Antihypertensive Drugs and Perinatal Outcomes in Hypertensive Women Attending a Specialized Tertiary Hospital

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Received: 21 April 2021
Accepted: 15 August 2021

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DOI 10.5001/omj.2022.43

Abstract

Objectives: This study aimed to identify the most commonly used antihypertensive medications in pregnant women and to determine the impact of these medications on perinatal (maternal and fetal) outcomes.

Methods: The medical records of 484 hypertensive pregnant women attended a tertiary university hospital during the study period were retrospectively evaluated for eligibility. Singleton pregnancies of women who were on antihypertensive medications and who delivered in the hospital were included in the study.

Results: Two hundred and ten women (mean age 32.4±5.6 years and mean BMI 34±8.1 Kg/m^2) were eligible. The most prevalent subtype of hypertension was preeclampsia (41.4%). Low birth weight (LBW), preterm delivery (PTD), intrauterine growth restriction (IUGR), small for gestational age

(SGA), respiratory distress syndrome and neonatal care unit admissions were significantly higher in women with preeclampsia than in the women with other types of hypertension. Labetalol was the most common prescribed antihypertensive drug. There were 101 (48.1%) women on combined therapy. Low birth weight, preterm delivery, IUGR, SGA, respiratory distress syndrome, absent end diastolic flow, neonatal care unit admission, preeclampsia and high dependency unit admissions of mothers were significantly higher in the women who received combined therapy.

Conclusion: This study showed that labetalol was the most commonly prescribed antihypertensive drug in this cohort and women on combined antihypertensive medications had significantly higher maternal and fetal complications. Larger prospective study including hypertensive women with or without antihypertensive medications in more than one center is needed to evaluate the affect of antihypertensive medications on perinatal outcomes.

Keywords: Preeclampsia; Antihypertensive medications, maternal and fatal outcomes

Introduction:

Hypertension is one of the common leading causes of morbidity and mortality and it is an important risk factor for cardiovascular and chronic kidney diseases. (1,2) Hypertension in pregnancy has been associated with higher risk for developing cardiovascular diseases later in life. (3,4) This might be due to the irreversible vascular and metabolic changes that may persist after the complicated pregnancy. Therefore, managing hypertension in pregnancy does not only improve the immediate affected pregnancy, but also improves the long-term maternal cardiovascular health. (4)

In pregnancy, hypertension is considered as the second most common cause of direct maternal death and causes complications in approximately 7% of pregnancies; (5,6) 3% of whom have preexisting

hypertension prior to pregnancy and 4% develop hypertension during the pregnancy, the latter increasing the risk of developing preeclampsia. (5)

Although the use of medications during pregnancy is generally avoided, normalizing blood pressure in pregnancy is crucial due to the major adverse perinatal outcomes that hypertension in pregnancy can cause. (5) Studies have shown that the use of methyldopa and labetalol in controlling blood pressure in pregnancy significantly reduces the incidence of preterm deliveries (PTD), small for gestational age (SGA) and admissions to neonatal unit. (7) However, studies have shown that Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) are teratogenic and linked to major fetal malformations. Therefore, their use in pregnancy is contraindicated. (5) In the management of gestational hypertension and preeclampsia, it is recommended to use labetalol as first line therapy but intravenous hydralazine and oral nifedipine can also be used. Moreover, methyldopa is recommended as first line therapy in managing pre-existing hypertension in pregnancy in addition to labetalol, nifedipine and a diuretic. (8) However, some studies have linked these antihypertensive medications used in pregnancy to potential adverse outcomes in the child such as, decreased birth weight, cognitive development delay, childhood depression, (9) higher risk for developing asthma and sleeping disorders during childhood, (6) neonatal seizures and hematological disorders. (5) Nonetheless, there is still no strong evidence supporting and confirming these associations and the potential adverse effects of these antihypertensive drugs on pregnancy and the newborn are still debatable. (5,6,9)

Despite all these guidelines and studies, the prescribing patterns for control of blood pressure during pregnancy is variable in each institution. The aim of our study was to determine the prescribing patterns of antihypertensive drugs during pregnancy in a tertiary university hospital, and to study the impact of these drugs on maternal and fetal outcomes.

