Hypertension arising after 20 weeks of gestation: gestational hypertension or masked chronic hypertension?

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Abstract

Objectives

the aims were 1- to evaluate the prevalence of masked chronic hypertension in pregnant women classified as gestational hypertension 2- to compare the risks of developing preeclampsia in true gestational hypertension vs those women classified as having gestational hypertension but who had had masked hypertension in the first half of pregnancy.

Methods

We conducted a cohort study in consecutive high-risk pregnancies who were evaluated before 20 weeks of gestation. Women who developed hypertension (office BP ≥ 140/90 mmHg and/or antihypertensive treatment) after 20 weeks of gestation was classified, according to the ABPM performed before 20 weeks of gestation, as having “true” gestational hypertension (if their ABPM before 20 weeks of gestation was normal) or “pseudo” gestational hypertension (if they had masked chronic hypertension). Risks for preeclampsia (PE) were estimated and compared with normotensive women.

Results

Before 20 weeks of gestation, 227 were analyzed (age 32 ± 6 years, median gestation age 15 weeks); 67 had chronic hypertension (29.5%). Of the remaining 160, 39 developed gestational hypertension (16 had true gestational and 23 pseudo gestational hypertension, because they had masked hypertension in the first half of pregnancy). Compared with normotensive pregnant women, true gestational hypertension did not increase the risk of developing PE (OR = 0.76, 95%CI = 0.16–6.65). Conversely, pseudo gestational hypertension increased the risk of PE more than 4 times (0R = 4.47 CI = 1.16–12.63). Risk estimation did not change substantially after the adjustment for multiple possible confounders.

Conclusion

59% of women diagnosed as gestational hypertensives had indeed masked chronic hypertension and a high risk of developing PE.

Introduction

Traditionally, hypertensive disorders of pregnancy have been divided into chronic arterial hypertension (women with hypertension that become pregnant) vs. gestational hypertension (pregnancy-induced hypertension), using the office blood pressure (BP) before 20 weeks of gestation to differentiate both conditions [1, 3]. Thus, according to the traditional definitions, a pregnant woman who has an office BP < 140/90 mmHg before 20 weeks of gestation and subsequently develops hypertension, should be defined

as gestational hypertensive. However, using this approach the possibility to have masked chronic hypertension (normal office BP and elevated BP on ambulatory BP monitoring before 20 weeks) is not considered. Recently, our group showed that masked hypertension is a frequent condition in high-risk pregnant women. Moreover, masked hypertension carries an important increase in maternal and fetal risk [4].

The clinical significance of different hypertensive disorders of pregnancy is not the same. While the risk of maternal and fetal complications of chronic hypertension has been shown [5], the risk associated with gestational hypertension is less well defined. Wu et al, using the National Inpatient Sample database, analyzed the association between different hypertensive disorders of pregnancy and adverse in-hospital maternal and fetal outcomes in more than 44 million deliveries. Women with chronic hypertension, but not those with gestational hypertension, had a higher risk of both, maternal and fetal adverse outcomes [6]. However, the International Society for the Study of Hypertension in Pregnancy (ISSHP) in their last position paper state that “outcomes in pregnancies complicated by gestational hypertension are normally good, but about a quarter of women with gestational hypertension will progress to preeclampsia and have poorer outcomes”. They also state that “gestational hypertension is not a uniformly benign condition” [3]. The risk of complications has been attributed to the gestational age at which it develops [7]. Also, some data suggest that different outcomes could be related to different out-of-office BP levels. Davis et al found that pregnant women with gestational hypertension who developed preeclampsia/eclampsia (PE) had higher awake and 24-hour systolic BP than those who did not [8]. However, the possibility that those women had chronic masked hypertension was not further analyzed.

We hypothesized that a proportion of women with gestational hypertension defined using current recommendations might have masked chronic hypertension, rather than pregnancy-induced hypertension. Furthermore, this distinction could explain the heterogeneity of PE risk and could be important for prognostic considerations. Consequently, the objectives of this study were 1- to evaluate the prevalence of masked chronic hypertension in high-risk pregnant women classified as gestational hypertension using the traditional definition. 2- to compare the risks of developing preeclampsia in true gestational hypertension vs those women classified as having gestational hypertension but who had had masked hypertension in an evaluation performed before 20 weeks of gestation (denominated in this paper as pseudo gestational hypertension).

Material And Methods

This is a cohort study of consecutive women with high-risk pregnancies derived between 1st January 2016 and 31st March 2020 to the Cardiometabolic Diseases Unit (San Martín Hospital, La Plata, Argentina) and evaluated before 20 weeks of gestation using a predesigned protocol. They had been referred to the High-risk Pregnancy Office of the Obstetrics Department at San Martín Hospital (La Plata, Argentina) by primary care physicians either because of their comorbidities, such as diabetes, hypertension, chronic kidney disease or others, or because of certain findings detected during the current pregnancy (gestational diabetes, gestational hypertension or multiple pregnancy).

