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A comparative analysis of antihypertensive drugs for hypertension and gestational hypertension among women in tertiary care hospitals in Lahore, Pakistan

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Abstract

Hypertension, characterized by persistently elevated blood pressure, poses severe risks, such as heart damage, artery hardening, and reduced blood and oxygen flow to the heart, which can also lead to kidney damage and stroke. Antihypertensive therapy for pregnant women differs from that for nonpregnant women because most antihypertensive medications used for nonpregnant hypertensive women are contraindicated for pregnant hypertensive patients. This study aimed to compare therapeutic regimens for treating hypertension between pregnant and nonpregnant women in various healthcare facilities. This cross-sectional study was conducted at several tertiary care hospitals in Lahore, Pakistan, recruiting 500 pregnant or nonpregnant female patients aged 18-55 years with hypertension. The data were collected through structured interviews and medical records reviews. Descriptive statistics and chi-square tests were used to analyze the data, with significance set at $p < 0.05$. A significant difference in area of residence was observed, with 83.2% of nonpregnant women residing in urban areas compared to 52.4% of pregnant women residing in urban areas. A systolic blood pressure between 120 and 139 mmHg was observed in 82.8% of pregnant women, compared to 51.2% of nonpregnant women ($p < 0.001$). Diastolic blood pressure between 80-99 mmHg was observed in 84.4% of pregnant women and 76.8% of nonpregnant women ($p < 0.001$). CVDs were more prevalent among nonpregnant women (38.8%), while anemia was more common in pregnant women (25.6%). Pregnant women were primarily prescribed methyldopa (58%), labetalol (56%), and amlodipine (40.4%), whereas nonpregnant women were more frequently prescribed valsartan (39.2%), metoprolol (28.8%), nebivolol (28%), and a combination of furosemide and spironolactone (24%). This study highlighted significant differences in comorbid conditions and antihypertensive treatment regimens between pregnant and nonpregnant women, emphasizing the need for tailored hypertension management approaches. Moreover, safer antihypertensive agents were prescribed to both groups, considering the Food and Drug Administration (FDA) drug categories and the observed comorbid conditions.

Keywords

Hypertension management; Pregnancy-related hypertension; Maternal hypertension; Gestational hypertension; Hypertension; Antihypertensive medication; Antihypertensive drugs

1. Introduction

Hypertension, characterized by persistently elevated blood pressure, poses severe risks, such as heart damage, artery hardening, and reduced blood and oxygen flow to the heart [1]. It can also cause kidney damage and stroke [2]. Pregnancy-related hypertension leads to significant hospitalization, morbidity, and mortality in mothers and fetuses, ac-

counting for more than 50,000 maternal deaths annually, and is the second most common cause of antenatal and postnatal death in developed countries [3].

Globally, 26% of the population has hypertension [4]. According to National Health and Nutrition Examination Survey (NHANES) data, women have lower hypertension control rates than men; 68% of hypertensive women are aware of their condition, while 67% of hypertensive men are aware of their condition, and 58% of hypertensive women take medication, while 52% of men do so [5]. The prevalence of hypertension is greater than that in other regions [6]. Approximately 7.7% of reproductive-aged women have hypertension, and 10% of pregnancies are complicated by this condition [7,8]. Chronic hypertension affects 1% to 2% of pregnancies, gestational hypertension affects 5% to 6%, and preeclampsia affects 2% to 4% of pregnancies [9]. In Pakistan, the prevalence of hypertension was 23% in urban areas and 18% in rural areas, with a prevalence of 14.5% among women [10,11].

Hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension, preeclampsia and eclampsia, and preeclampsia superimposed on chronic hypertension [12]. Gestational hypertension, which appears after 20 weeks of pregnancy, typically resolves after delivery [6]. Risk factors include preexisting cardiovascular, renal, or autoimmune disease; a history of hypertensive disorders in previous pregnancies; high BMI; diabetes; renal disease; chronic hypertension; maternal age over 40 years; and a family history of hypertension [13]. Preeclampsia, characterized by high blood pressure after 20 weeks of pregnancy and proteinuria or organ dysfunction, affects 2% to 5% of pregnancies [14]. Severe consequences include eclampsia with seizures and HELLP syndrome with significant maternal and fetal morbidity [13].