Methods:

This was a retrospective study conducted at Sultan Qaboos University Hospital (SQUH) in Muscat, Oman. All pregnant women who attended SQUH during the period from January 2015 to September 2018 were screened for eligibility for the study by reviewing the electronic medical records. The inclusion criteria included women who had singleton pregnancy, on antihypertensive medications and who delivered in the hospital. Women with multiple pregnancy, molar pregnancy, not on antihypertensive medications or who delivered elsewhere were excluded from the study.

The electronic medical records of the eligible patients were reviewed and data regarding antihypertensive drugs during pregnancy, type of hypertension and the perinatal outcomes, fetal and maternal outcomes were collected.

Patients were diagnosed according to the American college of obstetricians and gynecologists guidelines. Gestational hypertension is defined as new-onset hypertension (blood pressure ≥ 140/90 mmHg) after 20 weeks of gestation. Preeclampsia is new-onset gestational hypertension accompanied by proteinuria. Chronic hypertension (pre-existing hypertension) is hypertension detected before 20 weeks of gestation. Chronic hypertension with superimposed preeclampsia is chronic hypertension with proteinuria. Eclampsia is preeclampsia combined with seizures (10).

Descriptive statistics were used to obtain frequencies, means, medians, standard deviations, minimum and maximum of the different variables. The values of the continuous variables were described as mean ± standard deviation (SD). The associations of the categorized variables were assessed with the Chi-square test. One-way ANOVA and post hoc analysis were used to compare means of continuous variables and assess their associations with categorized variables. P-values < 0.05 were considered significant for all used statistical tests. IBM SPSS statistics software version 23 were used for the analysis.

The ethical approval was granted from the Medical Research Ethics committee, College of Medicine & Health Sciences, Sultan Qaboos University.

Results

The case notes of 484 women were reviewed to assess eligibility for the study according to the inclusion and exclusion criteria. Two hundred and seventy-four women were excluded from the study due to one or more of the exclusion criteria.

The final analysis included 210 women. The mean age of the women was 32.4 ± 5.6 years and the mean body mass index (BMI) was 34 ± 8.1 Kg/m^2. The gravidity ranged from 1 to 15 with a median of 3 and the parity ranged from 0 to 8 with a median of 2. The gestational age at birth ranged from 23 to 42 with a median of 37 weeks ***(Table 1).*** Diabetes mellitus (DM) was the most common associated comorbidity in the studied population, 82 (39%) of the women was diagnosed with DM, 58 women with gestational diabetes and 24 (11.4%) women with pre-existing diabetes. This was followed by fibroids (5.7%) and hypothyroidism (4.7%).

The most common type of hypertension was pre-eclampsia (41.4%) followed by chronic hypertension (22.4%), gestational hypertension (20.5%) and chronic hypertension with superimposed pre-eclampsia (15.7%). More than half of the women, 120 (57.1%) had developed pre-eclampsia. Only 27 (12.9%) women had normal spontaneous vaginal delivery while 183 (87.1%) women required an intervention. The interventions included medial induction of labor in 91 (43.3%) patients while 92 (43.8%) required caesarean section.

Pre-eclampsia was the most common maternal complication in the studied population (120 (57.1%) women) followed by postpartum hemorrhage (22 (10.5%) women). Two women developed eclampsia. Nearly half of the women (47.6%) required admission to the high dependency unit during pregnancy or post-delivery. ***(Figure 1)***

Fetal outcomes

There were 5 cases of intrauterine fetal deaths with 205 live births. The mean of the Apgar score at 1 minute was 8±1.7 and at 5 minutes was 9±1.1. The mean birth weight was 2.47±0.8 Kg.

The fetal outcomes are represented in ***figure 2***. The most common fetal outcome was low birth weight (LBW) followed by PTD, respiratory distress syndrome, Intrauterine growth retardation (IUGR) and SGA respectively. Twelve newborns had a congenital defect including patent ductus arteriosus (n=6), undescended testes (n=2), hypospadias (n=2), atrial septal defect (n=1) and cleft lips (n=1). Eighty-seven newborns required admission to neonatal care unit and there was one fetal mortality immediately after birth.

Types of hypertension and associated perinatal outcomes

Table 2 represent the risk factors, fetal and maternal outcomes in the studied population according to the type of hypertensive disorder. Women with preeclampsia were younger and had lower BMI compared to women with other types of hypertension ($P < 0.05$). Diabetes Mellitus was more frequent in women with chronic hypertension than other types of hypertensive disorders ($P < 0.05\%$).

