Articles

Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial

*The Magpie Trial Collaborative Group**

Summary

Background Anticonvulsants are used for pre-eclampsia in the belief they prevent eclamptic convulsions, and so improve outcome. Evidence supported magnesium sulphate as the drug to evaluate.

Methods Eligible women (n=10 141) had not given birth or were 24 h or less postpartum; blood pressure of 140/90 mm Hg or more, and proteinuria of 1+ (30 mg/dL) or more; and there was clinical uncertainty about magnesium sulphate. Women were randomised in 33 countries to either magnesium sulphate (n=5071) or placebo (n=5070). Primary outcomes were eclampsia and, for women randomised before delivery, death of the baby. Follow up was until discharge from hospital after delivery. Analyses were by intention to treat.

Findings Follow-up data were available for 10 110 (99·7%) women, 9992 (99%) of whom received the allocated treatment. 1201 of 4999 (24%) women given magnesium sulphate reported side-effects versus 228 of 4993 (5%) given placebo. Women allocated magnesium sulphate had a 58% lower risk of eclampsia (95% CI 40–71) than those allocated placebo (40, 0·8%, *vs* 96, 1·9%; 11 fewer women with eclampsia per 1000 women). Maternal mortality was also lower among women allocated magnesium sulphate (relative risk 0·55, 0·26–1·14). For women randomised before delivery, there was no clear difference in the risk of the baby dying (576, 12·7%, *vs* 558, 12·4%; relative risk 1·02, 99% CI 0·92–1·14). The only notable difference in maternal or neonatal morbidity was for placental abruption (relative risk 0·67, 99% CI 0·45–0·89).

Interpretation Magnesium sulphate halves the risk of eclampsia, and probably reduces the risk of maternal death. There do not appear to be substantive harmful effects to mother or baby in the short term.

Lancet 2002; **359:** 1877–90
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Introduction

Pre-eclampsia, a multisystem disorder of pregnancy usually associated with raised blood pressure and proteinuria, complicates 2–8% of pregnancies.[1] Although outcome is often good, pre-eclampsia is a major cause of morbidity and mortality for the woman and her child.[2] Eclampsia is defined as the occurrence of one or more convulsions superimposed on pre-eclampsia. In developed countries eclampsia is rare, affecting around one in 2000 deliveries,[3] while in developing countries estimates vary from one in 100 to one in 1700.[4,5] Worldwide an estimated 600 000 women die each year of pregnancy-related causes,[6] with 99% of these deaths occurring in developing countries. Pre-eclampsia and eclampsia probably account for more than 50 000 maternal deaths a year.[7] In places where maternal mortality is high, most of these deaths are associated with eclampsia. Where maternal mortality is lower, a higher proportion will be due to pre-eclampsia. For example, in the UK pre-eclampsia and eclampsia together account for 15% of direct maternal deaths, and two-thirds were related to pre-eclampsia.[2]

For decades anticonvulsant drugs have been given to women with pre-eclampsia, in the belief that they reduce the risk of seizure, and so improve outcome.[8] However, there has been little reliable evidence to support that belief. In 1998, a systematic review[9] of anticonvulsants for women with pre-eclampsia identified four trials (total 1249 women) comparing an anticonvulsant with no anticonvulsant or placebo. This review concluded that magnesium sulphate was the most promising choice for pre-eclampsia, and the priority for further evaluation. Additionally, magnesium sulphate is now the drug of choice for women with eclampsia, with strong evidence that it is better than either diazepam,[10] phenytoin,[11] or lytic cocktail.[12]

The use of magnesium sulphate for pre-eclampsia is increasing,[13] although a range of other anticonvulsant drugs continue to be used, including diazepam and other benzodiazepines, phenytoin, barbiturates, and lytic cocktail. There is also substantial variation in the severity of pre-eclampsia for which a prophylactic anticonvulsant is used. In the USA, for example, magnesium sulphate is given to an estimated 5% of pregnant women before delivery.[14] By contrast, a quarter of UK obstetricians never use any prophylactic anticonvulsants,[13] and those who do often restrict their use to women with severe pre-eclampsia, which is around 1% of deliveries.

The initial question about magnesium sulphate, as a prophylactic anticonvulsant for women with pre-eclampsia, is whether it reduces the risk of eclampsia. Even if it does, reliable information is required before magnesium sulphate can be safely recommended for clinical practice; in particular about the size of any risk reduction, effects on other important outcomes for the woman and child, and disease severity at which benefits outweigh the risks. The Magpie Trial (MAGnesium sulphate for Prevention of Eclampsia) was a large

international trial designed to evaluate the effects of magnesium sulphate on women and their babies. The aim was to find out if, overall, women with pre-eclampsia or their children, or both, do better if they are given magnesium sulphate rather than placebo, regardless of whether treatment is started before or after delivery and irrespective of any previous anticonvulsant therapy.

Methods

Trial organisation

Overall coordination of the trial was from the Resource Centre for Randomised Trials at the Institute of Health Sciences in Oxford, UK. Spanish speaking centres in Latin America were coordinated from the Centro Rosarino de Estudios Perinatales in Rosario, Argentina, and from the Instituto Argentino de Medicina Basada en las Evidencias in Buenos Aires, Argentina. Centres in South Africa were coordinated from the MRC Pregnancy Hypertension Unit in Durban. Throughout recruitment, a 24-h on-call service was provided by the Coordinating Centre in Oxford. Trial procedures were piloted at Kalafong Hospital, Pretoria, in South Africa (February to July, 1998). Recruitment to the pilot trial took place between Feb 23, and July 14, 1998 (n=101), and to the main trial between July 15, 1998, and Nov 29, 2001.

All hospitals were required to secure appropriate local ethics or research committee approval before recruitment could begin. In the UK, the trial was approved by the Northwest Multicentre Research Ethics Committee. It was also approved by the WHO Scientific and Ethical Review Group, Geneva, Switzerland.

Participants

Women were eligible for trial entry if they had pre-eclampsia and there was uncertainty about whether to use magnesium sulphate. We included women irrespective of whether they had had an anticonvulsant at a referring hospital, or whether the pregnancy was singleton or multiple. Most women were recruited whilst on the labour ward. Although the decision to offer participation was usually made by the obstetrician, women could be enrolled by either an obstetrician or a midwife. Eligibility criteria were: the woman had not given birth, or was 24 h or less postpartum; blood pressure was 90 mm Hg diastolic or 140 mm Hg systolic or more on at least two occasions; proteinuria was 1+ or more; and there was clinical uncertainty about whether magnesium sulphate would be beneficial. Women were excluded if they had hypersensitivity to magnesium, hepatic coma with a risk of renal failure, or myasthaenia gravis. Women with oliguria (urine output <25 mL/h) were eligible, but the volume of trial treatment was halved for each dose. All women provided written or oral informed consent.

It was anticipated that uncertainty about the use of magnesium sulphate would be affected by the presence of signs or symptoms of imminent eclampsia, such as hyper-reflexia, frontal headache, blurred vision, and epigastric tenderness. If the woman's initial blood pressure did not require immediate treatment, it was recommended that the two measurements should be 30 min apart, but up to 1 h between measurements was allowed. If the initial blood pressure was high enough to require consideration of immediate antihypertensive treatment, the second measurement was taken within 30 min. For assessment of proteinuria, a midstream sample was requested whenever possible. Because eligibility was highly dependent on the attending clinicians' beliefs about magnesium sulphate it was not possible to keep an accurate record of those eligible but not recruited.

Randomisation

Hospitals with reliable access to telephones used a central telephone randomisation service at the Clinical Trial Service Unit, in Oxford. Baseline details were collected during a 2–3 min call, and recorded on the central computer. Treatment allocation used a minimisation algorithm, balancing for severity of pre-eclampsia, gestation at randomisation, whether delivered, whether given anticonvulsant drugs before trial entry, whether a multiple pregnancy, and country. The allocated pack number was then given and recorded on the trial entry form. Hospitals without reliable access to telephones used a local pack system. Baseline information was collected on the trial entry form and the next consecutively numbered pack taken from the box of eight packs (with an allocation sequence based on a block size of eight, also generated by the Clinical Trial Service Unit). The pack number was recorded on the form, which was then faxed to the Coordinating Centre in Oxford. The woman was in the trial once this number had been recorded, regardless of whether the pack was opened or the allocated treatment started.

The boxes of eight treatment packs had a large lift-up flap on one side, to display all the pack numbers when using the telephone randomisation service. The other side had a small horizontal flap at the bottom, allowing only one box to be removed at a time for those using the local box system. Treatment packs were prepared and packed by an independent clinical trial supplies company (DHP Clinical Supplies, Abergavenny, Wales, UK). Each batch of active and placebo packs was tested by an independent biochemist before distribution.

Interventions

Women were randomly allocated to receive either magnesium sulphate or placebo. Each woman was assigned a uniquely numbered treatment pack, containing nine 10 mL ampoules labelled "Magpie Trial Treatment". Each 10 mL "active" ampoule contained 5 g magnesium sulphate heptahydrate ($MgSO_4 \cdot 7H_2O$) 50% solution, which is approximately 2 mmoL magnesium/mL. Each placebo ampoule contained 10 mL normal saline. The magnesium sulphate and placebo ampoules were identical, and the solutions looked the same. Each pack also contained 10 mL calcium gluconate, for use in the event of toxicity, and an eclampsia rescue pack (see below) for use in the event of eclampsia. Treatment packs were provided to collaborating hospitals in boxes of eight packs. Standard treatment was a loading dose followed by 24-h maintenance therapy, with clinicians at each hospital able to choose whether to use the intravenous (iv) or the intramuscular (im) routes for the maintenance regimen. These two magnesium sulphate regimens were chosen because they are both widely used internationally, and have been evaluated in trials for treatment of women with pre-eclampsia[9] and eclampsia.[10–12]

The loading dose was 8 mL trial treatment (4 g magnesium sulphate, or placebo). This solution was diluted with normal saline according to whatever was the usual local practice, and given iv over 10–15 min. For the iv maintenance regimen,[15] this preliminary dose was followed by an infusion over 24 h of 2 mL/h trial treatment (1 g/h magnesium sulphate, or placebo), again diluted with normal saline, according to usual local practice. For the im maintenance regimen[16] this initial iv dose of 8 mL trial treatment was combined with 20 mL trial treatment by im injection, given as 10 mL trial treatment (5 g magnesium sulphate or placebo) into each

buttock. This dose was followed by 10 mL trial treatment (5 g magnesium sulphate, or placebo) every 4 h, for 24 h.

