Review Article

The management of pregnancy in hypertensive patients

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Introduction

Social Trends reported that the average age of married primigravida in the UK has risen to 27.8, the highest ever recorded.1 The opportunity for recognizing hypertension and initiating preconception counselling before the first pregnancy has therefore increased. This review primarily addresses the management of women known to be hypertensive before conception, a group classified as chronic hypertension and chronic renal disease diagnosed before, during or persisting after pregnancy.2

Preconception counselling for hypertensive patients

The confidential enquiry into maternal deaths reported that hypertension is now the main direct cause of maternal death.3 There is an increased incidence of abruptio placentae in patients with chronic hypertension. The incidence increases with increasing severity of hypertension and again if superimposed pre-eclampsia occurs.4

Hypertensive patients in their first pregnancy face the risk of additional pre-eclampsia. At term, up to 1,392 out of 11,812, that is, 12% of singleton pregnancies are complicated by additional hypertension, this figure comprised 19% of primigravida and 6% of parous women.5 Multiple pregnancies and advanced maternal age increase the risk.6 Non-proteinuric hypertension seems to carry virtually no risk to the fetus7 but 25–30% of women with hypertension prior to pregnancy will develop proteinuria before term.8

Chronic renal disease and other causes of hypertension

Do the patients have a remediable cause for their hypertension? The question is pressing as the outcome of any pregnancy may be adversely affected by failure to find certain causes of hypertension. The search is for renal disease, renal artery stenosis, coarctation of the aorta, phaeochromocytoma and Conn’s syndrome, and an understanding of the mechanisms of secondary hypertension is helpful.9

Women who undertake pregnancy with a primary renal disease, most commonly glomerulonephritis or reflux nephropathy, have a higher risk of adverse fetal and maternal outcomes.10 In patients after renal transplantation with impaired renal function, the perinatal mortality rate was doubled compared with transplant recipients with normal renal function. Six out of 18 transplant patients with impaired renal function showed further deterioration in renal function after pregnancy.11

The natural history of patients with autosomal dominant polycystic disease revealed that women who had three or more pregnancies showed worse renal function in later life.12 No irreversible deterioration in renal function was reported in 26 pregnancies in 16 patients with pre-existing lupus nephritis, although the risk of obstetric and fetal complications was higher, especially in hypertensive pregnancies.13

Finding renal disease will warrant nephrological assessment. Remediable causes of impaired renal function should be treated prior to conception. Missing obstructive uropathy as a cause of hypertension and renal impairment in pregnancy remains a hazard.14

The prognosis for the mother will be that of the underlying renal disease. The fetal outcome in mothers with known renal disease but normal renal function will be indicated by the degree of associated hypertension, the development of proteinuria and the risks of additional pre-eclampsia.

Age and diabetes

The relation between maternal age and mortality from pregnancy hypertension showed a jump from 17.1 per million aged 30–34, to 36.0 per million.
aged 35–39 and to 40.7 for the 40+ age group. Yet, because of smaller numbers in the >35 age group, 86% of the hypertension-related deaths were in the under 35 age group.\textsuperscript{15}

Both hypertension and diabetes are major factors in the excess morbidity and mortality associated with childbearing in women over 40.\textsuperscript{16} Even patients with gestational diabetes showed an increased frequency of chronic hypertension, pregnancy-induced hypertension and pre-eclampsia, compared with 327 women with normal glucose tolerance at 28–32 weeks of gestation.\textsuperscript{17} In patients with both diabetes and hypertension in pregnancy there is an increased risk for developing retinopathic complications.\textsuperscript{18}

Teratogenic risks

Preconception counselling provides the opportunity of stopping anti-hypertensive medication before conception and thereby avoiding teratogenic effects. Of currently used anti-hypertensives, angiotensin converting (ACE) inhibitors cause concern.\textsuperscript{19} One study showed adverse effects on fetal outcome in two of 19 newborns whose mothers were exposed to ACE inhibitors. This indicates that the absolute risk may be high.\textsuperscript{20} A further report on three infants strongly suggested that ACE inhibitors are fetotoxic.\textsuperscript{21} It was proposed that the primary mechanism by which ACE inhibitors affect development of the fetal kidney is through decreased renal blood flow.\textsuperscript{22} ACE inhibitors have been associated with fetal growth retardation, neonatal respiratory failure and possible fetal deaths.\textsuperscript{23}

