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Quick Response Code:

Website: www.pogsjournal.org

DOI: 10.4103/pjog.pjog_32_23

Determining the risk of gestational hypertension, preeclampsia, and adverse perinatal outcomes in patients with antenatal lower threshold blood pressure elevations: A retrospective cohort study

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Abstract:

BACKGROUND: Diagnosing hypertensive disorders in pregnancy utilizes systolic blood pressure (BP) of >140 mmHg and/or diastolic of >90 mmHg. However, since 2017, the American College of Cardiology and the American Heart Association (ACC/AHA) have been endorsing lower BP thresholds for diagnosing hypertension.

OBJECTIVES: This study determines if antenatal lower threshold BP elevations under elevated BP and Stage 1 hypertension from ACC/AHA show an increased risk of gestational hypertension, preeclampsia, and adverse perinatal outcomes.

MATERIALS AND METHODS: This retrospective cohort study included service patients with prenatal consultations and deliveries at a private tertiary-level hospital from February 2016 to 2020. Antenatal BP measurements, categorized into "normal," "elevated BP," and "Stage 1 hypertension" under ACC/AHA classifications, had crude and adjusted relative risks (aRRs) and 95% confidence intervals (CIs) estimated to determine their associations with hypertensive disorders of pregnancy.

RESULTS: Stage 1 hypertension was twice more likely to develop gestational hypertension (aRR: 2.314, 95% CI: 1.08–4.98) and thrice more likely to develop preeclampsia (aRR: 3.673, 95% CI: 2.30–5.86), whether without (aRR: 3.520, 95% CI: 1.33–9.29) or with severe features (aRR: 3.717, 95% CI: 2.16–6.41). There was a slightly increased risk for adverse perinatal outcomes from Stage 1 hypertension, as well as all outcomes from elevated BP, but was not statistically significant. Majority of BP elevations were during the third trimester.

CONCLUSION: Lower threshold Stage 1 hypertension showed an increased risk of developing hypertensive disorders of pregnancy, with a three-fold increased risk for preeclampsia. There may be advantages in its application for diagnosing preeclampsia or having increased monitoring for these patients.

Keywords:

Gestational hypertension, lower threshold blood pressure, perinatal outcomes, preeclampsia

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Submitted: 20-May-2023
Revised: 20-Jun-2023
Accepted: 25-Jun-2023
Published: 17-Aug-2023

How to cite this article: Acosta AS, Zamora BB. Determining the risk of gestational hypertension, preeclampsia, and adverse perinatal outcomes in patients with antenatal lower threshold blood pressure elevations: A retrospective cohort study. Philipp J Obstet Gynecol 2023;47:47-56.

Introduction

Hypertensive disorders in pregnancy occur in 5% to 10% of all pregnancies worldwide. Locally, preeclampsia with severe features occurs in 2% to 5% of pregnancies. They are part of the leading causes of maternal and perinatal morbidity and mortality worldwide, specifically in developing countries.[1,2] Hypertensive disorders in pregnancy are mainly classified into four categories: (1) preeclampsia-eclampsia, (2) chronic hypertension, (3) chronic hypertension with superimposed preeclampsia, and (4) gestational hypertension.[3] Preeclampsia alone is further classified into with and without severe features, depending on the level of BP elevations and the presence of end-organ dysfunction.[4] Mechanisms proposed in the development of preeclampsia include abnormal trophoblastic invasion of uterine vessels, immunologic dysfunction between maternal, paternal, and fetal tissues, maternal maladaptation to cardiovascular or inflammatory changes of pregnancy, and genetic factors. These factors are believed to eventually become clinically apparent and lead to multiple major organ involvement and affectations that may cascade together, including eclampsia, the severe manifestation of preeclampsia manifested as convulsions.[5] These factors are also believed to contribute to the perinatal morbidity and mortality rates of preeclampsia, including intrauterine growth restriction, placental abruption, nonreassuring fetal status as evidenced on fetal cardiotocography or on biophysical scoring, preterm delivery, intrauterine fetal demise or stillbirth, small for gestational age, and low APGAR scores. These are, however, dependent on the age of gestation (AOG) wherein hypertension was diagnosed, disease severity, and the presence of other contributing factors.[6]

Current diagnosis of hypertensive disorders in pregnancy

The diagnosis of gestational hypertension and preeclampsia is established with fixed blood pressure (BP) criteria, the presence of proteinuria, and/or clinical or biochemical signs of end-organ damage. Based on the Philippine Obstetrical and Gynecological Society (POGS) Clinical Practice Guidelines (2015) and the American College of Obstetrics and Gynecology (ACOG) Practice Bulletin for Gestational Hypertension and Preeclampsia, (2020), hypertensive disorders of pregnancy are diagnosed using the following criteria:[7,8]

