Pre-eclampsia and the hypertensive disorders of pregnancy

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Pre-eclampsia is a multisystem disorder, of unknown aetiology, usually associated with raised blood pressure and proteinuria. Although outcome for most women and their babies is good, it remains a major cause of morbidity and mortality. A wide range of interventions for prevention and treatment of pre-eclampsia have been evaluated in randomized trials. This evidence provides the basis for a rational approach to care. Overall, there is insufficient evidence for any firm conclusion about the effects of any aspect of diet or lifestyle during pregnancy. Antiplatelet agents are associated with a 19% reduction in the risk of pre-eclampsia (relative risk 0.81; 95% CI 0.75, 0.88), a 7% reduction in the risk of preterm birth (RR 0.93; 95% CI 0.89, 0.98), a 16% reduction in the risk of stillbirth or neonatal death (RR 0.84; 95% CI 0.74, 0.96) and an 8% reduction in the risk of a small for gestational age baby (RR 0.92; 95% CI 0.85, 1.00). For mild to moderate hypertension, trials evaluating bed rest are too small for reliable conclusions about the potential benefits and hazards. Antihypertensive agents halve the risk of progression to severe hypertension (RR 0.52; 95% CI 0.41, 0.64), but with no clear effect on pre-eclampsia (RR 0.99; 95% CI 0.84, 1.18), or any other substantive outcome. For severe hypertension, there is no good evidence that one drug is any better than another. Plasma volume expansion for severe pre-eclampsia seems unlikely to be beneficial, although the trials are small. The optimum timing of delivery for pre-eclampsia before 34 weeks is unclear. Magnesium sulphate more than halves the risk of eclampsia (RR 0.41; 95% CI 0.29, 0.58) and probably reduces the risk of maternal death (RR 0.54; 95% CI 0.26, 1.10). It is also the drug of choice for treatment of eclampsia.

Introduction

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Pre-eclampsia is a multisystem disorder of unknown aetiology, unique to pregnancy. Women with pre-eclampsia usually develop raised blood pressure and proteinuria, but the condition is also associated with abnormalities of the coagulation system, disturbed liver function, renal failure and cerebral ischaemia[1]. It complicates an estimated 2–8% of pregnancies and is a major cause of maternal morbidity, perinatal death and premature

British Medical Bulletin 2003; **67**: 161–176
DOI: 10.1093/bmb/ldg005

delivery, although outcome for most women is good. Eclampsia, the occurrence of one or more convulsions superimposed on the syndrome of pre-eclampsia, occurs less frequently, complicating between 1 in 100–1700 pregnancies in the developing world[2] and about 1 in 2000 pregnancies in Europe and other developed countries. Eclampsia is often a serious and life-threatening condition. Compared to pre-eclampsia it carries a much higher risk of death and serious morbidity for the woman and her baby. In the UK, for example, 1 in 50 of the women who have eclampsia die[3].

Worldwide, over half a million women die each year of pregnancy-related causes, and 99% of these deaths occur in the developing world[4]. Put another way, women in industrialized countries have an average lifetime risk (calculated as the average number of pregnancies multiplied by the risk associated with each pregnancy) of dying from pregnancy-related causes of between 1 in 4000 and 1 in 10,000, whereas women in low income countries have a risk that is between 1 in 15 and 1 in 50. In poor countries, maternal mortality is 100–200 times higher than in Europe and North America. There is no other public health statistic for which the disparity between rich and poor countries is so wide.

Although rare, eclampsia probably accounts for 50,000 maternal deaths a year[5]. In areas where maternal mortality is very high, infection and haemorrhage are the main causes of death[6], but as deaths from these causes become less common, those associated with pre-eclampsia and eclampsia assume greater importance. Where overall maternal mortality is high, most deaths are associated with eclampsia[5]. In places where mortality is low, a greater proportion of deaths are related to pre-eclampsia. There are few reliable data on the maternal morbidity associated with pre-eclampsia and eclampsia, but it is likely that this is also substantial. In the UK, for example, pre-eclampsia accounts for an estimated one-fifth of antenatal admissions[7], two-thirds of referrals to day care assessment units[8], and a quarter of obstetric admissions to intensive care units[9]. Although maternal mortality in the UK is low, pre-eclampsia/eclampsia accounts for 10–15% of direct obstetric deaths[10,11] as it does in many developing countries[5]. Reducing the morbidity and mortality associated with these conditions is an important priority.

This chapter briefly discusses the classification and pathophysiology of pre-eclampsia and the hypertensive disorders of pregnancy. It then presents the evidence from systematic reviews and randomized trials of the effects of interventions to prevent and treat pre-eclampsia and its complications.

