How do South African obstetricians manage hypertensive disorders of pregnancy — a survey

S M Khedun, J Moodley, T Naicker, B Maharaj

Objective. To determine the current management of hypertensive disorders of pregnancy in South Africa.

Method. A postal questionnaire was sent to 600 South African obstetricians.

Results. The response rate was 72% (432/600), with 425 questionnaires suitable for analysis. South African obstetricians disagree on the definitions of various hypertensive disorders of pregnancy. Methyldopa was the antihypertensive used most frequently for the treatment of mild to moderate hypertension (diastolic blood pressure between 90 and 109 mmHg), while intravenous dihydralazine was preferred in severe hypertension (diastolic blood pressure ≥ 110 mmHg and proteinuria ≥ ++).

To stop convulsions in eclampsia, 256 respondents (60%) said they would use diazepam, 28 (11%) said they would continue with a diazepam infusion, and the remaining 228 (89%) preferred magnesium sulphate ($MgSO_4$) to prevent further convulsions. The intramuscular route was the preferred method of administration for $MgSO_4$.

In cases of eclampsia, 273 respondents (64%) said they would use intravenous dihydralazine to lower high blood pressure (≥ 160/110 mmHg) and proteinuria; 98 respondents (23%) said they would use methyldopa, 38 (9%) nifedipine, and 8 (2%) apresoline. Eight (2%) said they would not use antihypertensives.

In patients with severe pre-eclampsia and impending eclampsia, 330 respondents (78%) said they would use $MgSO_4$ as prophylaxis, 46 (11%) diazepam, and 6 (1.4%) phenobarbitone. Forty-three of the respondents did not prescribe prophylactic anticonvulsant therapy. To prevent

Department of Experimental and Clinical Pharmacology, University of Natal, Durban

S M Khedun, MMedSc

B Maharaj, MD

MRC Pregnancy Hypertension Research Unit, Department of Obstetrics and Gynaecology, University of Natal, Durban

J Moodley, MD

Optics and Imaging Centre, University of Natal, Durban

T Naicker, MMedSc

pre-eclampsia, 247 of the respondents (58%) said they would prescribe low-dose aspirin.

Conclusion. This study demonstrates that South African obstetricians show great uniformity in terms of the treatment of hypertensive disorders of pregnancy.

S Afr Med J 2000; **90:** 156-160.

Hypertensive disorders of pregnancy are a fairly common complication, especially in developing countries.[1] They are the major cause of maternal and perinatal mortality and morbidity worldwide. In the last decade, knowledge of antihypertensive drugs used in pregnancy has increased, and new drugs that may be useful in pregnancy have been introduced. Further non-invasive techniques such as Doppler for measuring blood velocity wave forms have enabled direct examination of drug effects on maternal uterine and fetal haemodynamics. In addition, magnesium sulphate ($MgSO_4$) has been shown to be the anticonvulsant of choice in the management of eclampsia.[1]

There is continuing controversy, however, regarding the use of anticonvulsants in other categories of the pre-eclampsia and eclampsia syndrome, viz. moderate and severe grades of the disease, as well as the level of diastolic blood pressure at which to initiate antihypertensive treatment and the choice of antihypertensive agent. The use of common management protocols based on broad consensus may result in a decrease in maternal and perinatal morbidity and mortality from this condition. The objective of this study was to determine how South African obstetricians manage hypertensive disorders of pregnancy.

Materials and methods

A postal questionnaire was sent to 600 South African obstetricians. Four hundred were members of the South African Society of Obstetricians and Gynaecologists (SASOG). The names of the remaining 200 obstetricians were obtained from the telephone directory. The mailing was done in November 1996 and the forms were returned by July 1997. The questions were about the definition of hypertension of pregnancy and pre-eclampsia, first-line antihypertensives for severe pre-eclampsia, use of anticonvulsants in eclampsia and for its prophylaxis, and use of management protocols.

Descriptive statistics were used and all results are presented as frequencies and percentages.

Results

The response rate was 72% (432/600). Four hundred and twenty-five questionnaires were analysed. Six replies were excluded because these obstetricians had retired from active medical practice. Data in another reply were incomplete and also excluded from the analysis.

Ninety-seven per cent of respondents defined hypertension in pregnancy as blood pressure ≥ 140/90 mmHg after 20 weeks' gestation, 2% used a cut-off blood pressure level of ≥ 160/90 mmHg after 20 weeks' gestation, and 1 respondent stated that hypertension in pregnancy was a blood pressure ≥ 140/90 mmHg, with proteinuria. Two hundred and ninety-eight respondents (70%) used methyldopa for mild to moderate hypertension, defined as a blood pressure of 140/90 - 160/109 mmHg, 96 respondents (23%) used nifedipine, 22 (5%) used apresoline, and 9 (2%) used prazosin.