1. Gestational hypertension – Systolic BP (SBP) of >140 mmHg and/or a diastolic BP (DBP) of >90 mmHg, taken at least on two occasions 4 h apart at 20 weeks AOG or beyond. BP should not reach 160/110 mmHg, and there is no proteinuria and no signs of end-organ damage
2. Preeclampsia – Presence of proteinuria, with a 24-h urine protein of >300 mg or a urine protein/creatinine ratio of >0.3. In the absence of proteinuria, the diagnosis stands if with maternal organ dysfunction (thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and new-onset cerebral or visual disturbances not attributed to other conditions). Preeclampsia is further divided into:
   a. Preeclampsia without severe features – SBP >140 mmHg or DBP >90 mmHg BP PLUS proteinuria
   b. Preeclampsia with severe features – With signs of end-organ damage or BP reaches SBP >160 mmHg or DBP >110 mmHg confirmed within 15 min, regardless if with proteinuria or not. The presence of any of the features of organ dysfunction that encompass hemolysis, elevated liver enzymes, and low platelet is termed as HELLP syndrome and is a severe manifestation, not a separate entity.[2]
3. Chronic hypertension with superimposed preeclampsia – New-onset signs of organ dysfunction, proteinuria, or abrupt increase in BP baseline for patients with known chronic hypertension.[4,7,8]

The new guidelines for the diagnosis of hypertension in adults

As of 2017, the American College of Cardiology and the American Heart Association (ACC/AHA) guidelines redefine the diagnosis of hypertension in nonpregnant adults, lowering the threshold of elevated BP.[9,10] These new ACC/AHA guidelines only focus on the nonpregnant, and pregnancy is outside of its scope due to a lack of available data.

1. Normal BP – SBP of <120 mmHg and DBP <80 mmHg
2. Elevated BP – SBP of 120 mmHg to 129 mmHg with a DBP <80 mmHg
3. Stage 1 hypertension – SBP of 130 mmHg to 139 mmHg or a DBP of 80 mmHg to 89 mmHg
4. Stage 2 hypertension – SBP of >140 mmHg or a DBP of >90 mmHg.

The latest POGS and ACOG guidelines still use the cutoff of SBP >140 mmHg or DBP >90 mmHg in diagnosing hypertension in pregnancy.[2] This is mainly derived from previous reports from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC), but note that the new ACC/AHA guidelines are meant to be an update to all prior JNC reports.[9,10] The other globally utilized guideline by the International Society for the Study of Hypertension in Pregnancy (ISSHP), updated in 2018, suggests that the implementation of the new Stage 1 hypertension threshold may increase unnecessary testing, hospitalization, and intervention in the absence of a proven benefit.[11] The ISSHP still follows the 140/90 mmHg cutoff, but tracing back to older versions shows that the cutoff is based on

a classification given by Davey and MacGillivray dating back in 1988.[12] The ACOG guidelines on chronic hypertension in pregnancy do give the option of diagnosing chronic hypertension if the pregnant patient presents with lower threshold BP elevations before 20-week AOG, but this should ideally be with a diagnosis of hypertension before pregnancy.[13] Studies suggesting the use of these lower thresholds in diagnosing hypertension in pregnancy are still very few. One is a systematic review by Sisti and Williams which shows increasing evidence of the use of the lower thresholds in diagnosing hypertension in pregnancy, but the evidence remains weak due to the few number of available studies, which are mainly retrospective in nature, owing to the ethical concerns of doing actual trials on the pregnant population.[14] This study further evaluates if there is indeed an increased risk for hypertensive disorders in pregnancy or adverse perinatal outcomes associated with them in patients who present with the ACC/AHA lower threshold BP measurements.

Objectives

General

To determine if the presence of lower threshold BP elevations of "elevated BP" and "Stage 1 hypertension" during the antenatal period is associated with an increased risk of gestational hypertension, preeclampsia, or any adverse perinatal outcomes.

Specific

1. To determine the prevalence and risk of developing
   a. Gestational hypertension
   b. Preeclampsia
      i. Preeclampsia without severe features
      ii. Preeclampsia with severe features
   c. Adverse perinatal outcomes in patients with antenatal BP elevations following the "elevated BP" and "Stage 1 hypertension" lower BP thresholds endorsed by the AHA/ACC taken at the second trimester (20–27 6/7 weeks), third trimester of pregnancy (28–36 6/7 weeks), and at term before the onset of labor (37 weeks onward) if available.
2. To determine at which AOG range with low threshold BP elevations is associated with an increased risk for gestational hypertension, preeclampsia, and/or adverse perinatal outcomes associated with hypertensive disorders in pregnancy
3. To determine which of the new lower thresholds ("elevated BP" and "Stage 1 hypertension") has a higher association with increased risk of gestational hypertension, preeclampsia without severe features, preeclampsia with severe features, and/or adverse perinatal outcomes.

Materials and Methods

Study design and data retrieval

A retrospective cohort study was done involving patients who delivered at the service wards of a private tertiary hospital from February 1, 2016, to February 29, 2020, and had prenatal care at the department's outpatient clinics. The specific time period was chosen to maintain uniformity in the diagnosis of preeclampsia within the institution, since the POGS and ACOG guidelines that use the preeclampsia with and without severe features categorization as compared to the older "mild preeclampsia" and "severe preeclampsia" were fully placed into practice in the institution's department beginning 2016. The institution's electronic medical records for outpatient consults were accessed to retrieve the BP measurements of the patients during their prenatal consults. The needed sample size was calculated using Epi Info StatCalc version 7.2.4.0 using values of prevalence and risk ratio of preeclampsia in the normotensive and in those with Stage 1 BP elevations, which were 5.4% and 15.3%, respectively, with a risk ratio of 2.66.[15] For a confidence level of 95%, the minimum sample size computed was 195 needed per arm.

