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PHARMACOTHERAPY OF HYPERTENSION IN PREGNANCY IN A SECONDARY HOSPITAL IN SOUTH WEST NIGERIA

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Abstract
Hypertension in pregnancy has damaging effects on the blood vessels of the expectant mother as well as the blood supply involving the placenta exchange of oxygen and nutrition from mother to baby. A retrospective study of five years of the management of hypertension in pregnancy at Adeoyo Maternity Hospital, Ibadan was made. Its primary purpose was to assess the rational pharmacotherapeutic approach to the management of hypertension in pregnancy at the secondary hospital during the period of 5 years (2003–2007). Three hundred 300 randomly selected case notes of pregnant hypertensive patients from the medical records within age bracket of 15 – 40 years admitted into the antenatal ward of Adeoyo Maternity Hospital, Ibadan were thoroughly studied. Gestational hypertension was 240 (80.0%), pre-eclampsia was thirty four (34) (11.3%), while eclampsia was twenty six (26) (8.7%). Methyldopa was the most frequently administered drug as it was administered to 43.0±4.4 patients, nifedipine was administered to 33.6±8.6 patients, while hydralazine was administered to 16.4±2.0 patients. F-Tests ($P<0.05$) indicated significant differences between the three drugs, with methyldopa being the most significantly used antihypertensive following Fisher's least significant differences test ($LSD_{0.05}$). Although not statistically significant ($P>0.05$), patients' response to methyldopa appeared better than any of the other two drugs with comparatively lower number of 2.1±0.4, 4.5±0.7, 3.3±2.1, 3.1±0.6 and 3.6±0.5 days spent on admission over the five year period. Patients on hydralazine spent 2.4±0.5, 3.4±0.8, 3.5±0.8, 3.8±1.2 and 4.3±1.4 days and patients on nifedipine spent 3.0±0.4, 3.7±0.4, 3.4±0.4, 2.5±0.4 and 4.2±0.6 days. It was discovered that patients on methyldopa spent the least number of days on admission. This was followed by patients on hydralazine and nifedipine who spent few more days respectively than those on methyldopa. Optional therapy for gestational hypertension requires early detection, especially during antenatal clinic. It also requires utilization of appropriate pharmacotherapeutic and non-pharmacotherapeutic measures such as bed rest. The findings from this study will serve a beneficial purpose in the long term management of hypertension in pregnancy.

Keywords: pregnancy, gestational hypertension, pharmacotherapy, antihypertensive.

INTRODUCTION

Hypertension is a heterogeneous disorder that may result from some underlying pathophysiologic mechanism stemming from an unknown etiology. This is known as primary or essential hypertension (Caulfield *et al.*, 1994). The diagnosis of hypertension is confirmed after screening when the average of two or more diastolic blood pressure (DBP) measurements is 90 mmHg or higher, or the average of two or more systolic blood pressure (SBP) measurements is consistently greater than 140 mmHg (NCDETHBP, 1993; Jensen *et al.*, 1997). Hypertension in pregnancy can be classified into four disorders, namely: Pre-eclampsia, Eclampsia, Gestational hypertension and Chronic hypertension. The cause of Pre-eclampsia is not known. Its occurrence is however related to maternal age and parity. Pre-eclampsia

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occurs predominantly in young primigravida and the incidence is double in the first pregnancy in relation to subsequent pregnancies. Its incidence rises again both for primigravida and multigravida after the age of thirty-five years. Incidence of hypertension in pregnancy increases with age (Attah, 2000).

The diagnosis of a hypertensive disorder in a pregnant woman depends, in part upon the gestational age at presentation. Pre-eclampsia refers to the syndrome of new onset of hypertension and proteinuria or pathological oedema after 20 weeks of gestation in a previously normotensive woman (Cunningham, 1983). The risk factors of pre-eclampsia include first pregnancy (up to 85%), young or older maternal age, multiple gestation, family history, diabetes mellitus, essential hypertension and molar pregnancies that is, tumor-like mass of cyst instead of embryo that grows from tissue of fertilized egg (Steyn and Odendaal, 1997). The complications of pre-eclampsia include intrauterine growth retardation, placenta insufficiency or abruption, and pre-term labour and delivery. The complications increase in direct proportion to increased blood pressure (Pangle, 2000).

