Management of pre-eclampsia

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Pre-eclampsia is part of a spectrum of conditions known as the hypertensive disorders of pregnancy (box 1).¹ A multisystem disorder usually associated with raised blood pressure and proteinuria, pre-eclampsia is relatively common, affecting 2-8% of pregnancies. Although outcome is often good, pre-eclampsia can be devastating and life threatening for both mother and baby (box 2), particularly in developing countries.² It may also lead to an increased risk of cardiovascular disease in later life.

Although the cause is not fully understood, factors thought to have a role include genes, the placenta, the immune response, and maternal vascular disease.³ Inadequate blood supply to the placenta leads to endothelial dysfunction, which accounts for the secondary changes in maternal target systems (such as platelet aggregation and vasoconstriction) responsible for the signs and symptoms of pre-eclampsia (box 3).

Effective care includes identification and referral of women at high risk, prompt diagnosis with prevention and treatment of complications, and timely delivery (the only definitive cure). This review summarises current evidence on management of pre-eclampsia.

Methods

We searched *The Cochrane Database of Systematic Reviews*, the trials register of the Cochrane Pregnancy and Childbirth Group, CENTRAL and EMBASE for systematic reviews and randomised trials. Searches were updated in November 2005. Details of the search strategy are summarised on bmj.com. We also identified systematic reviews of studies assessing risk factors for pre-eclampsia. References for trials and reviews are on bmj.com.^{w1-w28}

Screening and diagnosis

Assessment usually begins when a woman presents to a general practitioner or midwife requesting antenatal care (box 4). Women at high risk are then offered further visits and testing, with referral for specialist care.⁴ Screening of low risk women is based primarily on blood pressure measurement and urine analysis. The search for additional tests continues.⁵ Despite initial optimism for uterine artery Doppler ultrasonography, it has only limited accuracy in predicting pre-eclampsia.

Women with blood pressure >140/90 mm Hg should be referred for specialist assessment. A relative rise in blood pressure or oedema is not related to out-

Summary points

Pre-eclampsia is the commonest medical complication of pregnancy and is associated with substantial morbidity and mortality for both mother and baby. The only definitive "cure" is delivery

All pregnant women should have regular assessment of their blood pressure and urinary analysis for proteinuria. Women at high risk should be referred for specialist antenatal care

Low dose aspirin reduces the risk of pre-eclampsia and of the baby dying. Calcium supplements have moderate benefits for women with low dietary intake

Women with blood pressure >140/90 mm Hg or pre-eclampsia should be referred for specialist assessment. For mild to moderate hypertension, antihypertensive drugs help prevent hypertensive crisis

Women with severe hypertension should be admitted to hospital for monitoring and control of their blood pressure

Magnesium sulphate for women with pre-eclampsia halves the risk of eclampsia and is the drug of choice for treating eclamptic fits. Phenytoin, lytic cocktail, and diazepam should not be used

After a pregnancy complicated by pre-eclampsia, women should be advised of the risk of recurrence and assessed for chronic hypertension and other underlying conditions

come, and neither is an indication for routine screening.¹ Because of cardiovascular changes, automated blood pressure monitors systematically underestimate blood pressure in pregnancy and pre-eclampsia. If used, they should be calibrated regularly against a mercury sphygmomanometer (box 5).⁷

Extra references w1-w50, extra figures A-E, and details of the literature search, ongoing research, and the situation in developing countries appear on bmj.com

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Box 1: Classification of the hypertensive disorders of pregnancy**Gestational hypertension (pregnancy induced hypertension)**

- Hypertension detected for the first time after 20 weeks' gestation, in the absence of proteinuria
- Hypertension defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg
- Resolves within three months after the birth

Pre-eclampsia and eclampsia

- Hypertension and proteinuria detected for the first time after 20 weeks' gestation
- Hypertension defined as above
- Proteinuria defined as ≥ 300 mg/day or ≥ 30 mg/mmol in a single specimen or $\geq 1+$ on dipstick
- Eclampsia is the occurrence of seizures superimposed on the syndrome of pre-eclampsia

