



DRUG TREATMENT OF GESTATIONAL HYPERTENSION; IMPLICATIONS FOR MATERNAL AND FETAL WELLBEING

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ABSTRACT

Background: Hypertension in pregnancy carries high risk of adverse maternal and fetal outcomes. It is implicated in pre-eclampsia, proteinuria and eclampsia all of which carry high risk of maternal mortality. Gestational hypertension that is uncontrolled is often associated with low birth weight, intra-uterine growth retardation, still births and neonatal death. This study aims to assess antihypertensive utilization and their effect on maternal and fetal outcomes. **Methods:** This was a cohort observational study involving hypertensive women who received antenatal care in a tertiary hospital. Data was extracted from randomly selected medical records of eligible patients. The blood pressure, morbidity, drug(s), delivery method and fetal health data were used for analysis. **Analysis:** Data was analyzed using SPSS 21 for descriptive and inferential analysis. Pearson correlation test was used to assess relationship between antihypertensive drugs and maternal or fetal outcomes. **Results:** Maternal mortality and hypertensive complications remain relatively high, so also was prevalence of low birth weight and foetal deaths. A strong association was observed between aggressive blood pressure control and adverse foetal outcomes. Similar observation was noted for combination therapies involving diuretics. **Discussion:** The prescription of antihypertensives either contraindicated or of doubtful safety in pregnancy may potentially be contributing to adverse outcomes. There is need to emphasize the better management of hypertension in pregnancy to minimize the risk of adverse outcomes. **Conclusion:** There should be better use of drugs and improved blood pressure control among hypertensive pregnant women to improve maternal and fetal wellbeing.

KEYWORDS: Pregnancy, Gestational hypertension, Drug therapy, fetal outcomes, maternal outcomes.

INTRODUCTION

Chronic hypertension is globally estimated to be a complicating factor in 1–5% of all pregnancies.^[1, 2] Gestational hypertension is reported to be present in 5–10% of all pregnancies, though it is reported to vary widely among different populations depending on diagnostic criteria.^[3, 4] Recent demographic changes in developing countries reveal that chronic hypertension among women of reproductive age is increasing as age of first childbirth increase.^[5] The rise has been linked to the impact of rising cases of risk factors like obesity, metabolic disorders and socioeconomic factors among pregnant women.^[6,7,8,9] Hypertension in pregnancy is known to be associated with poor clinical outcomes and increased adverse events for both mother and fetus.^[10]

Global estimates indicate that uncontrolled hypertension is estimated to be directly responsible for 10–15% of pregnancy related complications.^[11] The most severe forms of complications included pre-eclampsia and

eclampsia both of which are associated with high mortality rate for both fetus and mother.^[12] Several studies has been linked uncontrolled gestational hypertension to poor pregnancy outcomes, making it a major risk factor for abnormal development and low fetal survival rate.^[13, 14, 15] Some studies have also suggested that in the presence of hypertension; high plasma uric acid level commonly found in affected pregnant women is not only an independent predictor of eclampsia, but also an indication of severity of gestational hypertension.^[16, 17, 18]

Fetal complications associated with uncontrolled gestational hypertension include intrauterine growth retardation, fetal distress, prematurity, hypoxia, low birth weight and perinatal death.^[19, 20] The severity of fetal complications is reported to correlate with severity of pre-eclampsia, duration of uncontrolled hypertension and level of maternal proteinuria.^[21]

Antihypertensive therapy play a critical role in not only improving maternal wellbeing, but also good fetal development and post-delivery survival.^[22, 23, 24, 25, 26] The risk of developing severe hypertension and its associated complications is significantly reduced with drug therapy, however the impact of blood pressure reduction on pre-eclampsia, neonatal death, preterm birth, low birth weight and overall pregnancy outcomes is less clear.^[27,28] Many experts still have concerns about how much blood pressure reduction is ideal for pregnancy related risks, because aggressive control of blood pressure raises the possibility of reducing placental blood flow which can lead to unintended consequences for the fetus.

The choice of therapy in gestational hypertension is largely based on best clinical evidence, however there is significant variability in clinical response.^[29, 30] In recent years, Labetolol and Nifedipine has been added to Methyl dopa as a safe antihypertensive drug in pregnancy in spite of concerns of possible intrauterine growth retardation generally associated with beta blockers^[31] Among the direct vasodilators, Hydralazine has found use in hypertensive emergencies or as third line drug for multidrug control of refractory hypertension.^[32] The use of ACEIs / ARBs is contraindicated because of their potential for teratogenicity and congenital malformations.^[33, 34]

While guidelines provide options for drug selection, literature evidence indicate that blood pressure control is less than optimal in gestational hypertension particularly in developing countries. Blood pressure control in pregnancy should therefore be a careful balance that produce the best clinical outcomes for both mother and the fetus. The major objectives of this study include assessment of antihypertensive drug prescription pattern as well as maternal and fetal outcomes.