The patient should have had at least one BP monitoring value done each during the following phases of prenatal care: the second trimester (20–27 6/7 weeks), third trimester of pregnancy (28–36 6/7 weeks), and at term before the onset of labor (37 weeks onward) if available (in the event that the patient delivered preterm). The highest available BP measurement was recorded per trimester. The patients were then categorized into "normal," "elevated BP," and "Stage 1 hypertension" as per the ACC/AHA guidelines. Patients who fit both elevated BP and Stage 1 hypertension were placed under the more severe category. The classification of the patients based on BP measurements is shown in Table 1. The ACC/AHA classification of Stage 2 hypertension was not used since its BP cutoff, by definition, already overlaps with the current criteria for diagnosing hypertensive disorders in pregnancy.[7-10]

Patients who did not have at least one BP measurement available in the second trimester and third trimester of pregnancy, at the extremes of age (<18 years or >35 years of age), with comorbidities known to increase the risk of preeclampsia such as multifetal pregnancy, preeclampsia

Table 1: Classifications of patients based on their antenatal blood pressure

Classification	Blood pressure criteria
Normal BP	SBP <120 mmHg and DBP <80 mmHg
Elevated BP	SBP 120–129 mmHg and DBP <80 mmHg
Stage 1 HTN	SBP 130–139 mmHg or DBP of 80–89 mmHg

BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP, HTN: Hypertension

in the previous pregnancy, known cases of chronic hypertension or with BP elevations of >SBP 140 mmHg or DBP 90 mmHg before 20-week AOG, with pregestational diabetes mellitus/overt diabetes mellitus, with a prepregnancy body mass index (BMI) of >30 kg/m, known case of systemic lupus erythematosus, antiphospholipid antibody syndrome, thrombophilia, obstructive sleep apnea or any maternal renal or cardiac anomaly disease before pregnancy, with history of smoking, alcohol or drug use, conceived pregnancy through any means of assisted reproductive technology, with fetal or neonatal congenital anomaly, and those who had uncertain AOG due to the last menstrual period not correlated with an available ultrasound done at up to 21 6/7-week AOG, were all excluded from the study.[2,16]

Evaluation for outcomes

After classifying the patients by their antenatal BP measurements, patient charts were then accessed to check if they were diagnosed with gestational hypertension, preeclampsia (further divided into preeclampsia with and without severe features), or a composite of adverse perinatal outcomes at delivery and up to 6 weeks postpartum. The definition of the outcomes is given in Table 2.

Participants received prenatal care according to the usual practice at the said private tertiary-level hospital. Prenatal consults were advised every 4 weeks until 28 weeks, every 2 weeks until 36 weeks, and weekly thereafter until term.[19] Timing of delivery, whether at term or preterm, was by the standard practice in the private tertiary-level hospital. Guidelines for diagnosis and management of the hypertensive disorders of pregnancy were followed using the latest POGS guidelines.[7] Measurement of BP s was done by trained residents and clinical clerks using a sphygmomanometer. BP was measured with the patient in a seated position after a 30-min rest using an appropriately sized cuff.