Chronic hypertension

- Hypertension known to be present before pregnancy or detected before 20 weeks' gestation
- "Essential" hypertension if there is no underlying cause
- "Secondary" hypertension if associated with underlying disease

Pre-eclampsia superimposed on chronic hypertension

- Onset of new signs or symptoms of pre-eclampsia after 20 weeks' gestation in a woman with chronic hypertension

If possible, proteinuria should be confirmed in a 24 hour collection. The diagnosis of pre-eclampsia is more certain if other organ systems are implicated (box 3). Onset of pre-eclampsia may be rapid, and prompt diagnosis and treatment often depends on awareness among women and primary care workers of these signs and symptoms.

Primary prevention of pre-eclampsia

Assessment of whether any intervention does more good than harm depends not only on whether the risk of pre-eclampsia is reduced (figure) but also on the impact on more substantive outcomes, such as perinatal death and preterm birth.

Lifestyle choices

Rest and exercise are known to affect hypertension. Whether changes in a woman's level of activity during pregnancy influences her risk of pre-eclampsia is less

Box 3: Symptoms and signs associated with pre-eclampsia

- Hypertension and proteinuria (see box 1)
- Persistent severe headache
- Persistent new epigastric pain
- Visual disturbances (such as blurred vision, diplopia, or floating spots)
- Vomiting
- Hyperreflexia, with brisk tendon reflexes
- Epigastric pain or tenderness
- Severe swelling of hands, face, or feet of sudden onset
- Serum creatinine concentration increased ($> 110 \mu\text{mol/l}$)
- Platelet count reduced to $< 100 \times 10^9/\text{l}$
- Evidence of microangiopathic haemolytic anaemia
- Liver enzyme activity elevated (alanine aminotransferase, aspartate aminotransferase, or both)

clear. For normotensive high risk women, two small trials of uncertain quality suggest that rest, for up to four hours a day at home, may reduce the risk of pre-eclampsia (figure). For those with hypertension, it is unclear whether rest in hospital offers any advantage over normal activity. Taking more exercise may reduce the risk of pre-eclampsia, although again data are sparse. As none of this evidence is strong, the balance between rest and exercise should depend on each woman's personal preference.

Diet and nutrition

There is no clear evidence that advising pregnant women to increase their energy intake, providing energy or protein supplements, or prescribing a low energy diet to overweight women protects against pre-eclampsia. Also unclear is whether advice to reduce dietary salt intake during pregnancy has any impact.

Several nutritional agents have been suggested to have a role in preventing pre-eclampsia. Dietary supplementation with at least 1 g of calcium a day reduces the relative risk of pre-eclampsia (figure), but with no clear effect on the risk of stillbirth or the baby dying before discharge from hospital (9 trials, 6763 babies; relative risk 1.04, 95% confidence interval 0.65 to 1.66).⁸ The effects seemed strongest for high risk

Box 2: Complications of pre-eclampsia**Central nervous system**

- Eclampsia (seizures)
- Cerebral haemorrhage (stroke)
- Cerebral oedema
- Cortical blindness
- Retinal oedema
- Retinal blindness

Renal system

- Renal cortical necrosis
- Renal tubular necrosis

Respiratory system

- Pulmonary oedema
- Laryngeal oedema

Liver

- Jaundice
- HELLP syndrome (haemolysis, elevated liver enzymes, and lowered platelets)
- Hepatic rupture

Coagulation system

- Disseminated intravascular coagulation
- Microangiopathic haemolysis

Placenta

- Placental infarction
- Placental abruption

Baby

- Death
- Preterm birth
- Intrauterine growth restriction

Box 4: Factors associated with an increased risk of pre-eclampsia (adapted from Duckitt et al⁶)

- First pregnancy
- Pre-eclampsia in a previous pregnancy
- ≥ 10 years since previous pregnancy
- ≥ 40 years of age
- Body mass index ≥ 35 at booking in
- Family history of pre-eclampsia (especially mother or sister)
- Diastolic blood pressure ≥ 80 mm Hg at booking in
- Proteinuria at booking in
- Multiple pregnancy
- Underlying medical condition:
 - Chronic hypertension
 - Renal disease
 - Diabetes
 - Presence of antiphospholipid antibodies