Gestational hypertension refers to elevated blood pressure first detected after 20 weeks of gestation without proteinuria or pathologic oedema[8]. Although, the exact cause of gestational hypertension is unknown, it seems to be an immunologic rejection of pregnancy, the baby seen as a hostile tissue-graft reaction. Brain swelling is the cause of seizures, lethargy and visual disturbances - the visual disturbances are not to be confused with the swelling of the cornea which results in blurred vision, which reverses after birth and it is harmless. The expectant mother's kidneys are especially vulnerable, affecting filtration, worsening the swelling and resulting in the loss of protein in the urine. The blood vessels develop abnormalities of constriction, affecting blood pressure and the reflexes become hyperactive (August, 2007). Chronic hypertension is defined as systolic pressure greater than 140 mmHg and /or diastolic pressure greater than 90 mmHg that antedates pregnancy. It is present or persists longer than 12 weeks post partum (Steyn and Odendaal, 1997). Eclampsia is the development of generalized seizures in a patient with gestational hypertension (Pangle, 2000).

Although fetal loss is about 16% in mild hypertension, and may reach 40% in severe hypertension, the primary goal of blood pressure management is to prevent maternal complications (Zuspan and Zuspan, 1992). Methyldopa is a central α – adrenergic agonist and it has a long history of use in treating hypertension in pregnancy. Using methyldopa reportedly increases fetal survival rates and decreases mid-trimester fetal loss. Hydralazine is a vasodilator. Intravenous form of hydralazine is useful when treating severe hypertension due to pre-eclampsia/eclampsia. It has a long record of safe use during pregnancy, but troublesome adverse effects could occur. Hydralazine could be used in conjunction with methyldopa when needed for chronic hypertension. Hydralazine causes direct arteriolar smooth muscle relaxation through mechanisms that increase the intracellular concentration of cyclic GMP. It exerts little effect, if any on the venous side of circulation (British National Formulary, 1998). Nifedipine is a dihydropyridine calcium channel

blocker which is effective in treating acute hypertension in near term patients. Nifedipine causes relaxation of cardiac and smooth muscles by blocking voltage-sensitive calcium channels, thereby reducing the entry of extracellular calcium into the cells. Vascular smooth muscle relaxation leads to vasodilation and a corresponding reduction in blood pressure (British National Formulary, 1998).

The purpose of the study was to assess the rational pharmaco-therapeutic approach to the management of hypertension in pregnancy and to provide means of prevention of complications associated with hypertension in pregnancy with the goal of providing and promoting pharmaceutical care.

PATIENTS AND METHODS

The study was a retrospective evaluation of randomly selected case notes of 300 pregnant hypertensive patients admitted into the antenatal ward of the hospital from January, 2003 to December 2007. The case notes containing the medical profiles of the patients were evaluated for the following information: age, occupation, number of times being pregnant (n^{th} pregnancy), gestational age, blood pressure on admission, blood pressure on discharge, number of days spent on admission, marital status, type of hypertension, and drugs that were prescribed/administered.

The data that were extracted were then subjected to one way analysis of variance completely randomized design where F – Tests was significant at 5% level of probability ($P<0.05$), Means were separated using Fisher's least significant difference. Means of the randomly sampled population were presented with ± standard error of the mean. Other descriptive statistics, such as proportions (percentages %), frequencies and cumulative frequencies were also used. They were presented in tables and figures as appropriate.