LBW, PTD, IUGR, respiratory distress syndrome and neonatal care unit admissions were significantly higher in women with preeclampsia than in women with other types of hypertension (p-value <0.05). The prevalence of SGA and fetal bradycardia were more among women with preeclampsia. However,

it was not statistically significant. The other fetal outcomes did not differ significantly between types of hypertension. There was a significant association between the type of hypertension and the admissions to the neonatal care unit for the newborns and to the high dependency unit (HDU) for the mothers (p-value <0.001). The other maternal outcomes were not significantly different between the types of hypertension.

Antihypertensive medications and the associated perinatal outcomes

Labetalol was the most common prescribed antihypertensive medication in the studied population, 170 (81%) of the women received labetalol, followed by methyldopa (74, 35.2%), hydralazine (43, 20.5%) and nifedipine (15, 7.1%). Magnesium sulphate was used in 77 (36.7%) women in order to prevent eclampsia. There were 101 (48.1%) women on combined therapy. Labetalol was prescribed as a single therapy for 71 (33.8%) women and methyldopa alone for 37 (17.6%) women and one woman had hydralazine alone.

Newborns of the women who received labetalol alone required admission to neonatal care unit more than those who were on methyldopa alone (31.1% vs. 12.2%, p-value = 0.021). As expected, fetal bradycardia was higher in fetuses of women who received labetalol. However, it was not statistically different (p-value = 0.079). The other fetal and maternal outcomes were not significantly different between the two antihypertensive medications. ***(Table 3)***

Low birth weight, PTD, IUGR, SGA, respiratory distress syndrome, absent end diastolic flow, congenital defects and neonatal care unit admissions were significantly more prevalent in newborns of women who received combination therapy than newborns of women who were on a single medication (p-value <0.05). Preeclampsia, placental abruption and HDU admissions were

significantly more prevalent in women who were on combination therapy than the women who received a single medication only (p-value <0.05). The other maternal outcomes did not differ significantly with the used treatment, single or combination. ***(Table 4)***

Discussion

Hypertension in pregnancy has been associated with perinatal, fetal and maternal, adverse outcomes. (1) The outcomes found in our study are partially in line with a previously reported retrospective study from Saudi Arabia, which found that preeclampsia was the most common hypertensive disorder in pregnancy (54.9%). However, it was followed by gestational hypertension (29.5%), chronic hypertension with superimposed preeclampsia (4%) and chronic hypertension (3.6%). (11) An earlier study from Canada found that the most prevalent hypertensive disorder in pregnancy among their studied population was gestational hypertension (44.4%) followed by chronic hypertension (23.6%), preeclampsia (25.7%) and chronic hypertension with superimposed preeclampsia (6.4%). (12)

The most common fetal outcomes in our study were LBW, PTD, IUGR and SGA which is consistent with what had been reported recently in a systemic review (5) and in another study from Ghana. (13) Preeclampsia and postpartum hemorrhage were the most common maternal outcomes in our study and that is in line with other studies. (7)

Most of the women in our study were on combination therapy (48.1%) which is similar to the study from Saudi Arabia (62.5%). (11) However, in our study, labetalol (33.8%) was the antihypertensive agent most commonly prescribed on its own followed by methyldopa (17.6%), while in Saudi Arabia

methyldopa was most commonly prescribed alone (22.8%) followed by nifedipine (8.5%) and Labetalol (6.3%).

A comparative observational study conducted in India comparing the effects of labetalol and methyldopa on perinatal outcomes showed a non-significantly higher prevalence of IUGR, neonatal care unit admissions, respiratory distress syndrome and SGA in newborns of women who were on methyldopa than newborns of women who were on labetalol. (14) However, as in our study, there was no significant statistical difference in perinatal outcomes except for neonatal care unit admissions that were higher in newborns of women who were on labetalol compared to methyldopa.

Diabetes in pregnancy is known to increase the risk of adverse perinatal outcomes. (15) Although there were significantly more women with diabetes who received methyldopa in our study ($p = 0.038$), this did not translate to higher adverse perinatal outcomes as compared to women on labetalol. Extreme maternal age has also been shown previously to be an independent risk factor for adverse fetal outcomes. (16) However, in our study, there was no significant difference in age between women who received labetalol or methyldopa. Therefore, the difference in the outcomes is unlikely to be attributed to the maternal age or associated diabetes mellitus.