Tailing off medication in well-controlled hypertensives is relatively easy as it often takes several months and sometimes up to a year before blood pressure returns to unacceptable levels. If conception is achieved during this period the fall in blood pressure which occurs in the first 16 weeks of pregnancy counteracts the hypertension. Half of the patients who have chronic hypertension during pregnancy can be expected to have normal blood pressures during the second trimester. Women whose blood pressure was previously unknown but who become hypertensive during the first 20 weeks of pregnancy are more likely to have underlying chronic hypertension.\textsuperscript{24}

Monitoring in pregnancy

If the patient attends for antenatal care then her blood pressure will be monitored. Obstetricians will recognize the increased risk of hypertension associated with twin pregnancies, and complete or even partial hydatidiform mole.\textsuperscript{25} Unfortunately, it is likely that blood pressure will be casually recorded as evidenced by 78% of blood pressure readings ending in 0.\textsuperscript{26} Diastolic blood pressures are still recorded using both muffling (phase IV) and the disappearance of sounds (phase V) as the end point. Most clinical trials of hypertension in pregnancy have used phase IV.\textsuperscript{24} There remains an urgent need for international consensus on how to measure the blood pressure accurately in pregnancy.\textsuperscript{27} This is unfortunate as precise recordings are as good a predictor of pre-eclampsia as any measure yet devised.

Ambulatory blood pressure monitoring in pregnancy demonstrates lower blood pressures when the patient is away from the medical centre. The same pattern is found in non-pregnancy hypertensives and the difficulties in comparing these measurements with traditional blood pressure readings remain unresolved.\textsuperscript{28}

Because antenatal care will include blood pressure monitoring, it should be unnecessary for patients to attend medical outpatients additionally. The well-structured care provided by antenatal services will include monitoring of fetal growth and maternal renal function. Both low and high systolic and diastolic pressures are associated with intrauterine growth retardation and preterm delivery.\textsuperscript{29} Mild to moderate hypertension carries little risk to the mother or fetus. The risk is in it progressing to severe hypertension (>160/100 mmHg) and pre-eclampsia, hence the need to monitor blood pressure carefully during pregnancy. All primigravida and women with known hypertension should have their blood pressure measured and urine checked for protein fortnightly from 24 weeks and then weekly as term approaches.\textsuperscript{30}

Proteinuria

The detection and quantification of proteinuria remains a useful monitor of early renal changes and acts as an indicator of pregnancy outcome.\textsuperscript{31} Protein excretion is best estimated from 24 hour specimens rather than from 8 hour collections.\textsuperscript{32} Dipstick urinalysis showed a false-negative rate of 7% even in the presence of 100 mg/dl and cannot be totally relied upon either to detect or exclude the presence of proteinuria in pregnant women.\textsuperscript{33}

In a study of renal disease, proteinuria and pregnancy outcome in 53 women, protein excretion of more than 500 mg/day was associated with renal insufficiency in 62% and chronic hypertension in 40%; 45% of infants were delivered pre-term and 23% had growth retardation; 62% developed clinical evidence compatible with superimposed pre-eclampsia; this figure rose to 100% if there was associated chronic hypertension.\textsuperscript{34} The management and pregnancy outcomes of 42 women with
pre-eclampsia and proteinuria of greater or equal to 5 g/24 hours showed that 83% were delivered by caesarean section; 91% of these sections were delivered urgently before the onset of labour; perinatal mortality was high but only one mother had significant proteinuria 3 months after delivery. Diabetic patients developing proteinuria in the range 190–499 mg/day before 20 weeks’ gestation identified a group with a subsequent 31% rate of pre-eclampsia, with protein excretion above 500 mg/day, the rate rose to 38%. If the patients in addition had chronic hypertension, the rates rose to 50% and 58%, respectively. In diabetic nephropathy control of hypertension is known to reduce protein excretion. Early diabetic nephropathy is associated with an increase in glomerular filtration rate similar to that found in early pregnancy, in subjects with pre-eclampsia this rise was absent.

The use of atenolol in 100 women who developed hypertension in late pregnancy was associated with a reduction in proteinuria. When labetalol was used in 57 pregnant women with diastolic pressure greater than 90 mmHg, the degree of proteinuria was no different from the control group. A double-blind controlled study of labetalol involving 144 women with mild to moderate pregnancy-induced hypertension did show a reduced incidence of proteinuria but no improvement in indices of clinical outcome.

Uric acid levels

Uric acid levels show diurnal variation. Sustained elevations are another marker of impaired renal function and hence are associated with a poor prognosis. Elevated uric acid levels in conjunction with substantial proteinuria can be used as a marker for superimposed pre-eclampsia in women already taking anti-hypertensive medication.