Permission to conduct the study was granted by the Ethical Committee of Adeoyo Maternity Hospital, Ibadan Nigeria, with the objective that the study aims at improving the overall pharmaceutical care received by pregnant hypertensive patients at Adeoyo Maternity Hospital.

RESULTS

Table 1 shows the distribution of patients based on the number of pregnancy at Adeoyo maternity hospital during the 5 year period of 2003 and 2007. Patients that had their first pregnancy in the study accounted for 109 (37%). The second, third, fourth, fifth, sixth and seventh pregnancies accounted for 39 (13.2%), 41 (113.9%), 50 (17.0%), 30 (10.2%), 16 (5.4%) and 8 (2.7%) respectively. The Eighth and tenth pregnancies accounted for 1 (0.3%) each. Fig. 1 shows the age group of pregnant hypertensive patients on admission during the 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, 5^{th}, 6^{th}, 7^{th}, 8^{th} and 10^{th} pregnancies.

The number of the pregnant hypertensive patients that were with their first pregnancies upon linear regression indicated equation: $0.2906 x + 20.735$, $R^2 = 0.1704$, thus indicating that gestational hypertension is a subtitle crucial factor in first pregnancy (Fig. 2)

Table 2 shows the total number of pregnant hypertensive patients that had gestational hypertension to be 240 (80.0%) while 34 (11.3%) had pre eclampsia and 26 (8.7%) had eclampsia during the study period. Table 3 shows anti hypertensive drug regimen prescribed to pregnant hypertensive patients admitted to Adeoyo Maternity Hospital during the study period. Methyldopa was

administered to 43.0 ± 4.4 mean number of patients, nifedipine was administered to 33.6 ± 8.6 mean number of patients while hydralazine was administered to 16 ± 2.4 mean number of patients. The number of pregnant hypertensive patients placed on the different drug was significantly different from one another (P<0.05). Table 4 shows the proportion of pregnant hypertensive patients administered with methyldopa, nifedipine and hydralazine. Patients who received nifedipine, a calcium channel blocker alone were 22.6% while hydralazine alone was given to 11.1% patients and 18.2% patients received a combination of methyldopa and nifedipine. A combination of methyldopa and hydralazine was given to 7.7% patients while 5.9% patients were given a combination of nifedipine and hydralazine.

Anxiolytics were administered to 41.2 ± 7.0 mean number of patients. Antimalarial drugs were given to 2.0 ± 0.0 while antibiotics were given to 6.0 ± 0.5 patients. The mean number of patients administered with haematinics/multivitamins was 12.6. 6 ± 4.6 while 9.6 ± 3.1 patients were given analgesics (Table 5).

Fig 3 shows the number of days the patients spent on admission. Patients seemed to respond very well to methyldopa compared to the other two drugs. Patients on methyldopa spent the least number of days on admission. In years 2003 through 2007, number of days spent on admission by patients on methyldopa were 2.1±0.4, 4.5±0.7, 3.3±2.1, 3.1±0.6 and 3.6±0.5 respectively. Patients on hydralazine spent 2.4±0.5, 3.3±0.8, 3.5±0.8, 3.8±1.2 and 4.3±1.4 days, while patients on nifedipine spent 3.0±0.4, 3.7±0.4, 3.4±0.3, 2.5±0.4 and 4.2±0.6 days on admission. The number on admission was however not significantly different from one another based on the antihypertensives administered ((P>0.05).

DISCUSSION

In this study, it was observed that the highest percentage of the pregnant hypertensive patients reviewed were those who were carrying their first pregnancy indicating first pregnancy to be a major risk/predisposing factor to hypertension in pregnancy. As seen in the study 37% of the patients had their first pregnancy, while the lowest were those with eighth and tenth pregnancies, as they both accounted for 0.3% each. The result supported the observation of Pangle (2000) that the first pregnancy accounted for the highest percentage of patients with pre-eclampsia, and that the hypertension in the first pregnancy constitutes a very important high risk factor.