LBW, PTD, IUGR, SGA, respiratory distress syndrome, absent end diastolic flow, congenital defects and neonatal care unit admission were significantly more prevalent in newborns of women who received combination therapy than newborns of women who were given a single medication. Preeclampsia, placental abruption and HDU admissions were significantly more prevalent in women who were on combination therapy than women who received a single medication only. These women

are more likely to have more severe uncontrolled hypertension that required more antihypertensive medications which may led to higher adverse perinatal, maternal and fetal, outcomes. However, this does not exclude the effect of medications that could also have contributed to the increase of the adverse outcomes in these women. Coexisting comorbidities such as diabetes mellitus and maternal age might contribute to higher adverse outcomes however our study showed no significant difference between those who were on single and combined therapy in terms of mean age and DM.

The result of this study and previous similar studies shall enhance the knowledge of the physicians to the perinatal outcomes associated with hypertension and antihypertensive medications and to be more cautious when selecting and using antihypertensive medication in pregnant women. They should be more vigilant to the commonly reported outcomes during the antenatal and postnatal follow up

Conclusion:

Preeclampsia was the most common type of hypertension and labetalol was the most commonly prescribed antihypertensive drug in this cohort of women who received specialized care in a tertiary university hospital. Majority of these patients were on combination therapy and associated with higher fetal and maternal outcome than women on single drug. Our study was conducted in a single specialized center therefore its findings cannot be generalized for women followed with general practitioner. For more robust conclusion, to determine whether these findings are attributed to the severity, chronicity or antihypertensive medication, a further prospective study including groups of normotensive women and hypertensive women with and without medications in more than one specialized and primary health care centers is needed.

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Tables

Table 1 Demographic characteristics of the hypertensive pregnant women in the studied population

Characteristic	Range	Mean ± SD
Age (years)	20-46	32.4 ± 5.6
BMI (Kg/m^2)	19.5-68	34 ± 8.1
SBP (mmHg)	127-235	160.4 ± 18.1
DBP (mmHg)	55-154	93.7 ± 14.8
Gravidity	1-15	4 ± 2.6
Parity	0-8	2 ± 2.0
Gestational Age (weeks)	23-42	36 ± 3.5
Time of diagnosis (weeks)	20-40	33 ± 4.9

SD: Standard deviation; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Table 2 Prevalence of risk factors, fetal and maternal outcomes in the studied population according to the type of hypertensive disorder

	G-HTN	PE	C-HTN	C-HTN + PE	Total	p-value
Risk factors						
Age (years), mean ± SD	32.3 ± 5.5	30.4 ± 5.6	34.1 ± 5.2	35.4 ± 4.3	32.6 ± 5.5	<0.001
BMI (Kg/m^2), mean ± SD	33.5 ± 5.5	31.5 ± 9.5	36.5 ± 7.5	36.4 ± 7.3	34.0 ± 8.1	0.008
Associated DM	13 (30.2%)	26 (29.9%)	28 (59.6%)	15 (45.5%)	82 (39.0%)	0.004
Fetal outcomes						
Low birth weight	9 (21.4%)	46 (55.4%)	10 (21.3%)	17 (51.5%)	82 (40.0%)	<0.001
Preterm delivery	5 (11.6%)	42 (48.8%)	12 (25.5%)	18 (54.5%)	77 (36.8%)	<0.001