Table 2: Definition of outcomes for evaluation

Outcome	Definition
GH	BP elevations with a SBP of >140 mmHg and/or a DBP of >90 mmHg, taken at least on two occasions 4 h apart in a patient with previously normal BP, with no evidence of proteinuria or end-organ dysfunction
	BP should not reach the SBP >160 mmHg or DBP >110 mmHg
Preeclampsia	BP elevations with a SBP of >140 mmHg and/or a DBP of >90 mmHg, taken at least on two occasions 4 h apart in a patient with previously normal BP, plus presence of proteinuria, as evidenced by protein of >300 mg or more in a 24 h urine collection sample or a urine protein/creatinine ratio of >0.3
	In the absence of proteinuria, if with signs of maternal organ dysfunction, such as thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema and new-onset cerebral or visual disturbances not attributed to other conditions
Preeclampsia without severe features	SBP of >140 mmHg and/or a DBP of >90 mmHg, taken at least on two occasions 4 h apart in a patient with previously normal BP
	Plus with the presence of proteinuria evidenced by a urine protein creatinine ratio >0.3 and without any of the features that would classify the BP elevation as severe
	In our department, proteinuria is routinely checked with the urine protein creatinine ratio beginning 2016
	BP should not reach the SBP >160 mmHg or DBP >110 mmHg
Preeclampsia with severe features	SBP of>140 mmHg and/or a DBP of >90 mmHg, taken at least on two occasions 4 h apart in a patient with previously normal BP with or without proteinuria (via urine protein creatinine ratio of ≥0.3) if one or more of the following are present
	Thrombocytopenia (platelet count <100,000)
	Impaired liver function that is not accounted for by alternative diagnoses and as indicated by abnormally elevated blood concentrations of liver enzymes (to more than twice the upper limit normal concentrations), or by severe persistent right upper quadrant or epigastric pain unresponsive to medications
	Renal insufficiency (serum creatinine concentration >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
	Pulmonary edema seen on chest radiograph
	New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
	Visual disturbances
	May also be diagnosed if the patient attains a higher threshold of BP elevations of SBP >160 mmHg or DBP ≥110 mmHg confirmed within 15 min, regardless if without proteinuria or end-organ dysfunction[2,7,8]
Adverse perinatal outcomes	Treated as a composite, the patient should have any one or more of the following adverse perinatal outcomes known to be associated with hypertensive disorders of pregnancy[17]
	IUGR-fetus with an estimated fetal weight of less than the 10th percentile for gestational age based on Hadlock 4 by ultrasound prior to delivery. This may be with or without abnormal Doppler velocimetry findings[18]
	Preterm delivery-delivery of the fetus at 36 6/7-week AOG or less, regardless of Ballard score[19]
	IUFD or stillbirth-fetus with no signs of life or death documented in utero via the absence of cardiac activity on ultrasound at 20 weeks gestation or greater. If not previously documented on ultrasound, delivery of a neonate with no signs of life falls under stillbirth[20]
	Small for gestational age-neonatal weight on delivery is below the 10th percentile for the neonate's Ballard score[18]

BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP, GH: Gestational hypertension, AOG: Age of gestation, IUGR: Intrauterine growth restriction, IUFD: Intrauterine fetal demise

Ethical considerations

Patient data were encoded using Microsoft Excel, and names were concealed. Electronic data were saved in a flash drive and to be stored with a lock and key at the department office for 10 years. Although the study involves human data, data were collected from the electronic records where patient anonymity is assured and maintained with no communication with the subjects in connection with the study and the rights of the subjects to privacy were not adversely affected; hence, a waiver for informed consent was applied.

Data processing and analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Crude and adjusted relative risks (aRRs) and their 95% confidence intervals (CIs) were estimated to determine potential associations between prenatal BP elevations and the incidence of hypertensive disorders of pregnancy. All valid data were included in the analysis. The only missing data were the Ballard scores for patients who delivered intrauterine fetal demise/stillbirth babies. This was neither replaced nor estimated. The null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 (StataCorp LLC, College Station, Texas, USA) was used for data analysis.

Results

A total of 2034 patients were delivered at the service wards of the private tertiary hospital's Department of Obstetrics and Gynecology from February 1, 2016, to February 29, 2020. Of these, a total of 829 patients were excluded from the study because of the following: no prenatal consults in the same institution (n = 259), had missing BP measurements at either the 20–27 6/7 weeks or 28–36 6/7-week AOG antenatal period (n = 36), were extremes of age (18 years old and below, n = 91, and 35 years old and above, n = 261), had prepregnant BMIs of >30 kg/m^2 (n = 26), had multiple pregnancies (n = 9), had maternal cardiac/renal anomalies or diseases (n = 11), diagnosed with chronic hypertension (n = 53), overt diabetes mellitus (n = 35), and systemic lupus erythematosus (n = 1), with fetal/neonatal congenital anomalies (n = 20), and had no prepregnant BMI recorded (n = 27). The remaining 1205 were included in this study.

The mothers had a median age of 27 years, ranging from 19 to 34 years old, and a median prepregnancy BMI of 23.75 kg/m^2. Primigravida comprised 41.08% of the study population. The neonates had a median weight of 3000 g, with 95% born term and appropriate for gestational age. Patients who delivered through spontaneous vaginal delivery comprised 60% of the population. Nearly all neonates had good APGAR scores (>98%). The characteristics of normal, elevated BP, and Stage 1 hypertension subgroups are enumerated in Table 3.

Of the 1205 patients in the study, 396 were under normal BP, 301 were under elevated BP, and 508 were under Stage 1 hypertension. Overall, there were 42 (3.49%) who developed gestational hypertension, 146 (12.12%) with preeclampsia, 36 (2.99%) with preeclampsia without severe features, 110 (9.13%) with preeclampsia with severe features, and 78 (6.47%) with adverse perinatal outcomes.