The main goal of managing hypertension is to reduce blood pressure and prevent cardiovascular complications. Therapeutic goals include achieving systolic BP < 140 mmHg and diastolic BP < 90 mmHg or < 130/80 mmHg for patients with diabetes and chronic kidney disease [13,14]. First-line agents typically consist of low-dose thiazide diuretics, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and angiotensin-converting enzyme (ACE) inhibitors. During pregnancy, methyldopa is preferred due to its safety profile, with labetalol and nifedipine as second-line options. ACE inhibitors and ARBs are contraindicated during pregnancy because of the risks of fetal renal damage and toxicity [15,16].

Treatment regimens for gestational hypertension should be beneficial and safe for both mothers and fetuses. Methyldopa and labetalol are considered safe, while ACE inhibitors and ARBs are contraindicated due to teratogenic effects [17,18,19]. There is a dearth of literature comparing therapeutic regimens for pregnancy-related and nonpregnancy-related hypertension. Therefore, this study aimed to address this gap by comparing regimens used for treating pregnant women with those used for treating nonpregnancy-related hypertension among women in various healthcare facilities.

2. Materials and methods

2.1. Study design and approval

This cross-sectional study was approved by the Research and Ethics Committee of Gulab Devi Institute of Pharmacy (No. REC/GDIP/22/DCP-06). The research was conducted at several tertiary care teaching hospitals, including Jinnah Hospital, General Hospital, Mayo Hospital, and Gulab Devi Hospital, specifically within the cardiology, obstetrics and gynecology, and diabetes outpatient departments and wards. The data were collected over two months, from May 2022 to June 2022.

2.2. Study population

The study included female patients aged between 18 and 55 years who had hypertension, either pregnant or nonpregnant, and who provided informed consent to participate. The inclusion criteria were female patients aged 18-55 years who were either pregnant or nonpregnant and who were diagnosed with hypertension. The exclusion criteria were female patients not taking any antihypertensive medication and those with complicated comorbid conditions such as chronic kidney disease (CKD), liver dysfunction, or hormonal imbalances.

2.3. Sample size and sampling method

The sample size was calculated using the Raosoft calculator, with an age-standardized prevalence of hypertension (i.e., 16.4%) among Punjabi women, a 5% margin of error, and a confidence interval of 95% [20]. The calculated sample size was 209, which was increased to 500 to enhance the study's robustness. Participants were selected using a convenient sampling method. We collected a proportionate sample of 250 participants for each category: pregnant women with hypertension and nonpregnant women with hypertension.

2.4. Data collection

The data were collected from the participants through structured interviews and medical records reviews. Demographic information, including age, residence, and body mass index (BMI), was recorded. Medical history, including antihypertensive medication usage, pregnancy status, and trimester of pregnancy, was documented for pregnant participants. Blood pressure measurements, both systolic and diastolic, were taken. Additionally, the prevalence of comorbid conditions such as diabetes, obesity, gastric issues, cardiovascular disease, and anemia was noted.

2.5. Data analysis

Descriptive statistics, including frequencies and percentages, were used to analyze the data. Comparative analysis was performed using the chi-square test to assess differences in therapeutic regimens between pregnant and nonpregnant women with hypertension. Statistical analysis was conducted using SPSS software, with significance set at $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

Table 1 shows the demographics and clinical characteristics of 500 pregnant and nonpregnant women. Pregnant women were predominantly younger, with 81.60% aged 18-30 years, whereas nonpregnant women were mainly older, with higher proportions in the 41-50 and 51-55 age ranges ($p < 0.001$). There was a significant difference in the area of residence, with a larger proportion of nonpregnant women residing in urban areas (83.20%) than pregnant women (52.40%) ($p < 0.001$). In terms of systolic blood pressure, 82.80% of pregnant women had systolic blood pressure readings between 120 and 139 mmHg, compared to 51.20% of nonpregnant women, while 36.40% of nonpregnant women had systolic blood pressure readings between 140 and 159 mmHg, compared to 17.20% of pregnant women ($p < 0.001$). For diastolic blood pressure, 84.40% of pregnant women had diastolic blood pressure readings between 80 and 99 mmHg, whereas 76.80%

of nonpregnant women had diastolic blood pressure readings between 80 and 99 mmHg ($p < 0.001$).

Table 1. Demographics and clinical characteristics of the study participants (n = 500).

