Articles

Randomised controlled trial of ketanserin and aspirin in prevention of pre-eclampsia

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Summary

Background Pre-eclampsia is associated with extensive endothelial-cell damage and platelet activation, resulting in lower production of vasodilator prostaglandins and increased release of the vasoconstrictors thromboxane A_2 and serotonin. Damage to endothelial-cell serotonin-1 receptors leaves vasoconstriction and platelet aggregation mediated by serotonin-2 receptors unopposed. We investigated the role of ketanserin, a selective serotonin-2-receptor antagonist, in lowering the rate of pre-eclampsia among pregnant women with mild to moderate hypertension.

Methods We recruited 138 pregnant women into a double-blind, randomised, placebo-controlled trial. They had diastolic blood pressure persistently more than 80 mm Hg before 20 weeks' gestation. 69 women received ketanserin and 69 received placebo. Both groups also received aspirin. Patients were initially given two tablets daily, increased to four tablets daily in diastolic blood pressure was more than 90 mm Hg. Primary outcomes were the development of pre-eclampsia and severe hypertension, and perinatal mortality.

Findings There were significantly fewer cases of pre-eclampsia (two *vs* 13; relative risk 0·15 [95% CI 0·04–0·66], p=0·006) and severe hypertension (six *vs* 17; p=0·02) in the ketanserin than in the placebo group. There was also a trend towards less perinatal mortality (one *vs* six deaths) but this was not significant (p=0·28). Rates of abruptio placentae and pre-eclampsia before 34 weeks' gestation were lower in the ketanserin group, and mean birthweight was significantly higher.

Interpretation We found an association between the addition of ketanserin to aspirin and a decrease in the number of cases of pre-eclampsia and severe hypertension, as well as improved pregnancy outcome among patients with mild to moderate midtrimester hypertension.

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Introduction

Pre-eclampsia is an important cause of perinatal and maternal morbidity and mortality in developed and developing countries,[1,2] especially among patients who present before 28 weeks' gestation.[3–5]

Pre-eclampsia is associated with widespread endothelial-cell damage, leading to decreased production of vasodilator prostaglandins.[6] Activation of platelets through increased release of thromboxane A_2 and serotonin, which are potent vasoconstrictors, is well described.[7] Low-dose aspirin inhibits biosynthesis of platelet thromboxane A_2 with little alteration to vascular prostacyclin production.[8] However, initial expectations that low-dose aspirin would decrease the incidence of pre-eclampsia were not proved.[9] Stimulation of the serotonin-2 receptors on platelets and vascular-smooth-muscle leads to further platelet aggregation[10] and vasoconstriction; vasodilatation after stimulation of endothelial serotonin-1 receptors generally counteracts this reaction. In pre-eclampsia, endothelial-cell damage leaves vasoconstriction, mediated by serotonin-2 receptors, and platelet aggregation unopposed.[11]

The role of antihypertensive therapy in pregnant women with mild to moderate hypertension is unclear. Although reviews conclude that antihypertensive therapy decreases blood pressure without other proven benefits, treatment was started after 20 weeks' gestation in most studies.[12,13] By combining data from studies in which participants were treated from early in pregnancy, Odendaal and colleagues[14] found that midtrimester losses occurred significantly less often among treated patients than in control groups.

Ketanserin is a selective serotonin-2-receptor blocker with some degree of α-1-blocker activity.[15] Ketanserin lowers blood pressure in various disorders including pre-eclampsia,[16,17] and inhibits serotonin-induced platelet aggregation in vitro[18] and in patients with hypertension.[19] We decided that ketanserin was a good choice to study the effect of antihypertensive therapy in mild to moderate midtrimester hypertension. We used a randomised, double-blind, placebo-controlled design to assess the value of ketanserin plus aspirin compared with placebo plus aspirin in the prevention of pre-eclampsia and its complications.

Patients and methods

Participants were selected from all women who attended antenatal clinics at Tygerberg Hospital, a tertiary centre serving a community of mainly lower socioeconomic class and mixed racial origin in the northern suburbs of Cape Town, South Africa. Initial inclusion criteria were diastolic blood pressure persistently above 80 mm Hg before 20 weeks' gestation, no proteinuria, and gestation of between 12 and 20 completed weeks. Blood pressure was measured with an appropriately sized

cuff; the patient lay in the right recumbent position. If the diastolic blood pressure was more than 80 mm Hg but less than 109 mm Hg twice, at least 30 min apart, measured by sphygmomanometer, with the fourth Korotkoff sound as the reference pressure, three further measurements were taken with a Dinamap Vital Signs monitor (Criticon, Tampa, FL, USA); these three measurements relied on diastolic blood pressure nearer to the fifth Korotkoff sound.[20] Patients were eligible for inclusion if all values were more than 80 mm Hg.