Two hospitals in Bangladesh used a loading dose of 20 mL trial treatment (10 g magnesium sulphate, or placebo), given as 8 mL trial treatment iv over 10–15 min followed by 5 mL trial treatment (2·5 g magnesium sulphate, or placebo) im into each buttock, and then 5 mL trial treatment (2·5 g magnesium sulphate, or placebo) every 4 h for 24 h.

If the woman had recently received a loading dose of magnesium sulphate at a referring hospital, she could be randomised and the trial treatment loading dose omitted. The iv regimen required six ampoules of trial treatment (58 mL), and the im regimen eight ampoules (78 mL). The extra ampoules in each pack could be used to continue trial treatment beyond 24 h, if this was considered necessary by the clinicians. An additional pack of nine ampoules could be allocated to the women if treatment was to continue for longer than was possible with one treatment pack, or if treatment was to be restarted some time later. In this situation, the central 24-h randomisation service (see above) or the Coordinating Centre in Oxford was contacted and an additional treatment pack allocated, which contained the same treatment as the first pack. If it was not possible to make this contact, the clinicians had to decide whether or not to use ward stock magnesium sulphate. All other aspects of care were at the discretion of the clinicians.

Magnesium sulphate is excreted by the kidneys and is a smooth muscle relaxant. Reduction or loss of tendon reflexes precedes respiratory depression, so reflexes were to be carefully monitored and magnesium sulphate administration adjusted as appropriate to prevent toxicity. Before starting Magpie Trial treatment, the clinician checked that knee or other tendon reflexes were present, the respiratory rate was normal (>16 respirations/min), and urine output was 100 mL or more during the past 4 h, or greater than 25 mL/h. Clinical monitoring continued throughout trial treatment, with reflexes and respiration to be checked at least every 30 min (or according to usual practice) and urine output measured hourly for the duration of treatment. The volume of trial treatment was reduced by half if tendon reflexes were slow, respiratory rate reduced but the woman well oxygenated, or urine output was less than 100 mL in 4 h. Blood monitoring of magnesium concentrations was not required.

Unblinding was available either by phoning the telephone randomisation service in Oxford or by using the 24-h emergency bleep, usually held by either the Clinical Coordinator or the Trial Manager. To preserve the blinding, clinicians were asked not to measure serum magnesium concentrations, unless clinically necessary, and to report if any measurements were taken.

If the woman had an eclamptic seizure, trial treatment was to be stopped and it was recommended that magnesium sulphate be used. Rather than unblind the allocation before initiation of treatment, which might have led to unacceptable delays, an eclampsia rescue pack was provided in each treatment pack, with two red labelled ampoules. One contained 5 g magnesium sulphate and the other 10 mL of either 50% magnesium sulphate (5 g) or placebo, whichever was the opposite of the trial allocation. For management of the acute fit, 4 mL from each ampoule were given iv over 5–10 min; 4 g magnesium sulphate for those originally allocated placebo and 2 g for those originally allocated magnesium sulphate. Magnesium sulphate maintenance therapy was then to be continued according to the normal clinical practice in that hospital. If the im Magpie Trial regimen had been used, the first unblinded im dose for eclampsia was given when the next trial treatment dose would have been due, to avoid overdose.

Outcomes

Primary outcomes were eclampsia and, for women randomised before delivery, death of the baby before discharge from hospital (including stillbirths). Maternal death was not specified as a primary outcome, because the study was not expected to have sufficient power to estimate reliably any effects on maternal mortality. Cause of death for the babies was classified using the system suggested by Wigglesworth.[17] Because most babies were from countries where normal birthweight tends to be lower than in the UK, where this classification system was devised, we used a birthweight of 2 kg or less (rather than ≤2·5 kg) for prematurity. Follow-up for women and children was until discharge from hospital after delivery. Long-term follow-up of a proportion of the women and children is also under way at selected centres.

Secondary outcomes were measures of serious maternal morbidity (respiratory depression, respiratory arrest, pneumonia, cardiac arrest, coagulopathy, renal failure, liver failure, pulmonary oedema, and cerebral haemorrhage), toxicity (need for calcium gluconate, stopped or reduced treatment due to toxicity, stopped or reduced treatment due to side-effects), and other side-effects of magnesium sulphate (nausea or vomiting, flushing of the skin, drowsiness, confusion, muscle weakness, abscess). A composite outcome of these nine measures of serious morbidity was also prespecified as a main outcome. Serious unexpected events thought possibly to be related to the trial treatment were reported immediately to the Coordinating Centre in Oxford.

For women randomised before delivery, additional secondary outcomes were complications of labour and delivery (induction and length of labour, caesarean section, retained placenta, blood loss, transfusion, and gestation at delivery), and neonatal morbidity (Apgar <7 at 5 min, intubation at place of delivery, ventilation, abnormal cerebral ultrasound, convulsions, and admission to special care baby unit).

Other outcomes included measures of the use of maternal health-service resources (number of days in hospital, admission to an intensive care unit or a high

Definition of severe pre-eclampsia

All women

Diastolic blood pressure ≥110 mm Hg on two occasions, or systolic blood pressure ≥170 mm Hg on two occasions and proteinuria ≥3+

or

Diastolic blood pressure ≥100 mm Hg on two occasions, or systolic blood pressure ≥150 mm Hg on two occasions and proteinuria ≥2+ and at least two signs or symptoms of imminent eclampsia

Or, for women who had an antihypertensive in the 48 h before randomisation

In 48 h before trial entry, highest diastolic blood pressure ≥110 mm Hg, or highest systolic blood pressure ≥170 mm Hg and proteinuria ≥3+ at trial entry

or

In 48 h before trial entry, highest diastolic blood pressure ≥100 mm Hg, or highest systolic blood pressure ≥150 mm Hg and proteinuria ≥2+ and at least two signs or symptoms of imminent eclampsia

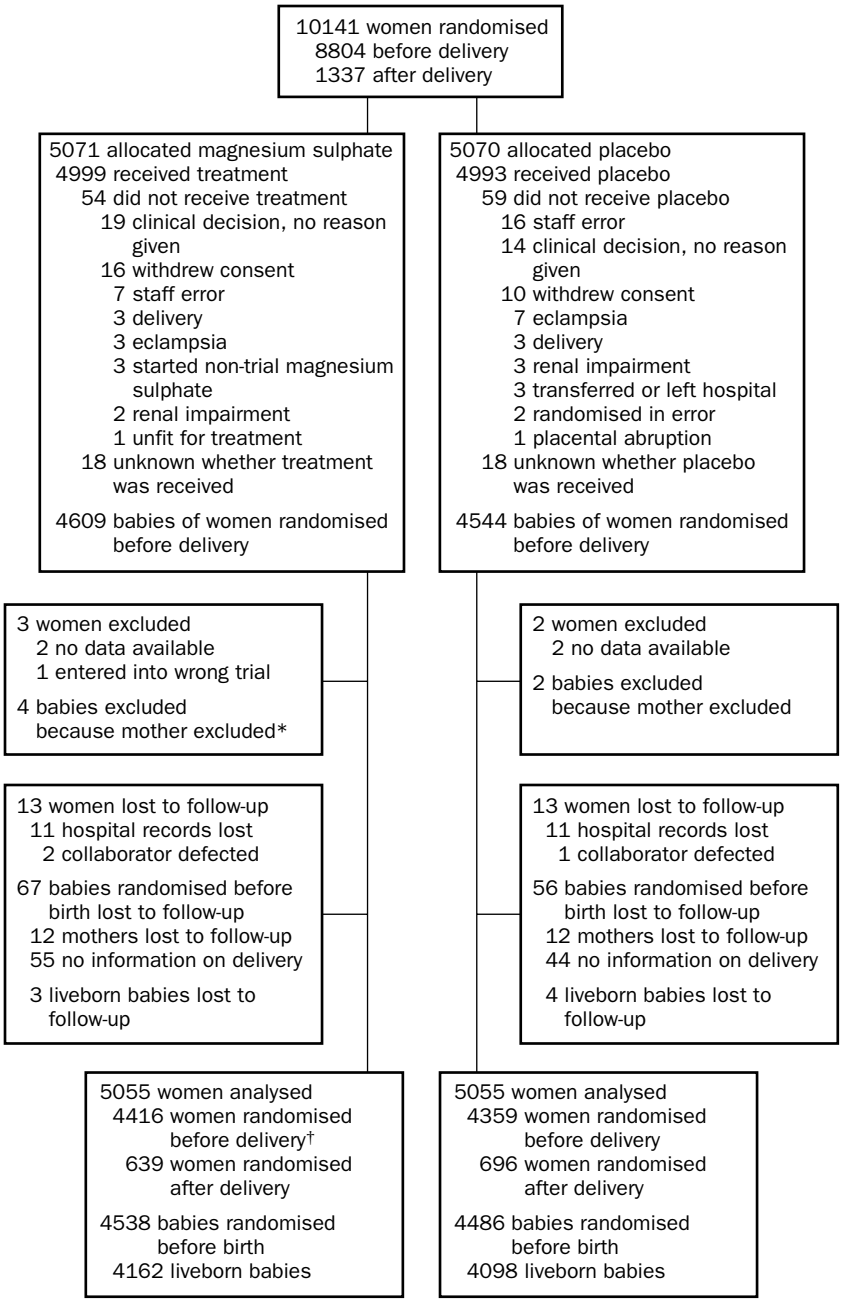

Figure 1: **Trial profile**
*Includes one pair of twins. † Includes one phantom pregnancy.

dependency unit, ventilation, and dialysis) and of neonatal health-service resources (days in special care baby unit and ventilation). An economic evaluation of the use of magnesium sulphate for women with pre-eclampsia is in progress.