Those with their second pregnancy accounted for 13.2%, third pregnancy 14.0%, fourth pregnancy 17.0%, fifth pregnancy10.2%, sixth pregnancy 5.4%, and seventh pregnancy 2.7% (Table 1). First pregnancy is observed as a very important risk factor for pre-eclampsia which is a type of hypertensive disorder in pregnancy [8]. Since the first foetus is seen as a hostile tissue graft which the mother's immune system tries to fight against as a foreign body, the first pregnancy thus constitutes a very high-risk factor. Therefore, women carrying first pregnancies should be encouraged to visit the antenatal clinic regularly so as to prevent the complications associated with first pregnancy as a crucial risk factor for gestational hypertension. There are reports that there is a multifactorial condition involving some sorts of immune response to pregnancy as a foreign material (the father's genetic component) just as in tissue graft rejection and that the varying intensities of the rejection are probably responsible for the numerous

ways the hypertension presents itself in different women. Geographic, Ethnic, Racial, Nutritional and Familial factors and pre-existing vascular disease may contribute to the development of pregnancy-induced hypertension

Table 1: Distribution of patients based on nth pregnancy at Adeoyo Maternity Hospital, Ibadan in 2003 – 2007.

Year	nth Pregnancy								
	1st	2nd	3rd	4th	5th	6th	7th	8th	10th
2003	21(35%)	7(11.7%)	6(10.0%)	9(15%)	11(18.3%)	4(6.7%)	2(3.3%)		
2004	20(33.3%)	11(18.3%)	6(10.0%)	10(17.0%)	6(10.0%)	5(8.3%)	1(1.7%)		1(1.7%)
2005	23(38.3)	12(20.0%)	9(15%)	8(13.3%)	2(3.3%)	2(3.3%)	4(6.7%)		
2006	18(30.5)	5(8.5%)	16(27.1%)	10(17.0%)	6(10.2%)	3(5.1%)	1(1.7%)		
2007	27(48.2%)	4(7.1%)	4(7.1%)	13(23.2%)	5(8.9)	2(3.6%)		1(1.8%)	
Total	**109**	**39**	**41**	**50**	**30**	**16**	**8**	**1**	**1**
(%)	(37.0%)	(13.2%)	(13.9%)	(17.0%)	(10.2%)	(5.4%)	(2.7%)	(0.3%)	(0.3%)

hypertensive patients studied were carrying their first pregnancy and first pregnancy is a very important risk factor in pregnancy-induced hypertension. Table 2 showed 11.3% had pre-eclampsia while 8.7% had eclampsia. Yearly breakdown of the data indicated that gestational hypertension is more common among pregnant women than pre-eclampsia/eclampsia. There was no incidence of chronic hypertension in the study. This might be because there was no gestational age of presentation that was less than twenty weeks. The study indicated that there were late

(Springhouse, 2005). This study further revealed that gestational hypertension is most common among the pregnant hypertensive patients as 80.0% of these patients had gestational hypertension. This could be due to the fact that most of the pregnant

Table 2: Number and proportion (%) of patients with different types of hypertension at Adeoyo Maternity Hospital, Ibadan in 2003 – 2007.

S/N	Type of hypertension	2003	2004	2005	2006	2007	Total
1	Gestational hypertension	52(86.7)	48(80.0)	52(86.7)	53(88.3)	35(58.3)	240(80.0)
2	Pre-eclampsia	5(8.3)	6(10.0)	0(0.0)	2(3.3)	21(35.0)	34(11.3)
3	Eclampsia	3(5.0)	6(10.0)	8(13.3)	5(8.3)	4(6.7)	26(8.7)

Table 3: Antihypertensive drug regimen prescribed to pregnant hypertensive patients admitted to Adeoyo Maternity Hospital, Ibadan from 2003 to 2007.