All women were also evaluated in the Cardiometabolic Disease Unit with a pre-defined protocol for office and ambulatory BP measurement. This protocol, that includes the routine use of ABPM after 10 weeks of gestation in all high-risk pregnancies, has been incorporated as usual medical practice at our hospital since 2016. The protocol has been previously described [9]. In brief: a specially trained nurse, at the end of a 15-min interview, performed three BP measurements employing a validated oscillometric automatic BP device (OMRON HEM 705 CP), in seated position with the arm at heart level and using appropriate arm sleeves. Office BP was defined as an average of these three determinations. Immediately after, an ABPM was initiated with a validated monitor (Spacelabs 90207). Measurements were scheduled every 15 min during the day and every 20 min at night. Only ABPMs with at least 70% successful measurements and at least one record per hour were considered valid. Only women who had at least one ABPM before 20 weeks of gestation and who were followed up until delivery at San Martín Hospital were included in this analysis.

Chronic hypertension was defined as office BP ≥ 140/90 mmHg and 24-h ABPM ≥ 130/80 mmHg, based on the ABPM before 20 weeks of gestation, or treatment with antihypertensive drugs started before the current pregnancy. Women without chronic hypertension was classified as normal BP (office BP < 140/90mmHg and 24-h ABPM < 130/80 mmHg), white-coat hypertension (office BP ≥ 140/90 mmHg and 24-h ABPM < 130/80 mmHg) or masked chronic hypertension (office BP < 140/90 mmHg and 24-h ABPM ≥ 130/80 mmHg). According to current guidelines, women who developed hypertension (office BP ≥ 140/90 mmHg and/or antihypertensive treatment) after 20 weeks of gestation were defined as gestational hypertension. According to the ABPM before 20 weeks of gestation, these women were divided in “true” gestational hypertension (if their ABPM before 20 weeks of gestation was normal) or “pseudo” gestational hypertension (if they had masked chronic hypertension).

PE was defined as the presence of any of the following: 1- preeclampsia (BP ≥ 140/90 mmHg associated with proteins in urine ≥ 300 mg/24 h), or 2- eclampsia (seizures in a patient with preeclampsia or gestational hypertension), or 3- HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet count). Data of the delivery and perinatal outcomes -APGAR score (Appearance, Pulse, Grimace, Activity and Respiration) and birth weight- were extracted from the default protocol used by the Obstetrics Department.

Continuous variables were expressed as mean and standard deviation (SD) and compared between groups using “t” test or ANOVA and post-hoc Scheffe test, as appropriate. Ordinal variables were expressed as median and interquartile range (IQR) and compared with Kruskal-Wallis H test. Categorical variables were expressed as percentage and were compared with x^2 or Fisher’s exact test, as appropriate.

The relative risks of women with normotension, chronic hypertension, true gestational hypertension, and pseudo gestational hypertension were estimated using logistic regression models and expressed as Odds-ratio with 95% confidence interval (OR, 95%CI). Normotension was the reference category. Two models were constructed: Model 1, unadjusted; Model 2, adjusted by relevant covariables (age, diabetes

mellitus, gestational diabetes, and use of low doses of acetylsalicylic acid (ASA) and/or calcium supplements).

The data were analyzed using SPSS (IBM, Armonk, New York, USA); P values < 0.05 (two-tailed) were considered significant.

This was an observational study which carries no risk for the patients and conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the medical bioethics committee of the Faculty of Medical Sciences, National University of La Plata (UNLP), Buenos Aires, Argentina (COBIMED 0/27).

Results

A total of 262 high-risk pregnant women (age 31 ± 7 years, with a median of 15 weeks, range 7–19 weeks) were evaluated before the 20th week of gestation. Of these, 30 patients were excluded because had not been followed up until the delivery, and 5 because they did not have a valid ABPM. The remaining 227 are included in the present analysis (age 32 ± 6 years, median gestation week 15, range 8–19).

At the evaluation in the first half of gestation, the prevalence of chronic hypertension was 29.5% (67/227); 45 women were under pharmacological treatment and 34 had office BP ≥ 140/90 mmHg, of which 12 had white-coat hypertension. The prevalence of masked hypertension in untreated normotensive pregnant women was 20.9% (31/148). The characteristics of the patients are shown in Table 1.