Classification of the hypertensive disorders of pregnancy

Eclampsia and pre-eclampsia are part of a spectrum of conditions associated with raised blood pressure during pregnancy, known as the

hypertensive disorders of pregnancy. Attempts to classify these disorders have, in the past, been confusing and sometimes misleading. More recently their classification has been rationalized and simplified to reflect the different situations encountered in clinical practice[12]. Raised blood pressure during pregnancy is generally defined as systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg, and proteinuria as >300 mg/24 h or ≥30 mg/mmol in a single specimen. There is agreement that the terms pregnancy-induced hypertension, or gestational hypertension, refer to raised blood pressure occurring for the first time in the second half of pregnancy, but without proteinuria (<300 mg/24 h). The term pre-eclampsia is reserved for the new occurrence of hypertension and proteinuria in the second half of pregnancy. The diagnosis of pre-eclampsia is strengthened if there is further indication of multisystem involvement, such as raised serum creatinine or liver enzymes, lowered platelets, or neurological symptoms (hyperreflexia, severe frontal headache, or visual disturbance). Eclampsia is the occurrence of convulsions superimposed on pre-eclampsia. Chronic hypertension is known hypertension before pregnancy. Pre-eclampsia superimposed on chronic hypertension is when a women with chronic hypertension develops new signs or symptoms of pre-eclampsia in the second half of pregnancy.

Women with pregnancy-induced hypertension generally have a good outcome. The risk to them and their baby increases only if they progress to pre-eclampsia, or have very high blood pressure.

Pathophysiology of pre-eclampsia

Although the exact mechanisms which lead to pre-eclampsia are not clear, several factors are known to play a part in determining who will develop this disease. Some women have predisposing factors. These include family history, age and parity. Current thinking is that the primary pathophysiology in pre-eclampsia is placental[13,14]. Pre-eclampsia occurs in women who have an abdominal pregnancy and in those with a hydatidiform mole, indicating that uterine and fetal factors are not essential. In addition, it is more common amongst women who have conditions associated with a large placenta (such as multiple pregnancies and hydrops fetalis), and in women who have microvascular disease (such as diabetes, hypertension and collagen vascular disease). In pre-eclampsia, trophoblastic implantation is abnormal, with reduced placental perfusion. As normal implantation is complete by around 20 weeks, this deficient implantation occurs weeks or months before the disease becomes clinically apparent.

The secondary pathology in pre-eclampsia appears to be endothelial cell injury. The proposed model is that reduced blood supply to the placenta

results in production of unknown factors which are released into the maternal circulation and act on endothelial cells, leading to endothelial dysfunction[1]. This results in vasospasm, with consequent reduction in plasma volume, and activation of the coagulation cascade. These changes antedate other clinical findings[1]. Recently, there has been interest in oxidative stress as the possible mechanism for this endothelial dysfunction[1,15].

Interventions to prevent and treat pre-eclampsia and hypertension during pregnancy

The evidence presented here is primarily derived from systematic reviews published on The Cochrane Library[16]. These reviews have a standard and extensive search strategy and methodology, which is described in detail in each of the reviews. Where reviews are not available, evidence is summarized from randomized trials identified by searching the Cochrane Central Controlled Trials Register within The Cochrane Library[16].

Prevention of pre-eclampsia

Diet and exercise

For decades, women have been advised to make a range of changes to their diet and lifestyle, in the expectation that it might reduce their risk of developing pre-eclampsia. Many of these are now obsolete. There is no reliable evidence that any are effective. Interventions that have been evaluated in randomized trials include aerobic exercise[17,18], protein restriction[19], protein supplementation[20,21], increasing or decreasing salt intake[22], magnesium supplementation[23] and zinc supplementation[24]. All the studies in these reviews were small and, even taken together, provide insufficient evidence to provide a reliable basis for clinical decisions. Therefore, in the absence of good evidence of either benefit or harm, women's diet and lifestyle during pregnancy should be determined by their own personal preferences.

Two further forms of supplementation have been evaluated in trials: sources of prostaglandin precursors such as fish oil, and calcium. Fish oil contains long chain fatty acids, which have antiplatelet and antithrombotic effects thought to be beneficial in prevention of pre-eclampsia. Observational studies suggested the possibility of a prophylactic effect of fish oil and prompted more rigorous randomized trials. Other sources of fatty acids, such as oil of evening primrose, have also been evaluated in randomized trials. Over 2000 women have now been randomized into these studies[25]. Taken together, the confidence intervals suggest that the true effect could be anything between a 40% reduction