	Number and proportion (%) of prescriptions per drug per year with sample mean ± standard error						
S/N	Drugs	2003	2004	2005	2006	2007	Mean ± SE
1	Aldomet	47(61.0%)	46(51.1%)	41(41.0%)	29(34.5%)	52(45.6%)	43..0±4.4
2	Nifedipine	8(0.4%)	25(27.8%)	41(41.0%)	43(51.2%)	51(44.7%)	33.6±8.6
3	Hydrallazine	22(28.6%)	19(21.1%)	18(18.0%)	12(14.3%)	11(9.7%)	16.4±2.4
	$LSD_{(0.05)}$						7.9

detection of gestational hypertension, pre-eclampsia/eclampsia, because many of the pregnant women did not visit the hospital/antenatal clinic early and regularly. Some pregnant women do not visit the health facility until seizures/convulsions set in. This is particularly risky because as revealed in this study, many pregnant women suffer gestational hypertension more than any form of hypertension.

It was also discovered that gestational hypertension is a crucial but subtle factor in first pregnancy (Fig.1). The small magnitude of the coefficient of determination indicated that the two variables are related and the prediction was good, because the smaller the variability of the residual values around the regression line relative to the overall variability, the better is the prediction; although the negativity of the regression equation indicated that gestational hypertension is a subtle, though crucial factor in first pregnancy (Fig.2).

In this study, it was found that methyldopa was the most frequently prescribed antihypertensive for these

Table 4: Drug combination therapy prescribed to pregnant hypertensive patients admitted to Adeoyo Maternity Hospital, Ibadan in 2003 to 2007.

S/N	Class of Drug	Frequency	Proportion (%)
I	Central α- adrenergic agonist	215	29.0
II	Calcium channel blocker	168	22.6
III	Vasodilator	82	11.1
IV	I + II	135	18.2
V	I + III	57	7.7
VI	II + III	44	5.9
VII	I + II + III	41	5.5

pregnant hypertensive patients because it was prescribed to 43.0 ± 4.4 mean number of patients. (Table 3) This could be due to the fact that methyldopa has a long history of use in treating hypertension in pregnancy, and using methyldopa reportedly increases fetal survival rates and decreases mid-trimester fetal loss (Paul, 2007). Methyldopa has tolerable side effects. Methyldopa has the least mean number of days spent by patients on admission. This shows that it is very effective for management of gestational hypertension. It is also cheap and easily affordable, thereby enhancing patients' compliance to the drug therapy for gestational hypertension.

Hydralazine was administered to 16.4 ± 2.4 mean number of pregnant hypertensive patients. (Table 3) The intravenous form of hydralazine is useful when treating severe hypertension due to pre-eclampsia/eclampsia. It has a long record of safe use during pregnancy (Paul, 2007). Hydralazine was the least frequently used antihypertensive drug in this study, as it is useful when treating severe hypertension due to pre-eclampsia/eclampsia. Patients on methyldopa had the least mean number of days spent on admission, although not statistically significant, it might be of crucial clinical consideration, followed by hydralazine and nifedipine (Fig.3).

The common regimes of therapy administered on the patients were in the order: single therapy > bitherapy > triple therapy. The combinations used were methyldopa + hydralazine or nifedipine + hydralazine in the case of bitherapy and all the three drugs in the case of the triple therapy. It was observed that methyldopa was the most frequently used drug, as it occurred in almost all the different combinations of the drug therapy (Table 4).