The definitions of pre-eclampsia varied. Eighty-eight per cent of respondents included hypertension plus proteinuria in their definition, but the diastolic blood pressure varied from 90 to 110 mmHg and above, even without proteinuria. Twelve per cent of the respondents defined pre-eclampsia as including at least two out of three of the clinical symptoms of hypertension, oedema and proteinuria. The level of diastolic blood pressure at which antihypertensive treatment would be initiated in pre-eclampsia varied between 90 and 110 mmHg or above, and the choice of antihypertensive is shown in Table I.

Table I. Level of diastolic blood pressure and choice of antihypertensive agent in pre-eclampsia

	Diastolic blood pressure (mmHg)			
Antihypertensives	90 - 99	100 - 109	110+	Total
Oral				
Methyldopa	155	105	35	295
Apresoline	10	11	1	22
Nifedipine	0	20	14	34
Minipress	7	3	0	10
Atenolol	0	1	0	1
Parenteral				
Dihydralazine	0	22	41	63

The use of rapid-acting antihypertensive agents in severe hypertension in pregnancy is shown in Table II.

In eclampsia, all respondents used anticonvulsants.

Table II. Rapid-acting antihypertensive agents used in severe hypertension in pregnancy*

Drug	No. of users†	%
Dihydralazine	290	68.2
Nifedipine	121	28.5
Labetalol	4	0.9
Diazoxide	6	1.4
No answer	4	0.9

* Severe hypertension: blood pressure ≥ 160/110 mmHg + proteinuria++.
†A further 90 respondents (21.2%) ticked more than one box implying the choice of more than one drug.

Diazepam was used by 256 respondents (60%) to stop fits, while 28 (11%) continued with diazepam to prevent further fits. $MgSO_4$ was used by 228 respondents (89%) to prevent further fits after the first fit was stopped with diazepam. One hundred and sixty-eight respondents (39.5%) used only $MgSO_4$ both for stopping the fit and preventing further fits. One respondent used phenytoin to stop fits and then $MgSO_4$ to prevent further fits. The preferred route of administration of $MgSO_4$ was intramuscular.

Four hundred and seventeen (98%) of the respondents said they would use antihypertensive agents concurrently with anticonvulsive therapy if the diastolic blood pressure was ≥ 160/110 mmHg with proteinuria, 273 (64%) said they would use dihydralazine, 98 (23%) methyldopa, 38 (9%) nifedipine, and 8 (2%) apresoline; 8 (2%) said they would use no antihypertensive therapy.

In patients with severe pre-eclampsia and impending eclampsia, 330 respondents (78%) used $MgSO_4$ and the preferred route of administration was intramuscular; 46 (11%) used diazepam and 6 (1.4%) used phenobarbitone. Forty-three respondents (10.1%) did not prescribe anticonvulsant therapy.

Three hundred and forty-five respondents (81%) said they would stop angiotensin-converting enzyme (ACE) inhibitors in chronic hypertensive women in early pregnancy, while 30 respondents (7%) said they would continue with the drug. Fifty-one obstetricians (12%) said they would stop antihypertensive medication in all chronic hypertensives and observe the patient at more frequent antenatal visits.

Two hundred and thirty-seven obstetricians (56%) said they would use β-blockers in hypertensive disorders of pregnancy. The choice of β-blocker is shown in Table III.

Table III. Beta-blockers used in hypertensive disorders of pregnancy

Drug	No. of users	%
Atenolol	110	46.4
Labetalol	87	36.7
Propranolol	22	9.3
Oxprenolol	16	6.8
Sotalol	1	0.4
Acebutolol	1	0.4

To prevent pre-eclampsia low-dose aspirin was prescribed as the first choice by 247 respondents (58%), followed by calcium as second choice (213, 50%), magnesium as third choice (183, 43%), and heparin as the fourth choice (51, 12%).

Two hundred and thirty-four respondents (55%) said they would recommend epidural analgesia during delivery in cases of severe pre-eclampsia for reasons other than pain relief; 166 (50%) said they would use it to stabilise blood pressure, 65 (28%) to calm the patient, 2 (1%) to improve placental blood flow, and 1 (0.4%) for its anticonvulsive effect.