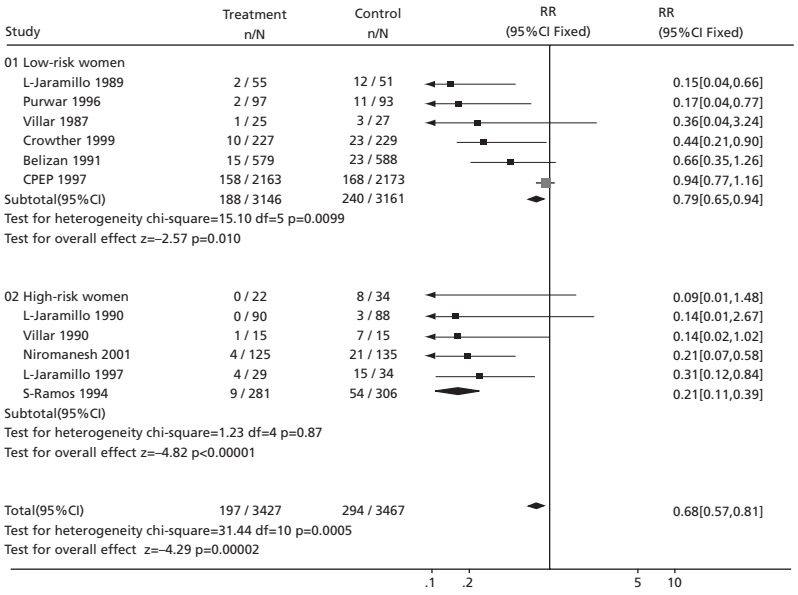

Fig. 1 Calcium supplementation *versus* none/placebo: effect on pre-eclampsia (subgroups by maternal risk).

in the risk of pre-eclampsia associated with these oils and a 28% increase [relative risk (RR) 0.87, 95% CI 0.59, 1.28].

The hypothesis that dietary calcium might be related to the risk of pre-eclampsia was also derived from observational studies. There are now 11 trials (6894 women) in the systematic review. Women in these trials received at least 1 g calcium/day[26]. Overall, there is a 30% reduction in the risk of pre-eclampsia (Fig. 1). The effect seems to be greatest for women who were high risk at trial entry (five trials, 587 women; RR 0.21, 95% CI 0.11–0.39), and for those with a previous low calcium intake (six trials, 1842 women; RR 0.32, 95% CI 0.21–0.49)[26]. This reduction in the risk of pre-eclampsia was not reflected in any overall effect on stillbirths or neonatal deaths (nine trials, 6763 women; RR 1.04, 95% CI 0.65, 1.66). A further multicentre trial of women with low dietary calcium was completed in 2003, results are awaited.

Aspirin and other antiplatelet agents

Pre-eclampsia is associated with deficient intravascular production of prostacyclin, a vasodilator, and excessive production of thromboxane, a platelet-derived vasoconstrictor and stimulant of platelet aggregation. These observations led to the hypotheses that antiplatelet agents, and low dose aspirin in particular, might be effective for prevention of pre-eclampsia. There are now 51 trials (36,500 women) in the systematic review[27]. Most women in these trials received low dose (<75 mg)