IUGR	6 (14.3%)	28 (33.3%)	5 (10.6%)	4 (12.1%)	43 (20.9%)	0.004
SGA	4 (9.5%)	17 (20.2%)	4 (8.5%)	2 (6.1%)	27 (13.1%)	0.088
Hypoglycemia	4 (9.5%)	6 (7.2%)	1 (2.1%)	4 (12.1%)	15 (7.3%)	0.349
Congenital defects	2 (4.8%)	3 (3.6%)	2 (4.3%)	5 (15.2%)	12 (5.9%)	0.100
Seizures	1 (2.4%)	1 (1.2%)	0	0	2 (1.0%)	0.639
RDS	3 (7.1%)	29 (34.9%)	6 (12.8%)	16 (48.5%)	54 (26.3%)	<0.001
Fetal bradycardia	6 (14.3%)	12 (14.5%)	0	4 (12.1%)	22 (10.7%)	0.058
Perinatal depression	1 (2.4%)	2 (2.4%)	2 (4.3%)	2 (6.1%)	7 (3.4%)	0.761
PPROM	3 (7.1%)	2 (2.4%)	3 (6.4%)	0	8 (3.9%)	0.286
Absent end diastolic flow	1 (2.4%)	3 (3.6%)	0	2 (6.1%)	6 (2.9%)	0.433
NNCU admission	7 (16.7%)	46 (55.4%)	15 (31.9%)	19 (57.6%)	87 (42.4%)	<0.001
Maternal outcomes						
Eclamptic seizures	0	1 (1.1%)	0	1 (3.0%)	2 (1.0%)	0.491
Postpartum hemorrhage	6 (14.0%)	4 (4.6%)	7 (14.9%)	5 (15.2%)	22 (10.5%)	0.138
Antepartum bleeding	4 (9.3%)	8 (9.2%)	4 (8.5%)	4 (12.1%)	20 (9.5%)	0.955
Placental abruption	0	4 (4.6%)	1 (2.1%)	1 (3.0%)	6 (2.9%)	0.511
HDU admission	7 (16.3%)	59 (67.8%)	9 (19.1%)	25 (75.8%)	100 (47.6%)	<0.001

G-HTN: gestational hypertension; PE: preeclampsia; C-HTN: chronic hypertension; BMI: body mass index; DM: diabetes mellites; IUGR: intrauterine growth restriction; SGA: small for gestational age; RDS: respiratory distress syndrome; PPROM: preterm premature rupture of membranes NNCU: neonatal care unit; HDU: high dependency unit

Table 3 Prevalence of fetal and maternal outcomes in the studied population according to Labetalol and Methyldopa when prescribed alone

	Labetalol	Methyldopa	Total	p-value

Risk factors				
Age (years), mean ± SD	31.9 ± 5.3	33.4 ± 4.8	32.4 ± 5.2	0.150
Associated DM	22 (31.0%)	19 (51.4%)	41 (38.0%)	0.038
Fetal outcomes				
Low birth weight	19 (28.8%)	8 (19.5%)	27 (25.2%)	0.283
Preterm delivery	7 (10.6%)	8 (19.0%)	15 (13.9%)	0.216
IUGR	11 (16.7%)	5 (12.2%)	16 (15.0%)	0.528
SGA	5 (7.6%)	2 (4.9%)	7 (6.5%)	0.583
Hypoglycemia	5 (7.6%)	1 (2.4%)	6 (5.6%)	0.262
Congenital defects	1 (1.5%)	2 (4.9%)	3 (2.8%)	0.306
Seizures	0	1 (2.4%)	1 (0.9%)	0.202
RDS	6 (9.1%)	3 (7.3%)	9 (8.4%)	0.748
Fetal bradycardia	8 (12.9%)	1 (2.4%)	9 (8.4%)	0.079
Perinatal depression	3 (4.5%)	0	3 (2.8%)	0.166
PPROM	2 (3.0%)	0	2 (1.9%)	0.261
Absent end diastolic flow	0	0	0	
NNCU admission	21 (31.8%)	5 (12.2%)	26 (24.3%)	0.021
Maternal outcomes				
Preeclampsia	33 (50.0%)	7 (16.7%)	40 (37.0%)	<0.001
Eclampsia	0	0	0	
Postpartum hemorrhage	10 (15.2%)	5 (11.9%)	15 (13.9%)	0.634
Antepartum bleeding	7 (10.6%)	5 (11.9%)	12 (11.1%)	0.834
Placental abruption	0	0	0	
HDU admission	16 (24.2%)	5 (11.9%)	21 (19.4%)	0.114

IUGR: intrauterine growth restriction; SGA: small for gestational age; RDS: respiratory distress syndrome; NNCU: neonatal care unit; HDU: high dependency unit

Table 4 Prevalence of fetal and maternal outcomes in the studied population in the women who received single medication and the women who received combination therapy