Compared to those under normal BP, women under Stage 1 hypertension were twice more likely to develop gestational hypertension (crude risk ratio [cRR]: 2.165, 95% CI: 1.02–4.59, P = 0.04), four times more likely to develop preeclampsia (cRR: 4.054, 95% CI: 2.56–6.42), whether without severe features (cRR: 3.742, 95% CI: 1.44–9.72), or with severe features (cRR: 4.157, 95% CI: 2.43–7.10, P < 0.001). After adjusting for age and BMI, the association between Stage 1 hypertension and gestational hypertension (aRR: 2.314, 95% CI: 1.08–4.98) was maintained. There was also still a three-fold risk of developing preeclampsia (aRR: 3.673, 95% CI: 2.30–5.86), preeclampsia without severe features (aRR: 3.520, 95% CI: 1.33–9.29), and preeclampsia with severe features (aRR: 3.717, 95% CI: 2.16–6.41) even after adjustments. Evidence showed a slight increase in risk but was insufficient to demonstrate a statistically significant association between those with elevated BP and the outcomes of gestational hypertension (aRR: 1.264, 95% CI: 0.49–3.27), preeclampsia (aRR: 1.403, 95% CI: 0.78–2.53), and adverse perinatal outcomes (aRR: 1.381, 95% CI: 0.76–2.5). Likewise, there was no significant association between Stage 1 hypertension with adverse perinatal outcomes (aRR: 1.442, 95% CI: 0.85–2.44). Tabulations of the prevalence of the outcomes with each of the exposure groups, with cRRs at 95% CIs of the different exposures and outcomes, are summarized in Table 4.

Within the composite of adverse perinatal outcomes, the most prevalent were small for gestational age and preterm delivery. Small for gestational age outcomes were at 32% for those with elevated BP and 37.66% for those with Stage 1 hypertension, while preterm delivery outcomes were at 48% for elevated BP and 46.75% for Stage 1 hypertension, as shown in Table 5.

Among the eight patients who developed gestational hypertension classified under elevated BP, the BP elevations were reported at 20–27 6/7 weeks in three patients (37.5%), 28–36 6/7 weeks in seven patients (87.5%),

Table 3: Characteristics of mothers and neonates (*n*=1205)

	Median (range), frequency (%)			
	Overall (*n*=1205)	Normal (*n*=396)	Elevated (*n*=301)	Stage 1 HTN (*n*=508)
Mothers				
Age group (years)	27 (19–34)	27 (19–34)	27 (19–34)	27 (19–34)
19–25	335 (27.8)	132 (33.33)	92 (30.56)	111 (21.85)
25–29	444 (36.85)	125 (31.57)	132 (43.85)	187 (36.81)
30–34	426 (35.35)	139 (35.1)	77 (25.58)	210 (41.34)
Prepregnant BMI (kg/m^2)	23.75 (15–29.94)	22.4 (16–29.2)	24.97 (17–29.85)	24.05 (15–29.94)
<18.5	68 (5.64)	35 (8.84)	11 (3.65)	22 (4.33)
18.5–23	416 (34.52)	183 (46.21)	83 (27.57)	150 (29.53)
23–27.5	248 (20.58)	67 (16.92)	57 (18.94)	124 (24.41)
27.5–29.99	473 (39.25)	111 (28.03)	150 (49.83)	212 (41.73)
Gravidity	2 (1–7)	2 (1–7)	2 (1–6)	2 (1–6)
1	495 (41.08)	173 (43.69)	112 (37.21)	210 (41.34)
>2	710 (58.92)	223 (56.31)	189 (62.79)	298 (58.66)
Parity	1 (0–5)			
0	246 (42.27)	191 (48.23)	129 (42.86)	233 (45.87)
1	190 (32.65)	113 (28.54)	84 (27.91)	171 (33.66)
2–4	144 (24.74)	91 (22.98)	87 (28.9)	104 (20.47)
>5	2 (0.34)	1 (0.25)	1 (0.33)	0
Neonates				
Birth weight (g)	3000 (640–4400)	3000 (1850–4150)	3000 (1780–4250)	2950 (640–4400)
<2500	88 (7.3)	24 (6.06)	14 (4.65)	50 (9.84)
≥2500	1117 (92.7)	372 (93.94)	287 (95.35)	458 (90.16)
Birth length	49 (33–56)	49 (38–55)	49 (39–55)	49 (33–56)
Gestational age at birth by week AOG				
Early preterm	4 (0.33)	0	1 (0.33)	3 (0.59)
Late preterm	52 (4.32)	8 (2.02)	11 (3.65)	33 (6.5)
Term	1148 (95.27)	388 (97.98)	289 (96.01)	471 (92.72)
Postterm	1 (0.08)	0	0	1 (0.2)
Ballard score				
Early preterm	4 (0.33)	0	2 (0.66)	2 (0.39)
Late preterm	15 (1.24)	2 (0.51)	6 (1.99)	7 (1.38)
Term	1182 (98.09)	393 (99.24)	292 (97.01)	497 (97.83)
IUFD (no Ballard)	4 (0.33)	1 (0.25)	1 (0.33)	2 (0.39)
Birth weight classification				
SGA	48 (3.98)	12 (3.03)	8 (2.66)	28 (5.51)
AGA	1146 (95.1)	381 (96.21)	288 (95.68)	477 (93.9)
LGA	11 (0.91)	3 (0.76)	5 (1.66)	3 (0.59)
Delivery				
NSD	730 (60.58)	243 (61.36)	213 (70.76)	274 (53.94)
CS	429 (35.6)	138 (34.85)	77 (25.58)	214 (42.13)
Assisted vaginal	46 (3.82)	15 (3.79)	11 (3.65)	20 (3.94)
Apgar (1 min)				
<7	17 (1.41)	6 (1.52)	1 (0.33)	10 (1.97)
≥7	1188 (98.59)	390 (98.48)	300 (99.67)	498 (98.03)
Apgar (5 min)				
<7	5 (0.41)	1 (0.25)	1 (0.33)	3 (0.59)
≥7	1200 (99.59)	395 (99.75)	300 (99.67)	505 (99.41)