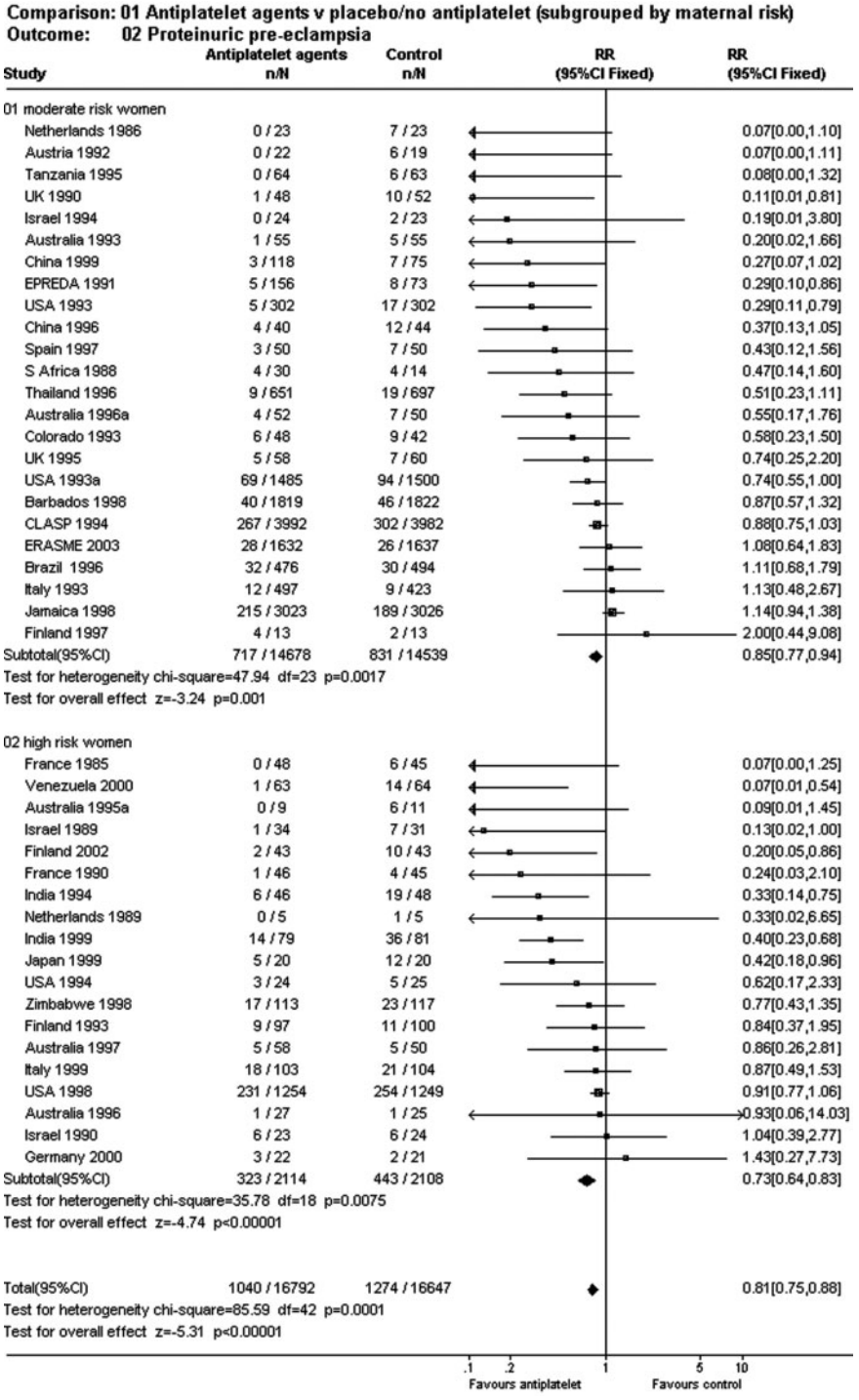

Fig. 2 Antiplatelet agents *versus* placebo or no antiplatelet agent: effect on pre-eclampsia (subgroups by maternal risk).

aspirin. Antiplatelet agents are associated with a 19% reduction in the risk of pre-eclampsia [43 trials, 33,439 women; RR 0.81, 95% CI 0.75, 0.88; number needed to treat (NNT) 69, 95% CI 51, 109] (Fig. 2). This reduction is consistent, regardless of risk status or gestation at trial entry. Other benefits associated with antiplatelet agents were: a small (7%) reduction in the risk of delivery before 37 completed weeks (28 trials, 31,845 women; RR 0.93, 95% CI 0.89, 0.98), a 16% reduction in fetal or neonatal deaths (38 trials, 34,010 women; RR 0.84, 95% CI 0.74, 0.96) and an 8% reduction in the risk of a small for gestational age baby (32 trials, 24,310 women; RR 0.92, 95% CI 0.85, 1.00). Low dose aspirin also appears to be reasonably safe.

Low dose aspirin does help prevent pre-eclampsia, and some of its complications. These results should be discussed with women, particularly those at high risk of developing pre-eclampsia. In countries with a high incidence of pre-eclampsia, recommending more widespread use may be worthwhile.

Antioxidant vitamins

One small trial has evaluated high doses of vitamins C and E as antioxidant agents for prevention of pre-eclampsia[28]. The results are promising, but require confirmation in larger studies before being recommended for clinical practice. Several such studies are currently planned or recruiting.

Treatment of mild or moderate hypertension

Mild or moderate hypertension carries little risk to the mother, unless there is superimposed severe hypertension or pre-eclampsia. For this reason, the aim of treatment for mild to moderate hypertension during pregnancy has been to defer or prevent the progression to severe hypertension or pre-eclampsia. Rest in bed and a variety of medications have been used.

Bed rest

Women with high blood pressure during pregnancy have often been advised to rest in bed, either at home or in hospital. Confinement to bed either at home or in hospital may result in financial or social costs for the woman and her family. Admission to hospital may be stressful and has, in addition, major cost implications for the health services. These interventions would only be justified if there were clear health benefits. Three small trials (408 women) have compared hospital admission with care at home for hypertension alone[29]. Two trials (145 women) have compared bed rest in hospital with normal ambulation for women with

pre-eclampsia. Even taken together, these trials are too small for any reliable conclusions[30].

Antihypertensive agents

Antihypertensive agents are used to lower blood pressure during pregnancy, in the belief that these delay progression to more severe disease, and so improve outcome. Twenty-four trials (2815 women) have compared an antihypertensive drug with placebo/no antihypertensive drug for women with mild–moderate hypertension during pregnancy[31]. Unsurprisingly, antihypertensive drugs reduce by half the risk of developing severe hypertension (17 trials, 2155 women; RR 0.52, 95% CI 0.41, 0.64), but with little evidence of a difference in the risk of pre-eclampsia (19 trials, 2402 women; RR 0.99, 95% CI 0.84, 1.18) (Fig. 3). Similarly, there is no clear effect on the risk of the baby dying (23 trials, 2727 women; RR 0.71, 95% CI 0.46, 1.09), being born too early (12 trials, 1738 women; RR 0.98, 95% CI 0.85, 1.13), or being small for gestational age (17 trials, 2159 women; RR 1.13, 95% CI 0.91, 1.42).