Bed rest

The tradition of bed rest for the patient with hypertension in pregnancy started in the 1950s and persists despite reports of it being ineffective. Recent studies continue to show no improvements in fetal growth or neonatal morbidity as a result of bed rest, nor did it prevent the development of proteinuria. Because of the cost and inconvenience of this traditional management, the National Health Service Research and Development department might wish to address the issue.

Improvements in the domiciliary midwifery services now provide better facilities for monitoring hypertensive patients outside hospital. Another alternative is the use of day hospitals. Studies of day hospital care have only identified relatively small cost savings but long experience in Glasgow has shown day care to be acceptable to women.

Home monitoring means that recordings can be made which do not reflect the stress of a hospital visit, but an attempt to measure anxiety levels between home and hospital monitoring showed no differences. Home monitoring of blood pressures requires common protocols of management to be agreed between the hospital and community services. Such protocols must stress that the development of proteinuric pre-eclampsia with symptoms warrants emergency admission to hospital.

Pre-eclampsia and aspirin

Does aspirin therapy reduce the risk of additional pre-eclampsia? Studies on the action of aspirin on platelet reactivity and prostaglandin production have given a theoretical basis for testing aspirin use and small studies on selected high-risk patients have been interpreted to show benefit. These promising early studies stimulated larger trials. In nulliparous women, 60 mg aspirin was given from 24 weeks once drug compliance had proved satisfactory. A positive outcome with 5/302 (1.7%) in the aspirin group developing pre-eclampsia compared with 17/302 (5.6%) in the placebo group (P = 0.0009) was reported. However, in an open study in which 50 mg of aspirin was given daily to 583 women judged to be at moderate risk of pre-eclampsia or intrauterine growth disorder gave little support for its use.

Use of aspirin after the diagnosis of pre-eclampsia is ineffective.

These uncertainties led to the National Institutes of Health Study of 3,135 nulliparous women, in which, 1,570 women were given aspirin 60 mg per day starting from 13 to 26 weeks gestation. The incidence of pre-eclampsia was 4.6% in the aspirin group and 6.3% in the placebo group (relative risk 0.7; 95% confidence intervals 0.6 to 1). The incidence of gestational hypertension was 6.7% and 5.9%, respectively. There was no significant difference in birth weight, fetal growth retardation, postpartum haemorrhage or neonatal bleeding problems. Eleven women in the aspirin group had abruptio placentae compared with two in the placebo group (P = 0.01). Subgroup analysis showed that pre-eclampsia occurred more commonly in those with initial systolic pressure 120–134 mmHg. Aspirin in this group reduced pre-eclampsia from 11.9% to 5.6% (P = 0.01). This more powerful trial gives little support for unselective aspirin use and is in line with earlier conclusions that its use should be selective.

The recently published Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) trial had
Key points

Hypertension is the main direct cause of maternal death, the risk doubles in the over-35 age group.

Non-proteinuric hypertension seems to carry virtually no risk to the fetus.

Women who undertake pregnancy with a primary renal disease have a higher risk of adverse fetal and maternal outcomes.

Where possible stop anti-hypertensives (especially ACE inhibitors) prior to conception.

Measure blood pressure to the nearest 2 mmHg. Check for proteinuria fortnightly from 24 weeks.

Aspirin prophylaxis was not shown to be of benefit in large studies.

Anti-hypertensive therapy with methyl dopa is safe and has been associated with reduced mid-term fetal loss, but has no effect on maternal outcome.

Beta-blocker therapy does reduce the risk of developing severe hypertension but not of developing pre-eclampsia.

Anti-hypertensive therapy should be reviewed within 2 weeks of delivery.

Both prenatal and postnatal counselling should be offered.

3,467 subjects in a trial of prophylactic aspirin therapy. This group included at risk patients selected on the basis of chronic hypertension (n = 933), renal disease (n = 223), diabetes (n = 129), maternal age, family history or multiple pregnancy. In the same group were women with a history of pre-eclampsia or intrauterine growth retardation. Using 60 mg aspirin from as early as 12 weeks, the conclusion was that this therapy would prevent proteinuric pre-eclampsia in about one women out of every 100 treated. The reduction in deliveries before 37 weeks estimated gestation would be 2.5 per 100 women treated. There was no increase in maternal or fetal bleeding disorders in women on aspirin but they did receive more post-delivery blood transfusions. There was a trend towards progressively greater reductions in proteinuric pre-eclampsia the more pre-term the delivery.

