GUIDELINES

Management of hypertensive disorders during pregnancy: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists Further information about the guidance, a list of members of the guideline development group, and the supporting evidence statements are in the full version on bmj.com.

Why read this summary?

Hypertensive disorders of pregnancy cover a spectrum of conditions, including chronic (pre-existing) hypertension, pre-eclampsia, and gestational hypertension (box 1). These conditions are associated with increased perinatal mortality and morbidity. Hypertensive disorders cause one in 50 stillbirths in normal babies and 10% of all preterm births. They contribute to a third of cases of severe maternal morbidity.[1] Pre-eclampsia is one of the most common causes of maternal death in the United Kingdom.[2] This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on how to manage hypertensive disorders during pregnancy.[3]

Box 1 | Definitions

Chronic hypertension: hypertension present at booking visit or before 20 weeks' gestation, or being treated at time of referral to maternity services; can be primary or secondary in aetiology

Clinically relevant proteinuria: more than 300 mg protein in a 24 hour urine collection or more than 30 mg/mmol in a spot urinary protein:creatinine sample

HELLP syndrome: haemolysis, elevated liver enzymes, and low platelet count

Gestational hypertension: new hypertension presenting after 20 weeks' gestation without clinically relevant proteinuria

Mild hypertension: diastolic blood pressure 90-99 mm Hg, systolic blood pressure 140-149 mm Hg

Moderate hypertension: diastolic blood pressure 100-109 mm Hg, systolic blood pressure 150-159 mm Hg

Pre-eclampsia: new hypertension presenting after 20 weeks' gestation with clinically relevant proteinuria

Severe hypertension: diastolic blood pressure 110 mm Hg or greater, systolic blood pressure 160 mm Hg or greater

Severe pre-eclampsia: pre-eclampsia with severe hypertension or with symptoms, biochemical abnormalities, or haematological impairment (or any combination thereof)

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Reducing the risk of hypertensive disorders in pregnancy

- Advise pregnant women of their risk of developing hypertensive disorders during pregnancy (in particular pre-eclampsia; see box 2) and of the need to seek immediate advice from a healthcare professional if they experience symptoms of pre-eclampsia (severe headache; problems with vision, such as blurring or flashing before the eyes; severe pain just below the ribs; vomiting; sudden swelling of face, hands, or feet).
- Advise women with at least one high risk factor for pre-eclampsia or at least two moderate risk factors for pre-eclampsia (box 2) to take 75 mg of aspirin daily from 12 weeks until the birth of the baby.
- Although several drugs (nitric oxide donors, progesterone, diuretics, and low molecular weight heparin) and vitamin and nutrient supplements (such as vitamin C, vitamin E, folic acid, magnesium, fish oils, algal oils, and garlic) have been studied as preventive treatments for hypertensive disorders, these have not shown benefit and should not be given for this purpose. The evidence for added calcium in the prevention of hypertensive disorders is conflicting and confusing, and more research is needed in this area.

Chronic hypertension

Preconception

- Tell women taking angiotensin converting enzyme inhibitors and angiotensin II receptor blockers that taking these drugs during pregnancy increases the risk of congenital abnormalities, and that they should discuss other antihypertensive treatments with their healthcare professional if they are planning pregnancy.
- Tell women taking chlorothiazide diuretics that taking these drugs during pregnancy increases the risk of congenital abnormalities and neonatal

complications, and that they should discuss other antihypertensive treatments with their healthcare professional if they are planning pregnancy.
- Reassure women taking antihypertensive treatments other than angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or chlorothiazide diuretics that the limited evidence available has not shown an increased risk of congenital malformation with such treatments.

Antenatal care
- Antihypertensive treatment should be offered but be dependent on pre-existing treatment, side effect profiles, and teratogenicity.
- If women taking angiotensin converting enzyme inhibitors or angiotensin II receptor blockers become pregnant, stop these drugs and offer alternatives.
- Aim to keep blood pressure lower than 150/100 mm Hg in pregnant women with uncomplicated chronic hypertension but do not lower diastolic blood pressure below 80 mm Hg.
- Schedule additional antenatal consultations on the basis of the woman and her baby's needs.
- Do not offer birth before 37 weeks' gestation if blood pressure is lower than 160/110 mm Hg, with or without antihypertensive treatment.

