induced hypertension stimulates the uteroplacental renin-angiotensin system, which both increases peripheral vascular resistance and hence perfusion pressure directly and stimulates vasodilator synthesis within the pregnant uterus, allowing increased perfusion. The fact that the administration of angiotensin converting enzyme inhibitors to pregnant women lowers maternal blood pressure, but at cost to the fetus,[34] supports this hypothesis.

What then turns a protective mechanism into a rapidly worsening cascade of events? The fetus's absolute metabolic demands increase rapidly in the third trimester. Placental inadequacy will be of varying severity so that its effects will become apparent at different gestations. If hypoxia develops early or there is considerable endothelial damage, or both, then compensatory mechanisms may be unable to cope. There is thus no need to postulate the existence of two distinct conditions having different pathophysiologies. Rather, they may be ends of a spectrum, the high incidence of the disease being explained in terms of the potential benefit of a protective mechanism whose cost is high when it breaks down.

**Diagnosis**

So how does this basic research help improve the care of pregnant women? It provides useful pointers for diagnosis (box).

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**Early antenatal care**

● Is there a family history of pregnancy induced hypertension or pre-eclampsia?

● Measure blood pressure using a standardised method

● Make sure urine is checked for protein

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Firstly, genetics. The simple question "Did your mother suffer from high blood pressure, which might have been called pre-eclamptic toxaemia (PET) or toxaemia, in any of her pregnancies?" will immediately identify a group of women at higher risk when the answer is "yes." Further probing may reveal a positive history for a grandmother(s) or sister(s), and such women will merit extra care.

Secondly, reliable readings of maternal blood pressure are needed from early in pregnancy, and certainly before 20 weeks' gestation. This will allow the identification of women with borderline, and previously undiagnosed chronic hypertension, as such women will have systemic arterial pressures of 140/90 mm Hg or more at a time when maternal pressure is normally at the nadir. It will also provide a baseline from which to assess the rise in pressure as pregnancy progresses for each woman. Women who develop pre-eclampsia have significantly higher systolic and diastolic blood pressures as a group during the second trimester. This, however, is not especially helpful as a predictor because of the "white coat hypertension" effect of hospitals, the normal fluctuation in blood pressure over short times, the fact that blood pressure may still be within the normal range, and the commonly found inadequacies of blood pressure measurement. Techniques of measuring blood pressure vary widely, even within one hospital. The technique used must therefore be standardised to

allow accurate identification of changes. Standardisation should be relatively straightforward in terms of posture; bladder size; and use of Korotkoff sound IV or V. The measurement should be recorded as accurately as possible.

The British Hypertension Society recommends that blood pressure in pregnancy should be measured with the woman seated or lying on her left side. This is because profound hypotension can occur in late pregnancy if a woman lies supine because of the mechanical obstruction of the inferior vena cava by the gravid uterus. It is probably advisable to measure the blood pressure after taking the history and before other clinical examination.

General practitioners and clinicians should have available two sizes of cuff, with inflation bladders of 35 cm and 42 cm wide. The cuff used should depend on the arm circumference, with the bladder length being at least 80% of that circumference.

The question of whether to use Korotkoff sound IV or V remains highly controversial. The use of the fourth sound avoids the problem of the occasionally encountered failure of disappearance of sound in pregnancy, but the frequency of occurrence of this problem is disputed. Consistency in measurement throughout pregnancy should be the aim, and so perhaps the fourth sound is to be preferred.

The rounding off of blood pressure measurements should be avoided as it can lead to wide variability. It is preferable to attempt to record the blood pressure as accurately as possible, even though such accuracy will vary between observers.

If these simple standardisations are applied by all who measure the blood pressure in pregnancy, it becomes much easier to identify potentially sinister trends with time.

The woman's weight and height should be measured at least at the first visit. The initial body mass index (weight (kg)/(height (m))$^2$) is quite a useful predictor of hypertension later in gestation, women developing hypertension having higher body mass indices.[23] Again, however, normal and abnormal overlap, and hypertension identified from body mass index is likely to indicate the development of chronic hypertension.

A fall in platelet count is characteristic of the disease in its later stages. There is, however, wide individual variability, so that an early, baseline, measurement will aid later interpretation.

## Treatment

Hypertension arising in pregnancy is not usually the same as hypertension outside pregnancy and should not be regarded in the same light (box). Although many women will never progress beyond mild disease, some will, and since identifying them is currently unreliable, any pregnant woman developing high blood pressure anew needs careful attention and referral for specialist assessment. In general terms, the earlier hypertension develops in pregnancy the more severe the disease is likely to be.

When pregnancy induced hypertension is first diagnosed, bed rest has been suggested to be beneficial,

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**Treatment of hypertension alone**

● Hypertension alone may well be benign, but it needs careful monitoring and, if possible, referral to a pregnancy assessment clinic

● If it occurs before 37 weeks patients should be referred for specialist review

● If proteinuria develops patients must be referred to a specialist

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although its value has been questioned. Regular monitoring of blood pressure and of proteinuria should be instituted in an outpatient department. If proteinuria develops, the woman needs to be referred urgently to a specialist centre. The proteinuria of severe disease can be spectacular, reaching the full blown symptoms of the nephrotic syndrome very quickly. The progression of proteinuria is best monitored in 24 hour urine collections, a value in excess of 500 mg/l being clinically important. Dipsticks are not accurate, though values designated + + + and + + + + do indicate severe disease.