Demographic and Clinical Characteristics		Pregnancy Status		Degree of Freedom	Pearson Chi-Square	*p* Value [*, **]
		Nonpregnant (N = 250)	Pregnant (N = 250)			
		Frequency (%)	Frequency (%)			
Age (years)	Below 18	0 (0.00)	0 (0.00)	3	386.52	< 0.001 **
	18 – 30	5 (2.00)	204 (81.60)			
	31 – 40	48 (19.20)	46 (18.40)			
	41 – 50	123 (49.20)	0 (0.00)			
	51 – 55	74 (29.60)	0 (0.00)			
Area of residence	Urban	208 (83.20)	131 (52.40)	1	54.32	< 0.001 **
	Rural	42 (16.80)	119 (47.60)			
BMI	Less than 18	0 (0.00)	0 (0.00)	2	54.64	< 0.001 **
	18 – 24.99	54 (21.60)	133 (53.20)			
	25 – 29.99	128 (51.20)	84 (33.60)			
	Above 30	68 (27.20)	33 (12.20)			
Trimester (n = 250)	First	-	0 (0.00)	2	500.00	< 0.001 **
	Second	-	135 (54.00)			
	Third	-	115 (46.00)			
Systolic blood pressure (mmHg)	Less than 120	9 (3.60)	0 (0.00)	4	66.82	< 0.001 **
	120 – 139	128 (51.20)	207 (82.80)			
	140 – 159	91 (36.40)	43 (17.20)			
	160 – 179	16 (6.40)	0 (0.00)			
	Above 179	6 (2.40)	0 (0.00)			
Diastolic blood pressure (mmHg)	Less than 80	11 (4.40)	0 (0.00)	3	17.95	< 0.001 **
	80 – 99	192 (76.80)	211 (84.40)			
	100 – 119	41 (16.40)	39 (15.60)			
	120 – 140	6 (2.40)	0 (0.00)			

[*] The *p* values were calculated using the chi-square test to compare the distribution of each medication between the pregnant and nonpregnant groups. [**] A *p* value of less than 0.05 indicates a statistically significant difference in the distribution of the medication between the two groups.

3.2. Comorbid conditions of the study participants

Table 2 presents the comorbid status of the study participants. CVD was more common among nonpregnant participants (38.80%) than among pregnant participants (1.20%). In contrast, anemia was observed only in the pregnant group, with 25.60% affected. Compared with nonpregnant participants, pregnant participants also had greater frequencies of no comorbid conditions (10.00%) and gastric issues (11.60%) (4.00% and 2.80%, respectively). Diabetes was present in 10.00% of both groups, while obesity was more common in pregnant participants (6.00%) than in nonpregnant participants (2.00%). Complex comorbidities, such as diabetes combined with gastric issues, were more frequent in pregnant participants (10.40%) than in nonpregnant participants (4.40%). Additionally, pregnant participants exhibited significant incidences of combinations involving anemia, diabetes, and obesity (10.80%), which were absent in the nonpregnant group.

Table 2. Comorbid status of the study participants (n = 500).

Comorbid Conditions	Pregnancy Status	
	Nonpregnant (N = 250)	Pregnant (N = 250)
	Frequency (%)	Frequency (%)
No comorbid condition	10 (4.00)	25 (10.00)
Diabetes	20 (8.00)	25 (10.00)
Obesity	5 (2.00)	15 (6.00)
Gastric issues	7 (2.80)	29 (11.60)
Cardiovascular disease (CVD)	97 (38.80)	3 (1.20)
Diabetes and obesity	14 (5.60)	2 (0.80)
Diabetes and gastric issues	11 (4.40)	26 (10.40)
CVD and diabetes	31 (12.40)	-
CVD and gastric issues	6 (2.40)	1 (0.40)
CVD, diabetes, and obesity	20 (8.00)	-
CVD, diabetes, and gastric issues	4 (1.60)	-
CVD, diabetes, obesity, and gastric issues	7 (2.8)	-
Anemia	-	64 (25.60)
Anemia and diabetes	-	19 (7.60)
Anemia, diabetes, and obesity	-	27 (10.80)
CVD and obesity	11 (4.40)	-
Other	7 (2.80)	14 (5.60)