Box 5: How to measure blood pressure during pregnancy

- Mercury sphygmomanometers are preferable to automated blood pressure monitors
- If automated devices are used they should be calibrated, and checked regularly, against a mercury sphygmomanometer
- Use an appropriate size cuff
- Woman should be seated or lying at 45° angle, with arm at level of the heart
- Record blood pressure to the nearest 2 mm Hg
- Use phase V Korotkoff sound (sound disappearance) to measure diastolic blood pressure

women and those with low dietary calcium. Data from the recent World Health Organization trial of women with low calcium intake support a modest reduction in the risk of pre-eclampsia associated with calcium supplementation rather than placebo (171/4151 *v* 186/4161; relative risk 0.91, 0.69 to 1.19).⁹ There were also reductions in the risk of severe gestational hypertension (relative risk 0.71, 0.61 to 0.82), eclampsia (0.68, 0.48 to 0.97), and delivery before 32 weeks (0.82, 0.71 to 0.93).⁹ Antioxidants, primarily vitamins C and E, also seem to reduce the risk of pre-eclampsia (figure). This seems to be associated with an increase in

preterm birth (3 trials, 585 women; relative risk 1.38, 1.04 to 1.82), but there is insufficient evidence for conclusions about the impact on perinatal mortality. Several large trials are currently recruiting (see bmj.com for details of ongoing research).

Drugs

Antiplatelet drugs, primarily low dose aspirin, reduce the relative risk of pre-eclampsia by 19% (95% confidence interval 12% to 25%) and of stillbirth or neonatal death by 16% (4% to 26%; 38 trials, 34 010 women) (figure). This means that 69 women (51 to 109) would need to be treated with low dose aspirin to prevent one case of pre-eclampsia; for high risk women 18 (13 to 30), for moderate-low risk 188 (74 to 303). To prevent one baby death 227 women (128 to

* Excludes quasi-random studies, which were included in the review

[†] Random effects model, due to heterogeneity

[‡] Data reported for "pregnancy hypertension" not specified whether gestational hypertension or pre-eclampsia

Summary of results from controlled trials of interventions for preventing pre-eclampsia. Data from Cochrane reviews^{w1-w11}

Patients' stories

Katherine Walker

"I thought I was an ordinary pregnant woman experiencing some swelling at 28 weeks. Apparently not, as I quickly transformed from ordinary to becoming a swollen, frightened woman, terrified of losing not only her baby but her own life as well. I was a classic case—proteinuric, high blood pressure, and extremely swollen. I gave birth by caesarean at 29+ weeks—a boy, tiny yet strong and willful, thankfully. Nine days later, I returned home, battle-worn but a survivor, still on stack-loads of medication.

"I found myself pregnant again just 16 months later. I was under expert care at St Thomas's, who cared for me, not only medically with low dose aspirin and Doppler scans, but also emotionally. Those Doppler scans were so reassuring when the blood flow showed no notches. I became very anxious approaching 29 weeks and was able to self check my urine at home; again reassuring—except when I had a urine infection and turned up 2+ (I nearly fell off my chair). I also took part in the vitamins in pre-eclampsia trial. Best of all was the spontaneous labour on my due date, resulting in a beautiful little girl and a well mother."

Nancy Owens

"I was 25 weeks pregnant when a routine scan flagged up concerns about the baby's size, and further examination indicated I had pre-eclampsia. I was lucky to be in Oxford and was thus admitted under the care of Professor Redman and his team. I was placed on medication for my high blood pressure and told the team would work to keep me pregnant as long as possible. This proved to be one additional week before I developed HELLP syndrome and my condition deteriorated, necessitating surgery to deliver my daughter at just over 26 weeks.