New onset hypertension during pregnancy

Assessment of proteinuria
- To diagnose pre-eclampsia and distinguish it from gestational hypertension, use an automated reagent strip reading device or spot urinary protein:creatinine ratio for estimating proteinuria in secondary care.
- If an automated reagent strip reading device is used to detect proteinuria and a result of 1+ or more is obtained, use a spot protein:creatinine ratio or 24 hour urine collection to quantify proteinuria.
- Diagnose clinically relevant proteinuria if the urinary protein:creatinine ratio is greater than 30 mg/mmol or a validated 24 hour urine collection shows greater than 300 mg protein.
- Where 24 hour urine collection is used to quantify proteinuria, a recognised method of evaluating completeness of the sample should be used.

Box 2 | Risk factors for pre-eclampsia

Moderate risk
Age 40 years or more
First pregnancy
Multiple pregnancy
Interval since last pregnancy of more than 10 years
Body mass index of 35 or more at presentation
Family history of pre-eclampsia

High risk
Chronic hypertension
Chronic kidney disease
Hypertensive disease during a previous pregnancy
Diabetes
Autoimmune disease

Management of gestational hypertension
- Offer an integrated package of care covering assessment in hospital by a healthcare professional trained in managing hypertensive disorders; possible hospital admission; treatment; and monitoring of blood pressure, proteinuria, and blood tests as indicated in table 1.

Management of pre-eclampsia
- Assess women with pre-eclampsia at each consultation; assessment should be performed by a healthcare professional trained in the management of hypertensive disorders of pregnancy.
- Offer an integrated package of care covering admission to hospital; treatment; and monitoring of blood pressure, proteinuria, and blood tests as indicated in table 2.
- Manage pregnancy conservatively (do not plan same day delivery of the baby) until 34 weeks' gestation.
- Consultant obstetric staff should document in the woman's notes maternal and fetal biochemical, haematological, and clinical thresholds for birth before 34 weeks' gestation and write a plan for fetal monitoring during birth.

Fetal monitoring
- In women with chronic hypertension, carry out ultrasound assessment of fetal growth and amniotic fluid volume and umbilical artery Doppler velocimetry between 28 and 30 weeks' gestation and between 32 and 34 weeks' gestation. If results are normal, do not repeat after 34 weeks' gestation, unless clinically indicated.
- In women with mild or moderate gestational hypertension diagnosed at less than 34 weeks' gestation, carry out ultrasound assessment of fetal growth and amniotic fluid volume and umbilical artery Doppler velocimetry. If results are normal, do not repeat after 34 weeks' gestation, unless clinically indicated.
- In women with severe gestational hypertension or pre-eclampsia, carry out cardiotocography at diagnosis. If conservative management is planned, carry out ultrasound assessment of fetal growth and amniotic fluid volume and umbilical artery Doppler velocimetry at diagnosis; if results are normal, do not repeat more than every two weeks. Do not repeat cardiotocography more than weekly if results of all fetal monitoring are normal.

Intrapartum care
- During labour, measure blood pressure hourly in women with mild or moderate hypertension, and continually in women with severe hypertension.
- Continue antenatal antihypertensive treatment during labour.
- Determine the need for haematological and biochemical tests during labour in women with mild

Table 1 | Management of gestational hypertension

Management option	Degree of hypertension*		
	Mild hypertension	Moderate hypertension	Severe hypertension
Admit to hospital	No	No	Yes (until blood pressure is ≤159/109 mm Hg)
Treat	No	With oral labetalol as first-line treatment to keep diastolic blood pressure between 80 and 100 mm Hg, and systolic blood pressure <150 mm Hg	With oral labetalol as first line treatment to keep diastolic blood pressure between 80 and 100 mm Hg, and systolic blood pressure <150 mm Hg
Measure blood pressure	Not more than once a week	At least twice a week	At least four times a day
Test for proteinuria	At each visit using automated reagent strip reading device or urinary protein:creatinine ratio	At each visit using automated reagent strip reading device or urinary protein:creatinine ratio	Daily using automated reagent strip reading device or urinary protein:creatinine ratio
Blood tests	Only those for routine antenatal care	Test kidney function, electrolytes, full blood count, transaminases, bilirubin; do not carry out further blood tests if no proteinuria is seen at subsequent visits	At presentation and then weekly, test kidney function, electrolytes, full blood count, transaminases, and bilirubin

*Mild hypertension is 140/90-149/99 mm Hg; moderate hypertension is 150/100-159/109 mm Hg; severe hypertension is ≥160/110 mm Hg.