Anti-hypertensive therapy during pregnancy

Patients with hypertension at the start of pregnancy will tend to show increasing levels of blood pressure after the 16th week. The rate of rise cannot be predicted but needs monitoring to determine the optimal point for initiating anti-hypertensive therapy. Unfortunately, despite the high prevalence of hypertension in pregnancy, there remain few powerful controlled studies of the results of anti-hypertensive treatment in pregnancy. The bulk of the evidence relates to methyl dopa. This shows that initiating methyl dopa therapy once blood pressure levels exceed 170/110 mmHg in early pregnancy reduced mid-term fetal loss by four out of 242 pregnancies but had no effect on maternal outcome. The fetal outcome, and subsequent growth and development until aged 7 has been reported.

Beta-blockers provide an alternative to methyl dopa. The best studied of these is atenolol. Concern has been expressed about the adverse effects of beta-blockers on fetal outcome, especially in uncontrolled studies. A small study compared the haemodynamic effects of atenolol in 13 patients with pindolol in 16. The finding of reduced placental weight in the atenolol group has been given undue emphasis. Small uncontrolled drug studies claiming adverse fetal effects are still being published. Controlled studies in late pregnancy have shown improved blood pressure control that resulted in reduced admission to hospital and no detected long-term adverse effects on fetal outcome. More recent studies in which therapy was started early in pregnancy were reported as indicating an increased risk to the fetus but the study did not reach its intended size and the adverse effects are interpreted on the basis of two adverse events from a group of 15 pregnant women on atenolol compared with a similar-sized control group. Meta-analysis of 11 trials involving 1,200 women with moderate hypertension in pregnancy indicated that beta-blocker therapy reduced the risk of developing severe hypertension but not of developing pre-eclampsia.

Studies of other hypotensive drugs for the treatment of hypertension in pregnancy again suffer a lack of power and absence of long-term follow-up data. A recent study of 100 patients treated with nifedipine (unlicensed for use in pregnancy in the United Kingdom) showed a reduction in maternal blood pressure but no improvement in perinatal outcome compared with 100 patients treated with bed rest. Ultrasound studies of the effects of hypotensive drugs on blood flow in uterine, umbilical and fetal blood pressures are being used to detect alterations in blood flow that might be considered detrimental.

Hypotensive drug pharmacokinetics may be altered in pregnancy. Studies on nifedipine showed reduced terminal elimination half life, which indicates that it would need to be administered at shorter intervals in pregnant than in the non-pregnant women. Peak plasma metoprolol concentrations were four times higher after the same oral dose in the non-pregnant state. Studies of the
transplacental transfer of hypotensive drugs with, for example, isradipine showed that its concentration is considerably lower in fetal compared with maternal plasma.\textsuperscript{27}

The scope of anti-hypertensive therapy in pregnancy is therefore limited to protecting the mother from the dangers of severe hypertension, particularly cerebral haemorrhage in the context of pre-eclampsia.\textsuperscript{72} Current UK practice favours oral labetalol (35%), oral methyl dopa (23%) and parenteral hydralazine (29%),\textsuperscript{73} although oral nifedipine may have some advantages.\textsuperscript{74} Women with mild hypertension in pregnancy, no hypertension before pregnancy and who do not develop proteinuria can with close supervision be treated conservatively.\textsuperscript{75}

In established hypertensives in early pregnancy it is realistic to expect the patient to run higher blood pressure levels than the accepted 140/90 mmHg. Setting a higher target reduces anxiety in both patients and their carers. Obstetricians rightly remain concerned about the risk of eclampsia and will have to make the difficult clinical decision on when to intervene. One definition of pregnancy-induced hypertension is a rise of \( > 30 \) mmHg systolic or \( > 15 \) mmHg diastolic compared with readings taken early in pregnancy.\textsuperscript{76}

In severe pre-eclampsia prior to delivery, American practice has relied on magnesium sulphate,\textsuperscript{77} whereas UK or New Zealand practice\textsuperscript{73} has deployed i.m./i.v. hydralazine or short-term use of sodium nitroprusside both backed by phenoxytin therapy. Experimentation into the mode of action of magnesium sulphate has shown that it acts as a local vasodilator of the vascular bed distal to the maternal middle cerebral arteries.\textsuperscript{78} Hydralazine given by either constant infusion or intermittent injection can accumulate causing hypotension. Bolus doses of from 5 to 10 mg should not be given more frequently than 20–30 minutes.\textsuperscript{72} The use of these agents however remains limited to controlling blood pressure over the immediate pre- and post-partum period.