3.3. Comparison of drugs

Table 3 presents a comparative analysis of antihypertensive drug prescriptions among pregnant and nonpregnant women. Methyldopa, an alpha-2 agonist, was prescribed exclusively to pregnant participants (58.00%, $p < 0.001$). Diuretics had distinct effects: furosemide was given to 24.80% of pregnant participants and 0.64% of nonpregnant participants, while a combination of furosemide and spironolactone was prescribed to 24.00% of nonpregnant participants ($p = 0.011$). Selective beta-blockers, such as metoprolol (28.80%) and nebivolol (28.00%), were prescribed only to nonpregnant participants ($p < 0.001$), and bisoprolol was also more commonly prescribed to nonpregnant participants (13.20%) than to pregnant participants (3.20%).

There was a significant difference in the use of nonselective beta blockers: labetalol was prescribed to 56.00% of pregnant participants and to none of the non-pregnant participants ($p < 0.001$). Angiotensin II receptor blockers such as valsartan (39.20%) and losartan (20.00%) were prescribed only to nonpregnant participants ($p < 0.001$). Angiotensin-converting enzyme inhibitors, such as lisinopril (4.80%) and ramipril (2.40%), were exclusive to nonpregnant participants ($p < 0.001$).

Calcium channel blockers had a more balanced distribution, with amlodipine prescribed to 40.40% of pregnant participants and 34.00% of nonpregnant participants ($p = 0.032$), while nifedipine was only prescribed to pregnant participants (10.00%). Direct vasodilators such as nitrates were given exclusively to nonpregnant participants (21.60%), whereas hydralazine was more common in pregnant participants (8.40%) than in nonpregnant participants (0.40%, $p < 0.001$).

Table 3. Comparative analysis of antihypertensive drug classes and active ingredients prescribed among study participants.

Name of Active Ingredient Prescribed	Name of Medicine	N	Pregnancy Status		*p* Value [**, ***]
			Pregnant (N = 250)	Non-Pregnant (N = 250)	
Alpha-2 agonists	Methyldopa	145	145 (58.00)	0 (0.00)	< 0.001 [***]
Diuretics	Furosemide and spironolactone	60	0 (0.00)	60 (24.00)	0.011 [***]
	Hydrochlorothiazide	19	0 (0.00)	19 (7.60)	
	Amiloride and hydrochlorothiazide	4	0 (0.00)	4 (1.60)	
	Furosemide	62	62 (24.80)	1 (0.64)	
	Spironolactone	3	0 (0.00)	3 (1.20)	
Selective beta-blockers	Metoprolol	72	0 (0.00)	72 (28.80)	< 0.001 [***]
	Nebivolol	70	0 (0.00)	70 (28.00)	
	Bisoprolol	41	8 (3.20)	33 (13.20)	
	Atenolol	1	0 (0.00)	1 (0.40)	
Nonselective beta-blockers	Carvedilol	2	0 (0.00)	2 (0.80)	< 0.001 [***]
	Nadolol	1	0 (0.00)	1 (0.40)	
	Labetalol	140	140 (56.00)	0 (0.00)	
Angiotensin II receptor blockers	Valsartan	98	0 (0.00)	98 (39.20)	< 0.001 [***]
	Losartan	50	0 (0.00)	50 (20.00)	
	Telmisartan	14	0 (0.00)	14 (5.60)	
	Irbesartan	1	0 (0.00)	1 (0.40)	
Angiotensin-converting enzyme inhibitors	Lisinopril	12	0 (0.00)	12 (4.80)	< 0.001 [***]
	Ramipril	6	0 (0.00)	6 (2.40)	
	Sacubitril	1	0 (0.00)	1 (0.40)	
Calcium channel blockers	Amlodipine	186	101 (40.40)	85 (34.00)	0.032 [***]
	Diltiazem	2	0 (0.00)	2 (0.80)	
	Nifedipine	25	25 (10.00)	0 (0.00)	
Direct vasodilators	Nitrates	54	0 (0.00)	54 (21.60)	< 0.001 [***]
	Hydralazine	22	21 (8.40)	1 (0.40)	

[*] The frequency and percentage indicate the number of patients within each group (pregnant and non-pregnant) taking the specified medication out of the total 250 patients in each group. [**] The *p* values were calculated using the chi-square test to compare the distribution of each medication between pregnant and nonpregnant groups. [***] A *p* value of less than 0.05 indicates a statistically significant difference in the distribution of the medication between the two groups.