"During my two weeks in hospital, before and after the birth, I was well looked after, and the midwives were especially caring, informative, and supportive. I sometimes felt that I was getting inconsistent or incomplete information from the doctors, particularly about my prognosis—in one week three doctors on the same team gave estimates for delivery ranging from 48 hours to four weeks, without explaining the data that supported these predictions. I am sure my stress and anxiety impaired my ability to process information, but it was only later, when I read more about pre-eclampsia, that I began to fully understand my condition and its ramifications for both my own health and the baby's. Overall, I felt I received excellent care; the only change I would have asked for is more complete and consistent communication."

909) need to be treated. Follow up of children at 2 years of age is reassuring that low dose aspirin is safe during pregnancy. This is the only intervention shown to reduce the risk both of pre-eclampsia and its complications. Women at high risk should be offered low dose aspirin. From a public health perspective, it may also be worth considering for more widespread use.

Heparin, alone or in combination with an antiplatelet, has been suggested for certain women at exceptionally high risk, such as those with renal disease plus previous pre-eclampsia. Trials to date have been too small for reliable conclusions.

Secondary prevention of pre-eclampsia

Blood pressure falls early in a normal pregnancy and then climbs slowly back up to pre-pregnancy levels by term. Hypertension is therefore uncommon in the first half of pregnancy, but occurs in about 10% of pregnancies after 20 weeks. Provided this does not progress to pre-eclampsia or severe hypertension, outcome is similar to, or perhaps slightly worse than, that for normotensive women.

Antihypertensive drugs

Antihypertensive drugs are used for mild to moderate hypertension during pregnancy in the belief they pre-

vent or delay progression to pre-eclampsia or severe hypertension, thereby improving outcome. Whether this is true is unclear. Antihypertensive drugs halve the risk of severe hypertension compared with placebo or no drug treatment (fig A on bmj.com), as would be expected of drugs known to lower blood pressure for non-pregnant people. Whether there are reductions in related outcomes such as admission to hospital (3 trials, 306 women; relative risk 0.94, 0.78 to 1.12) and stroke (no data) is uncertain. They are unlikely to have a major impact on the risk of progression to pre-eclampsia. A small but clinically important reduction in the risk of fetal or neonatal death is possible but does not achieve statistical significance.

It has been argued that lowering maternal blood pressure may cause fetal growth restriction.¹⁰ This hypothesis is based on meta-regression, however. So, although it used data from randomised trials, the analysis is prone to all the biases of observational studies. Also, when data from all trials are combined using meta-analysis, taking antihypertensive drugs has no overall effect on the relative risk of having a baby who is small for gestational age (relative risk 1.13, 0.91 to 1.42). Among the trials of β blockers, however, an increased risk does seem likely (8 trials, 810 women; relative risk 1.56, 1.10 to 2.22).¹¹ It therefore remains plausible that the observed association with fetal growth restriction is related to β blockers in particular rather than any general effect of antihypertensive drugs.

For mild to moderate hypertension, the antihypertensive methyldopa is often recommended.¹ Drowsiness is a common side effect—perhaps not a major disadvantage if the woman is hospitalised, but more problematic if she is not. Methyldopa can also cause depression, a risk not properly quantified during pregnancy. Alternative choices include labetalol and calcium channel blockers. There is insufficient evidence to conclude which is better.¹¹ Drugs to be avoided are atenolol, because of concern about fetal growth restriction, and angiotensin converting enzyme inhibitors and angiotensin receptor antagonists, which are contraindicated in pregnancy.

Other drugs

Diuretics are no longer advised for gestational hypertension. As for non-pregnant people, these drugs do reduce blood pressure, but with insufficient evidence of improvement in other outcomes. Antiplatelet drugs and abdominal decompression have been advocated for secondary prevention, but the evidence on their possible effects is inconclusive.

Admission to hospital or day care unit

Traditionally, women with either proteinuric or non-proteinuric hypertension were admitted to hospital for assessment and treatment. In many developed countries this process now takes place in day care units. Two trials (of 449 women) have compared these policies, with the main difference being shorter length of antenatal stay (in hospital or day care unit) for those allocated day care. Allocation to day care was not associated with cost savings.¹² Where both options are available, women should be offered a choice.