Possible adverse effects are not well reported in these trials. There is a trend towards an increase in small for gestational age babies, largely confined to the beta blocker group of drugs[31]. Meta-regression within a systematic review has suggested that lowering blood pressure may increase the risk of a small for gestational age baby[32]. There are few data to provide reassurance on long-term follow-up for either the mother or baby.

It remains unclear whether antihypertensive drug therapy for mild–moderate hypertension during pregnancy is worthwhile. Whether the reduction in the risk of severe hypertension is considered sufficient to warrant treatment is a decision that should be made by women in consultation with their obstetrician. If an antihypertensive is used, there is little good evidence that one antihypertensive is clearly better than another. The choice should therefore depend on the previous experience of the clinician and the woman's preference.

Treatment of severe hypertension/pre-eclampsia

Antihypertensive drugs

Although treatment of hypertension does not strike at the basic disorder, it may still benefit the mother and fetus. An important objective in the care of a woman with severe hypertension, with or without proteinuria, is to reduce blood pressure in order to avoid hypertensive encephalopathy and cerebral haemorrhage. For this reason, the aim in treating severely hypertensive women is to keep the blood pressure below dangerous levels (< 170/110 mmHg).

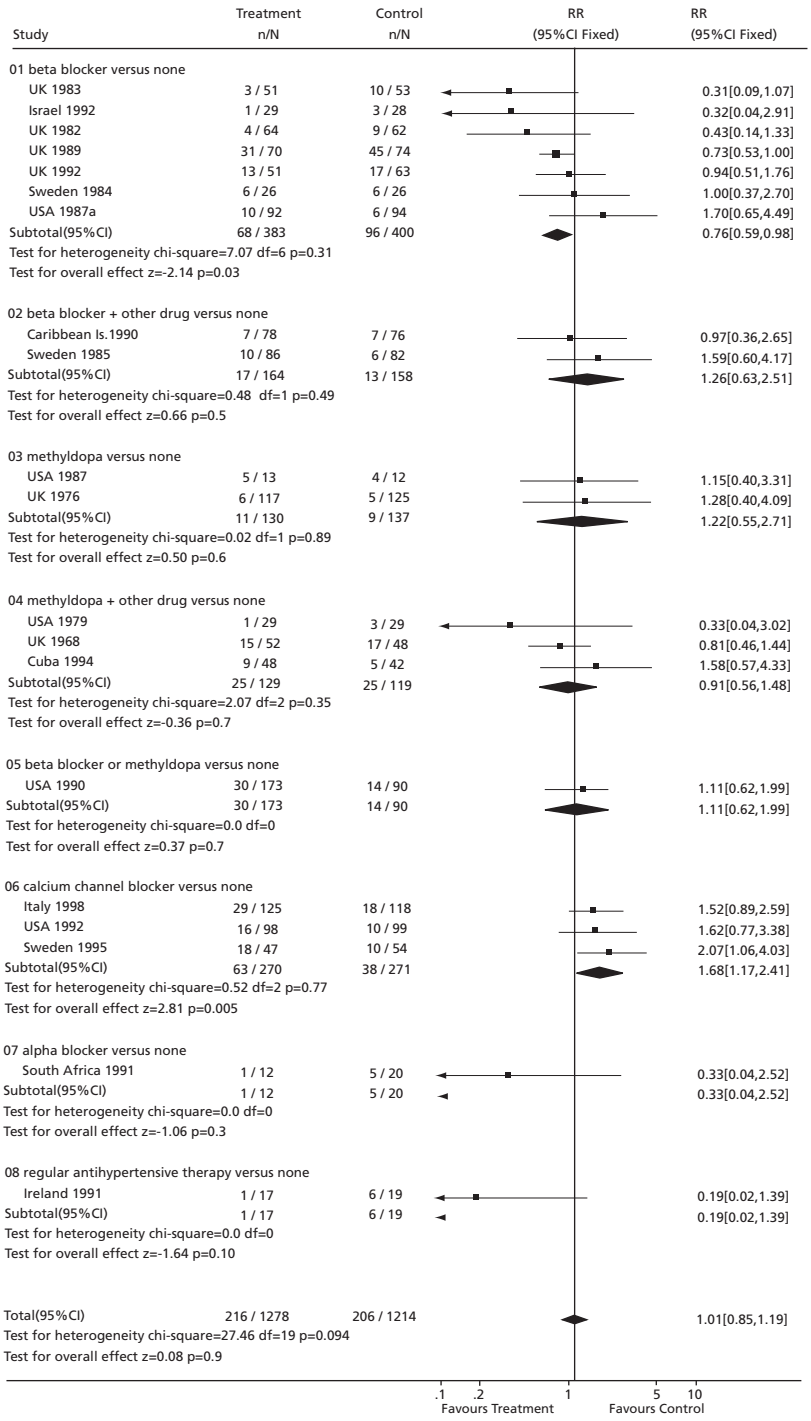

Fig. 3 Antihypertensive drugs *versus* none/placebo: effect on pre-eclampsia (subgroups by type of drug).