METHODS

Setting: The study was conducted at the obstetrics and gynaecology ward of the University of Maiduguri Teaching Hospital Borno State, North East Nigeria.

Study Design: This is a cross-sectional observational study using information obtained from medical record of hypertensive pregnant women receiving antenatal care in the hospital.

Sample Size/Sampling: A total of five hundred women diagnosed with gestational hypertension during antenatal

care were identified from medical records and selected using simple random method.

Exclusion criteria

- Women who attended less than 70% of scheduled antenatal visits
- Those who are on highly active antiretroviral therapy
- Patients being managed for chronic diseases
- Patients referred to the hospital for specialized care in pregnancy
- Women who only came to the hospital for delivery related complications

Data Collection: The blood pressure, morbidity, drug(s), delivery method and fetal data were extracted from medical record, laboratory tests and delivery notes.

Data analysis: The data was analyzed using SPSS version 20 for descriptive and inferential analysis. Pearson correlation was used to determine the association between antihypertensive medications and adverse maternal and fetal outcomes. P values ≤ 0.05 was considered statistically significant.

Ethical Issues: Approval for this study was obtained from the health research committee of the University of Maiduguri teaching hospital.

RESULTS

Majority of women with gestational hypertension were housewives with intermediate level education. The mean age of subjects was 35.5 ± 6.6 years with a mean parity 3.2 ± 1.8 . The mean PCV [31.3 ± 4.7] was well below the recommended level indicating high levels of anaemia [Table 1].

The most prevalent comorbidity was peptic ulcer disease which affected about a third of pregnant women followed by asthma and gestational diabetes with a prevalence of 14.2% and 5.8% respectively. The major hypertension induced complication was pre-eclampsia [15.6%], while low birth weight was observed in almost half of all babies. The prevalence of still births and early neonatal deaths was observed in 28% of all deliveries [Table 2].

Table 1: Demographic characteristics (n = 500).

Variable	Description	Outcome
Education		
	Primary	118 [23.6%]
	Secondary	254 [50.8%]
	Tertiary	128 [25.6%]
Occupation		
	Housewife	453 [90.6%]
	Business	39 [7.8%]

	Civil service	6 [1.2%]
	Farming	2 [0.4%]
Mean age [yrs.]		35.5 ± 6.6
Parity		3.1 ± 1.8
Packed cell volume [%]		31.3 ± 4.7
Time of first antenatal visit [weeks]		13.2 ± 4.3

Table 2: Maternal and fetal outcomes (n = 500)

Variable	Description	Outcome
Maternal outcomes		
	Maternal death	64 [12.8%]
	Normal delivery	436 [87.3%]
Delivery route		
	Vaginal delivery	322 [64.4%]
	Cesarean section	178 [35.6%]
Maternal complications		
	Pre-eclampsia	78 [15.6%]
	Post-partum hemorrhage	39 [7.8%]
	Convulsions	24 [4.8%]
Fetal outcomes		
	Healthy births	343 [68.6%]
	Still births	137 [27.4%]
	Early neonatal death	6 [1.2%]
	Miscarriage	14 [2.8%]
	Low birth weight [kg]	234 [46.8%]
	Birth weight [kg]	2.1 ± 1.3
	APGA score [5 minutes]	6.0 ± 3.9

Antihypertensive drugs prescription pattern showed that Methyldopa [56.2%] and Nifedipine [24%] were the most prescribed, however use of other drugs like

Bendrofluthiazide, Amlodipine and Lisinopril were also documented raising concerns about potential adverse fetal risks [Table 3].

Table 3: Antihypertensive drugs prescription pattern.

Drug[s]	Number [%]
Monotherapies	
Methyldopa	281 [56.2]
Nifedipine	120 [24]
Labetolol	6 [1.2]
Amlodipine	6 [1.2]
Bendrofluthiazide	17 [3.4]
Lisinopril	8 [1.6]
Dual therapies	
Methyldopa + Bendrofluthiazide	25 [5]
Nifedipine + Bendrofluthiazide	21 [4.2]
Amlodipine + Bendrofluthiazide	16 [3.2]

A comparison of blood pressure between first antenatal visit and time of delivery showed significant reduction in both SBP and DBP [Table 4].