Considering the concomitant drugs that were prescribed, anxiolytics had the highest number of prescription, and this may be because this class of drugs has sedating and calming effects, which would be of great benefit to pregnant hypertensive patients, because it serves as an adjunct in the

Table 5: Concomitant drugs prescribed to pregnant hypertensive patients admitted to Adeoyo Maternity Hospital, Ibadan in 2003 to 2007

	Number and proportion (%) of prescriptions per drug per year with sample mean ± standard error						
S/N	Drugs	2003	2004	2005	2006	2007	Mean ± SE
1	Anxiolytics	47(67.1%)	52(58.4%)	48(64.9%)	42(46.7%)	17(65.4%)	41.2±7.0
2	Haematinics/ Multivitamins	7(10.0%)	19(21.4%)	14(18.9%)	23(25.6%)	0(0.0%)	12.6±4.6
3	Antibiotics	5(7.1%)	7(7.9%)	5(6.8%)	7(7.8%)	6(23.1%)	6.0±0.1
4	Antimalaria	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2(7.7%)	2.0±0.0
5	Analgesics	11(15.7%)	11(15.7%)	7(9.5%)	18(20.0%)	1(3.9%)	9.6±3.1

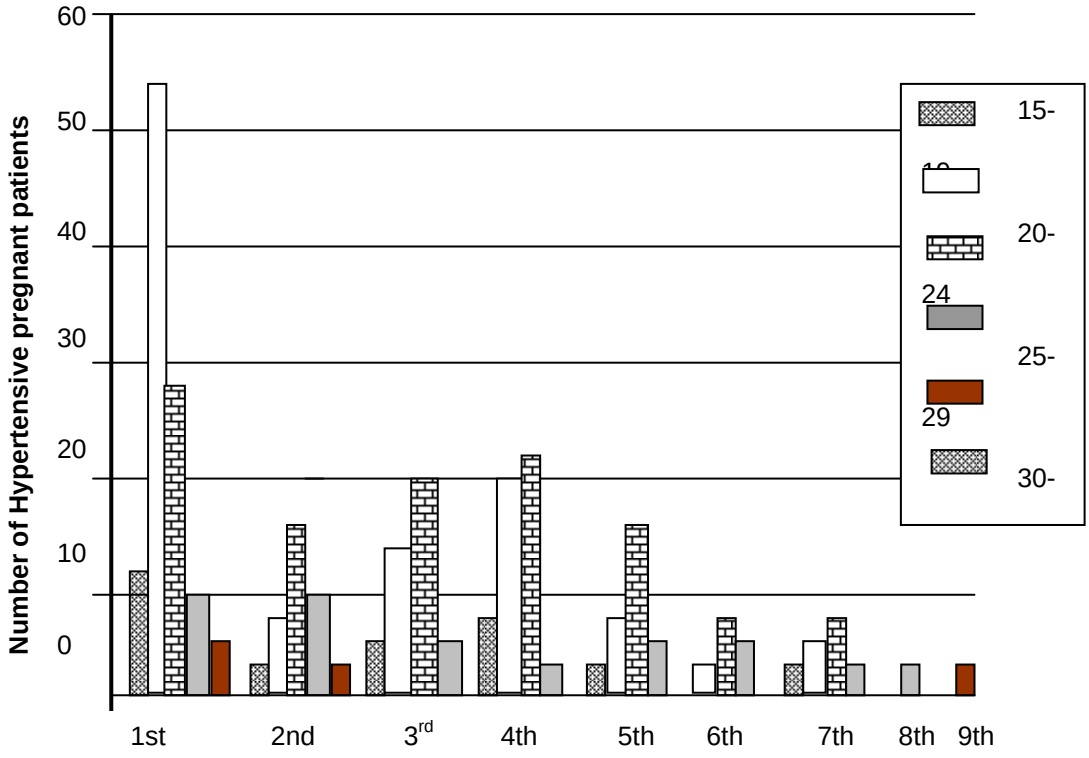

Figure 1: Distribution of patients based on age-group and Nth pregnancy at Adeoyo Maternity Hospital, Ibadan in 2003 – 2007.

therapy of their hypertension. Haematinics/multivitamins were prescribed so as to boost the packed cell volume of these patients.