Subgroup and sensitivity analyses

Women were classified, a priori, into subgroups based on their characteristics at trial entry: severity of pre-eclampsia, imminent eclampsia, gestational age, whether they had an anticonvulsant in the previous 48 h, and whether they had already given birth. The protocol defined severe pre-eclampsia at randomisation according to the criteria in the panel. Imminent eclampsia was taken as two or more signs or symptoms of imminent eclampsia regardless of hypertension and proteinuria.

Outcome was also compared on the basis of the country's perinatal mortality, as reported by WHO.[18] Although these subgroups were not specified until just before the final analysis, a similar strategy had been used successfully in an earlier perinatal trial.[19] Low perinatal mortality was taken as less than 20 deaths per 1000 births, moderate as 20–40 per 1000 births, and high as more than 40 per 1000 births. Countries with low perinatal mortality were Albania, Australia, Canada, Cuba, Denmark, Israel, Italy, Singapore, The Netherlands, UK, and USA. Countries with moderate perinatal mortality were Argentina, Colombia, Jordan, Malaysia, Mexico, Sri Lanka, Thailand, United Arab Emirates, Venezuela, and Zimbabwe. Countries with high perinatal mortality were Bangladesh, Brazil, Egypt, Ghana, India, Malawi, Nigeria, Pakistan, Sierra Leone, South Africa, Uganda, and Yemen.

Statistical analysis

We initially estimated that the risk of convulsions for women allocated placebo might be around 1%, and that to have 90% power to show a 50% decrease in this risk would require 14 000 women (α=0·05). In February, 2000, the sample size estimate was revisited, because the overall risk of eclampsia among trial participants was 1·2%. After consultation with the chair of the data monitoring committee, target recruitment was revised to between 10 800 and 12 750 women. We expected that most women (90%) would be randomised before delivery. If total mortality for their babies was 12%, as in previous trials,[9] our enrolment target would give a power of 90% to detect a 15% proportional reduction to 10·2% (α=0·05). If total mortality for the babies was reduced from 10% to 8·5% (15% reduction), the power would be 80% (α=0·05).

Data were monitored, in strict confidence, by an independent data monitoring committee. Meetings of the committee were arranged as considered appropriate by the chair. The committee's terms of reference were that they should inform the chair of the steering committee if, in their view: there was proof beyond reasonable doubt that treatment with magnesium sulphate was clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially affect patients' management; or if it was evident that no clear outcome would be obtained. Proof beyond reasonable doubt required a difference of at least 3 SE in at least one of the primary outcomes, which corresponds to a p value of about 0·003.

At their fifth meeting on Nov 27, 2001, after review of data for 8483 women with follow-up to discharge from hospital after delivery, the data monitoring committee

	Magnesium sulphate (n=5068)*	Placebo (n=5068)†
Characteristic		
Age (mean, SD) (years)	27·1 (6·7)	27·2 (6·7)
Primiparous‡	2604 (52%)	2591 (51%)
Multiple pregnancy	217 (4%)	203 (4%)
History of epilepsy	56 (1%)	56 (1%)
Systolic BP at entry ⩾170 mm Hg	801 (16%)	808 (16%)
Diastolic BP at entry ⩾110 mm Hg	1119 (22%)	1146 (23%)
Proteinuria		
Trace/none	2 (0·04%)	5 (0·1%)
1+	1571 (31%)	1568 (31%)
2+	1704 (34%)	1721 (34%)
3+	1310 (26%)	1270 (25%)
4+	481 (9%)	504 (10%)
Severe pre-eclampsia	1303 (26%)	1349 (27%)
Imminent eclampsia§	816 (16%)	833 (16%)
Oliguria	131 (3%)	129 (3%)
Previous treatment with anticonvulsant	440 (9%)	435 (9%)
Magnesium sulphate	242 (5%)	241 (5%)
Other anticonvulsant	196 (4%)	192 (4%)
Unknown	2 (0·04%)	2 (0·04%)
Previous treatment with antihypertensive	2508 (49%)	2502 (49%)
If treated with antihypertensive, highest BP before entry		
Systolic BP ⩾170 mm Hg	1149 (23%)	1172 (23%)
Diastolic BP ⩾110 mm Hg	1540 (30%)	1554 (31%)
Unknown	8 (0·2%)	4 (0·1%)
Postpartum at randomisation	640 (13%)	697 (14%)

BP=blood pressure. *Three women excluded. †Two women excluded. ‡n=5055 for both groups. §Two or more of frontal or severe headaches, epigastric pain, blurred vision, or hyper-reflexia (irrespective of BP or proteinuria).

Table 1: **Baseline characteristics**

decided to reveal the results to the chair of the steering committee. The steering committee met on Nov 29, 2001, and decided to stop the trial. Recruitment through the telephone randomisation service closed that evening, and during the next 24 h all collaborators were informed of the decision to stop.

All analyses were based on the groups as randomly allocated (ie, an intention to treat analysis). For the principal comparisons statistical significance was taken as the 5% level with 95% CI, and for the secondary comparisons the 1% level with 99% CI. For the analysis of multiple births, outcome was assessed for total babies and for total pregnancies. Where appropriate, results are presented as relative risk (RR) with 95% CI, risk difference (RD) with 95% CI, number of events prevented (compared with placebo) per 1000 women with 95% CI, or number needed to treat (NNT).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Magnesium sulphate (n=4427)*	Placebo (n=4371)
Characteristic		
Gestation at entry		
<34 weeks	1211 (27%)	1213 (28%)
⩾34 weeks	3216 (73%)	3158 (72%)
Severe pre-eclampsia at entry	1150 (26%)	1182 (27%)
Multiple pregnancy†	173 (4%)	167 (4%)
Fetal heartbeat not heard at entry‡	143 (3%)	151 (3%)

Data are number (%). *Excludes one woman with a phantom pregnancy. †Magnesium sulphate: 168 twins, five triplets; placebo: 165 twins, two triplets. ‡n=4605 magnesium sulphate and n=4542 placebo (includes two babies where mother randomised between delivery of twin one and two).

Table 2: **Characteristics at trial entry for women randomised before delivery**

Results

Overall, 10 141 women were randomised at 175 secondary and tertiary level hospitals in 33 countries. Recruitment of 101 women in the pilot occurred from Feb 23, to July 14, 1998, and of the remaining women from July 15, 1998, to Nov 29, 2001. Altogether, 2037 women were recruited through the telephone service and 8104 through the local pack system. 4762 (47%) women were recruited in Africa, 2735 (27%) in the Americas, 1583 (15%) in the Asia-Pacific region, and 1061 (10%) in Europe. Of these, five women have been excluded from this analysis (three from the magnesium sulphate group and two from placebo). The reasons for exclusion are listed in figure 1. A further six treatment packs are not accounted for. 15 women randomised in two different pregnancies appear twice. 18 women who did not fully meet the entry criteria are included; five were allocated magnesium sulphate (two had proteinuria <1+ [<30 mg/dL]), three were >24 h after delivery) and 13 placebo (five had proteinuria <1+, three did not meet blood pressure criteria, five were >24 h after delivery). Also included is a woman with a phantom pregnancy. 17 women with a history of a possible convulsion before trial entry are also included. For eight of these women the history of a possible convulsion was only obtained after trial entry; the other nine were randomised in error. Information at trial entry is available for 10 136 women, and follow-up data are available for 10110 (99·7%). 9153 babies were born to women randomised before delivery, and data are available for 9024 (98·6%). Of these, 127 may have died in utero before randomisation, because the fetal heart beat was not heard at trial entry and the baby was a macerated stillbirth born less than 24 h later. For secondary outcomes, missing data for individual items is only reported if they constituted 1% of total data available. For most outcomes, less than ten were missing per group, with the exception of steroid use and manual removal of retained placenta, which were not available for the 101 women recruited to the pilot study.

	Magnesium sulphate (n=640)	Placebo (n=697)*
Characteristic		
Gestation at birth		
<34 weeks	112 (18%)	135 (19%)
⩾34 weeks	519 (81%)	556 (80%)
Unknown	9 (1%)	6 (1%)
Randomised >24 h after delivery†	3 (0·5%)	5 (0·7%)
Severe pre-eclampsia at entry	152 (24%)	166 (24%)
Multiple pregnancy	44 (7%)	36 (5%)
Birthweight (g)‡		
<1500	94 (14%)	107 (15%)
<2500	340 (49%)	354 (48%)
Total baby deaths‡	58 (8%)	85 (12%)
Perinatal death‡	48 (7%)	78 (11%)
Stillbirth	32	56
Early neonatal death	16	22
Late neonatal deaths‡	8	3
Post neonatal deaths‡	2	4
Cause of death‡		
Congenital malformation	1	4
Asphyxia	23	29
Macerated stillbirth	14	33
Prematurity	16	17
Other	4	2

*Includes two women randomised between delivery of twin one and twin two. †n=639 magnesium sulphate, n=696 placebo. ‡n=687 magnesium sulphate, 40 twins and four triplets; n=731 placebo, 33 twins and one triplet, plus twin one for two women randomised between delivery of twin one and twin two.