Further inclusion criteria were a live singleton fetus of less than 20 weeks' gestational age, without obvious major defects on ultrasonography. Patients were excluded if the electrocardiogram showed any signs of pathological bradycardia of less than 50 beats per min, such as grade 1 or 2 atrioventricular block or sick sinus syndrome, ventricular tachycardia, or increased QT time. Patients who required antihypertensive therapy when examined were excluded, but a history of previous hypertension was not necessarily an exclusion criterion.

We included 138 women in the trial. They were randomly assigned either ketanserin (n=69) or a similar-looking placebo (n=69). All women also received aspirin. Once each woman had given written consent, the next successively numbered sealed box containing study drug or placebo was opened. Random numbers were computer generated in a way unknown to the clinicians and assigned to the boxes. A balanced block method was used, which ensured five patients were assigned to each study group after every ten recruitments. The study code was kept by Janssens Pharmaceutical, Belgium. Copies were given to the study's monitoring committee in envelopes, which were opened only when analysis was done, according to protocol, after 60 and 120 deliveries, and at the end of the study. Each woman received medication only from the container assigned to her. All women were started on two tablets per day—a total of 40 mg ketanserin daily in the study group—plus 75 mg aspirin. The drugs were distributed by a research nurse who was involved in the study.

Women were first seen for follow-up 1 week after starting treatment, after which they were seen every 2 weeks until 36 weeks' gestation, and thereafter every week. Diastolic blood pressure was taken three times at each visit with the Dinamap Vital Signs monitor with 5 min intervals. If each of these readings was more than 90 mm Hg, three more measurements were done after at least 30 min rest. If all six values were more than 90 mm Hg, we increased the medication to two tablets twice daily (80 mg ketanserin daily in the study group). If diastolic blood pressure was persistently more than 90 mm Hg at subsequent visits, treatment was deemed to have failed and the study drug was stopped and replaced with methyldopa, distributed by the clinic pharmacy. These women were included in the analysis. Women continued to receive aspirin after the study drug was withdrawn. Other management decisions, such as induction of labour, were taken on clinical grounds.

The main outcomes were the development of pre-eclampsia and severe hypertension, and perinatal mortality. Secondary outcomes were birthweight, perinatal morbidity, and the development of abruptio placentae. Hypertensive disease was defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP).[21] This classification was a single diastolic-blood-pressure measurement of 110 mm Hg or more, or two consecutive measurements of 90 mm Hg or more, at least 4 h apart, without inclusion of the initial diastolic-blood-pressure or any systolic-blood-pressure value. Proteinuria is deemed to be important if it is more than 300 mg per 24 h. Alternatively, the ISSHP suggest measurement of specific gravity or use of a high limit, such as 2+ or more, on dipsticks when random samples are used. Severe hypertension is defined as a single diastolic-blood-pressure measurement of 120 mm Hg or more, or two consecutive measurements of 110 mm Hg or more at least 4 h apart. We also investigated rates of hypertension before 34 weeks' gestation, according to the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) classification.[9] Only proteinuria is required in the presence of hypertension. Diastolic blood pressure has to be at least 90 mm Hg; it must be accompanied by a rise of at least 25 mm Hg if the baseline

