Hypertension in pregnancy: the NICE guidelines

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Hypertension in pregnancy may indicate a chronic medical problem, gestational hypertension (new hypertension without proteinuria) or pre-eclampsia (new hypertension with new proteinuria). Chronic hypertension can mimic gestational hypertension and strongly predisposes to superimposed pre-eclampsia. Gestational hypertension is often benign but may also be an early stage in the development of pre-eclampsia.

Pre-eclampsia is not benign. Previously the first cause of maternal death in the UK, it is now the second.[1] Maternal deaths from pre-eclampsia have not fallen recently and, most disturbingly, are associated with the highest rates of substandard care, of all causes of maternal deaths.[1] It is also the most important reason for iatrogenic prematurity, a major contributor to perinatal mortality and a substantial cause of fetal growth restriction, especially with preterm disease.[2] Pre-eclampsia cannot be reliably prevented or reversed once it is established except by delivery, which removes the cause—namely, the placenta. Nevertheless, the past 30 years have seen considerable advances in its management. For both mother and baby the outlook is better than it was, at least in the developed world.

The new NICE guidelines for the management of hypertension in pregnancy (available on line at http://www.nice.org.uk/guidance/CG1), comprising more than 1000 pages including appendices, ambitiously review every aspect of management and the evidence upon which recommendations are based. The breadth of the guidelines reflects the complexities of their subject. They deal with many specific obstetric issues but of course the management of hypertension itself is a primary focus. Cardiovascular, obstetric or intensive care doctors will, or may be, involved at some stage, and these guidelines are also addressed to them.

Hypertension is defined as in table 1. Methods of measuring blood pressure are specified separately in the NICE guidelines on antenatal care[3], where the need to use devices validated specifically for use in pregnancy is highlighted. The grading of hypertension is important because the guidelines adopt the principle that moderate hypertension requires treatment (table 1), except for women with chronic hypertension and end-organ damage for whom the blood pressures should be normalised. It is not stated how many readings within what time frame are needed to change a pregnant woman's classification.

PREVENTION

To reduce the risks of hypertensive disorders of pregnancy, specifically of pre-eclampsia, the use of low-dose aspirin, 75 mg/day, from 12 weeks is recommended for women at higher risk. These include those with medical disorders (chronic hypertension, renal disease, diabetes and autoimmune conditions such as lupus); or women with two or more moderate risk factors: first pregnancy, multiple pregnancy, high body mass index (BMI), family history of pre-eclampsia, aged ≥40 years or a prolonged interval between pregnancies of ≥10 years. The benefit of low-dose aspirin is modest, but based on reliable evidence and a good safety profile. There is little evidence for other measures such as nitric oxide donors, progesterone, diuretics or low molecular weight heparin. Nutritional supplements given solely to prevent pre-eclampsia are also not recommended. Lifestyle recommendations are those that apply to all pregnant women.

CHOICE OF ANTIHYPERTENSIVE AGENTS

The problems specific to pregnancy are teratogenicity (first trimester), fetotoxicity (throughout pregnancy) and breast feeding.

ACE inhibitors and angiotensin II receptor blockers are moderately teratogenic and substantially fetotoxic and are therefore contraindicated throughout pregnancy. Women receiving such agents for chronic hypertension should be reviewed before pregnancy and offered alternative medication before conception or advised to consult as soon as pregnancy is confirmed to change treatment at that time. Chlorothiazide is identified as a possible teratogen and therefore best avoided.

These issues are analysed in a reasonably balanced overview, while acknowledging repeatedly that there is not much high-quality evidence upon which to base recommendations. None is made about which drug to use during pregnancy for pre-existing hypertension because of lack of specific evidence. Labetalol is recommended as the first choice for gestational and pre-eclamptic hypertension. Alternatives include methyldopa or nifedipine.

POSTNATAL ISSUES

Postnatal issues include continuing management of hypertension, medication in relation to breast feeding and long-term cardiovascular health of the mother. The guidelines interpret what little evidence there is pragmatically. They advise against the use of methyldopa not because of breast feeding concerns but because of its potential to aggravate postnatal depression. The other antihypertensive drugs used during pregnancy appear to be safe, as do, captopril and enalapril, which are contraindicated before delivery.