Table 3: **Characteristics at trial entry for women randomised after delivery**

	Magnesium sulphate (n=5055)	Placebo (n=5055)
Received allocated treatment*	4999 (99%)	4993 (99%)
Unknown	2 (0·04%)	3 (0·06%)
Received allocated treatment plus		
No other drug	4736 (94%)	4742 (94%)
Non-trial magnesium sulphate	126 (2%)	104 (2%)
Non-trial magnesium sulphate and diazepam	2 (0·04%)	8 (0·2%)
Diazepam	104 (2%)	114 (2%)
Phenytoin	7 (0·1%)	4 (0·08%)
Barbiturates	14 (0·3%)	13 (0·3%)
Other†	10 (0·2%)	8 (0·2%)
Did not receive allocated treatment	54 (1%)	59 (1%)
No other anticonvulsant	46 (0·9%)	48 (0·9%)
Non-trial magnesium sulphate alone	6 (0·1%)	9 (0·2%)
Other‡	2 (0·04%)	2 (0·04%)
Duration of treatment (median, IQR) (h)§	24·2 (24·0–25·6)	24·2 (24·0–25·6)
Additional treatment pack used¶	31 (0·6%)	27 (0·5%)
⩽2 h from end of first pack to start of second	10 (0·2%)	11 (0·2%)
Serum magnesium measured	39 (0·8%)	41 (0·8%)
Volume of treatment		
Intravenous regimen, given 58 mL‖	1688 (62%)	1678 (62%)
Intramuscular regimen, given 78 mL‖	1427 (65%)	1532 (70%)
Treatment stopped early		
Total	785 (16%)	631 (13%)
Woman's request or side-effects	317	118
Oliguria or renal failure	114	148
Woman stable	72	68
Staff error**	69	56
Absent tendon reflexes	47	50
Decided to use magnesium sulphate	29	28
No bed space or equipment failure	28	35
Respiratory depression or arrest	26	14
Eclampsia	16	54
Hypotension	16	7
For caesarean section	15	8
Severe medical problem	7	10
Transferred or left hospital	7	9
Eclampsia before trial entry, randomised in error	1	2
Woman died	2	0
Other	10	7

*Includes six women in each group given wrong pack with wrong allocated treatment. †Includes lytic cocktail, carbamazepine, chlorpromazine, nitrazepam; seven women (five magnesium sulphate, two placebo) not known which anticonvulsant used, and five (two magnesium sulphate and three placebo) had two additional anticonvulsants. ‡Magnesium sulphate plus diazepam, diazepam alone, or unknown. §Calculated either up to time infusion stopped, or 4 h after last intramuscular injection; includes additional treatment if started within 2 h of finishing first pack. ¶For 16 women additional one pack was not allocated correctly; of these, seven allocated magnesium sulphate had placebo in additional pack, one allocated placebo had magnesium sulphate in additional pack. ‖Includes additional treatment if started within 2 h of finishing the first pack; for intravenous route n=2719 magnesium sulphate, n=2720 placebo; for intramuscular route n=2193 magnesium sulphate, n=2184 placebo (excludes two centres in Bangladesh, which used a different regimen). **20 women allocated magnesium sulphate and 17 placebo from one centre where protocol initially misunderstood.

Table 4: **Compliance with allocated treatment**

The groups were well balanced at trial entry (table1). Just over half the women were in their first pregnancy, 4% had multiple pregnancies, 26% had severe pre-eclampsia, and 16% imminent eclampsia, 9% had received an anticonvulsant before trial entry, and 13% were recruited postpartum. Only 3% (138 of 5068 magnesium sulphate *vs* 155 of 5068 placebo) of women had blood pressure of 140/90 mm Hg and 1+ protein, the minimum criteria. The proportion of women with severe pre-eclampsia at trial entry in each country ranged from none of 43 in the USA and three of 261 (1%) in Cuba to 58 of 108 (54%) in Egypt and 21 of 37 (57%) in Sierra Leone. This variation probably reflects the local clinicians' prior belief about the value of magnesium sulphate; so, for example, in the USA and Cuba most women with severe pre-eclampsia were given magnesium sulphate rather than recruited to the trial. 26% (2524 of 9690) of women with singleton pregnancies had severe pre-eclampsia, as did 28% (118 of 420) of those with multiple pregnancies. For women randomised before delivery, a quarter were less than 34 weeks at trial entry (table 2). Of those randomised after delivery, 18% were less than 34 weeks at delivery (table 3). The small imbalance between the groups for women randomised before (4428 *vs* 4371) or after delivery (640 vs 697) appears to be due to the chance accumulation of slight imbalances in a small number of centres using the local pack system (data not shown).

	Magnesium sulphate (n=4999)	Placebo (n=4993)
Side-effects	1201 (24%)	228 (5%)
Flushing	987	98
Nausea or vomiting, or both	160	18
Muscle weakness	72	6
Absent or reduced tendon reflexes	59*	60
Respiratory depression or other problems	51*	26
Thirst	37	11
Headache	36	17
Hypotension or palpitations or tachycardia	36	9
Dizziness	37	10
Drowsiness or confusion	20	9
Itching or tingling	15	1
Other	20	9
Problems at injection site—intravenous regimen†	125 (5%)	41 (2%)
Pain or burning	95 (3%)	15 (0·6%)
Drip tissued	22 (0·8%)	17 (0·6%)
Inflammation or phlebitis	7 (0·3%)	8 (0·3%)
Bruising	1 (0·04%)	1 (0·04%)
Problems at injection site—intramuscular regimen‡	271 (12%)	181 (8%)
Pain or burning	244 (11%)	176 (8%)
Inflammation or phlebitis	17 (0·7%)	4 (0·2%)
Bruising or bleeding	9 (0·4%)	0
Abscess	1 (0·04%)	1 (0·04%)

Some women had more than one side-effect. *Four women had respiratory depression and absent tendon reflexes. †n=2719 magnesium sulphate, n=2720 placebo. ‡n=2280 magnesium sulphate, n=2273 placebo.

Table 5: **Side-effects and problems at injection site, for women who received trial treatment**

	Magnesium sulphate (n=5055)	Placebo (n=5055)	Relative risk (95% CI)
Eclampsia	40 (0·8%)	96 (1·9%)	0·42 (0·29 to 0·60)*
Unknown	4 (0·08%)	3 (0·06%)	
Number of fits			
1	27	63	
2	10	24	
3	2	7	
⩾4	1	1	
Unknown	0	1	
Maternal death	11 (0·2%)	20 (0·4%)	0·55 (0·26 to 1·14)†
Unknown	2 (0·04%)	2 (0·04%)	
Main cause of death			
Cardiac arrest or failure	4	6	
Stroke	3	2	
Eclampsia or pre-eclampsia	1	2	
Anaemia or postpartum haemorrhage	1	1	
Anaesthetic death	1	0	
Respiratory failure or pneumonia	1	1	
Renal failure	0	3	
Pulmonary embolism	0	3	
Infection	0	2	

Risk difference (95% CI) is *–1·1 (–1·6 to –0·7), †–0·2 (–0·4 to 0·04).

Table 6: **Eclampsia and maternal death**

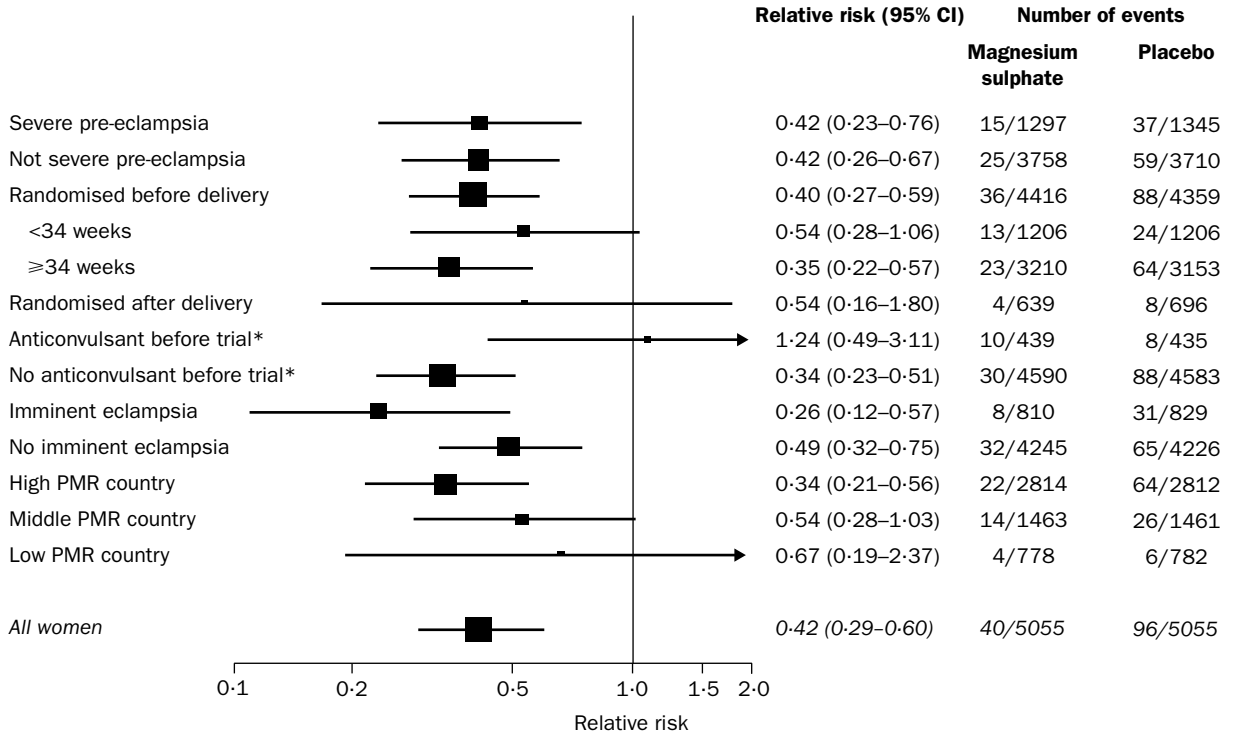

Figure 2: **Effects of treatment on eclampsia**
PMR=Perinatal mortality rate. *Not known whether previous anticonvulsant was given to 26 women allocated magnesium sulphate and to 37 allocated placebo.