Table 2 | Management of pre-eclampsia

Management option	Degree of hypertension*		
	Mild hypertension	Moderate hypertension	Severe hypertension
Admit to hospital	Yes	Yes	Yes
Treat	No	With oral labetalol as first line treatment to keep diastolic blood pressure between 80 and 100 mm Hg, and systolic blood pressure <150 mm Hg	With oral labetalol as first line treatment to keep diastolic blood pressure between 80 and 100 mm Hg, and systolic blood pressure <150 mm Hg
Measure blood pressure	At least four times a day	At least four times a day	More than four times a day, depending on clinical circumstances
Test for proteinuria	Do not repeat measurement of proteinuria	Do not repeat measurement of proteinuria	Do not repeat measurement of proteinuria
Blood tests	Monitor kidney function, electrolytes, full blood count, transaminases, and bilirubin twice a week	Monitor kidney function, electrolytes, full blood count, transaminases, and bilirubin three times a week	Monitor kidney function, electrolytes, full blood count, transaminases, and bilirubin three times a week

*Mild hypertension is 140/90-149/99 mm Hg; moderate hypertension is 150/100-159/109 mm Hg; severe hypertension is ≥160/110 mm Hg.

or moderate hypertension using the same criteria as for the antenatal period (even if regional analgesia is being considered).
- If low dose epidural analgesia or combined spinal epidural analgesia is needed in women with severe pre-eclampsia, do not preload with intravenous fluids.

Medical management of severe hypertension or severe pre-eclampsia in critical care

- The full guideline includes recommendations on criteria for referral to critical care, management of severe hypertension (including antihypertensive treatment and blood pressure measurement), anticonvulsants, corticosteroids (use betamethasone for fetal lung maturation but do not use betamethasone or dexamethasone for treatment of HELLP syndrome (box 1)), and fluid balance and volume expansion.
- Choose the mode of birth (induction of labour or caesarean section) according to the clinical circumstances and the woman's preference.

Postnatal care and follow-up care

- The full guideline includes recommendations on antihypertensive treatment and blood pressure measurement in the postnatal period.
- Tell women that labetalol, nifedipine, enalapril, captopril, atenolol, and metoprolol have no known adverse effects on babies receiving breast milk.
- Tell women that there is insufficient evidence on the safety of angiotensin II receptor blockers, amlodipine, and angiotensin converting enzyme inhibitors other than enalapril and captopril in babies receiving breast milk.
- Offer a medical review at the postnatal review (six to eight weeks after the birth).
- At transfer to community care tell women who have had gestational hypertension or pre-eclampsia that they have an increased risk of these conditions occurring in future pregnancies and an increased risk of developing high blood pressure and its complications in later life.

Overcoming barriers

Management of hypertensive disorders in pregnancy is thought to vary considerably, with many practices reflecting tradition rather than being evidence based. The recommendations and the supporting evidence should give healthcare professionals confidence to reduce the frequency of unnecessary tests and assessments in women with mild or moderate disease, yet emphasise an escalating approach to care that is centred more on individual women. The guidance may reduce interventions that result in morbidity, such as preterm birth, and may better target interventions that are likely to benefit the woman and her baby. Such changes are more likely to be adopted by clinicians, as are the many cost saving aspects of this guidance. Informed dialogue is another powerful driver of change: emphasising prevention, increasing information for women themselves, and increasing awareness of signs and symptoms from existing NICE guidance for routine antenatal care[4] should empower pregnant women to have such dialogue with their healthcare professionals.

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Previous articles in this series

- Diagnosis and management of adults with chronic heart failure (*BMJ* 2010;341:4130)
- Diagnosis, prevention, and management of delirium (*BMJ* 2010;341:c3704)
- Management of bacterial meningitis and meningococcal septicaemia in children and young people (*BMJ* 2010;340:c3209)

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RATIONAL TESTING

Investigating fatigue in primary care

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School.

Tiredness is a common presentation in general practice, but how useful are investigations, and what tests should be done and how soon?

A 48 year old teacher with a two month history of continuing tiredness visits her general practitioner. She has an unremarkable medical history and no history of recent infection, and she denies unusual stress. She has not lost any weight. Clinical examination is normal with a blood pressure of 130/75 mm Hg, a regular pulse at 70 beats per minute, and no lymphadenopathy.

The problem

Fatigue is a normal part of life, but it can also be a symptom of disease, including serious illnesses. It is a common complaint in primary care, exceeded only by complaints of cough.[1] Five to seven per cent of patients attending primary care have a primary complaint of fatigue, with this proportion being remarkably consistent across Western countries[2-5] and over time.[4] The proportion of patients presenting with fatigue as an additional complaint is nearly three times as high.[3 6] Almost three quarters of consultations for fatigue are isolated episodes, with no follow-up consultations on the subject.[5] This is presumably because most patients' fatigue improves,[7] especially if there is a time limited explanation, such as a recent infection.[8 9]