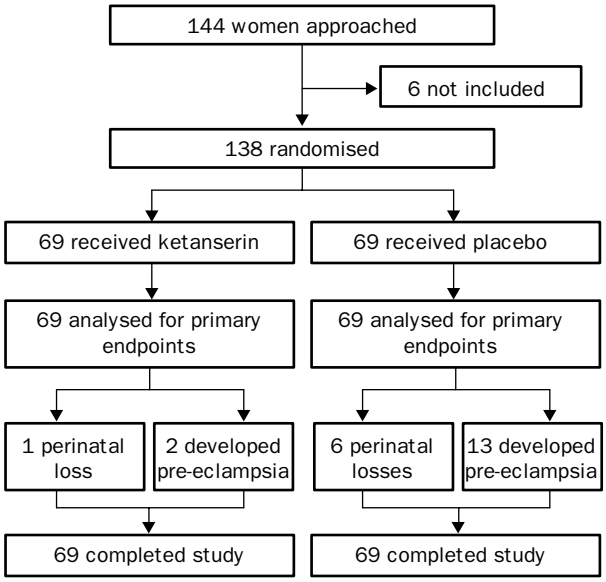

Figure 1: **Trial profile**

diastolic blood pressure is less than 90 mm Hg, or a rise of at least 15 mm Hg if the initial diastolic blood pressure is more than 90 mm Hg.

We defined neonatal deaths as occurring within the first 28 days of life and early neonatal deaths as occurring within the first 7 days. Neonatal morbidity was defined as any one or more of: intracranial haemorrhage, convulsions, intraventricular haemorrhage, intubation and ventilation, pneumonia, pulmonary haemorrhage, pulmonary hypertension, pneumothorax, patent ductus arteriosus, congestive cardiac failure, sepsis, or necrotising enterocolitis. A paediatrician diagnosed neonatal complications. All stillbirths and miscarriages were examined by a geneticist who was unaware of treatment status. Necropsies were not done in these cases, but were offered in cases of neonatal death. All physicians involved in management of patients were unaware of treatment status. All babies were followed up until discharge from hospital.

Based on the results of a similar,[14] we calculated that 112 patients were needed in each group to show a decrease from 25% to 10% in the rate of pre-eclampsia, with 80% power. A monitoring committee, of clinicians not involved in the management of the patients and an epidemiologist, assessed the data after every 60 deliveries to find out whether or not the study had to be continued, without disclosing any data if continuation was recommended. The study was to be discontinued when a significant result was reached for the main outcomes, or if an obvious benefit or harm from ketanserin became apparent.

We used logistic regression to assess the influence of various factors on the development of pre-eclampsia according to the ISSHP classification. Pre-eclampsia was modelled as a function of a set of possible confounders. We analysed data with SAS PROC CATMOD (version 6.01) with two approaches. First, the predictive value of confounders for development of pre-eclampsia known at recruitment were selected. Possible confounders were: the use of ketanserin; previous pregnancy losses in the different trimesters; previous pre-eclampsia; and gestational age at recruitment. Second, we analysed confounders known at the time of delivery. These confounders were: which drug was initially received; previous pregnancy losses; previous pre-eclampsia; gestational age at recruitment and delivery; the need for methyldopa; and the development of severe hypertension. We compared discrete data by calculating relative risks and 95% CIs. We used Fisher's exact test when the expected value in any cell was less than five. Continuous data were compared with Student's t -test for normally distributed data, and the Mann-Whitney U test for data without a normal distribution. Where applicable, p values of $<0{\cdot}05$ were taken as significant.

	Ketanserin group (n=69)	Placebo group (n=69)
Median (range) age in years	32 (19–46)	32 (21–44)
Median (range) number of previous pregnancies	3 (1–6)	3 (1–8)
Median (range) number of births	2 (0–5)	2 (0–7)
Median (range) gestation*	16 (12–19)	15 (12–19)
Number of smokers	12 (17%)	14 (20%)

*Completed weeks

Table 1: **Characteristics of women at start of study**

The study was approved by the ethics committee of Tygerberg Hospital and the University of Stellenbosch.

Results

144 women were eligible for inclusion. Six women who otherwise qualified were not randomised for participation. The reasons for exclusion were gestation beyond 20 weeks (two), an undiagnosed twin pregnancy before ultrasonography (one), and prolonged QT time on electrocardiogram (one). Two other patients from rural areas were not willing to attend Tygerberg Hospital for all antenatal visits. 138 women were, therefore, recruited. At this stage, the monitoring committee advised that the study could be discontinued after 120 births. We did not enrol any further participants; the extra 18 patients were managed according to protocol.

69 patients were randomly assigned to each treatment group. Once included, all patients completed the study (figure 1) The two study groups were similar at the time of entry (table 1, figure 2). Both treatment groups had a high rate of previously complicated pregnancies (table 2). Although more women in the placebo group than in the ketanserin group had previous pregnancies complicated by hypertensive disease, this difference was not significant for pre-eclampsia (p=0·13) or hypertension (p=0·06).