Compliance with the allocated treatment

In both groups, 99% of women received the allocated treatment, and of these 5% also had another anticonvulsant (table 4). 16 women (eight in each group) were given the wrong pack in error: four women (two in each group) received the correct treatment, and 12 did not. All 16 women were analysed as part of the group to which they were initially allocated. 75 women were allocated an additional treatment pack, which was used for 58 women (31 magnesium sulphate, 27 placebo). 113 women (1%) did not start the allocated treatment (figure 1). The im route for maintenance therapy was used at centres in Argentina, Bangladesh, Brazil, Ghana, India, Malawi, Malaysia, Mexico, Nigeria, Pakistan, Sierra Leone, South Africa, Thailand, Uganda, and Zimbabwe. The iv route was used in Albania, Argentina, Australia, Bangladesh, Brazil, Canada, Colombia, Cuba, Denmark, Egypt, India, Israel, Italy, Jordan, Nigeria, Pakistan, Singapore, South Africa, Sri Lanka, Netherlands, United Arab Emirates, UK, USA, Venezuela, and Yemen.

For ten women treatment was unblinded, seven allocated magnesium sulphate and three placebo. Reasons for unblinding in the magnesium sulphate group were reaction to the trial treatment (six) and massive haemorrhage (one). Reasons in the placebo group were reaction to trial treatment (one), baby hypotensive (one), and possible stroke (one).

785 women (16%) allocated magnesium sulphate stopped treatment early, compared with 631 (12%) of those allocated placebo. The most common reason was the woman's request or side-effects (317 of 5055, 8%, *vs* 118 of 5055, 2%; table 4). Respiratory depression or absent tendon reflexes was the reason for stopping treatment for 73 of 5055 women allocated magnesium sulphate and 64 of 5055 allocated placebo. Overall, 1201 of 4999 (24%) women allocated magnesium sulphate reported side-effects compared with 228 of 4993 (5% allocated placebo (table 5). More women experienced side-effects with the im rather than the iv regimen (im 637 of 2280, 28%, *vs* 109 of 2273, 5%; iv 564 of 2719, 20%, *vs* 119 of 2720, 4%). Flushing, the most common side-effect, was more frequent with the im regimen (im 541 of 2280, 24%, *vs* 45 of 2273, 2%; iv 446 of 2719, 16%, *vs* 53 of 2720, 2%). There was little difference between the regimens for nausea or vomiting (im 61 of 2280, 3%, *vs* five of 2273, 0·2%; iv 99 of 2719, 4%, *vs* 13 of 2720, 0·5%). For women using the im regimen, magnesium sulphate was more likely than placebo to be stopped early (430 of 2280, 19%, *vs* 298 of 2273, 13%). There was little difference between the groups for the iv regimen (355 of 2719, 13%, *vs* 333 of 2720, 12%). Serious unexpected events were reported for six women allocated magnesium sulphate and three allocated placebo. For the magnesium sulphate group these were problems during the infusion (two women), fetal heartbeat stopped (one), stroke (one), cardiac arrest (one), and pulmonary oedema (one). For the placebo group they were anaphylactic shock (one), cardiac arrest (one), and stroke (one).

Outcomes

There were significantly fewer eclamptic convulsions among women allocated magnesium sulphate than among those allocated placebo (40, 0·8%, *vs* 96, 1·9%; ie, 11 fewer women with eclampsia per 1000 women, 95% CI 7–16 women; p<0·0001; table 6). This represents a 58% lower relative risk of eclampsia (95% CI 40–71% reduction), NNT 91 (95% CI 63–143). The NNT for women with severe pre-eclampsia was 63 (95% CI 38–181) and for those without severe pre-eclampsia it was 109 (95% CI 72–225). Excluding the 17 women reported to have possibly had eclampsia before trial entry, six of whom also had a convulsion after trial entry, makes little difference (39 of 5051, 0·8%, *vs* 91 of 5042, 1·8%; 57%

	Magnesium sulphate (n=5055)	Placebo (n=5055)
Outcome		
Any serious morbidity*	196 (3·9%)	183 (3·6%)
Respiratory depression	46 (0·9%)	27 (0·5%)
Respiratory arrest	5 (0·1%)	2 (0·04%)
Pneumonia	14 (0·3%)	6 (0·1%)
Pulmonary oedema	32 (0·6%)	33 (0·7%)
Cardiac arrest	4 (0·1%)	5 (0·1%)
Renal failure	49 (1·0%)	61 (1·2%)
Liver failure	52 (1·0%)	67 (1·3%)
Coagulopathy	73 (1·4%)	86 (1·7%)
Cerebrovascular accident	3 (0·1%)	6 (0·1%)
Antihypertensives after trial entry	3720 (74%)	3823 (76%)
1	2209	2182
2	1285	1383
3	174	204
⩾4 drugs	20	22
Unknown	32	32
Calcium gluconate	14 (0·3%)	11 (0·2%)
Other maternal problems		
Ascites	44	39
Infection	21	31
Myocardial infarction or cardiac failure	10	6
Blindness or retinopathy	6	4
Thromboembolism	4	3
Airway obstruction or laryngeal oedema	3	0
Ruptured uterus or scar or cervical tear	3)	6
Major psychiatric illness	2	5
Transient neurological symptoms	1	1
Other†	17	19

*Some women had more than one. †Includes pancreatitis, haematuria, pleural effusion.

Table 7: **Secondary outcome for all women**

lower relative risk, 95% CI 38–71% reduction). Overall, 3·6% (15 of 420) of women with a multiple pregnancy had eclampsia (four of 217, 2%, *vs* 11 of 203, 6%), as did 1·2% (121 of 9690) of those with a singleton pregnancy (36 of 4838, 1%, *vs* 85 of 4852, 2%). The effect on eclampsia was consistent regardless of severity of pre-eclampsia, stage of gestation at trial entry, whether an anticonvulsant had been given before trial entry, or whether the woman had delivered at trial entry (figure 2). It was also consistent regardless of parity (para=0: 27 of 2604, 1·0%, *vs* 62 of 2591, 2·4%; para 1–3: ten of 1941, 0·5%, *vs* 27 of 1896, 1·4%; para >3: three of 504, 0·6%, *vs* six of 558, 1·1%). Most women with eclampsia received non-trial magnesium sulphate after their first convulsion (115 of 136, 84%), and for 34 this drug was combined with diazepam; three women were given phenytoin.

Maternal mortality was lower among women allocated magnesium sulphate than in those allocated placebo (11, 0·2%, *vs* 20, 0·4%; relative risk reduction 45%, 95% CI –74% to 14; p=0·11). Of the women who died, one allocated magnesium sulphate also had eclampsia, as did three allocated placebo. Overall, 45% of the women who

	Magnesium sulphate (n=5055)	Placebo (n=5055)
Stay in hospital (median, IQR) (days)*	6 (4–9)	6 (4–9)
Discharged before delivery†	200 (4%)	191 (4%)
Admission to an intensive care unit	83 (2%)	86 (2%)
Ventilated	30 (0·6%)	18 (0·4%)
Dialysis	4 (0·08%)	5 (0·1%)
High dependency area/unit		
Admission	2803 (55%)	2800 (55%)
Length of stay (median, IQR) (days)	2 (2–3)	2·0 (2–3)
Re-admission	22 (0·4%)	28 (0·6%)

*For first admission only. †146 allocated magnesium sulphate readmitted for delivery, 150 allocated placebo.

Table 8: **Hospital stay and use of intensive care facilities, for all women**

died had severe pre-eclampsia at trial entry; 39% had imminent eclampsia, 42% were less than 34 weeks' gestation, 13% were postpartum, and 19% had had an anticonvulsant in the previous 48 h. Overall, 1% of women with a multiple pregnancy died (one of 217, 0·5%, *vs* three of 203, 1·5%) and 0·3% of those with a singleton pregnancy (ten of 4838, 0·2%, *vs* 17 of 4852, 0·4%). There were no maternal deaths in low perinatal mortality countries. Maternal mortality was highest in countries with high perinatal mortality, but the relative reduction in risk was consistent (for moderate perinatal mortality countries two of 1463 maternal deaths *vs* four of 1461, relative risk 0·50, 95% CI 0·90–2·72; for high perinatal mortality countries nine of 2814 *vs* 16 of 2812, relative risk 0·56, 95% CI 0·25–1·27).

There were no clear differences between the groups in any measure of maternal morbidity, or in the composite measure of any serious morbidity (table 7). Renal failure, liver failure, and coagulopathy are closely related to pre-eclampsia, and again there was no difference (117, 2·3%, *vs* 136, 2·7%). There were no clear differences in length of stay in hospital or use of hospital resources (table 8). The analysis presented here is based on all women, but there are no substantive differences when women who died are excluded.

The most frequently used antihypertensive drugs after trial entry were methyldopa (magnesium sulphate group 2373 *vs* placebo 2439), nifedipine (1469 *vs* 1560), and hydralazine (977 *vs* 1040). 58 women were reported to have hypotension associated with trial treatment (38 *vs* 20). Around half of them had had antihypertensive drug(s) (18 of 38 *vs* 11 of 20), of which the most common were methyldopa (eight *vs* seven) and nifedipine (six *vs* four).