Two hundred and fifty-two respondents (59%) said they would use furosemide in hypertensive disorders of pregnancy when the main indication was pulmonary oedema. Of the 252 respondents, 102 (40%) said they would also use it for cardiac failure, 11 (4.4%) for oliguria and 6 (2.4%) for anuria. Two respondents (0.8%) gave no answer.

Ninety-seven respondents (22.8%) had protocols for the management of hypertensive disorders of pregnancy. Of this number 31 (32%) were private specialists, 58 (60%) were hospital specialists and 8 (8%) were both private and hospital specialists.

Discussion

The response rate of 72% observed in this study is comparable with rates obtained in affluent countries such as the UK,[2] Sweden[3] and Australia.[4] Hutton *et al.*[2] and more recently Gulmezoglu and Duley[5] undertook similar studies in the UK and obtained 70% response rates. Our study therefore demonstrates that response rates for postal questionnaire studies in developing countries are feasible. However, we could not establish whether 600 was the total number of obstetricians in South Africa. The names and addresses of only 600 were available. The present survey provides a national picture of the current management of hypertension, pre-eclampsia and eclampsia during pregnancy. Although the actual management of patients can only be truly revealed by a prospective audit, our study showed considerable uniformity regarding treatment and strategies.

There are no adequately sized trials assessing the benefits and risks of antihypertensive drugs in the management of pregnancy hypertension. However, antihypertensive drug therapy is now routine practice in the management of women with hypertensive disorders of pregnancy in the USA and UK.[2,5,6] In our survey, 361 respondents (85%) used antihypertensive agents. Methyldopa was the most commonly used drug for mild to moderate hypertension (diastolic blood pressure between 90 and 109 mmHg). This is in keeping with international trends, as methyldopa is the most commonly used antihypertensive for the management of essential hypertension in pregnancy and is considered the standard against which other antihypertensives should be tested.[6]

Fifteen per cent of the obstetricians said they would stop all antihypertensive medication at their first antenatal visit and observe blood pressure levels frequently. Presumably this is done in the belief that during pregnancy a proportion of women with essential hypertension will not require antihypertensive treatment.

Hutton *et al.*[2] found that labetalol (a combination α-, β-blocker) was the most commonly used oral antihypertensive

agent in the UK. In our survey oral labetalol was not commonly used, probably because this drug is not registered for use in pregnancy in South Africa and is also not commonly used in non-pregnant hypertensives. On the other hand, it was surprising that 237 respondents (56%) used β-blockers in our survey. Atenolol was the most commonly used β-blocker, probably because it is freely available in South Africa and commonly used in the non-pregnant state. The use of β-blockers in pregnancy is still contentious; some consider that if there are other safe and effective agents available for use in pregnancy, women on β-blockers who become pregnant should be offered an alternative. Although atenolol has been evaluated in randomised controlled trials in pregnancy and has been shown to have no adverse effects,[7,8] a placebo-controlled trial using atenolol from the first trimester in women with essential hypertension was associated with reduced birth weight.[9] More information is required before this drug can be used as first-line antihypertensive therapy in pregnancy. It was surprising that 22 obstetricians used propranolol in pregnancy. There is good evidence associating this β-blocker with fetal growth restriction, depression of fetal heart rate, fetal hypoglycaemia and increased perinatal mortality rates.

New classes of antihypertensive drugs have recently become available. One of these is nifedipine. Twenty-three per cent of South African obstetricians said they used this drug for hypertension in the antenatal period, while 28.5% used it for severe hypertension. These figures compare favourably with figures from the UK[2] and New Zealand.[10] In Sweden isradipine, a new oral and intravenous calcium channel blocker, is a popular choice for very high blood pressure in pregnancy.[3] A number of trials investigating its use in pregnancy have shown promising results.[11,12] There is, however, continuing concern that nifedipine may have a synergistic action with $MgSO_4$. A number of studies have reported severe hypotension,[13] neuromuscular blockade[14] and cardiac depression[15] with the combined use of $MgSO_4$ and nifedipine. Twenty-eight respondents (7%) said they would use nifedipine concurrently with anticonvulsive therapy ($MgSO_4$) if the diastolic blood pressure was in excess of 110 mmHg, with proteinuria.

In South Africa, the most commonly used intravenous agent for lowering high blood pressure is dihydralazine; 68% of respondents used this drug. Its popularity stems from the fact that it has been in the market for a long time, it is inexpensive, and despite shortcomings, most obstetricians are familiar with its use.

Use of ACE inhibitors in pregnancy is associated with serious side-effects such as intra-uterine death, leucopenia and renal failure. Surprisingly, a few of the respondents said they would continue treatment with this group of drugs. We strongly suggest that this agent should not be used in pregnancy as there are alternative agents that are safer for the fetus.