Referral should also be instituted if the blood pressure does not settle to 140/90 mm Hg or below. Hypertension of 160/100 mm Hg or any additional complaints of frontal headache, visual disturbance, photophobia, vomiting, or epigastric discomfort are cause for major concern and merit urgent referral to a specialist unit on the same day. Increasingly, pregnancy assessment or day case units are available, which permit closer monitoring of mother and fetus without formal admission, while facilitating admission when necessary.

When considering the use of any drugs in pregnancy, doctors must always remember that they are treating two patients, one of whom has immature hepatic and renal function while the other may develop impaired hepatic and renal function. When pre-eclampsia develops relatively late in gestation, when the prognosis for the baby is good, and a well equipped neonatal intensive care unit is to hand, delivery may be better than drug treatment, especially if steroids can be used to reduce the risk of the respiratory distress syndrome. Delivery is also the preferred choice when the disease is fulminating earlier in pregnancy and the avoidance of irreversible complications in the mother may need to take precedence. Drug treatment is useful in the grey area between these two extremes (box). Hypertension is only a late manifestation of a long ongoing disease. It is the need to prevent a cerebral vascular accident in the mother while trying to achieve a clinically useful prolongation of pregnancy for the baby that dictates the use of antihypertensive agents.

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**Prophylactic treatment**

● Low dose aspirin may be useful in women with previous early onset pre-eclampsia

● Sympatholytics may be used, especially in chronic hypertension, but they do not influence disease progression

● Calcium channel blockers have also been successfully used, but there is much less experience with them

● Do not use diuretics

● Do not use angiotensin converting enzyme inhibitors

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The use of diuretics does not affect perinatal mortality. As the plasma volume is reduced in severe pre-eclampsia, it also seems illogical on scientific grounds to consider using diuretics unless the disease has progressed to renal failure, in which case care should be given in a specialist high risk obstetric or intensive care unit.

Sympatholytic agents, especially methyldopa and labetalol, are widely used to treat pregnancy induced hypertension and pre-eclampsia. They have a limited effect on the hypertension, which is not mediated by the sympathetic nervous system, but it may be sufficient to allow useful prolongation of gestation. Their comparatively short term use is not associated with intrauterine growth retardation, although growth retardation has been reported after longer use of β blockers in pregnant women with chronic hypertension.

Vasodilators seem to be a more logical treatment, but in the absence of controlled trials, their use in the United Kingdom in pregnant women is usually as an adjunct to methyldopa or a β blocker. Calcium channel blockers are increasingly used, especially nifedipine or nitrendipine. Nifedipine has also been used for obstetric hypertensive emergencies.

The angiotensin converting enzyme inhibitors are contraindicated in pregnancy because of their adverse effects on the fetus. Their use in pregnant women has been associated with oligohydramnios, stillbirth, and neonatal anuria.[34]

The fall in prostacyclin produced in pre-eclampsia, and the observation that low doses of aspirin (60-150 mg daily) inhibit thromboxane synthase but not prostacyclin synthase led to the suggestion that aspirin might be a suitable prophylactic agent against pre-eclampsia. Early small trials proved encouraging, but the multicentre collaborative low dose aspirin study in pregnancy failed to support the routine prophylactic or therapeutic administration of low doses of aspirin.[35] Aspirin may, however, have a place in treating women with a history of severe pre-eclampsia before 30-32 weeks' gestation. Such women should probably start prophylactic treatment early in the second trimester. The dose used in the multicentre study was 60 mg daily.[35]

Additional important warning features of deterioration in maternal or fetal condition, or both, are: the development of hyperreflexia or clonus, or both; a fall in platelet count to below $100 \times 10^9/l$; and any rise in plasma transaminase activities. These again require urgent and immediate specialist attention.

The pregnancy induced hypertension and pre-eclampsia can progress with the frightening rapidity of a truly malignant hypertension. Each successive report on the confidential enquiries into maternal deaths identifies deaths that could probably have been prevented had those delivering the primary care to the women been more alert. Eclampsia, the thunderbolt, and fulminating pre-eclampsia can still strike apparently from the blue.

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# A MEMORABLE WARD ROUND

## Certainty and doubt

As a medical student in training much emphasis is placed on the detection of physical signs. This potentially can lead to feelings of inadequacy when you fail to hear the reverse splitting of the second heart sound which is so obvious to the rest of the group.

As a houseman in Oxford I can clearly remember one particular ward round with an eminent consultant physician in which he was joined by three equally eminent professors in the specialty from various parts of the globe. After the four of them had examined the abdomen of a patient a heated discussion broke out regarding the presence or absence of a palpable spleen. Essentially two firmly believed they could feel a spleen while the other two equally firmly asserted that it was not palpable. As the junior houseman I resisted any temptation to step in with the casting vote. What the incident did teach me, however, was that even among the world's most distinguished clinicians the elicitation of physical signs is by no means consistent. Ever since then I have encouraged medical students to stand by what they believe they have, or have not, found on examination. Even when the rest of the students (and the professors) are marvelling at the emperor's outfit he may yet have no clothes on.—DAVID GRIMSHAW is a general practitioner in Abingdon