For women randomised before delivery, there was no clear difference in the risk of the baby dying (576, 12·7%, *vs* 558, 12·4%; relative risk increase of 2%, 95% CI –8% to 14%). This result a 0·3% in absolute risk (95% CI –1·1% to 1·6%, table 9). Excluding the 127

	Magnesium sulphate (n=4538)*	Placebo (n=4486)	Relative risk (95% CI)
Baby death			
Total	576 (12·7%)	558 (12·4%)	1·02 (0·92 to 1·14)‖
Likely in-utero death before trial entry†	57 (1·3%)	70 (1·6%)	
Baby death, excluding likely in-utero death before trial entry‡	519 (11·6%)	488 (11·1%)	1·05 (0·93 to 1·18)**
Perinatal death	518 (11·4%)	516 (11·5%)	0·99 (0·88 to 1·11)††
Stillbirth§	373 (8·2%)	384 (8·6%)	
Early neonatal death	145 (3·2%)	132 (2·9%)	
Late neonatal death	42 (0·9%)	27 (0·6%)	
Post neonatal death	16 (0·4%)	13 (0·3%)	
Infant death	0	1 (0·02%)	
Unknown	0	1 (0·02%)	
Causes of death			
Asphyxia	220	215	
Macerated stillbirth	163	168	
Prematurity¶	161	131	
Congenital malformation	15	21	
Other	14	19	
Unknown	3	4	
Still in hospital at 6 weeks	1	1	
Unknown	4	0	

*No baby for one phantom pregnancy. †Based on fetal heart beat not heard at trial entry and macerated stillbirth <24 h later. ‡n=4481 magnesium sulphate, n=4416 placebo. §For two babies allocated magnesium sulphate and one allocated placebo, the mother died before delivery. ¶Includes all liveborn babies with birthweight ⩽2 kg, unless clearly some other cause of death. Risk difference (95% CI) is ‖0·3 (–1·1 to 1·6); **0·5 (–0·8 to 1·8); ††0·09 (–1·4 to 1·2).

Table 9: **Baby deaths before discharge from hospital for those randomised before delivery**

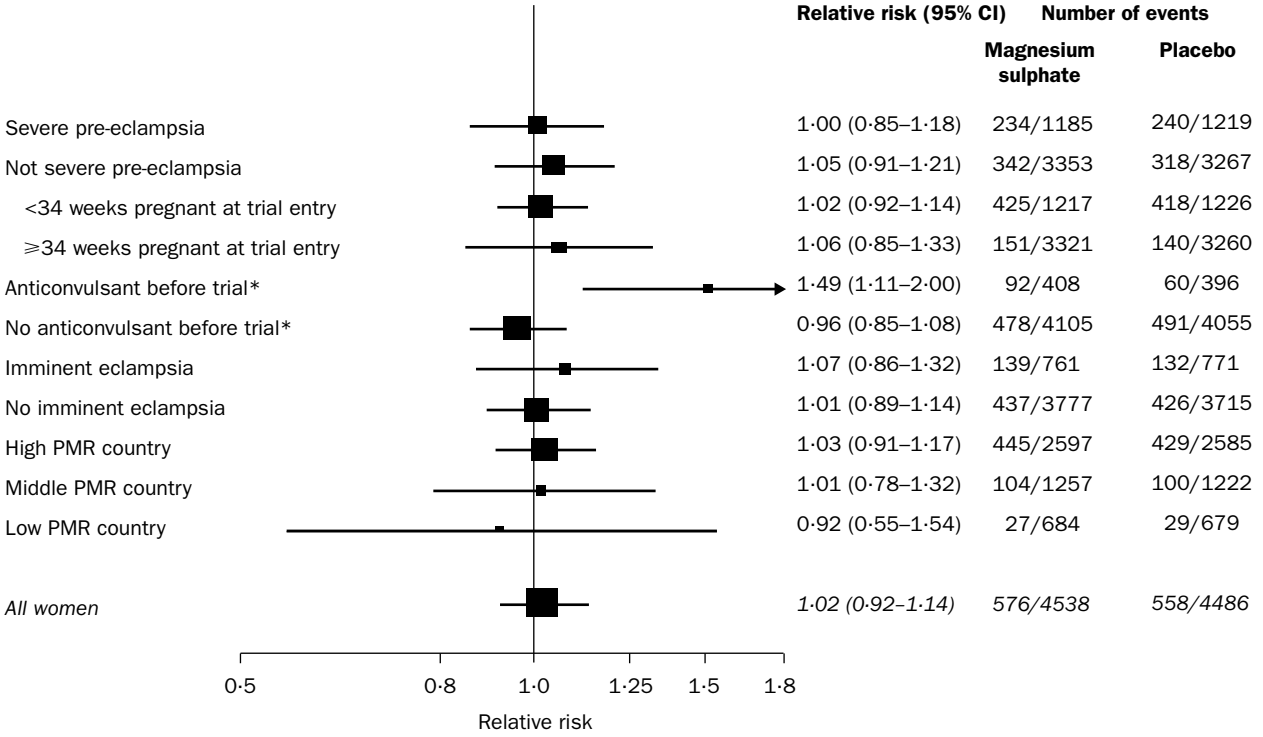

Figure 3: **Effects of treatment on baby death, for those randomised before birth**
PMR=perinatal mortality rate. *Not known whether previous anticonvulsant was given to two of 25 babies allocated magnesium sulphate and to seven of 36 allocated placebo.

babies likely to have died in utero before trial entry makes little difference (519, 11·6%, *vs* 488, 11·1%; relative risk 1·05, 95% CI 0·93–1·18; table 9). The effect on baby death was consistent regardless of severity of pre-eclampsia or gestation at trial entry (figure 3). The only exception is the small subgroup of women who had received an anticonvulsant before trial entry, where there appears to be an increase in the relative risk of baby death (relative risk 1·49, 95% CI 1·11–2·00). This group is the only outlying subgroup of many tested, however, a result that may well have occurred by chance. Also, mortality in this subgroup does not seem to be related to the use of magnesium sulphate before trial entry (magnesium sulphate before entry 49 of 229, 21·4%, *vs* 34 of 230, 14·8%; other anticonvulsant(s) before entry 42 of 177, 23·7%, *vs* 25 of 165, 15·2%).

These results were similar when outcome was looked at by pregnancy, taking a bad outcome as being any pregnancy in which at least one baby died (561 of 4415, 12·7%, *vs* 547 of 4359, 12·5%; relative risk 1·02, 95% CI 0·91–1·13). This includes twin pregnancies in which both babies died (12 of 168 *vs* ten of 165) and triplet pregnancies in which all three babies died (two of five *vs* none of two). Baby mortality was particularly high for women with eclampsia (six of 40, 15%, *vs* 12 of 96, 12%) and for maternal deaths (six of 11, 55%, *vs* seven of 20, 35%).

619 babies died after trial entry and before delivery (313 of 4466 *vs* 306 of 4395), excluding the 127 likely to have died before trial entry and 36 with lethal congenital malformations. Risk of death in utero after trial entry for severe pre-eclampsia was twice that for not severe pre-eclampsia (severe 132 of 1159, 11·5%, not severe 181 of 3307, 5·4%, *vs* 142 of 1187, 11·9%, *vs* 164 of 3208, 5·1%). A fifth of these stillbirths were born less than 12 h after trial entry (67 of 2092, 3·2%, *vs* 66 of 2160, 3·1%), and a third were born less than 24 h after trial entry (110 of 2839, 4·0%, *vs* 115 of 2882, 4·1%). Another third were born more than 71 h after trial entry (117 of 811, 14·3%, *vs* 119 of 802, 14·2%). For liveborn babies without a lethal congenital malformation, mortality was highest in the first week after birth and for those born before 30 weeks' gestation (table 10).

The only clear difference in outcome related to pregnancy, labour, or delivery was a lower risk of placental abruption in the magnesium sulphate group than in the placebo group (90, 2·0%, *vs* 141, 3·2%; ie, 12 fewer women with an abruption per 1000 women, 99% CI 3–21). This figure represents a 27% lower relative risk of abruption (99% CI 11–55; table 11). Of the 237 babies

	Magnesium sulphate (n=4153)			Placebo (n=4089)		
	Died 0–6 days	Died ⩾7 days	Proportion who died	Died 0–6 days	Died ⩾7 days	Proportion who died
Gestation at birth (weeks)						
<28	23	14	37/65 (57%)	27	9	36/67 (54%)
28–30	49	24	73/275 (27%)	35	12	47/227 (21%)
31–33	19	7	26/448 (6%)	27	9	36/474 (8%)
34–36	24	10	34/1060 (3%)	17	3	20/988 (2%)
>36	20	1	21/2290 (1%)	16	4	20/2314 (1%)
Unknown	0	0	0/15 (0%)	1	1	2/19 (11%)

Final outcome not known for 11 liveborn babies allocated magnesium sulphate and 14 allocated placebo.

Table 10: **Gestation at birth and age at death for liveborn babies, without lethal congenital malformation**

	Magnesium sulphate (n=4415)*	Placebo (n=4359)
Outcome		
Placental abruption	90 (2%)	141 (3%)
Of which, unclear if before or after entry	28 (0·6%)	28 (0·6%)
Antenatal steroids, in 7 days before delivery	787 (18%)	799 (18%)
Unknown	58 (1%)	59 (1%)
No information about delivery†	54 (1%)‡	41 (1%)‡
Labour		
Induced	1892 (43%)	1892 (43%)
Augmented	892 (20%)	851 (20%)
Length >8 h§	874 (41%)	922 (41%)
Caesarean section	2224 (50%)	2082 (48%)
Before labour	1486 (34%)	1373 (31%)
In labour	738 (17%)	709 (16%)
Delivery <24 h after entry	2797 (63%)	2863 (66%)
Entry to delivery (median, IQR) (h)‖	12·5 (4·5–33·9)	11·3 (4·2–32·0)
Blood loss after delivery >500 mL	750 (17%)	774 (18%)
Manual removal of placenta	148 (3%)	162 (4%)
Unknown	57 (1%)	54 (1%)
Platelet transfusion after trial entry	38 (1%)	38 (1%)
Blood transfusion after trial entry	224 (5%)	242 (6%)

Data are number (%) unless otherwise indicated. *Excludes one woman with a phantom pregnancy. †Includes two women allocated magnesium sulphate and three allocated placebo where only information about delivery is whether baby was liveborn. ‡Three women died before delivery; two allocated magnesium sulphate, one allocated placebo. §n=2135 magnesium sulphate, n=2228 placebo had a vaginal delivery. ¶Five women allocated magnesium sulphate had vaginal delivery for twin one and a caesarean section for twin two. ‖Only for those not discharged before delivery.