In 1995 the Eclampsia Collaborative Group (ECG) published their study entitled 'Which anticonvulsant for women with eclampsia?',[1] showing $MgSO_4$ to be the anticonvulsant of choice for the treatment of this condition. It was surprising to find, therefore, that obstetricians were still using diazepam for the prevention of further fits and that one respondent was using phenytoin. In the UK the most commonly used anticonvulsant in the management of eclampsia was diazepam. However, a recent study has shown that $MgSO_4$ is now the commonest anticonvulsant for this purpose, although diazepam and phenytoin are still used in the UK.[5] In our study, diazepam was used by 60% of respondents to stop or shorten fits. There is no evidence in the literature to indicate the benefit of this practice, although the clinical setting often warrants a situation in which a drug is given to shorten a seizure. However, it is enlightening to know that 89% of respondents used $MgSO_4$, as there is now good evidence to suggest that this agent probably works by causing cerebral vasodilation.[16]

For the prevention of fits in severe pre-eclampsia and impending eclampsia, 376 respondents (89%) used prophylactic $MgSO_4$. Recently a questionnaire study similar to ours undertaken in the UK found that 77% of the respondent obstetricians used anticonvulsives for severe pre-eclampsia and eclampsia.[5] There is both descriptive evidence and a limited amount of clinical data suggesting that prophylactic anticonvulsants are effective in severe pre-eclampsia. A South African trial of 822 women with severe pre-eclampsia in a tertiary hospital[17] and a meta-analysis study[18] suggest that at least some women with severe pre-eclampsia benefit from $MgSO_4$ therapy. However, the Cochrane library shows that there are important outstanding issues.[19] In particular, there is considerable uncertainty surrounding the value of $MgSO_4$ in mild to moderate pre-eclampsia. Furthermore, the equally important questions of whether the drug is safe for mother and baby and its cost-effectiveness have not been addressed by previous studies. It is for this reason that large randomised trials on women with mild to moderate pre-eclampsia should be performed before recommending the use of $MgSO_4$ for all grades of pre-eclampsia.

The use of drugs in clinical practice with and without evidence is of concern. On the one hand, the ECG study provided compelling evidence that $MgSO_4$ is the anticonvulsant of choice in eclampsia, and clinical management in various countries has seen a greater use of $MgSO_4$. On the other hand, despite a growing body of evidence suggesting that low-dose aspirin has no effect on the prevention of pre-eclampsia, many doctors continue to use it routinely for the prevention of this condition. Our survey showed that 58% of South African obstetricians are still using low-dose aspirin for the prevention of pre-eclampsia in women with chronic hypertension. This presumably arises from the fact that aspirin for the management of pre-eclampsia shot into the limelight in the 1980s when two small-scale studies using aspirin for the prevention of pre-eclampsia showed dramatic success, almost

eliminating the condition in treated women. Since then, however, several large-scale studies, in particular the Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP) involving 9 000 patients, failed to detect any major effect of aspirin because they included low-risk women.[20] In 1998 three large studies provided evidence that preventive treatment with aspirin does not work. The study from the USA is of particular importance as it included 2 539 women at high risk of pre-eclampsia; no significant differences from placebo were found in the women recruited on the basis of pre-pregnancy diabetes, hypertension or multiple pregnancies or women with previous pre-eclampsia. There was also no increased incidence of preterm babies or babies who were small for dates. These studies suggest that there is no place for the use of low-dose aspirin in the prevention of pre-eclampsia.[20-25] Furthermore, our survey showed that obstetricians frequently used calcium and magnesium supplementation for prevention of pre-eclampsia when there is no real evidence of their efficacy.

In conclusion, although there is general disagreement on the definition of various disorders of pregnancy, there are many similarities in their management; hopefully this will lead to a national standardised policy of management. It would seem to be generally accepted that $MgSO_4$ should be used for the prevention of recurrent convulsions in eclampsia and dihydralazine to lower very high blood pressure, and that oral methyldopa is still the antihypertensive drug of choice for hypertensive disorders of pregnancy.

The study was supported by grants from the Medical Research Council/University of Natal Pregnancy Hypertension Research Fund, University of Natal Medical School.