Treatment of pre-eclampsia

As the cause of pre-eclampsia is unclear, treatment remains symptomatic with little evidence that any intervention alters the underlying pathophysiology. Complementary medicines, such as Chinese herbal medicines, offer alternative strategies that are attracting growing interest, but none has been evaluated in randomised trials.

Women with severe hypertension or pre-eclampsia

Choice of antihypertensive

Once blood pressure rises above a certain level it may lead to direct vascular damage, which leads to life threatening complications such as renal failure, stroke, and fetal distress. This risk is not specific to pregnancy. Antihypertensive drugs are mandatory for systolic blood pressure ≥ 170 mm Hg or diastolic pressure ≥ 110 mm Hg, although lower thresholds are advisable if signs or symptoms are present. The aim is to bring about a smooth reduction in blood pressure to levels that are safe for both mother and fetus, avoiding sudden drops.

Antihypertensive drugs do lower high blood pressure during pregnancy, but with insufficient evidence about effects on other outcomes to conclude that one drug is preferable to another (fig B on bmj.com). Best avoided are diazoxide at high doses, since it is associated with a greater risk of hypotension and caesarean section than labetalol, and the serotonin receptor antagonist ketanserin, which led to far more persistent hypertension than hydralazine.¹³ An alternative analysis suggested avoiding hydralazine as first line treatment¹⁴ but this review included quasi-random designs and pooled studies comparing hydralazine with various drugs, regardless of whether they were likely to be better or worse. There has been concern about the combined use of nifedipine and magnesium sulphate, but this seems unfounded.¹⁵

Timing of delivery for women with early onset, severe pre-eclampsia

Optimal timing for delivery of women with severe pre-eclampsia before 32-34 weeks' gestation remains a dilemma—a precarious balance between protecting the mother by ending pregnancy and maximising maturity for the baby by delaying delivery. Data from trials are insufficient for reliable conclusions about the comparative effects of these alternative policies (fig C on bmj.com).

Other interventions for severe pre-eclampsia

Trials have failed to confirm any benefit associated with plasma volume expansion and suggest that it may increase the risk of caesarean section. This practice should therefore be abandoned. Corticosteroids and antioxidants have been suggested for women with severe pre-eclampsia, but trials to date have not shown any benefit.

Prevention and treatment of eclampsia

Eclampsia, the occurrence of seizures superimposed on the syndrome of pre-eclampsia, is rare, complicating 1 in 2000 pregnancies in the United Kingdom.¹⁶ In

Additional educational resources

- National Institute for Clinical Excellence (NICE). Clinical guideline 6: Antenatal care. Routine care for healthy pregnant women (www.nice.org.uk/page.aspx?o=89310)—Includes guidance on screening low risk women for pre-eclampsia
- Cochrane Library (www.thecochranelibrary.com)—Includes a comprehensive set of reviews covering prevention and treatment of pre-eclampsia and eclampsia
- Confidential Enquiries into Maternal and Child Health (CEMACH) (www.cemach.org.uk/publications.htm)—Site includes recent reports from the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) and the Confidential Enquiry into Maternal Deaths (CEMD)
- Royal College of Obstetricians and Gynaecologists. Clinical green top guidelines: Management of eclampsia (www.rcog.org.uk/index.asp?PageID=516)
- Geneva Foundation for Medical Education and Research. Preeclampsia, eclampsia, hypertension in pregnancy (www.gfmer.ch/Guidelines/Pregnancy_newborn/Preeclampsia_eclampsia_hypertension_in_pregnancy.htm)—Comprehensive and international listing of web based resources on pre-eclampsia, including information for patients, from a not-for-profit organisation and World Health Organization collaborating centre

Information resources for patients

Action on Pre-eclampsia (www.apec.org.uk)—Website for UK consumer group providing information about pre-eclampsia to women, affected families, and health professionals. Also has a telephone helpline, and a network of "local befrienders"

Similar organisations are in Australia (www.aapec.org.au) and New Zealand (www.nzapec.com)