IUFD: Intrauterine fetal demise, SGA: Small for gestational age, AGA: Appropriate for gestational age, LGA: Large for gestational age, NSD: Normal spontaneous delivery, CS: Cesarean section, BMI: Body mass index, AOG: Age of gestation, HTN: Hypertension

and at term with one patient (12.5%). Meanwhile, there were 25 patients who developed gestational hypertension under the Stage 1 hypertension group, with BP elevations at 20–27 6/7 weeks in 4 (16%) patients, at 28–36 6/7 weeks in 18 (72%) patients, and at term in 12 (48%) patients.

Among 22 patients who developed preeclampsia with elevated BP, the BP elevations were reported at 20–27 6/7 weeks in 5 (22.73%) patients, 28–36 6/7 weeks in 19 (86.36%) patients, and at term with 5 (22.73%) patients. Meanwhile, in the 104 patients who developed

Table 4: Relative risks and 95% confidence intervals of lower threshold blood pressure elevation with the development of hypertensive diseases of pregnancy (*n*=1205)

	GH (*n*=42)		*P*	PE (*n*=146)		*P*	PE without severe features (*n*=36)		*P*
	n (%)	Relative risk (95% CI)		*n* (%)	Relative risk (95% CI)		*n* (%)	Relative risk (95% CI)	
Crude									
Normal (*n*=396)	9 (2.27)	Reference		20 (5.05)	Reference		5 (1.26)	Reference	
Elevated (*n*=301)	8 (2.66)	1.169 (0.46–3.00)	0.744	22 (7.31)	1.447 (0.80–2.60)	0.217	7 (2.33)	1.842 (0.59–5.75)	0.293
Stage 1 HTN (*n*=508)	25 (4.92)	2.165 (1.02–4.59)	0.044	104 (20.47)	4.054 (2.56–6.42)	<0.001	24 (4.72)	3.742 (1.44–9.72)	0.007
Adjusted (by age and BMI)									
Normal (*n*396)	9 (2.27)	Reference		20 (5.05)	Reference		5 (1.26)	Reference	
Elevated (*n*=301)	8 (2.66)	1.264 (0.49–3.27)	0.628	22 (7.31)	1.403 (0.78–2.53)	0.260	7 (2.33)	1.816 (0.58–5.72)	0.308
Stage 1 HTN (*n*=508)	25 (4.92)	2.314 (1.08–4.98)	0.032	104 (20.47)	3.673 (2.30–5.86)	<0.001	24 (4.72)	3.520 (1.33–9.29)	0.011

	PE with severe features (*n*=110)		*P*	Adverse perinatal outcome (*n*=78)		*P*
	n (%)	Relative risk (95% CI)		*n* (%)	Relative risk (95% CI)	
Crude						
Normal (*n*=396)	15 (3.79)	Reference		20 (5.05)	Reference	
Elevated (*n*=301)	15 (4.98)	1.316 (0.65–2.65)	0.442	21 (6.98)	1.381 (0.76–2.50)	0.286
Stage 1 HTN (*n*=508)	80 (15.75)	4.157 (2.43–7.10)	<0.001	37 (7.28)	1.442 (0.85–2.44)	0.174
Adjusted (by age and BMI)						
Normal (*n*396)	15 (3.79)	Reference		20 (5.05)	Reference	
Elevated (*n*=301)	15 (4.98)	1.270 (0.63–2.57)	0.505	21 (6.98)	1.381 (0.76–2.50)	0.286
Stage 1 HTN (*n*=508)	80 (15.75)	3.717 (2.16–6.41)	<0.001	37 (7.28)	1.442 (0.85–2.44)	0.174

HTN: Hypertension, GH: Gestational HTN, PE: Preeclampsia, CI: Confidence interval, BMI: Body mass index

Table 5: Summary of adverse perinatal outcomes (number %)

BP criteria	Adverse perinatal outcomes (*n*=78)			
	IUGR, *n* (%)	SGA, *n* (%)	Preterm delivery, *n* (%)	IUFD, *n* (%)
Normal	8 (28.57)	11 (39.29)	8 (28.57)	1 (3.57)
Elevated	4 (16)	8 (32)	12 (48)	1 (4)
Stage 1 HTN	10 (12.99)	29 (37.66)	36 (46.75)	2 (2.6)

HTN: Hypertension, IUFD: Intrauterine fetal demise, SGA: Small for gestational age, BP: Blood pressure, IUGR: Intrauterine growth restriction

preeclampsia under the Stage 1 hypertension group, the BP elevations were recorded at 20–27 6/7 weeks in 27 (26%) patients, at 28–36 6/7 weeks in 83 (79.81%) patients, and at term in 64 (62%) patients.