13 women (19%) in the placebo group developed pre-eclampsia, according to the ISSHP classification, compared with two (3%) in the ketanserin group (relative risk 0·15 [95% CI 0·04–0·66], p=0·006; table 3). Pre-eclampsia occurred before 34 weeks' gestation in five of the 13 women in the placebo group. In two of these women, intrauterine deaths occurred and six required antihypertensive therapy to maintain diastolic blood pressure of less than 110 mm Hg. The time of onset of pre-eclampsia was not related to gestation at recruitment. One woman in the ketanserin group, in her first pregnancy, developed pre-eclampsia before 34 weeks' gestation; the study drug was stopped according to protocol at 31 weeks' gestation and substituted with methyldopa. She developed 2+ proteinuria on dipstick (Multistix, Ames, Elkhart, IN, USA) at 33 weeks' gestation and was successfully managed according to local clinic policy.[22]

In the logistic regression of the predictive value of confounders for development of pre-eclampsia, only initial assignment to ketanserin was significant (recruitment p=0·009; delivery p=0·02). The only other factor approaching significance was the need for methyldopa (p=0·11).

	Ketanserin group (n=63)	Placebo group (n=60)
Midtrimester miscarriage	9 (14%)	9 (15%)
Stillbirth	11 (18%)	7 (12%)
Caesarean section	14 (22%)	18 (30%)
Pre-eclampsia	18 (29%)	26 (43%)
Hypertension	16 (25%)	26 (43%)
Abruptio placentae	5 (8%)	6 (10%)
Multigravid women without living children	14 (22%)	15 (25%)

Table 2: **Outcome of previous pregnancies**

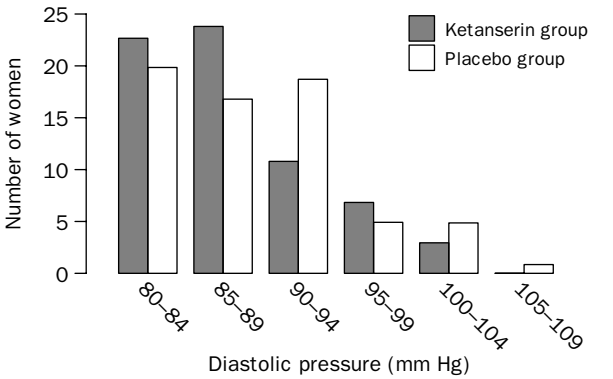

Figure 2: **Distribution of diastolic blood pressure at recruitment**

According to the CLASP definition, another six women in the placebo group and another one in the ketanserin group also developed pre-eclampsia. One woman in the placebo group underwent induction of pregnancy at 25 weeks' gestation because of severe hypertension with repeated + proteinuria, absent end-diastolic-flow velocity on umbilical artery doppler examination, advanced oligohydramnios, and intrauterine growth retardation. The fetus died during the induction process and weighed 520 g. Eight women (12%) in the placebo group presented with pre-eclampsia before 34 weeks' gestation compared with one (1%) in the ketanserin group (p=0·02).

34 (24·6%) of the 138 women required other antihypertensive therapy before the onset of labour; 23 were in the placebo group (0·48 [0·25–0·90], p=0·03; table 4). 12 of these 23 women developed pre-eclampsia compared with one in the ketanserin group (p=0·02). Four had fetal losses (table 4) and 17 advanced to severe hypertension, compared with six in the ketanserin group (0·35 [0·15–0·84], p=0·02); 11 women in the placebo group and three in the ketanserin group needed parenteral therapy. A further five patients in the placebo group and two in the ketanserin group who had not

Gestational age (weeks)	ISSHP definition		CLASP definition	
	Ketanserin	Placebo	Ketanserin	Placebo
<28	0	0	0	1
28–29	0	1	0	2
30–31	0	2	0	3
32–33	1	2	1	2
34–35	0	2	0	3
36–37	0	3	0	5
38–39	1	3	2	3

Table 3: **Distribution of pre-eclampsia according to ISSHP classification and CLASP classification**