- Preeclampsia Foundation (www.preeclampsia.org)—Provides support and education for families, as well as funding for research, from a US not-for-profit organisation
- Maternity Wise (www.maternitywise.org)—US consumer oriented site to promote evidence based maternity care. Includes explanations of the role of systematic reviews, and chapters on pre-eclampsia
- NHS Direct (<http://www.nhsdirect.nhs.uk/>)—Information and advice from the UK National Health Service

developing countries it is more common, and accounts for more than 50 000 maternal deaths each year (see bmj.com for further details).²

Prevention of eclampsia

There is now robust evidence that, for women with pre-eclampsia, magnesium sulphate more than halves the risk of eclampsia (number needed to treat 100, 95% confidence interval 50 to 100) and probably reduces the risk of maternal death (fig D on bmj.com). However, no overall difference has been found in the risk of stillbirth or neonatal death. A quarter of women allocated magnesium sulphate had side effects, primarily flushing.

Choice of anticonvulsant for treating eclampsia

Magnesium sulphate is clearly the anticonvulsant of choice for treating eclampsia, with substantial reductions in the risk of further seizures compared with diazepam, phenytoin, and lytic cocktail (fig E on bmj.com). It is also better at preventing maternal death than diazepam. Compared with phenytoin, magnesium sulphate has a lower risk of pneumonia and ventilation, as well as being safer for the baby. Lytic cocktail has no place in treatment of eclampsia. Training of healthcare staff by means of practice drills and on-site simulation may also improve care.¹⁷

Although magnesium sulphate is affordable and effective, it is not available in all low and middle income countries.¹⁸ Governments and international agencies should ensure that barriers to its use are removed.

Treatment of postpartum hypertension

The only definitive “cure” for pre-eclampsia is to deliver the placenta. However, the risk of hypertension or pre-eclampsia does not resolve immediately. Pre-eclampsia and eclampsia can both present for the first time after the birth. Whether antihypertensive drugs should be offered routinely after delivery to women who had antenatal hypertension is unclear, as is the choice of drug.

Assessment and counselling after pre-eclampsia

Women who have had pre-eclampsia are at increased risk of developing it again in subsequent pregnancies and should be advised of this, ideally before conception. They should also be assessed for underlying chronic hypertension and other medical conditions.

Conclusion

Women should be screened regularly throughout pregnancy for pre-eclampsia, and those at high risk should be referred early for specialist care. Awareness of the signs and symptoms is important at all levels in the maternity services, and for women themselves. Once pre-eclampsia develops, prompt referral for assessment and monitoring will help ensure that women receive appropriate care. The information summarised here should be available to women, clinicians, and policy makers to enable them to make more informed decisions about care during pregnancy and childbirth.

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A major medical decision

About 30 years ago, I was part time occupational physician to a big chemical complex in Bristol. Late one afternoon, some workers reported to the medical inspection room complaining of an irritating dusky rash on exposed areas of skin (neck, face, and arms).

They worked in a plant which used arsenic trioxide in the circulating fluid in a multitude of pipework. I went to the plant and saw in the failing light a fine bluish mist descending from the overhead pipes. I decided that the workers had contact dermatitis and went to see the general manager, a doctor of chemistry. He called the plant managers to discuss my findings and diagnosis. Their opinion was that the pipes were puncture proof.

The general manager asked me, “Freddy, are you sure?”

“As certain as can be,” I replied.

“Well”, he said, “I’ll have to ring the main board and stop the plant—at a cost of £28 000.” (A lot of money in those days.)

I confirmed my opinion and left the plant. I then had my usual busy evening surgery, but I still spent a rather worried and sleepless night thinking about the implications of my action.

The next morning I telephoned the general manager (who was also a patient and a friend) with a slightly anxious question: “What happened?”

“Well,” he replied, “it shut itself off.”

I felt that the good lord and the fail-safe system had intervened to save me.

Leaks were subsequently found in the pipes and repaired; the workers recovered quickly; and I breathed a long sigh of relief.

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