It is not surprising, therefore, that general practitioners perform investigations in only half of patients complaining of fatigue[10] and that few of these tests yield abnormal results.[10 11] Even so, the high incidence of the fatigue complaints means that laboratory tests for fatigue account for almost 5% of the total number of laboratory tests ordered by general practitioners.[12]

The likelihood of finding a diagnosis

A diagnosis is made in less than half of patients with fatigue; furthermore, many of the diagnoses are descriptive, such as stress, or are one of the many synonyms for fatigue itself.[6] Patients understand that an underlying identifiable disease may not be present,[6] though patients' and doctors' beliefs are sometimes mismatched, with a higher proportion of doctors than patients considering the particular problem to be psychological.[13]

Precipitating factors for consultation can be stressful life events (underlying about two thirds of fatigue complaints)—for example, work disputes, family problems, bereavement, or financial difficulties; or they can be illnesses such as respiratory tract infections. Hypothyroidism and anaemia are identified in under 3% of patients.[10] Other conditions, such as Addison's disease, renal failure, liver failure, carbon monoxide poisoning, coeliac disease, pregnancy, domestic abuse, and sleep apnoea are all rare, though each may (rarely) present with fatigue as a predominant complaint. Indeed, almost any condition can do so.

History and examination

After the initial history taking, ask questions about the main organ systems, particularly about bleeding (menorrhagia, gastrointestinal), gastrointestinal symptoms, urinary symptoms (including polyuria and polydipsia), quality and length of sleep (sleep apnoea being characterised by episodes of night-time breathlessness, daytime sleepiness, and often snoring), recent infections, joint pains or swelling, and mental health problems including concentration, motivation, stressful events, and mood. Review prescribed and over the counter medications for iatrogenic fatigue and ask specifically about alcohol consumption. Examine the patient,

LEARNING POINTS

Tiredness is a common complaint, reported in 5-7% of general practice encounters
Investigations may exclude diagnosis and reassure the patient, but they have a low rate of identifying any underlying disease
Investigations are warranted in those who have not recovered after one month or whose initial presentation is atypical or is associated with "red flag" symptoms
Be alert for important but easily missed conditions such as carbon monoxide poisoning, coeliac disease, pregnancy, and sleep apnoea
Further evidence is needed to establish best practice in the investigation of the tired patient

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Previous articles in this series

- Investigating mildly abnormal serum aminotransferase values (*BMJ* 2010;341:c4039)
- Investigating symmetrical polyarthritis of recent origin (*BMJ* 2010;340:c3110)
- Investigating hirsutism (*BMJ* 2009;338:b912)

Investigations requested after four weeks for patients who presented to their general practitioner with fatigue

Investigations	Proportion (%) of patients for whom test is requested[12]	Abnormality rate (%)[12]	When to consider test	Type of evidence
Full blood count	74	12.0	Always	Randomised trial evidence from primary care[15]
Thyroid function tests	47	6.8	Always	
Random glucose	19	Not known	If symptoms suggest or if the patient is obese	
Erythrocyte sedimentation rate or plasma viscosity	12	32.0	Always	
C reactive protein	Not known	Not known	If persistent infection is suspected	Cohort studies in primary care[21]
Coeliac disease	Not known	Not known	Second line or if any gastrointestinal symptoms	Cohort studies in primary care[22]
Creatinine and electrolytes	23	10.9	Age >60 years or if other symptoms such as itching or polyuria[14]	Randomised trial evidence from primary care[15]
Liver function tests	34	9.7	Age >60 years or with alcohol excess or drug misuse[14]	
Calcium	Not known	Not known	If symptoms suggest hypercalcaemia	Case reports
Ferritin	20	9.1	Women of childbearing age	Randomised trial evidence from primary care[23]
Glandular fever*	Not known	Not known	Patients aged <40 years with recent infection[14]	Cohort studies in primary care[24]
Depression screening tool, often PHQ-9[25]	Not known	17[26]	If symptoms suggest	Cohort studies in primary care[26]

*The heterophil antibody (Monospot) test is the most appropriate test, though this may be negative in the first week of glandular fever. Epstein-Barr virus IgM may be detectable at an earlier stage, but this is unlikely to be needed in the context of a fatigue complaint.

including urine analysis and blood pressure measurement. Patients with Addison's disease may have postural hypotension, as well as increased pigmentation.

What is the next investigation?

Rational investigation aims to allow most patients to forgo testing and improve spontaneously, while identifying the few patients with underlying disease reasonably quickly. Younger patients are less likely to have underlying disease, as are patients who consult frequently.[1 10] Recent infection or stressful events can justify deferral of testing. Time can be a diagnostician as well as a healer, although it is probably advisable to offer a specific time for review rather than a vague "return if you don't improve." Take action accordingly when red flag symptoms or signs are detected; most are obvious (box).