Table 11: **Outcomes relevant only to women randomised before delivery**

from these pregnancies, a third died (33 of 93, 35·5%, *vs* 52 of 144, 36·1%). There was also a 5% higher risk of caesarean section, which was borderline for significance at the 1% level (relative risk 1·05, 99% CI 1·00–1·11, p=0·02). There were no clear differences in any measure of neonatal morbidity (table 12). The analysis presented here is based on all babies, but the only difference when liveborn babies who died are excluded is that a smaller proportion was ventilated (119 of 3959, 3%, *vs* 96 of 3924, 2%).

Overall, centres using the im maintenance regimen had a higher risk of eclampsia and of baby death than those using the iv regimen. However, there was no evidence that route of administration influenced the effectiveness of magnesium sulphate compared with placebo. For the im regimen: eclampsia 20 of 2301, 0·9%, versus 54 of 2292, 2·4%; baby death 380 of 2171, 17·5%, versus 368 of 2159, 17·0%. For the iv regimen: eclampsia 20 of 2754, 0·7%, versus 42 of 2763, 1·5%; baby death 197 of 2367, 8·3%, versus 190 of 2327, 8·2%.

	Magnesium sulphate (n=4162)	Placebo (n=4098)
Birthweight (g)*		
<1500	753 (17%)	707 (16%)
<2500	2255 (50%)	2177 (49%)
Apgar <7 at 5 min	235 (6%)	227 (6%)
Intubated at place of delivery	175 (4%)	171 (4%)
Cerebral ultrasound imaging	322 (8%)	317 (8%)
Abnormal ventriculomegaly	28	25
Persistent parenchymal echogenicity	31	28
Neonatal convulsion(s)	40 (1·0%)	52 (1·3%)
Length of stay in hospital (median, IQR) (days)	5 (3–9)	5 (3–9)
Admission to special care baby unit	1629 (39%)	1591 (39%)
In special care baby unit >7 days	810 (19%)	783 (19%)
Death or in special care baby unit >7 days*	1330 (29%)	1302 (29%)
Ventilation	389 (9%)	359 (9%)

Data are number (%). *n=4538 magnesium sulphate and n=4486 placebo, total births.

Table 12: **Neonatal morbidity for liveborn babies of women randomised before delivery**

Discussion

The Magpie Trial was designed to assess the effects, on women and their babies, of magnesium sulphate when used for women with pre-eclampsia. To provide reliable evidence to guide the care of women with pre-eclampsia the trial needed to recruit very large numbers of women. The study also aimed to provide results that would be generalisable to a wide range of clinical settings, in both rich and poor countries. In order to achieve our target recruitment, and to include collaborators from developed and developing countries, the protocol was simple, flexible, and integrated into the existing health services. The high compliance, completeness of data collection, and breadth of the collaboration reflect the success of this approach.

This study is the largest trial ever conducted for the hypertensive disorders of pregnancy. 12 times larger than the previous biggest trial of magnesium sulphate versus placebo,[20] it took 3·5 years to complete recruitment. The success of the Magpie Trial hinged critically on the active and enthusiastic collaboration of obstetricians, midwives, and other busy hospital staff, often working in difficult circumstances in many low-middle income countries. These researchers endorsed the concept that it is not ethical to continue to use an unproven treatment if the opportunity arises to assess the safety and effectiveness of that intervention in a rigorous and unbiased fashion.

Results from the Magpie Trial demonstrate clearly that magnesium sulphate is effective in considerably reducing the risk of eclampsia for women with pre-eclampsia. Overall, 11 per 1000 fewer women allocated magnesium sulphate had an eclamptic convulsion. Despite the inevitable reduction in power of a subgroup analysis, the results were consistent regardless of the severity of pre-eclampsia at trial entry or whether treatment was before or after delivery. The relative reduction in risk was also consistent across low, middle, and high perinatal mortality countries. Combining data from the Magpie Trial with those from the earlier systematic review[9] makes little change to the results presented here. For eclampsia, the combined relative risk is 0·41 (95% CI 0·29–0·58). The trend in maternal mortality also favoured magnesium sulphate, although a small increase in mortality has not been excluded.

One of the concerns about magnesium sulphate has been the risk of respiratory depression. Although in this study more women allocated magnesium sulphate had respiratory depression or respiratory arrest, the actual numbers were small, and there was no overall difference in serious maternal morbidity. Similarly, there was no clear difference in ventilation for the babies of women randomised before delivery. However, a quarter of women allocated magnesium sulphate had unwanted side-effects, compared with 5% allocated placebo. 8% also had problems at the injection site, compared with 4% allocated placebo. Although very few of these side-effects were life threatening, most of them were unpleasant and many women experienced multiple side-effects. Hence, the higher number of women allocated magnesium sulphate who stopped treatment early. Although there is no evidence that effectiveness is influenced to a clinically important degree by the choice of regimen, the iv route for maintenance therapy does appear to be associated with

fewer problems. Nevertheless, the decision about which regimen to use is likely to be influenced by a range of other factors, including cost, availability of trained staff, and safety. The apparent reduction in problems may anyway be related more to the higher dose of the im regimen, than to any difference per se.

These comparisons between women who received the iv rather than the im regimen should be interpreted with caution, as the route for maintenance therapy was not allocated at random.

The Magpie Trial aimed to assess the effects of magnesium sulphate for the child, as well as the mother. One of the beliefs supporting the unevaluated use of magnesium sulphate over many decades has been that it improves outcome for the child. Recent support for this belief has come from case-control studies, suggesting that in-utero exposure to magnesium sulphate might reduce the risk of cerebral palsy for low birthweight (<1500 g) babies.[21] However, there is also concern that magnesium sulphate exposure for these vulnerable babies might be associated with an increased mortality.[22] Data presented here suggest that, overall, there is little or no effect on mortality, although a small increase or decrease has not been excluded. The small subgroup of babies exposed to an anticonvulsant before trial entry do appear to have an increased mortality in the active group, but these deaths were not restricted to those who had received magnesium sulphate before randomisation. This apparent difference may reflect the play of chance. We observed a reduction in the risk of placental abruption, but this is not reflected in any effect on total mortality for the baby. There was no evidence of a difference in any other measure of neonatal morbidity. In particular, there was no evidence of a difference in the predefined outcome of death or in a special care unit for more than 7 days. We now need reassurance that there are no adverse consequences for the child's later development. Follow-up of a proportion of the children whose mothers were recruited to the Magpie Trial is underway.

There was little evidence to support the hypothesis that magnesium sulphate, administered according to the regimens in this trial, might be useful either as a tocolytic or an antihypertensive agent. The small (5%) increase in the relative risk of caesarean section is supported by data from the systematic review.[9] As there is no evidence of an effect on induction of labour, length of labour, blood loss at delivery, or retained placenta this increase may be related to other factors. Similarly, there was no clinically useful reduction in the use of antihypertensive drugs. There has been concern, based on just a tiny number of case reports,[23,24] about severe hypotension related to the simultaneous use of magnesium sulphate and nifedipine. In the Magpie Trial, 30% of women received nifedipine after trial entry and no associated adverse events were reported. For the few women who did have hypotension there was no association with the combination of nifedipine and magnesium sulphate.

Although the trial was placebo controlled, it is possible that the occurrence of side-effects allowed the allocation to be guessed for about one-fifth of women allocated magnesium sulphate. It is unlikely that this would have substantially influenced the assessment of outcome, as the main outcome measures were objective.

The aetiology of pre-eclampsia and eclampsia remains elusive. Exactly how magnesium sulphate might control eclamptic convulsions is also unclear. Magnesium may have a localised cerebral effect. For example, it may cause vasodilatation with subsequent reduction of cerebral ischaemia,[25] and/or block some of the neuronal damage associated with ischaemia.[26,27] A possible mechanism for vasodilatation is relaxation of smooth muscle. That magnesium may have a generalised effect on all smooth muscle, including the peripheral vasculature and uterus, has also been suggested. Hence the hypotheses that it may have antihypertensive and tocolytic effects. This generalised effect now seems unlikely. Alternatively, any effects of magnesium sulphate in control of eclamptic convulsions may be, wholly or part, through its role as a blocker of N-methyl-D-aspartate receptors in the brain.[26] These receptors are activated in response to asphyxia, leading to calcium influx into the neurons, which causes cell injury. It is suggested that magnesium may block these receptors, so reducing calcium influx and protecting the neurons from damage.[26,27]

An unexpected finding was that so few of the women who died had had eclampsia. A possible explanation is that magnesium sulphate may also have beneficial effects on other organs implicated in pre-eclampsia, a suggestion supported by the reduction in placental abruption. Fewer women allocated magnesium sulphate rather than placebo had renal failure, liver failure, or coagulopathy, but the difference was small and could have occurred by chance. Pre-eclampsia is associated with endothelial dysfunction.[28] Magnesium sulphate may somehow improve local perfusion by improving endothelial function or micro-vascular perfusion.

Magnesium sulphate is remarkably effective at reducing the risk of eclampsia, whether this is the first seizure or recurrence of convulsions.[29] In the Magpie Trial, as in the Collaborative Eclampsia Trial,[29] management of the acute convulsion was with magnesium sulphate. It has been argued that diazepam should be used for treatment of the actual convulsion.[30] There is no evidence to support this suggestion. Data from the Magpie Trial present further evidence that magnesium sulphate alone should be used for women with eclampsia: both to control the seizure and to prevent recurrence.