Table 4: Blood pressure reduction [mm/Hg]

Blood pressure	First Antenatal BP [mm/Hg]	Delivery BP [mm/Hg]	Mean drop [mm/Hg]	P value
Systolic BP	151 ± 20.4	123.5 ± 12.9	35.5 ± 19.6	0.0001
Diastolic BP	102.2 ± 12.5	80.7 ± 7.7	20.3 ± 12.4	0.0001

Adverse fetal outcomes was found to be strongly associated with Bendrofluthiazide monotherapy and its combination with Nifedipine. A similar association of

adverse fetal outcome was found when there was a simultaneous drop in SBP [> 20 mm/Hg] and DBP [> 30 mm/Hg] [Table 5].

Table 5: Antihypertensive drugs and association with adverse fetal outcomes.

Variable	R	P value	Outcome
Bendrofluthiazide	0.405*	0.001	Still birth
Amlodipine	0.220	0.179	
Nifedipine	0.266	0.102	
Methyldopa	0.180	0.273	
Nifedipine + Bendrofluthiazide	0.431**	0.006	Still birth
Drop of SBP [> 20 mm/Hg]	0.034	0.836	
Drop in DBP [> 30 mm/Hg]	0.069	0.676	
Drop in SBP and DBP [SBP [> 20] and DBP [> 30]]	0.593**	0.001	Still birth

Key: *Significant at 0.05, ** Significant at < 0.01

In case of adverse maternal outcome, the presence of anaemia and/or hypertension related eclampsia showed a significant association with high risk of maternal mortality [Table 6].

Table 6: Maternal factors and their association with maternal mortality.

Maternal factors	R	P value
Packed cell volume	0.192**	0.002
Eclampsia	0.167**	0.007
Cesarean delivery	1.400	0.024

Key: ** = Significant at < 0.01

DISCUSSION

Antihypertensive therapy is indicated for all women with gestational hypertension; however it remains unclear if drug therapies independently improved fetal outcomes.^[35] The prevalence of complications such as pre-eclampsia found in this study is comparable to previous studies.^[27] Maternal mortality associated with pre-eclampsia in this study is much higher than previously reported.^[4] The high mortality rate found in this study was also considerably higher than 1–8% earlier reported in similar studies.^[8, 36]

Fetal and neonatal mortality rate was comparably lower than previously reported, while stillbirth prevalence in this study was more than twice the rates reported.^[36] Overall, prevalence of adverse fetal outcomes occurred in about a third of pregnancies which is an unacceptably high figure. This may be partly due to either late presentation and/or late referral from lower level health facilities. Clinical evidence suggests that early and adequate prenatal control of blood pressure can significantly reduce adverse outcomes for both mother and foetus.^[37, 38]

There is significant association between maternal eclampsia and/or anaemia and high maternal mortality. While there is inherent risk of death from cesarean delivery from complications of anaesthesia, puerperal infection, post-partum haemorrhage and venous thromboembolism^[39], its contribution to overall maternal mortality vary widely.^[40,41,42,43] The overall contribution of these various factors in the observed high maternal mortality remain unclear.^[44, 45] Furthermore, the presence

of pre-delivery complications can considerably increase the risk of mortality.^[46]

Adverse fetal outcomes observed involved still births, low birth weight, low APGAR score and early neonatal death. These adverse fetal outcomes have been reported, particularly where there is superimposed pre-eclampsia and excessive reduction in blood pressure.^[47] There is also evidence that steep fall in blood pressure is associated with low birth weight and high level of perinatal mortality.^[47, 48] The steep fall in both systolic and diastolic blood pressure observed coupled with maternal anaemia may be contributory factors to high level of fetal adverse outcomes.

Antihypertensives most prescribed included Methyldopa and Nifedipine monotherapy; however the prescription rate of equally safe Labetolol was relatively low.^[49,50] The efficacy of antihypertensive drugs is well established, however their impact following fetal exposure in-utero remain unclear.^[51,52] The combination of commonly prescribed antihypertensives with Bendrofluthiazide was strongly associated with stillbirths. While thiazide diuretics are not absolutely contraindicated in pregnancy, their use as add on drug may cause a bigger fall in blood pressure, further reducing placental blood flow and consequently increase the risk of fetal death.

Gestational hypertension and its associated risks remain a common clinical challenge among all women of reproductive age, so appropriate selection of drugs and effective management of complications remain the cornerstone of reducing unnecessary mortality.

CONCLUSION

Maternal and foetal mortality was unacceptably high and aggressive antihypertensive therapy management may be one of the many contributory factors. The use of thiazide based therapies was strongly associated with adverse fetal outcomes, so utmost care should be taken in all drug therapies.

Author's contributions

Author¹—concept, study design, literature review, data analysis, draft manuscript, manuscript editing.

Author²–Data collection and analysis, literature review, final manuscript revision.

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