Twenty trials (1637 women) have compared one antihypertensive agent with another for severe hypertension[33]. Most of these studies were small. There are 10 comparisons in the review, five of which compared hydralazine with another drug. Other agents included were nifedipine, labetolol, methyldopa, diazoxide, prostacyclin, ketanserin, urapidil, magnesium sulphate, prazosin and nimodipine.

There is no good evidence that one antihypertensive is better than any of the others for reducing blood pressure. Until better evidence is available, the best choice of drug for an individual woman probably depends on the experience and familiarity of her clinician with a particular drug, and on what is known about adverse maternal and fetal side-effects. Diazoxide is probably best avoided, however, as although the numbers are small it does seem to be associated with an increased risk of very low blood pressure and of caesarean section when compared to labetolol. Also, ketanserin is less effective in reducing blood pressure than hydralazine.

Plasma volume expansion

Women with severe pre-eclampsia often have a restricted circulating plasma volume. This has led to the recommendation that plasma volume should be expanded with either colloid or crystalloid solutions, in an effort to improve maternal systemic and uteroplacental circulation. However, intravascular volume expansion carries a serious risk of volume overload, which may lead to pulmonary or cerebral oedema. Also, large volume expansion often requires invasive monitoring of intravascular pressure, procedures carrying risks of their own.

Three small trials (61 women) have compared a colloid solution with placebo or no infusion. These studies were too small for reliable conclusions, but suggest plasma volume expansion is not beneficial[34]. Systematic reviews of volume expansion for critically ill non-pregnant people found a higher mortality than either not using any plasma expander or expansion with a crystalloid[35,36]. Although none of these studies included pregnant women, it would seem prudent to avoid colloid solutions until data from randomized trials involving women with pre-eclampsia become available.

Timing of delivery

For women who have severe pre-eclampsia before 34 weeks, the decision about the best time to deliver the baby is often difficult. The hazards to the baby of being born too early need to be balanced against the risks to both the woman and the baby if the pregnancy is continued for too long. Two trials (133 women) have compared a policy of early elective delivery by induction of labour or by caesarean section, with a policy of delayed delivery. There are insufficient data for any reliable recommendation about which policy of care should be used for women with severe early onset pre-eclampsia.

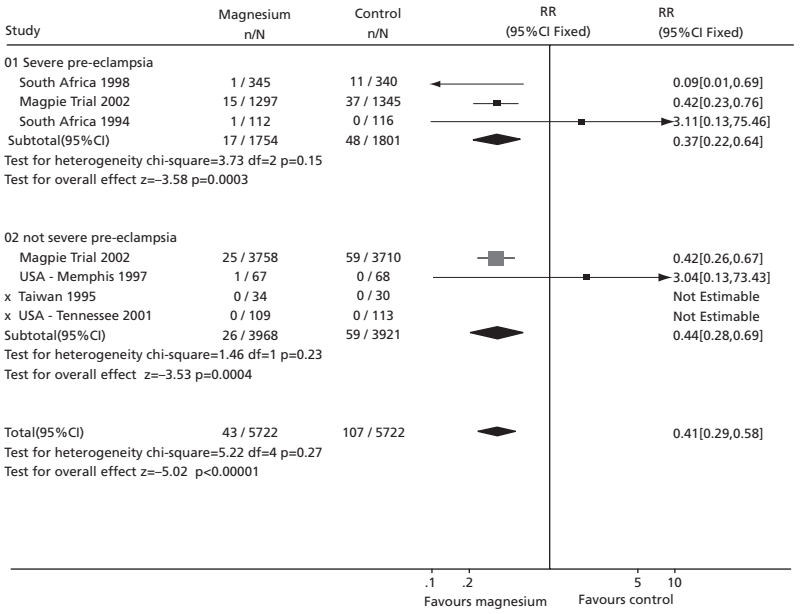

Fig. 4 Magnesium sulphate *versus* none/placebo: effect on eclampsia (subgroups by severity of pre-eclampsia).

Prevention and treatment of eclampsia

Anticonvulsant drugs are widely used in the management of eclampsia, as well as in severe hypertensive disease and pre-eclampsia, in an attempt to prevent the occurrence of eclamptic seizures. Magnesium sulphate has recently emerged as the anticonvulsant of choice for eclampsia.