	Ketanserin (n=69)	Placebo (n=69)	p
Antihypertensive drugs required before labour			
Oral	11 (16%)	23 (33%)	0·03
Parenteral (excluding intrapartum)	3 (4%)	11 (16%)	0·048
Intrapartum	2 (3%)	5 (7%)	0·44
Any antenatal drugs	13 (19%)	28 (41%)	0·01
Severe hypertension	6 (9%)	17 (25%)	0·02
Complications developed after treatment			
Pre-eclampsia on oral medication	1/11 (9%)	12/23 (52%)	0·02
Perinatal losses on oral medication	0	4/23 (17%)	0·28

Table 4: **Distribution of complications associated with hypertension**

	Characteristics of pregnancies						
Treatment group	Placebo	Placebo	Placebo	Placebo	Placebo	Ketanserin	Placebo
Number of previous pregnancies	5	3	3	7	2	3	3
Maternal age (years)	24	36	26	40	21	33	30
Previous midtrimester losses	1	0	0	0	0	2	0
Previous perinatal losses	0	0	2	0	1	0	0
Gestation at delivery (weeks)	33	28	28	23	31	22	25
Perinatal outcome	IUD	NND	IUD	IUD	IUD	IUD	TOP
Pre-eclampsia	Yes	No	No	No	Yes	No	Yes
Severe hypertension	Yes	Yes	No	No	No	No	Yes
Other drugs needed	Yes	Yes	No	No	Yes	No	Yes
Last umbilical-artery doppler assessment	Normal	Normal	More than P95	Too early	More than P95	Too early	AEDF
Birthweight (g)	1720	1240	980	150	1500	520	520
Cause of loss	Abruptio placentae	Abruptio placentae	Placental insufficiency	Unknown	Abruptio placentae	Cervical incompetency	TOP

IUD=intrauterine death; NND=neonatal death; TOP=termination of pregnancy; P95=95th percentile; AEDF=absent end-diastolic-flow velocity.

Table 5: **Summary of perinatal losses**

required methyldopa before labour needed parenteral dihydralazine sulphate during labour. 28 women in the placebo group and 13 in the ketanserin group needed additional antihypertensive therapy during the rest of pregnancy (0·46 [0·26–0·82], p=0·009). Although severe hypertension occurred more often in women with a history of hypertension during previous pregnancies, this difference was not significant in either group (three of 16 women in the ketanserin group, p=0·17; nine of 26 women in the placebo group, p=0·51).

Delivery was significantly earlier in the placebo group (mean gestation 36·2 [SD 3·6] *vs* 37·6 [2·6] weeks; p=0·02), even when births before 28 weeks' gestation were excluded. Mean birthweight for babies born between 28 and 34 weeks was 3074 g (655) in the ketanserin group and 2791 g (751) in the placebo group. 13% and 10% of babies, respectively, had birthweights below the tenth percentile.

There was one perinatal death, due to cervical incompetence, and six perinatal deaths in the placebo group, attributed to hypertension and requiring induction of delivery (one), abruptio placentae (three), placental insufficiency (one), unknown cause (one). The proportion of neonatal deaths was significantly higher in the placebo group, but most deaths were related to prematurity.

The rate of abruptio placentae in the ketanserin and placebo groups did not differ significantly (one [1%] *vs* six [8%]). Perinatal deaths occurred in three cases in the placebo group (table 5). One woman in the placebo group on methyldopa was admitted to hospital at 28 weeks' gestation to assess blood-pressure control. A sudden deterioration in the short-term variability of the fetal heart rate on routine cardiotocogram was followed by abruptio placentae. The baby, delivered by caesarean section, died due to complications of prematurity. In five of the six patients in the placebo group, the study drug had been substituted by methyldopa by the time abruptio placentae occurred. The mean gestational age at the time of abruptio placentae in the placebo group was 33 weeks (range 28–38). The only case of abruptio placentae in the ketanserin group occurred in the one woman with severe pre-eclampsia; no serious maternal morbidity related to pre-eclampsia or the treatment occurred.

Three patients in the ketanserin group were taken off their treatment after complaining of severe dizziness.

Discussion

There is, as yet, no evidence that pre-eclampsia is entirely preventable or predictable. Hypertension and proteinuria, the traditional diagnostic requirements, are only two features of the pathophysiological process characterised by dysfunction in many systems.[23] Even the effective prevention of hypertension and proteinuria may be associated with increased morbidity and mortality. If an intervention decreases the rate of hypertension and proteinuria before delivery, but has no documented impact on maternal and fetal morbidity and mortality or on the need for or cost of admission to hospital, it will probably not be judged to be useful.