Investigations are warranted in those who have not recovered at about four weeks,[15 16] although they may be warranted at presentation if this is atypical (an older patient or a patient who consults infrequently)[17] or if clinical features suggest a diagnosis (such as polyuria and polydipsia). Clinical intuition has also been shown to have a useful role: the "art of general practice" is in noting a slightly unusual presentation from knowledge of the individual.[18]

First line investigations should be targeted at picking up the relatively common diagnoses. Evidence from one randomised trial suggests that a limited set of blood tests (haemoglobin, erythrocyte sedimentation rate, glucose, and thyroid stimulating hormone) is almost as useful diagnostically as a more extensive set of tests.[15] Whether mild hyperglycaemia causes fatigue is not clear, but one study of fatigue complaints in primary care found abnormalities of blood glucose more often than anaemia or hypothyroidism.[15] The National Institute for Health and Clinical Excellence also recommends testing for coeliac disease in people with persistent fatigue, even when no other suggestive symptoms are present.[19] Depending on the circumstances, additional first line tests may be appropriate (table).

If first line tests are normal, a period of watchful waiting can sensibly follow. If tiredness has persisted for three months or if further suggestive symptoms have developed, then a second line of testing is reasonable. If tiredness persists for at least four months without a clear explanation, a diagnosis of chronic fatigue syndrome should be considered.[20] Referral may be indicated if the patient or doctor continues to be concerned.

Outcome

In this case, as the patient has no red flag or suggestive symptoms and no abnormal findings, the likely temporary nature of the fatigue is discussed, together with some of the

Red flags*

- Weight loss
- Lymphadenopathy (such as a lymph node that is non-tender, firm, hard, >2 cm in diameter, progressively enlarging, supraclavicular, or axillary)
- Any other features of malignancy (such as haemoptysis, dysphagia, rectal bleeding, breast lump, postmenopausal bleeding)
- Focal neurological signs
- Features of inflammatory arthritis, vasculitis, or connective tissue disease
- Features of cardiorespiratory disease
- Sleep apnoea
- *All the above are supported by narrative reviews from cohort and/or case-control studies conducted in primary or secondary care or are population based (sleep apnoea).[14]

possible common precipitating factors. She is happy with a plan to return after one month for routine blood tests (full blood count, thyroid function tests, and erythrocyte sedimentation rate and viscosity) if things have not improved. In fact, she attends a couple of months later for a different problem and comments that her fatigue has improved, probably as she has resolved a difficulty at work.

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ANSWERS TO ENDGAMES, p 511. For long answers go to the Education channel on bmj.com

ANATOMY QUIZ

Sagittal T2 weighted magnetic resonance image of the brain

A Genu corpus callosum
B Lateral ventricle
C Pituitary stalk
D Splenium
E Quadrigeminal plate

STATISTICAL QUESTION

Prevalence and incidence

a, *b*, *c*, and *d* are all true.

ON EXAMINATION QUIZ

Penicillins

Answers A, B, and C are all true, whereas D and E are false.

CASE REPORT Persistent cough and weight loss

1 **Multidrug resistant tuberculosis is defined as *M tuberculosis* that is resistant to at least rifampicin and isoniazid. Extensively drug resistant tuberculosis is defined as *M tuberculosis* that is resistant to rifampicin, isoniazid, any fluoroquinolone, and at least one of the three injectable second line agents (amikacin, kanamycin sulphate, and capreomycin). This patient has extensively drug resistant tuberculosis.**
2 **The patient will require therapy with second line agents and admission to a negative pressure room for infection control. She should also be referred to a tertiary centre experienced in the management of drug resistant tuberculosis.**
3 **Public health services must be informed without delay. Cases of multidrug resistant or extensively drug resistant tuberculosis warrant a formal case conference to identify issues relating to patient isolation, contact tracing, and media liaison. Contacts at risk of infection need to be identified and offered screening.**
4 **Cure rates for aggressively managed extensively drug resistant tuberculosis are 60% among patients who do not have HIV.**
5 **The 2006 National Institute for Health and Clinical Excellence (NICE) guidelines identify six key risk factors for drug resistance in the UK: a history of previous drug treatment for tuberculosis; birth in a foreign country (particularly sub-Saharan Africa and the Indian subcontinent); HIV infection; residence in London; age 25-44 years; and male gender.**
6 **Tests based on the polymerase chain reaction can be performed on sputum samples to detect resistance mutations in three tuberculosis genes associated with resistance to rifampicin *(rpoB)* and isoniazid *(katG and inhA)*.**