4. Discussion

The current study highlighted notable demographic and clinical differences between pregnant and nonpregnant women. There were significant differences in the area of residence, with a larger proportion of nonpregnant women living in urban areas. BMI variations were observed, with nonpregnant women having higher BMI than pregnant women. Blood pressure profiles also differed, with pregnant women generally having lower systolic and diastolic blood pressure readings than nonpregnant women. Furthermore, CVDs were more common among nonpregnant women, while anemia was more common in pregnant women. Medication prescriptions varied significantly between the groups, with methyldopa, labetalol, and amlodipine being commonly prescribed to pregnant women, whereas nonpregnant women were more frequently prescribed valsartan, amlodipine, metoprolol, nebivolol, and a combination of furosemide and spironolactone.

Hypertension is a leading cause of various comorbid conditions, such as diabetes, CVD, and obesity, particularly in nonpregnant women [21,22]. Studies have shown that individuals with hypertension often have insulin resistance and are more likely to de-

velop diabetes. Gestational diabetes mellitus (GDM) is a common complication of pregnancy, and women with GDM are more likely to be obese [23]. Both insulin resistance and insulin secretion deficits have been associated with an increased risk of hypertension [24]. Our findings regarding the prevalence of diabetes and cardiovascular diseases among women align with previous studies highlighting a significant percentage of pregnant women with hypertension and cardiovascular conditions [25,26]. The comorbidities among pregnant women can be attributed to altered physiology, age, and nongestational diabetes, making hypertension management more challenging [27,28]. Moreover, poor access to resources and lack of quality healthcare further complicate the diagnosis and management of pregnancy-related comorbidities [29].

Medications that act on centrally located alpha-2 adrenoceptors, such as methyldopa, are commonly used to treat primary hypertension in difficult-to-treat patients. Methyldopa is primarily used for pregnancy-related hypertension. However, evidence for the effectiveness of centrally acting medications is limited, and side effects are common [30]. Our findings suggest that a significant percentage of pregnant women with hypertension use methyldopa, classified as a pregnancy Category B medication [31]. The National High Blood Pressure Education Program (NHBPEP) and the Food and Drug Administration (FDA) recommend methyldopa as a first-line agent for pregnancy-related hypertension [15]. In nonpregnant hypertensive women, these drugs are less common due to the availability of more effective medications that target the renin-angiotensin system (RAS) pathway.

Diuretics are the third most commonly used pharmaceutical agents for treating hypertension [32]. Our study revealed that furosemide, either as a single agent or in combination, was prescribed to a significant proportion of women to reduce blood pressure in hypertensive females. Furosemide is not teratogenic and is categorized as pregnancy category C. In nonpregnant hypertensive females, combinations of diuretics, such as furosemide and spironolactone, are mainly used to treat edema or fluid excess caused by pulmonary hypertension [33]. A combination of amiloride and hydrochlorothiazide was used for a small number of females. Additionally, hydrochlorothiazide was prescribed as a single agent to a limited number of nonpregnant females. These agents efficiently reduce excess fluid levels, lower blood pressure, and lessen the risk of future heart attack, stroke, or angina [34,35].

The study included a substantial number of participants who visited various healthcare facilities, allowing a robust comparison between pregnant and nonpregnant women regarding their hypertension status, comorbidities, treatment regimens, and prescribed medications. However, the study's limitation lies in not considering the dosage forms, prescribed dosages, or frequency of usage. Future studies may fill this research gap by incorporating these variables to provide a more comprehensive understanding of hypertension management in pregnant and nonpregnant women.

5. Conclusions

The study revealed that pregnant women commonly had anemia and hypertension, while nonpregnant women were more likely to suffer from cardiovascular diseases and hypertension. Pregnant women were primarily prescribed alpha-2 agonists and nonselective beta-blockers, with methyldopa and labetalol being the preferred drugs. Nonpregnant women were more frequently prescribed diuretics, with furosemide and spironolactone being common choices. These findings highlight the distinct differences in comorbid conditions and treatment regimens between pregnant and nonpregnant women, emphasizing the need for tailored hypertension management approaches for these populations.

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Consent to participate: Written informed consent was obtained from all participants prior to data collection.

Data availability: The data supporting this study's findings are available from the corresponding author, Iram, upon reasonable request.

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