There is some laboratory evidence that a combination of a selective serotonin-2-receptor antagonist with aspirin may be beneficial for disorders in which platelet aggregation plays a critical part. Tanaka and colleagues[24] reported that DV-7028, a selective serotonin-2-receptor antagonist without serotonin-1-receptor antagonism, inhibited reduction in cyclic flow resistant to low-dose aspirin in the coronary artery after experimental induction of thrombi in dogs. The combined regimen was significantly more effective than aspirin alone.

In our study, we found an association between the addition of ketanserin to aspirin and a significant decrease in the occurrence of pre-eclampsia, severe hypertension, and the need for additional antihypertensive therapy. In the placebo group, pre-eclampsia occurred significantly earlier in pregnancy and complications related to pre-eclampsia were more common than in the ketanserin group. Abruptio placentae and perinatal mortality were also more frequent in the placebo group, but not significantly so. Despite this lack of significance, in at least five of the six perinatal deaths in the placebo group, the deaths could be attributed to a cause that we hoped ketanserin would prevent. Furthermore, the only loss in the ketanserin group was not related to hypertensive disease.

There is no consensus on exactly what constitutes hypertension in pregnancy. Classification systems do not agree on whether both diastolic and systolic blood pressure should be taken into account; there is agreement that a diastolic-blood-pressure value of persistently more than 90 mm Hg at any stage in pregnancy is a sign that indicates hypertension.[18,25] This definition does not take into account the midtrimester fall in diastolic blood pressure in normal pregnancy. Few large longitudinal studies of blood pressure in pregnancy have been done. MacGillivray and colleagues[26] studied changes in blood pressure in 226 women throughout their first pregnancy by a standard method of measurement. The lowest systolic and diastolic blood pressure values occurred between 16 and 20 weeks' gestation. A diastolic-blood-pressure value of 90 mm Hg before 20 weeks' was 3·5 SD

above the mean; the value of the mean diastolic blood pressure plus 2 SD was 75 mm Hg.

Our study population probably consisted primarily of patients with mild chronic hypertension, although only 32% were previously diagnosed as such. A review by Chari and colleagues[9] and a meta-analysis by Duley[10] concluded that the medical treatment of chronic hypertension decreases maximum blood pressure, but that the rates of pre-eclampsia and abruptio placentae were not affected, and that evidence of other benefits was inadequate. The role of antihypertensive therapy in pregnant women with mild to moderate hypertension remains unresolved, but prevention of pre-eclampsia is more likely if therapy is started early in pregnancy.

The results of our study are encouraging. However, they were obtained in a carefully selected and motivated group of participants. Women were known to have had previous pregnancies affected with proteinuric hypertension.[19] The higher number of women in their first pregnancy in the placebo group did not affect our results since only one primigravida in the ketanserin group and two in the placebo group developed pre-eclampsia. Women with underlying hypertension who are treated from early in the second trimester are most likely to benefit from ketanserin. Whether the antihypertensive or antiserotonin effects of ketanserin brought about the improved outcome is not clear. A combination of these effects with that of aspirin may have improved the outcome. Further studies are needed to confirm our results and address the combined use of different drugs in different populations.

Contributors

D Wilhelm Steyn and Hein J Odendaal participated in the initial planning of the study and the writing of the study protocol. Both were also involved in the clinical management of patients, either as outpatients or after admission to hospital, and both worked on the final manuscript. Mariette Smith assisted the investigators in the statistical analysis of the data.

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References

1 DHSS. Report on confidential inquiries into maternal deaths in the United Kingdom 1985–1987. London: HMSO, 17–27.

2 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.

3 Moore MP, Redman CWG. Case control study of severe pre-eclampsia of early onset. *BMJ* 1983; **287:** 580–83.

4 Sibai BM, Taslimi M, Abdella TN, Brooks TF, Spinnato JA, Anderson GD. Maternal and perinatal outcome of conservative management of severe pre-eclampsia in midtrimester. *Am J Obstet Gynecol* 1985; **152:** 32–37.

5 Pattinson RC, Odendaal HJ, Du Toit R. Conservative management of severe proteinuric hypertension before 28 weeks' gestations. *S Afr Med J* 1988; **73:** 516–18.