Abnormalities of platelet function are a well-recognized complication of severe pre-eclampsia.\textsuperscript{79} A study of severe pre-eclampsia occurring between 26 and 32 weeks in 67 pre-term pregnancies showed this to be associated with chronic hypertension and renal disease, and adverse effects on fetal outcome.\textsuperscript{80}

Occurrence of the HELLP syndrome (acute haemolysis, abnormal liver function and thrombocytopenia\textsuperscript{81}) is associated with high maternal mortality, a greater incidence of eclamptic crisis, severe hypertension, higher protein excretion and episodes of acute renal failure.\textsuperscript{82} Not surprisingly a case can be made for managing such patients in an intensive care unit.\textsuperscript{83} Fortunately blood pressure normally settles rapidly after delivery but can occur for the first time postpartum.\textsuperscript{84} Despite being in common use it is sometimes forgotten that rebound hypertension occurs on methyl dopa withdrawal. A regime of gradual withdrawal spread over 4 days is recommended. Methyl dopa is not expressed in significant quantities in breast milk. Atenolol withdrawal does not precipitate rebound hypertension to the same degree. Again its concentration in breast milk is not sufficient to affect the baby.\textsuperscript{85} In patients with extensive oedema it is tempting to introduce a diuretic at this stage. These drugs are likely to interfere with lactation and should therefore be avoided if the mother wishes to breast feed.\textsuperscript{86}

Hypertension may recur as a problem around the time of planned discharge. Unless related to drug withdrawal or unrecognized changes in renal function, the blood pressure elevation may be no more than an indicator of stresses placed on the mother at this vulnerable time.

The sixth week postnatal visit is too long a delay before monitoring the changes in blood pressure after delivery. It is unkind or even dangerous to render the mother hypotensive in this period. The midwife will record blood pressure for a 10-day period. The rate of decline in blood pressure and the rate at which anti-hypertensive medication have to be withdrawn can be variable. An assessment around 2 weeks after delivery is necessary and this may have to be repeated before the traditional 6 week postnatal visit. One definition of chronic hypertension in pregnancy requires the patient to remain hypertensive 42 days after delivery.\textsuperscript{87}

In the longer term, certain patients' blood pressure may take as long as 6 months or even a year to return to pre-pregnancy levels. The interrelation between weight and blood pressure is important, an increase in weight of 6 kg is associated with a 9 mmHg increase in diastolic pressure. The speed with which proteinuria declines can be as varied as that of the blood pressure. It is realistic to wait for 6 months before making a final quantification of proteinuria and considering nephrological referral if proteinuria remains above 300 mg/24 hours.

**Postnatal counselling**

During the follow-up period, further counselling will be needed. Patients are likely to have received contraceptive advice at their postnatal visit. An absolute ban on the use of combined oral contraceptive medication for women who have a history of hypertension is often given. These patients are likely to have their blood pressure monitored and, if they request oral contraceptives, can be given a trial course so that the effects on their blood pressure can be assessed. Low-dose oral contraceptives can usually be used safely in non-
smoking younger hypertensives whose blood pressure is well controlled. Women with diabetes and hypertension should not use the combined pill. Older women, smokers and patients with poorly controlled blood pressure can be given progesterin only pills or advised on non-pharmacological alternatives.

Women will also want to know the risk of recurrence of hypertension in subsequent pregnancies. Careful collection of the evidence has shown that hypertension is less likely to be a problem in the second or third pregnancies. A pattern of hypertension increasing in severity with each successive pregnancy, however, is a pointer to severe hypertensive problems both in pregnancy and in later life. The subsequent history of 223 women who had eclampsia is described in a review by Sibai. From a total of 366 subsequent pregnancies 1.9% had eclampsia. Pregnancy outcomes were worse in those women who had experienced eclampsia before 37 weeks' gestation. The question again as to whether an underlying cause of hypertension in the first pregnancy was missed needs to be answered before giving advice concerning future pregnancies. The conundrum of low birth weight and higher placental weight at term as a marker for the development of hypertension in later life independent of maternal blood pressure during pregnancy as described by Barker remains topical.

The wheel has returned full circle to counselling. The process needs to be undertaken early or, as my obstetric colleagues know, you will be confronted with a second pregnancy before having fully evaluated the effects of the first. Although maternal hypertension has adverse effects on perinatal outcome, a small study of 37 children showed that most had normal growth and development in childhood. Recurrent mild hypertension in successive pregnancies remains a marker for the development of chronic hypertension in these women in later life. The pregnancy outcome of 13 women who had chronic hypertension before developing eclampsia showed an alarmingly high risk of severe pre-eclampsia and poor fetal outcome in subsequent pregnancy. The management of hypertension in women should include preconception counselling, the identification of high-risk pregnancies and their continuous monitoring right through to postnatal reassessment.

References