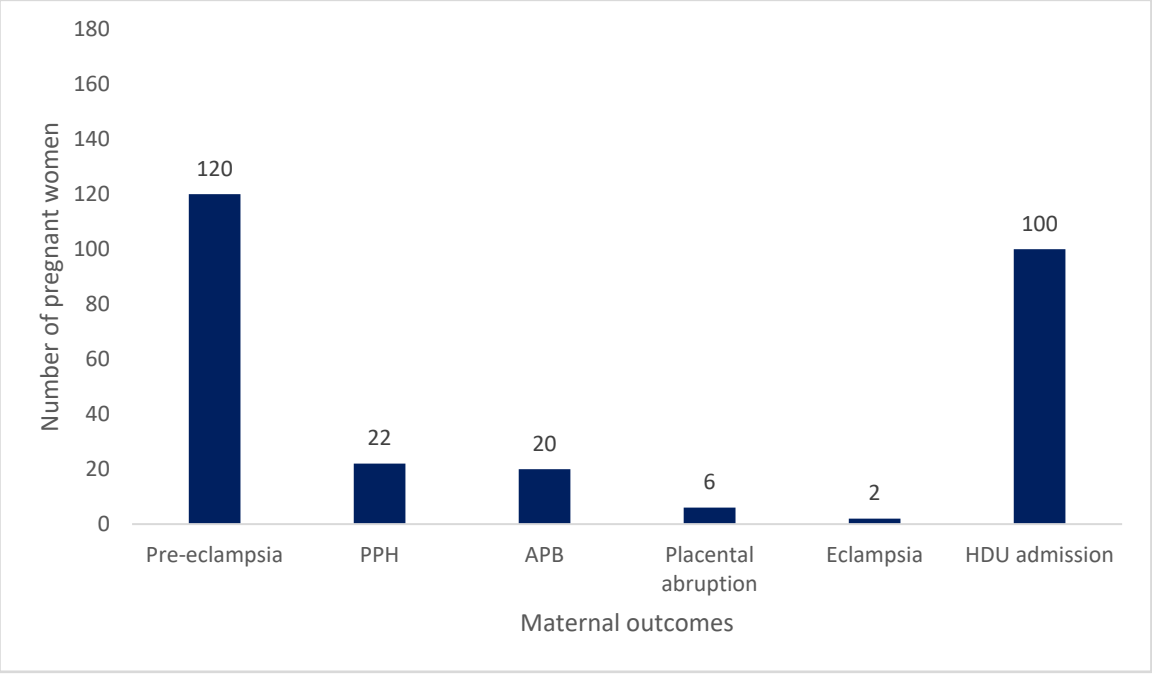
	Single medication	Combination therapy	Total	p-value
Risk factors				
Age (years), mean ± SD	32.4 ± 5.2	32.4 ± 6.1	32.4 ± 5.6	0.952
Associated DM	41 (37.6%)	41 (40.6%)	82 (39.0%)	0.658
Fetal outcomes				
Low birth weight	27 (25.0%)	55 (56.7%)	82 (40.0%)	<0.001
Preterm delivery	15 (13.8%)	62 (62.0%)	77 (36.8%)	<0.001
IUGR	16 (14.8%)	27 (27.6%)	43 (20.9%)	0.025
SGA	7 (6.5%)	20 (20.4%)	27 (13.1%)	0.003
Hypoglycemia	6 (5.6%)	9 (9.3%)	15 (7.3%)	0.307
Congenital defects	3 (2.8%)	9 (9.3%)	12 (5.9%)	0.048
Seizures	1 (0.9%)	1 (1.0%)	2 (1.0%)	0.939
RDS	9 (8.3%)	45 (46.4%)	54 (26.3%)	<0.001
Fetal bradycardia	10 (9.3%)	12 (12.4%)	22 (10.7%)	0.472
Perinatal depression	3 (2.8%)	4 (4.1%)	7 (3.4%)	0.605
PPROM	2 (1.9%)	6 (6.2%)	8 (3.9%)	0.110
Absent end diastolic flow	0	6 (6.2%)	6 (2.9%)	0.009
NNCU admission	26 (24.1%)	61 (62.9%)	87 (42.4%)	<0.001
Maternal outcomes				
Preeclampsia	40 (36.7%)	80 (79.2%)	120 (57.1%)	<0.001
Eclampsia	0	2 (2.0%)	2 (1.0%)	0.140
Postpartum hemorrhage	15 (13.8%)	7 (6.9%)	22 (10.5%)	0.106

Antepartum bleeding	13 (11.9%)	7 (6.9%)	20 (9.5%)	0.218
Placental abruption	0	6 (5.9%)	6 (2.9%)	0.010
HDU admission	22 (20.2%)	78 (77.2%)	100 (47.6%)	<0.001