6 Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. *Am J Obstet Gynecol* 1989; **161:** 1200–04.

7 Dekker GA. The pharmacological prevention of pre-eclampsia. *Baillieres Clin Obstet Gynaecol* 1995; **9:** 509–28.

8 Viinikka L, Hartikainen-Sorri A-L, Lumme R, Hiilesma V, Ylikorkala O. Low dose aspirin in hypertensive pregnant women: effect on pregnancy outcome and prostacycline: thromboxane balance in mother and newborn. *Br J Obstet Gynaecol* 1933; **100:** 809–15.

9 CLASP (Collaborative low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: A randomised trial of low-dose aspirin for the prevention and treatment of preeclampsia among 9364 pregnant women. *Lancet* 1994; **343:** 619–29.

10 Middlelkoop CM, Dekker GA, Kraayenbrink AA, Popp-Snijders C. Platelet poor plasma serotonin in normal and preeclamptic pregnancy. *Clin Chem* 1993; **39:** 1675–78.

11 Dekker GA, Van Geijn HP. Endothelial dysfunction in preeclampsia, part II: reducing the adverse consequences of endothelial cell dysfunction in preeclampsia—therapeutic perspectives. *J Perinat Med* 1996: **24:** 119–39.

12 Chari RS, Friedman SA, Sibai BM. Antihypertensive therapy during pregnancy. *Fetal Mat Med Rev* 1995; **7:** 61–75.

13 Duley L. Any hypertensive therapy in chronic hypertension. In: Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C, eds. Pregnancy and childb orth module. In: Cochrane Library (CDROM and online): Cochrane Collaboration, Issue 2. Oxford: Update Software, 1995.

14 Odendaal HJ, Schabort I, Pattinson RC. Prazosin for the treatment of hypertension in pregnancy: a randomised controlled trial. In: Oxford Database of Perinatal Trials, Version 1.2, Disk Issue 6, Autumn. Chalmers I, ed. Oxford: Oxford University Press, 1991.

15 Frishman WH, Huberfeld S, Okin S, Wang Y-H, Kumar A, Shareef B. Serotonin and serotonin antagonism in cardiovascular and non-cardiovascular disease. *J Clin Pharmacol* 1995; **35:** 541–72.

16 Weiner CP, Socol ML, Vaisrub N. Control of preeclamptic hypertension by ketanserin, a new serotonin receptor antagonist. *Am J Obstet Gynecol* 1984; **149:** 496–500.

17 Hulme VA, Odendaal HJ. Intrapartum treatment of preeclamptic hypertension by ketanserin. *Am J Obstet Gynecol* 1986; **155:** 260–63.

18 De Clerck F, Xhonneu x B. Continuous inhibition of platelet S2 serotonergic receptors during chronic administration of ketanserin in humans. *J Cardiovasc Pharmacol* 1985; **7:** S23–25.

19 Dzurik R, Fetkovska N, Brimichova G, Tison P. Blood pressure, 5-Oh indoleacetic acid, and vanilmandelic acid excretion and blood platelet aggregation in hypertensive patients treated with ketanserin. *J Cardiovasc Pharmacol* 1985; **7:** S29–31.

20 Franx A, Van der Post J, Elfering I, et al. Validation of automated blood pressure recording in pregnancy. *Br J Obstet Gynaecol* 1994; **101:** 66–69.

21 Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynaecol* 1988; **158:** 892–98.

22 Odendaal HJ, Steyn DW, Norman K, Kirsten GF, Smith J, Theron GB. Improved perinatal outcome in 1001 patients with severe pre-eclampsia. *S Afr Med J* 1995; **85:** 1071–76.

23 Roberts JM. Pregnancy-related hypertension. In: Creasy RK, Resnik R. Maternal fetal medicine: principles and practice. Philadelphia: WB Saunders, 1994; 804–43.

24 Tanaka T, Morishima Y, Watanabe K, Shibutani T, Yasuoka M, Shibano Y. Combined effect of the 5-HT_2 receptor antagonist DV-7028 and aspirin or heparin on coronary cyclic flow reductions in dogs. *Cardiovasc Res* 1993; **23;** 1374–79.

25 National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 1990; **163:** 1689–1712.

26 MacGillivray I, Rose GA, Rowe B. Blood pressure survey in pregnancy. *Clin Sci* 1969; **37:** 395–407.