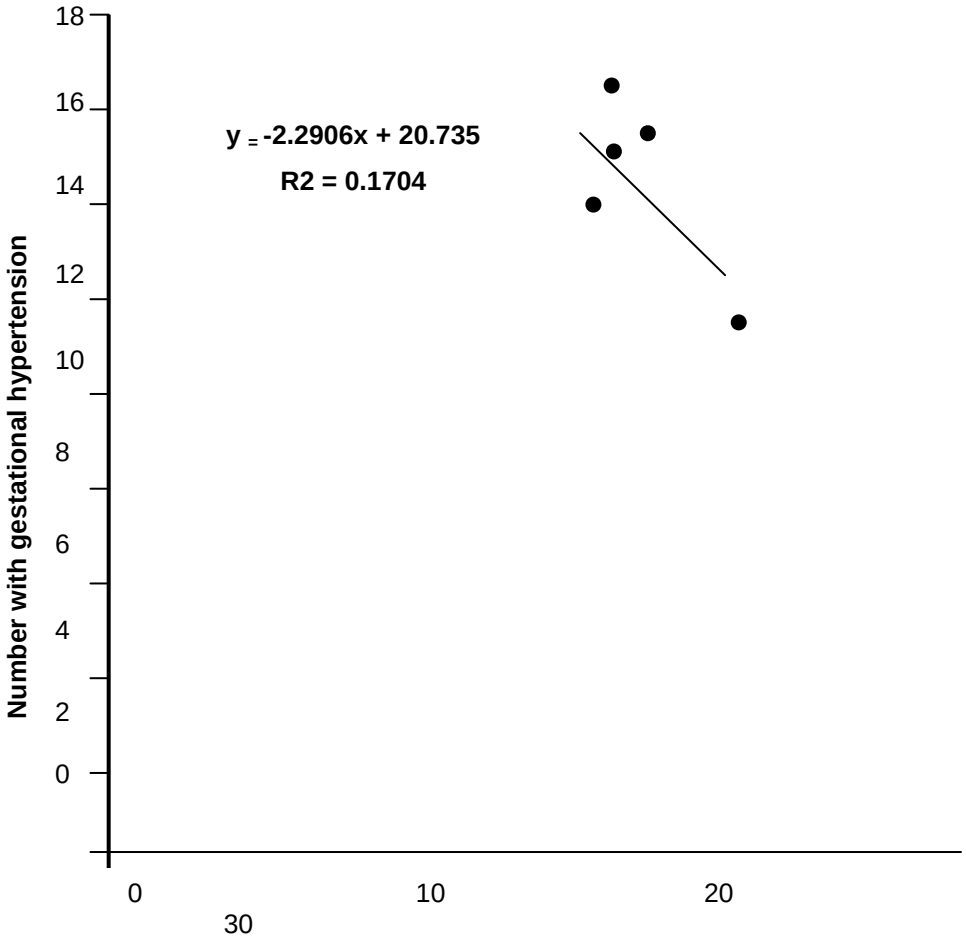

Figure 2: Comparison (linear regression) of number of hypertensive pregnant women in admission at Adeoyo Maternity hospital, Ibadan with gestational hypertension in the first pregnancy in 2003 to 2007.

Antibiotics were given to cure any existing infections and analgesics were prescribed for pain relief (Table 5). Low-dose aspirin may be prescribed as well. Its use has been suggested for patients at high risk for the development of the disorder (Felmeden, 2005).

Low-dose aspirin has been shown to decrease thromboxane A_2 synthesis to a greater degree than the decrease in prostacyclin synthesis, which would theoretically normalize the ratio of prostacyclin and thromoxane A_2 (Lubbe, 1987; Sibbai *et al.*, 1989). The usefulness of low-dose aspirin (60 mg/day) in preventing pre-eclampsia by virtue of its property of blocking the enzyme cyclooxygenase has now been verified in a number of studies (Gaziano *et al.*, 2000; ATC, 2002).