Magnesium sulphate was little used in many countries, including the UK, before the results of the Collaborative Eclampsia Trial were published in 1995.[29] This situation arose partly because of concerns about respiratory depression in the mother. The Magpie Trial has further dispelled these concerns. Importantly, safe monitoring was achieved without serum magnesium measurement, using simple clinical assessment of tendon reflexes, respiratory rate, and urine output. This achievement has obvious implications for care, particularly in low-income and middle-income countries.

Two magnesium sulphate regimens were used in this trial. Both are widely used in clinical practice and both were also used in the Collaborative Eclampsia Trial.[29] At the dosages and duration of treatment used here magnesium sulphate is both safe and effective in preventing eclampsia in women with pre-eclampsia. Whether or not a higher dose regimen, as has been argued for,[31] would be more effective is unclear. But, as the size of the risk reduction reported here was so large, this seems unlikely. Higher doses are unlikely to be safer, even if they are more effective. The reassurance about safety for both woman and child from these data cannot be extrapolated to higher doses, or to a longer duration of treatment.

The Magpie Trial Collaborative Group involved a wide range of people from four continents with a common interest in improving the care of women with pre-eclampsia. Results from this study confirm the high morbidity and mortality associated with this devastating condition. Outcome was particularly poor for women with

severe pre-eclampsia, and those from high perinatal mortality countries. We did attempt to subdivide the women without severe pre-eclampsia, based on blood pressure and proteinuria at randomisation. Although this successfully distinguished women with low and intermediate mortality for the baby, the relative risk of eclampsia changed little. 85% of recruitment to the Magpie Trial was from low-middle income countries, where the risk of eclampsia, maternal death, and baby death were highest. Magnesium sulphate is the drug of choice for eclampsia, but is not easily available in some countries.[32] To ensure that women recruited to the trial had optimum care if they developed eclampsia, we provided some collaborators in Africa and Asia with extra magnesium sulphate. Having now shown that magnesium sulphate also benefits women with pre-eclampsia, removing barriers in the supply and use of magnesium sulphate should be a priority for those responsible for maternal health services in developing countries, including international agencies such as the United Nations Population Fund (UNFPA), the United Nations Children's Fund (UNICEF), and WHO.

Implications for clinical practice

The results of this trial should be made available to women with pre-eclampsia, and those responsible for their care. Magnesium sulphate should be considered for women with pre-eclampsia for whom there is concern about the risk of eclampsia. As it is an inexpensive drug, it is especially suitable for use in low-income countries. iv administration is preferable, where there are appropriate resources, as side-effects and injection-site problems seem lower. Duration of treatment should not normally exceed 24 h, as the reassurance about safety applies only to the regimens used in this trial. Serum monitoring is not necessary. Administration and clinical monitoring of magnesium sulphate can be done by medical, midwifery, or nursing staff, provided they are appropriately trained.

This trial included women only after admission to hospital. Whether a loading dose of magnesium sulphate should be used for women at primary-care level before they are transferred to hospital is unclear. Other factors in this decision are likely to include how long it will take to get the woman to hospital, the support that is available during transfer, and severity of her pre-eclampsia.

Implications for research

Remaining questions about the use of magnesium sulphate include: what is the minimum effective dose? When is the optimal time to give it? Should it be used at primary-care level for women being transferred for secondary of tertiary care? What are the long-term consequences of exposure for the mother and her child? Many clinicians reserve magnesium sulphate for women for whom delivery is planned in the next 24 h. In the Magpie Trial some women were given 24-h treatment and the pregnancy was allowed to continue, if preterm and stable. Few of these women had any further treatment with magnesium sulphate.

Additional research is continuing on the long-term follow-up of a proportion of the women and children in the Magpie Trial, and on the cost implications of the findings for a range of settings.

Conclusions

Magnesium sulphate reduces the risk of eclampsia, and it is likely that it also reduces the risk of maternal death. At the dosage used in this trial it does not have any substantive harmful effects on the mother or child, although a quarter of women will have side-effects.

Magpie Trial Collaborative Group

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Conflict of interest statement

None declared.

Acknowledgments

This report is dedicated to the women who participated in the trial, and to Richard Johanson who died just a few months before publication. His enthusiasm and generosity are much missed. We thank José Belizán, John Bell, Enrique Ezcurra, Anibal Faundes, Muir Gray, David Henderson-Smart, Henry Halliday, Ann Johnson, Sara Kenyon, Mary Hannah, Rona McCandlish, Patrice Matchaba, Stephen Munjanja, Christopher Redman, Andrew Shennan, Philip Steer, Sarah Stewart-Brown, Walfrido Sumpaico, David Taylor, and Martin Whittle. Our thanks also to the Clinical Trial Service Unit, Oxford, and Action for Pre-eclampsia.

The work was funded by the UK Medical Research Council, UK Department for International Development, the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP).

References

1 WHO. WHO International Collaborative Study of Hypertensive Disorders of Pregnancy. Geographic variation in the incidence of hypertension in pregnancy. *Am J Obstet Gynecol* 1988; **158:** 80–83.

2 The National Institute for Clinical Excellence, The Scottish Executive Health Department, The Department of Health, Social Services and Public Safety, Northern Ireland. Why mothers die 1997–1999: the confidential enquiries into maternal deaths in the United Kingdom. London: RCOG Press, 2001.

3 Douglas K, Redman C. Eclampsia in the United Kingdom. *BMJ* 1994; **309:** 1395–400.

4 Crowther CA. Eclampsia at Harare maternity hospital. *S Afr Med J* 1985; **68:** 927–29.

5 Bergström S, Povey G, Songane F, Ching C. Seasonal incidence of eclampsia, its relationship to meteorological data in Mozambique. *J Perinat Med* 1992; **20:** 153–58.

6 WHO, UNICEF. Revised 1990 estimates of maternal mortality: WHO/FRH/MSM/96.11. Geneva: WHO, 1996.

7 Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *Br J Obstet Gynaecol* 1992; **99:** 547–53.

8 Roberts JM. Magnesium for preeclampsia and eclampsia. *N Engl J Med* 1995; **333:** 250–51.

9 Duley L, Gülmezoglu AM, Henderson-Smart D. Anticonvulsants for women with pre-eclampsia (Cochrane Review). In: *The Cochrane Library*, Issue 1. Oxford: Update Software, 2002.

10 Duley L, Henderson-Smart D. Magnesium sulphate versus diazepam for eclampsia (Cochrane Review). In: *The Cochrane Library*, Issue 1. Oxford: Update Software, 2002.

11 Duley L, Henderson-Smart D. Magnesium sulphate versus phenytoin for eclampsia (Cochrane review). In: *The Cochrane Library*, Issue 1. Oxford: Update Software, 2002.

12 Duley L, Gülmezoglu AM. Magnesium sulphate versus lytic cocktail for eclampsia (Cochrane Review). In: *The Cochrane Library*, Issue 1. Oxford: Update Software, 2002.

13 Gulmezoglu AM, Duley L. Anticonvulsants for women with eclampsia and pre-eclampsia: a survey of obstetricians in the UK and Ireland. *BMJ* 1998, **316:** 975–76.

14 Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med* 1995; **333:** 201–05.

15 Zuspan FP. Problems encountered in the treatment of pregnancy: induced hypertension. *Am J Obstet Gynecol* 1978; **131:** 591–97.

16 Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. *Am J Obstet Gynecol*. 1984; **148:** 951–63.

17 Wigglesworth JS. Monitoring perinatal mortality: a pathophysiological approach. *Lancet* 1980; **2:** 684–86.

18 WHO. Perinatal mortality: a listing of available information: WHO/FRH/MSM/96.7. Geneva: WHO, 1996.

19 Hannah ME, Hannah WJ, Hewson SA, et al. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. *Lancet* 2000; **356:** 1375–83.

20 Coetzee EJ, Dommisse J, Anthony JA. Randomised controlled trial of intravenous magnesium sulphate versus placebo in the management of women with pre-eclampsia. *Br J Obstet Gynaecol* 1998; **105:** 300–03.

21 Nelson K. Magnesium sulfate and risk of cerebral palsy in very low-birth-weight infants. *JAMA* 1996; **276:** 1843–44.

22 Scudiero R, Khoshnood B, Pryde PG, Lee KS, Wall S, Mittendorf R. Perinatal death and tocolytic magnesium sulfate. *Obstet Gynecol* 2000; **96:** 178–82.

23 Waisman GD, Mayorga LM, Camera MI, Vignolo CA, Martinotti A. Magnesium plus nifedipine: potentiation of hypotensive effect in preeclampsia? *Am J Ostet Gynecol* 1988; **159:** 308–09.

24 Ben-Ami M, Giladi Y, Shalev E. The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. *Br J Obstet Gynaecol* 1994; **101:** 262–63.

25 Belfort MA, Moise KJ. Effect of magnesium sulfate on maternal brain blood flow in preeclampsia: a randomised, placebo-controlled study. *Am J Obstet Gynecol* 1992; **167:** 661–66.

26 Sadeh M. Action of magnesium sulfate in the treatment of preeclampsia-eclampsia. *Stroke* 1989; **20:** 1273–75.

27 Goldman R, Finkbeiner SM. Therapeutic use of magnesium sulfate in selected cases of cerebral ischaema and seizure. *N Engl J Med* 1988; **319:** 1224–25.

28 Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet* 1993; **341:** 1447–51.

29 The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; **345:** 1455–63.

30 Fox R, Draycott T. Prefer diazepam for initial control of eclamptic fits. *BMJ* 1995; **311:** 1433.

31 Graham KM. Magnesium sulphate in eclampsia. *Lancet* 1998; **351:** 1061.

32 Mahomed K, Garner P, Duley L. Tocolytic magnesium sulphate and paediatric mortality. *Lancet* 1998; **351:** 293.