It is now known that pre-eclampsia is a harbinger of later arterial disease and the guidelines summarise the evidence clearly. Women should be advised of

Table 1 Grading of severity of hypertension and the need for antihypertensive treatment

Grade of hypertension	Blood pressure levels EITHER systolic OR diastolic at stated levels (mm Hg)	Treat	Levels after treatment
Mild	Diastolic: 90–99 Systolic: 140–149	No*	Not applicable*
Moderate	Diastolic: 100–109 Systolic: 150–159	Yes	<150 systolic* <100 diastolic*
Severe hypertension	Diastolic: ≥110 Systolic: ≥169	Yes	<150 systolic* <100 diastolic*

*Women with chronic hypertension and end-organ damage should be treated even if blood pressure is mild with the aim of normalising the blood pressure.

these risks but specific plans of follow-up cannot yet be recommended without better evidence. However, pre-eclampsia is an important component of a woman's medical history if or when she comes under cardiovascular review in later life.

THRESHOLD FOR ANTIHYPERTENSIVE TREATMENT: A CONTENTIOUS ISSUE

The author believes that the low threshold set for treating all hypertension regardless of cause or stage of pregnancy is inappropriate. Principles of antihypertensive treatment developed for older people of both sexes to accrue long-term benefit are probably less relevant to young women for the brief duration of pregnancy, when the welfare of the fetus must also be taken into account. A primary reason for controlling blood pressure in pregnancy is to prevent severe hypertension and maternal haemorrhagic strokes, which are more common in pregnancy, specifically in relation to pre-eclampsia. One of the top 10 recommendations of the confidential enquiry into maternal deaths for 2003–2005[4] was based on a key paper,[5] which provided evidence that systolic pressures of ≥160 mm Hg, in the context of severe pre-eclampsia or eclampsia only, should be treated to prevent cerebral haemorrhage. However, the authors of the confidential enquiry into maternal deaths report broadened the proposal to include all pregnant hypertensive women. Now NICE have moved the goal posts even further by lowering the threshold for treatment to 150 mm systolic (for all stages of pregnancy and all causes of hypertension) or below 140/90 if there is evidence for secondary end-organ damage.

But the guidelines clearly indicate that there is not sufficient evidence to assess the effectiveness of such treatment while other evidence, not cited by NICE, does not support this broad brush that is nevertheless adopted. Of more than 35 000 000 pregnancies in the USA (1998–2006), gestational hypertension alone, without pre-eclampsia, was not associated with a significantly increased risk of cerebral haemorrhage.[6] Chronic hypertension was so associated, but to a lesser extent than pre-eclampsia. This category included all cases with superimposed pre-eclampsia, which might fully explain this statistic. The risks of hypertensive haemorrhagic stroke in pregnancy appear to be more or less specific to pre-eclampsia/eclampsia. Pre-eclampsia is more than hypertension,[7] being a profound vascular inflammatory state[8] involving, among other changes, coagulopathy, and also a predisposition to cerebral haemorrhage. The vulnerability of cerebral arteries to hypertensive damage appears to be increased in this context. The threshold is right for pre-eclampsia, superimposed or not, but too low for gestational hypertension or uncomplicated chronic hypertension.

For pre-existing hypertension the main concern is the prevention of superimposed pre-eclampsia or placental pathology, such as abruption. There is as yet no evidence that antihypertensive treatment confers such benefits. Gestational hypertension may precede the onset of pre-eclampsia, but the later it develops the less likely is this progression.[9] Safe treatment that hinders this progression is much needed. A 'high-quality' trial (the only one) is

Box 1 Key guideline points for physicians

Reducing the risk of hypertensive disorders in pregnancy

- Advise women at high risk of pre-eclampsia to take 75 mg of aspirin daily from 12 weeks until the birth of the baby. High risk includes those with:
  - Hypertensive disease during a previous pregnancy
  - Chronic kidney disease
  - Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
  - Type 1 or type 2 diabetes
  - Chronic hypertension

Management of pregnancy with chronic hypertension

- Tell women who take ACE inhibitors or angiotensin II receptor blockers:
  - That there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy
  - To discuss other antihypertensive treatment with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy
- In pregnant women with uncomplicated chronic hypertension aim to keep blood pressure lower than 150/100 mm Hg

Assessment of proteinuria in hypertensive disorders of pregnancy

- Use an automated reagent-strip reading device or a spot urinary protein: creatinine ratio for estimating proteinuria in a secondary care setting

Management of pregnancy with gestational hypertension

- Offer women with gestational hypertension an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests

Management of pregnancy with pre-eclampsia

- Offer women with pre-eclampsia an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests
- Consultant obstetric staff should document in the woman's notes the maternal (biochemical, haematological and clinical) and fetal thresholds for elective birth before 34 weeks in women with pre-eclampsia
- Offer all women who have had pre-eclampsia a medical review at the postnatal review (6–8 weeks after the birth)

Advice and follow-up care at transfer to community care

- Tell women who had pre-eclampsia that their risk of developing:
  - Gestational hypertension in a future pregnancy ranges from 13% to 53%
  - Pre-eclampsia in a future pregnancy is 16%
  - Pre-eclampsia in a future pregnancy is 25% if their pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks, and 55% if it led to birth before 28 weeks

cited to show that, indeed, tighter blood pressure control[10] does just this, and seems strongly to have influenced the recommendations for relatively low thresholds for antihypertensive treatment. But certain biases are not considered. If high blood pressure alone is a trigger to obstetric intervention then tight control may prolong pregnancy or reduce hospitalisation not because of a beneficial effect on the pregnancy but by preventing inappropriate clinical interventions. Similarly, early and effective use of antihypertensive treatment for gestational hypertension, may delay recognition of pre-eclampsia, because its diagnosis depends on blood pressure levels.

Pre-eclampsia causes not only severe hypertension, but dysfunction of other systems, such as eclampsia (convulsions) or the HELLP syndrome (hepatocellular damage and coagulopathy). The latter results from acute endothelial dysfunction (not hypertension) secondary to placental derived circulating factors.[11] They are driven by placental oxidative stress. It is not clear why blood pressure control, which treats processes downstream from this pathology, may affect the upstream problems.

AN UNACKNOWLEDGED TIME BOMB

With lower thresholds for antihypertensive treatment many more pregnant women (and their fetuses) with moderate hypertension will be exposed to medication without clear evidence of benefit. Drug exposure is likely to be short for pre-eclampsia (usually no longer than 2 weeks) but longer for gestational or pre-existing hypertension (for months or even throughout pregnancy). The numbers needed to treat women with uncomplicated moderate gestational or chronic hypertension to prevent one cerebrovascular haemorrhage are not quantified, but likely to be very high. The drugs used, labetalol, methyldopa or nifedipine seem to be safe in the short-term. But long-term intrauterine exposure might affect intrauterine programming, with consequences not manifest until adult life. Fetal programming has been studied in relation to fetal nutrition, metabolism and stress[12] but it is likely that intrauterine drug exposure could have epigenetic effects with long-term consequences. Whether they matter is not known. They have not been considered. In such circumstances it would be wise to avoid large-scale, long-term drug use in pregnancy as these guidelines recommend, without better evidence than is presented. By focusing on the sign (hypertension) not the disease (pre-eclampsia) the imperative to treat pre-eclamptic hypertension adequately is blurred. The latter is the only situation where the lower thresholds are clearly justified.

STRENGTHS AND WEAKNESSES

Box 1 summarises the key guideline points that are relevant to physicians involved with managing pregnant women with hypertension. The guidelines inform inexperienced clinical staff of a minimum standard of practice that is firmly guided away from unvalidated or poorly validated 'fringe practices'. They highlight the absence of research in this area. For this reason they are inevitably in many respects a consensus statement based on opinion rather than facts.

Although they are a huge achievement, they should not be accepted uncritically. Large randomised controlled trials (RCTs) and statistical analyses, especially meta-analyses, are blunderbuss tools. They mean little without clear insights into pathogenic mechanisms. It is significant that the word mechanism is not mentioned once in the entire document. RCTs are extremely expensive because they must be large. They have two benefits: where there is good evidence for benefit which is denied irrationally, as that for magnesium sulphate to prevent eclampsia[13]; or to refute clinical management that is based on tradition or conviction without evidence. The guidelines call for RCTs that compare antihypertensive agents against each other for the control of relatively moderate hypertension in pregnancy. These are not going to revolutionise the outlook for pregnant women.

This guideline does not state its limitations. The weaknesses of the methods are not highlighted. Young clinicians will consider this to be 'the gospel' and managers who know nothing of the issues except the burden on their budgets will consider this to be the law. The danger is that management will be immobilised in a strait jacket and a new set of prejudices will replace the old, while real progress may be hindered.

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