Among 21 patients who had adverse perinatal outcomes under the elevated BP group, the BP elevations were seen at 20–27 6/7 weeks in 12 (57%) patients, 28–36 6/7 weeks in 16 (76%) patients, and at term with 7 (33.33%) patients. Adverse perinatal outcomes were seen in 37 under Stage 1 hypertension, with BP elevations recorded at 20–27 6/7 weeks in 13 (35.14%) patients, at 28–36 6/7 weeks in 27 (73%) patients, and at term in 19 (51%) patients. A summary of this can be found in Table 6.

Discussion

Hypertensive disorders of pregnancy are a major contributor to perinatal and maternal morbidity and mortality worldwide. The results of our study show an increased risk of gestational hypertension and preeclampsia in patients with antenatal BP elevations that fall under Stage 1 hypertension, which is defined as having an SBP of >130 mmHg OR even just a DBP of >80 mmHg. This cutoff is currently lower than the POGS and ACOG-endorsed cutoff of SBP >140 mmHg or DBP >90 mmHg in diagnosing hypertensive disorders in pregnancy.[7,8] Although there was an association between elevated BP and hypertensive disorders, there was not enough statistical significance to establish a link between the two, and there may be a need for a bigger sample size. The same applies to the adverse perinatal outcomes composite.

The new guidelines released by ACC/AHA as of 2017, though beneficial in the diagnosis and management of adults who are at high risk for such cardiovascular diseases, do not encompass the pregnant population due to a lack of available studies.[9,10] Note that our own local POGS guidelines for hypertensive disorders in pregnancy

Table 6: Blood pressure elevation, according to the age of gestation during which the blood pressure elevation was recorded

	n	20–27 6/7 weeks, *n* (%)	28–36 6/7 weeks, *n* (%)	≥37 weeks, *n* (%)
GH				
Elevated	8	3 (37.50)	7 (87.50)	1 (12.50)
Stage 1 HTN	25	4 (16)	18 (72)	12 (48)
Preeclampsia				
Elevated	22	5 (22.73)	19 (86.36)	5 (22.73)
Stage 1 HTN	104	27 (25.96)	83 (79.81)	64 (61.54)
Adverse perinatal outcome				
Elevated	21	12 (57.14)	16 (76.19)	7 (33.33)
Stage 1 HTN	37	13 (35.14)	27 (72.97)	19 (51.35)

HTN: Hypertension, GH: Gestational HTN

are heavily reliant on the international guidelines set by ACOG. Moreover, note that the cutoff used by ACOG for these disorders references the old JNC guidelines for hypertension, which the ACC/AHA guidelines are meant to replace. These cutoffs, when cross-referenced, date back to a report by Davey and MacGillivray from 1988.[12] The need to further evaluate if we may need to update our current guidelines for the pregnant population in light of these new lower threshold cutoffs arises.

The results of our study support the outcomes of the few studies on the subject matter. These include a randomized controlled trial by Sutton *et al*. using secondary analysis of existing data from a multicenter randomized, placebo-controlled trial of low-dose aspirin for preeclampsia prevention in nulliparous low-risk women. Their study shows that there is an increased risk of preeclampsia and preterm delivery in patients under the lower threshold Stage 1 hypertension category (relative risks, 2.66, 95% CI: 1.56–4.54, $P < 0.001$).[15] A more recent 2020 retrospective cohort study by Reddy *et al*. done in 18,243 singleton pregnancies in Australia shows that there is at least a three to six times increased risk for developing preeclampsia in patients under the Stage 1 hypertension category (aRR: 6.60, 95% CI: 4.98, 8.73 at 34–36 weeks of gestation) and that the development of preeclampsia was not limited to those with BPs of 140/90 mmHg.[21] Another retrospective cohort study done by Porcelli *et al*. also showed a two-fold increased risk for developing hypertensive disorders in pregnancy at delivery for all singleton pregnancies in 2014–2018 for those which fit the Stage 1 hypertension definition of ACC/AHA (aRR: 2.41, 95% CI: 2.02–2.85).[22] Our study, despite also including multiparous patients that Sutton *et al.*'s and Reddy *et al.*'s[15,21] studies did not include, still showed a similar increased risk for the development of hypertensive disorders in pregnancy for those with Stage 1 hypertension.

Although not statistically significant, our study also points to a higher risk for developing adverse perinatal outcomes; specifically, more prominent are preterm deliveries and small for gestational age. Similar results were seen in Reddy *et al*.'s study for the Stage 1 hypertension group, with an increased risk for those at 28–32-week AOG (aRR: 1.56, 95% CI: 1.23–1.97), along with an overall preterm birth that was significantly higher across all gestational ages in the Stage 1 hypertension (aRR: 1.69, 95% CI: 1.43–2.01). This was mainly due to indicated preterm deliveries. In their study, however, the association between small for gestational age and Stage 1 hypertension was weak.[21]

Our data further indicate that measurements of these lower threshold BP elevations were more prominent from 28 to 36 6/7-week AOG for those who developed hypertensive disorders of pregnancy. This may indicate the ideal time frame to be more adamant in the monitoring and surveillance of patients for gestational hypertension and preeclampsia, especially for those who have other concomitant risk factors for developing these disorders.