Preventing the onset of eclampsia

The main question about magnesium sulphate as a prophylactic anticonvulsant for women with pre-eclampsia is whether overall it does more good than harm. Six trials (11,444 women) have compared magnesium sulphate with placebo or no anticonvulsant[37]. Most women in these studies had moderate–severe pre-eclampsia. The magnesium sulphate regimen was usually 4 g as a slow intravenous bolus, followed by either an intravenous infusion of 1 g/h, or by intramuscular injections of 10 g and then 5 g every 4 h. The total duration of therapy was usually 24 h, with clinical monitoring alone.

There was more than a halving in the risk of eclampsia associated with the use of magnesium sulphate, rather than placebo or no anticonvulsant (RR 0.41, 95% CI 0.29, 0.58; NNT 100, 95% CI 50–100). This

reduction is consistent regardless of severity of pre-eclampsia (Fig. 4) and irrespective of gestation or whether the women were antepartum at trial entry. The risk of maternal death was also reduced for women allocated magnesium sulphate, although this did not achieve statistical significance (two trials, 10,795 women; RR 0.54, 95% CI 0.26, 1.10). There was no clear evidence of any overall difference in maternal morbidity between the two groups.

For women randomized before delivery, the risk of placental abruption was reduced for those allocated magnesium sulphate rather than placebo (RR 0.64, 95% CI 0.50–0.83). Women allocated magnesium sulphate also had a small (5%) increase in the risk of caesarean section (six trials, 10,108 women; RR 1.05, 95% CI 1.01, 1.10). There was no evidence of a clinically important effect on the risk of induction of labour, postpartum haemorrhage or manual removal of placenta. There was no overall difference in the risk of stillbirth or neonatal death (three trials, 9961 women; RR 1.04, 95% CI 0.93, 1.15) or in the risk of the baby dying or being in a special care baby unit for >7 days (RR 1.01, 95% CI 0.95–1.08). There was no clear difference in neonatal morbidity between the two groups. Follow-up after discharge from hospital is being conducted for one large trial[38], but data are not yet available.

Toxicity was uncommon with magnesium sulphate. There was no clear difference in the risk of absent or reduced tendon reflexes. Although respiratory depression was rare (52/5344 *versus* 26/5333), the risk was higher for women allocated magnesium sulphate (RR 1.98, 95% CI 1.24–3.15; NNH 206, 95% CI 100–1000). A quarter of women who received magnesium sulphate had side-effects, compared to 5% of those given placebo. By far the most common side-effect was flushing.

Trials have also compared magnesium sulphate with phenytoin (two trials, 2241 women) with nimodipine (one trial, 1750 women), and with diazepam (two trials, 66 women). These studies all support magnesium sulphate as the anticonvulsant of choice for women with pre-eclampsia. One trial has compared magnesium chloride with methyldopa (31 women).

Magnesium sulphate should be considered for women with severe pre-eclampsia, and for others about whom there is concern about the risk of eclampsia.

Controlling the acute convulsion and preventing recurrence of eclampsia

When a woman has an eclamptic convulsion, the immediate question is how best to control the acute fit. Once the first convulsion has subsided, the next question is how best to reduce the risk of her having another. In the past, the choice of anticonvulsant was controversial, but magnesium sulphate is now well established as the drug of choice.