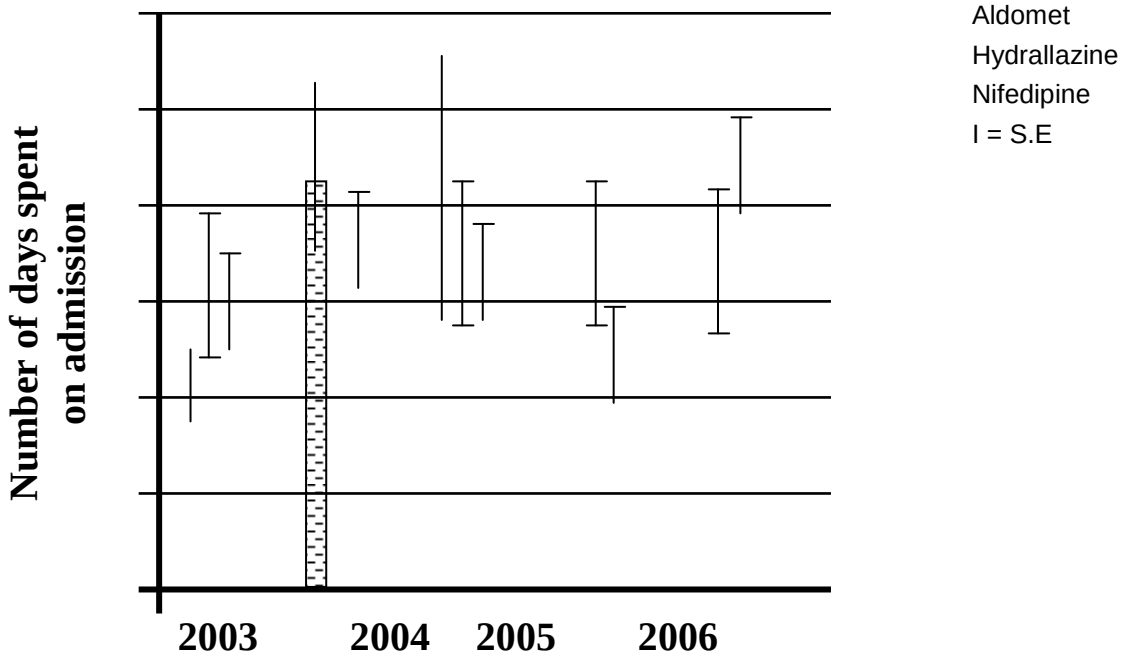

Figure 3: Response of pregnant hypertensive patients at Adeoyo Maternity Hospital, Ibadan, Nigeria to commonly used antihypertensive drugs in 2003 to 2007.

Since patients with first pregnancy are at high risk of gestational hypertension, pre-eclampsia/eclampsia, it is suggested that these patients should be started on low-dose aspirin anytime from the end of the second trimester till birth as prophylaxis to prevent gestational hypertension, pre-eclampsia/eclampsia. The management of hypertension in pregnancy aims principally at reducing both maternal and fetal morbidity and mortality. Methyldopa still remains drug of choice in the management of hypertension in pregnancy as seen in this study where 71.7% of the patients were administered methyldopa. Diazepam seems to be the choice of skeletal muscle relaxant that was administered to the patients with seizures (eclampsia) to control the seizures.

Bed rest can be used as an adjunct to drug therapy in patients with hypertension in pregnancy to augment uteroplacental blood flow if made in the lateral decubitus position and can be of value if there is uteroplacental insufficiency. In the management of patients with hypertension in pregnancy, possible drug-drug interactions must be taken into consideration as calcium channel blockers must not be used concurrently with magnesium sulphate as using them together may potentiate therapeutic effects and cause a precipitous fall in blood pressure which is not desirable in the management of hypertension in pregnancy.

CONCLUSION

Women of child bearing age should be encouraged to check their blood

pressure on a consistent basis as this would help in the early detection of hypertension in pregnancy in such women. Delivery is the best therapy for hypertension in pregnancy because hypertension resolves shortly after delivery (Janet, 1997).

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