In addition, hypertension in pregnancy is not reliant on BP measurements alone, as there are many risk factors that influence their development. A multifactorial screening assessment that includes BP measurements along with other risk factors may be of more benefit for better monitoring of patients. At present, the Fetal Medicine Foundation has a risk assessment tool for preeclampsia available for public use, which includes consideration of pregnancy type, pertinent history and comorbidities that point to a higher risk of preeclampsia, the patient's mean arterial pressure (MAP), uterine artery PI, and biochemical measurements (if available). This tool, however, has a 75%–92% false-positive rate and is not widely used due to possibly causing undue anxiety in patients and unnecessary treatment.[23] Although the BP alone cannot establish the disorder, the presence of these BP elevations may alert the physician to which patients need more attentive monitoring. Similar to this risk classification, the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial showed a markedly decreased odds for the diagnosis of preterm preeclampsia in patients given aspirin at 11–14-week AOG for their patients with high risk for preeclampsia. The risk prediction algorithm for preeclampsia used

in their study included factors such as maternal characteristics, MAP, uterine artery pulsatility index, maternal serum pregnancy-associated plasma protein A, and placental growth factor, but not concrete or specific BP measurements.[24] The use of aspirin for the prevention of preeclampsia, as endorsed by ACOG for those at risk for the disease, may also be considered in these patients with lower threshold BP elevations, but this will entail additional research.[25]

Important to note is that present studies on these lower threshold BP elevations have BP measurements mainly at or beyond 20-week AOG. This cutoff is chosen specifically due to the completion of spiral artery remodeling by 20–22-week AOG, wherein the trophoblastic invasion establishes a low-resistance vascular blood flow causing reduced BP at around 20 weeks of gestation and reaching a nadir. In patients with the defective remodeling of the spiral arteries, it is widely accepted to be one of the primary underlying pathologies in preeclampsia.[26] However, one study by Hauspurg *et al.* analyzed instead BP elevations taken at the first trimester and then their trajectories beyond 20-week AOG. Their results show that Stage 1 hypertension and its trajectory increased the risk to two-fold for hypertensive disorders in pregnancy (aRR: 2.16, 95% CI: 1.31–3.57).[27] This may indicate that the presence of these lower threshold BP elevations is not limited to beyond 20-week AOG. Taking this into conjunction with the ASPRE trials that evaluated preeclampsia risk during the first trimester and showed benefit in aspirin use beginning as early as 11-week AOG, the earlier detection and intervention for patients with these BP elevations is also a consideration for further study.

Conclusion

The lower threshold BP elevation of "Stage 1 hypertension" shows a definite increased risk of developing hypertensive disorders of pregnancy, showing a two-fold risk of developing gestational hypertension. With preeclampsia, the risk increases three-fold, including both preeclampsia without severe and with severe features. The risk is higher for those with Stage 1 hypertension than those with elevated BP. There is a tendency for a higher risk of developing gestational hypertension and preeclampsia with elevated BP, although not statistically significant. This is similar to the tendency to develop adverse perinatal outcomes, particularly small for gestational age, among those with elevated BP and Stage I hypertension. Majority of BP elevations were during the third trimester at 28–36 6/7-week AOG.

Limitations

This study is a retrospective cohort that relies heavily on prerecorded data, which may be subject to inaccuracies in record-keeping and inter-observer bias in the recording of patients' BP s. There is also the risk of misclassification bias since the measurements are based on prerecorded data only.

Recommendations

The BP cutoffs being used to diagnose hypertensive disorders of pregnancy, though effective, have been referenced from guidelines that date back all the way to 1988. Given this scenario, there may be a benefit in considering to follow the lower "Stage 1 hypertension" BP levels for the diagnosis of hypertensive disorders in pregnancy. Immediate application may bring about an increase in the incidence of hypertension in pregnancy, and would potentially increase unnecessary testing, hospitalization, and intervention. Further research, such as a prospective study, may also be considered in order to limit inaccuracies in BP measurement as well as maintain a more controlled environment for the observation of patients, as well as to determine if there will be an improvement in maternal and fetal outcomes for these patients. One option would be to increase the surveillance or monitoring of our pregnant patients that fall under Stage 1 hypertension and increase the anticipation of their possible development of gestational hypertension and preeclampsia while local and international guidelines have not yet been updated. Patients identified as high risk with the presence of these BP elevations may be encouraged to address any modifiable risk factors, be educated on the signs and symptoms of preeclampsia, and be scheduled for a more frequent clinic follow-up schedule. Further research if there is benefit in using aspirin for these patients may also be considered.

Authorship contributions

Abigail Sandra Yao Acosta - involved in the conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing of the original draft, review and editing, visualization, supervision and project administration.

Brenda Bernadette B. Zamora - involved in the conceptualization, methodology, validation, formal analysis, investigation, data curation, writing of the original draft, review and editing, visualization, supervision and project administration.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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