IUGR: intrauterine growth restriction; SGA: small for gestational age; RDS: respiratory distress syndrome; NNCU: neonatal care unit; HDU: high dependency unit

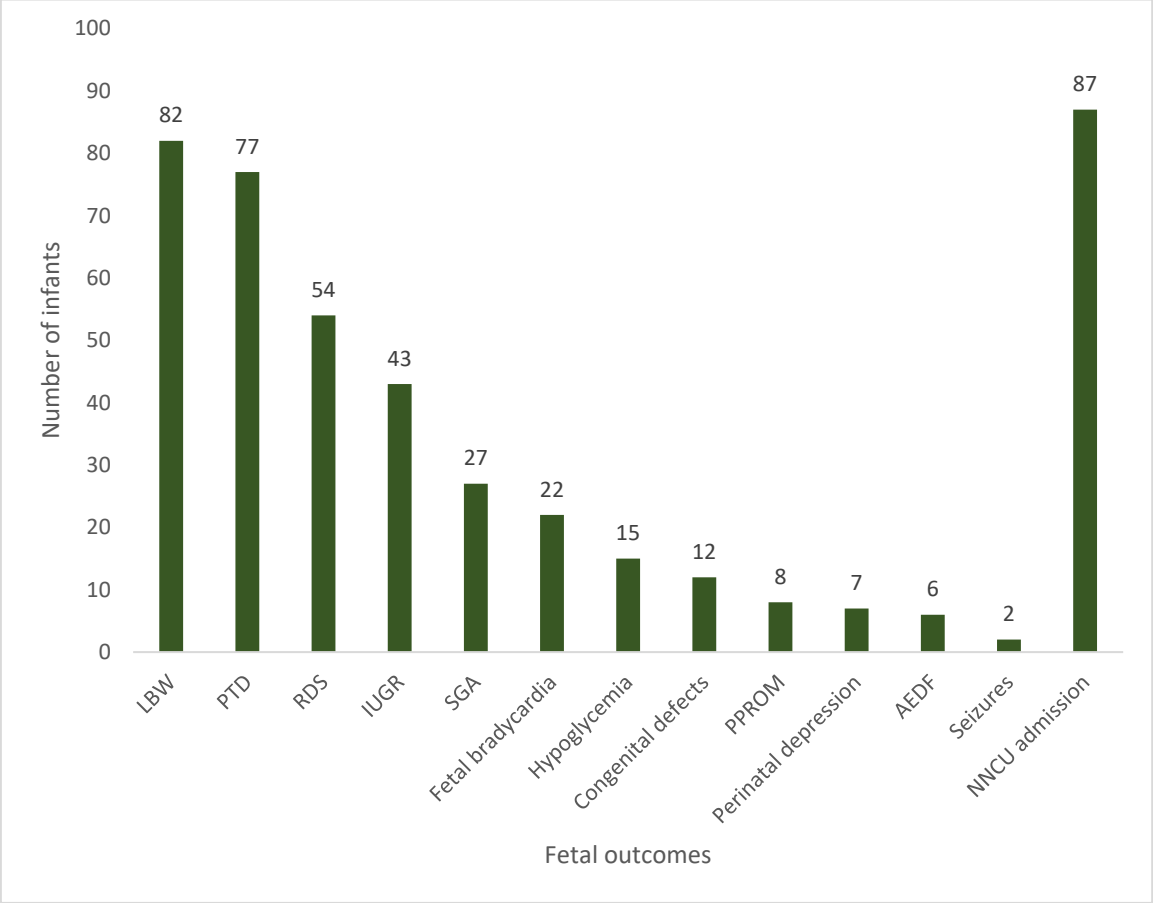
Figures

Figure 1 Maternal outcomes of the hypertensive pregnant women in the studied population



PPH: postpartum hemorrhage; APB: antepartum bleeding; HDU admission: high dependency unit admission

Figure 2 Fetal outcomes of the infants of the hypertensive pregnant women in the studied population



LBW: low birth weight; PTD: preterm delivery; RDS: respiratory distress syndrome; IUGR: intrauterine growth restriction; SGA: small for gestational age; PPROM: preterm

premature rupture of membranes; AEDF: absent end diastolic flow; NNCU admission: Neonatal care unit admission.