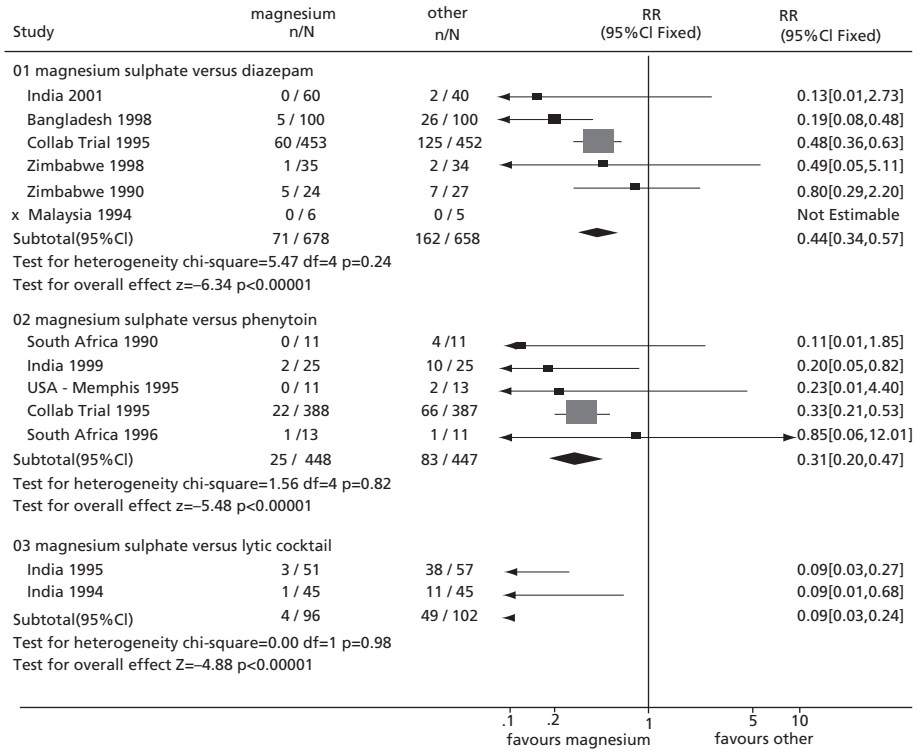

Fig. 5 Magnesium sulphate *versus* other anticonvulsants: effect on recurrence of convulsio

Magnesium sulphate has been compared with diazepam, with phenytoin, and with lytic cocktail in randomized trials. Six trials (1336 women) have compared magnesium sulphate with diazepam[39]. Magnesium sulphate was associated with a reduction in the risk of maternal death, when compared to diazepam, although the confidence intervals are wide (RR 0.59, 95% CI 0.37, 0.94). There is also a substantial reduction in the risk of recurrence of convulsions associated with magnesium sulphate (RR 0.44, 95% CI 0.34–0.57) (Fig. 5). On average, for every seven women treated with magnesium sulphate rather than diazepam, one recurrence of convulsions will be prevented (95% CI 6–10 women). There was no clear evidence of a difference in any other measure of maternal morbidity.

For the baby, there was no clear difference between the treatment regimens in the risk of perinatal death for babies randomized whilst *in utero* (RR 1.04, 95% CI 0.80, 1.36). The only clear differences associated with the use of magnesium sulphate, rather than diazepam, were a reduction in the risk of an Apgar score <7 at 5 min (RR 0.72, 95% CI 0.55–0.94), and in length of stay in a special care baby unit >7 days (RR 0.66, 95% CI 0.46–0.95).

Six trials (897 women) have compared magnesium sulphate with phenytoin[40]. Magnesium sulphate was associated with a 70% reduction in the relative risk of recurrent convulsions, compared to phenytoin (RR 0.31, 95% CI 0.20–0.47) (Fig. 5). On average, for every eight women treated with magnesium sulphate rather than phenytoin, one recurrence of convulsions will be prevented (95% CI 6–13 women). The trend in maternal mortality also favoured magnesium sulphate, but the difference did not achieve statistical significance (RR 0.50, 95% CI 0.24–1.05). In addition, the use of magnesium sulphate, rather than phenytoin, was associated with a reduction in the risk of pneumonia (RR 0.44, 95% CI 0.24–0.79), the need for ventilation (RR 0.66, 95% CI 0.49–0.90) and admission to an intensive care unit (RR 0.67, 95% CI 0.50–0.89).

For the baby, there was no clear difference in the risk of perinatal death between the two regimens (RR 0.85, 95% CI 0.67, 1.09). Babies whose mothers were allocated magnesium sulphate, rather than phenytoin, had fewer admissions to a special care baby unit (RR 0.73, 95% CI 0.58–0.91) and fewer died or were in SCBU for >7 days (RR 0.77, 95% CI 0.63–0.95).

Two trials (199 women) compared magnesium sulphate with lytic cocktail[41], usually a mixture of chlorpromazine, promethazine and pethidine. Magnesium sulphate was substantially better at preventing further fits than lytic cocktail (RR 0.09, 95% CI 0.03, 0.24). There was also a non-significant trend to fewer maternal deaths with magnesium sulphate rather than lytic cocktail (RR 0.25, 95% CI 0.04–1.43), and fewer baby deaths (for stillbirth RR 0.55, 95% CI 0.26–1.16; for neonatal death RR 0.39, 95% CI 0.14–1.06).

Magnesium sulphate is the drug of choice for women with eclampsia. In these trials, women allocated magnesium sulphate had magnesium sulphate for treatment of the acute fit, for maintenance therapy and for control of any recurrent fits. The treatment regimens were similar to those discussed above for pre-eclampsia. It has been argued that diazepam should be used for control of the acute fit[42], but this view is not supported by evidence[43].

Conclusions

A wide range of interventions has been suggested for the prevention and treatment of pre-eclampsia. Many thousands of women have now been entered into randomized trials evaluating some of these interventions, and this evidence provides the basis for a more rational approach to some aspects of care. Many important unanswered questions remain,

however. Further improvement in the care of women with pre-eclampsia will come from implementing the existing evidence, and from conducting further large trials to evaluate interventions not yet tested in large trials.

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