References

1. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; **345:** 1455-1462.
2. Hutton JD, James DK, Stirrat GM, Douglas KA, Redman CWG. Management of severe pre-eclampsia and eclampsia by UK consultants. *Br J Obstet Gynaecol* 1992; **99:** 554-556.
3. Wide-Swensson D, Montan S, Ingemarrson I. How Swedish obstetricians manage hypertensive disorders in pregnancy. A questionnaire study. *Acta Obstet Gynecol Scand* 1994; **73:** 619-624.
4. Tradinger BJ, Parik I. Attitudes to the management of hypertension in pregnancy: a survey of Australian fellows. *Aust N Z J Obstet Gynaecol* 1982; **22:** 191-197.
5. Gulmezoglu AM, Duley L. Use of anticonvulsants in eclampsia and pre-eclampsia: a survey of obstetricians in the United Kingdom and Republic of Ireland. *BMJ* 1998; **316:** 975-976.
6. Consensus Report. National High Blood Pressure Education Program. Working Group Report on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 1990; **163:** 1689-1712.
7. Rubin PC, Butters L, Clark DM. Placebo controlled trial of atenolol in treatment of pregnancy associated hypertension. *Lancet* 1983; **1:** 431-434.
8. Wichman K, Ryden G, Karlberg BE. A placebo controlled trial of metoprolol in the treatment of hypertension in pregnancy. *Scand J Clin Lab Invest* 1984; **169:** 90-95.
9. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. *BMJ* 1990; **301:** 587-589.
10. Hutton JD, Ngan Kee DG, Wilcox FL. New Zealand obstetricians' management of hypertension in pregnancy — a questionnaire survey. *Aust N Z J Obstet Gynaecol* 1990; **29:** 5-8.
11. Wide-Swenson D, Ingemarrson I, Lunnel NO, *et al*. Calcium channel blockade (isradipine) in the treatment of hypertension in pregnancy: a randomised placebo controlled study. *Am J Obstet Gynecol* 1995; **173:** 872-878.
12. Maharaj B, Khedun SM, Moodley J, van der Byl K, Rapiti N. A comparative study of intravenous isradipine and dihydralazine in the treatment of severe hypertension of pregnancy in black patients. *Hypertension in Pregnancy* 1997; **16**(1): 1-9.
13. Waisman G, Mayorga L, Camera L, Vignola ML, Martinotti A. Magnesium plus nifedipine: potentiation of hypotensive effect in pre-eclampsia? *Am J Obstet Gynecol* 1989; **159:** 308-309.
14. Snyder SW, Cardwell MS. Neuromuscular blockade with magnesium sulfate and nifedipine. *Am J Obstet Gynecol* 1989; **161:** 35-36.
15. Davis WB, Wells SR, Kuller JA, Thorp JM jun. Analysis of the risks associated with calcium channel blockade for the obstetrician-gynaecologist. *Obstet Gynecol Surv* 1997; **52:** 198-201.
16. Naidu K, Moodley J, Corr P, Hoffman M. Single photon emission and cerebral computerised tomographic scan and transcranial Doppler sonographic findings in eclampsia. *Br J Obstet Gynaecol* 1997; **104:** 1165-1172.
17. Duley L, Gulmezoglu AM, Henderson-Smart D. Anticonvulsives for pre-eclampsia (Cochrane Review). In: The Cochrane Library, Issue 3, 1998, Oxford update.
18. Coetzee EJ, Dommisse J, Anthony J. A randomised controlled clinical trial of intravenous $MgSO_4$ versus placebo in the management of women with severe pre-eclampsia. *Br J Obstet Gynaecol* 1998; **105:** 300-303.
19. Chien PF, Khan KS, Arnott N. Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomised trials. *Br J Obstet Gynaecol* 1996; **103:** 1085-1091.
20. Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP) Collaborative Group. CLASP: a randomised trial of low dose aspirin for the prevention and treatment of pre-eclampsia among 9 364 women. *Lancet* 1994; **343:** 619-629.
21. Cartis S, Sibai B, Hauth J, *et al*. Low dose aspirin to prevent pre-eclampsia in women at high risk. *N Engl J Med* 1998; **338:** 701-705.
22. Rotchell YE, Cruickshank JK, Gay MP, *et al*. Barbados low dose aspirin study in pregnancy (BLASP): A randomised trial for the prevention of pre-eclampsia and its complications. *Br J Obstet Gynaecol* 1998; **105:** 286-292.
23. Golding J. A randomised trial of low dose aspirin for primiparae in pregnancy. *Br J Obstet Gynaecol* 1998; **105:** 293-299.
24. Duley L. Aspirin for preventing and treating pre-eclampsia. Large trials continue to show no benefit. *BMJ* 1999; **318:** 751-752.
25. Bower H. Studies rejecting aspirin for the prevention of pre-eclampsia. *BMJ* 1998; **316:** 885.

Accepted 24 July 1999.