Table 1
Comparison of patients with and without chronic hypertension at the initial evaluation

	Chronic Hypertension		
	Yes n 67	No n 160	p
Age, years, mean ± SD	31 ± 6	34 ± 6	0,001
Gestational age at evaluation, weeks, mean ± SD	15 ± 3	15 ± 3	0,342
Diabetes mellitus, n (%)	5 (8,2)	19 (2,6)	0,362
Collagen disease /SAF, n (%)	1 (1,5)	7 (4,4)	0,283
Chronic kidney disease, n (%)	4 (6,8)	5 (3,5)	0,299
Systolic office BP, mmHg, mean ± SD	120 ± 12	134 ± 16	< 0,001
Diastolic office BP, mmHg, mean ± SD	76 ± 8	87 ± 12	< 0,001
Systolic 24hs-ABPM, mmHg, mean ± SD	119 ± 12	129 ± 16	< 0,001
Diastolic 24hs-ABPM, mmHg, mean ± SD	71 ± 8	79 ± 13	< 0,001
Antihypertensive treatment, n (%)	45 (67,2)	0 (0)	NA
Low doses of acetylsalicylic acid, n (%)	62 (92,5)	123 (79,6)	0,006
Calcium supplements, n (%)	29 (43,3)	64 (40,0)	0,646

BP: blood pressure. Continuous variables are shown as mean and standard deviation (SD) and are compared with independent samples t test. Proportions are shown as n and percent and compared with Chi^2 test or Fisher's exact test

In the second half of pregnancy, 39 developed gestational hypertension defined by traditional criteria. According to the ABPM performed at the first half of pregnancy, 16 were defined as true gestational hypertension and 23 (59%) were defined as pseudo gestational hypertension because they had had masked hypertension in the first half of pregnancy (Fig. 1). Table 2 compares the characteristics of patients with true vs pseudo gestational hypertension.

Table 2
Comparison of pregnant women without chronic hypertension at the initial evaluation according to their evolution after 20 weeks of gestation.

	Normotension n 121	True gestational hypertension n 16	Pseudo gestational hypertension n 23	p	p true vs pseudo hypertension
Age, years, mean ± DS	30 ± 6	30 ± 5	32 ± 9	0,591	NA
Diabetes mellitus, n (%)	15 (12,4)	0 (0)	4 (17,4)	0,240	NA
Diabetes gestational, n (%)	11 (9,1)	2 (12,5)	2 (8,7)	0,901	NA
Systolic office BP, mmHg, mean ± SD	120 ± 11	124 ± 16	122 ± 13	0,207	NA
Diastolic office BP, mmHg, mean ± SD	75 ± 8	79 ± 10	78 ± 7	0,135	NA
Systolic 24hs-ABPM, mmHg, mean ± SD	115 ± 9	118 ± 7	138 ± 10	< 0,001	< 0,001
Diastolic 24hs-ABPM, mmHg, mean ± SD	69 ± 6	71 ± 6	84 ± 9	< 0,001	< 0,001
Antihypertensive treatment, n (%)	0 (0)	11 (68,8)	22 (95,7)	< 0,001	0,022
Low doses of acetylsalicylic acid, n (%)	91 (75,2)	13 (81,2)	19 (82,6)	0,675	NA
Calcium supplements, n (%)	49 (40,5)	7 (43,8)	8 (39,4)	0,832	NA

BP: blood pressure (at baseline evaluation). Continuous variables are shown as mean and standard deviation (SD) and are compared with independent samples t test. Proportions are shown as n and percent and compared with Chi2 test or Fisher's exact test

The prevalence of PE in the whole cohort was 23.3%. The prevalences of PE analyzed by categories were15.7%, 12.5%, 43.5%, and 32.8% for women with normotension, true gestational hypertension, pseudo gestational hypertension, and chronic hypertension, respectively. Table 3 shows the adjusted and unadjusted risks of developing PE according to the condition in the second half of pregnancy. Compared with pregnant women with normotension, true gestational hypertension did not increase the risk of developing PE (OR 0.76, 95% CI 0.16–6.65). Conversely, pseudo gestational hypertension increased the risk for PE more than 4 times (0R 4.47 CI 1.16–12.63). Risk estimation did not change substantially after the adjustment for multiple possible confounders.

Table 3
Absolute risk and adjusted and not adjusted odds ratio for developing preeclampsia/eclampsia according to the different categories of blood pressure in pregnancy.

Categories	Absolute risk (% pregnancies)	OR no adjusted	CI 95%	OR adjusted (*)	CI 95%
Normotension, n 121	15,7	1		1	
True gestational hypertension, n 16	12,5	0,76	(0,16 – 3,65)	0,72	(0,15 – 3,45)
Pseudo gestational hypertension, n 23	43,5	4,13	(1,58 – 10,77)	4,47	(1,16 – 12,63)
Chronic hypertension, n 67	32,8	2,63	(1,29 – 5,32)	2,81	(1,30 – 6,07)
(*) Adjusted by maternal age, diabetes mellitus, gestational diabetes, and use of low doses of acetylsalicylic acid and/or calcium supplements					

Discussion

Our study shows that more than half of the women that had been classified based on office BP measurement as gestational hipertensives had masked chronic hypertension according to the results of an ABPM performed before 20 weeks of gestation. Thus, these women did not have true gestational hypertension because they were not strictly normotensives in the first half of gestation (pseudo gestational hypertension). Moreover, women with pseudo gestational hypertension, but not those with true gestational hypertension, had a very high risk to developed PE (~ 4 times more risk). Physiological BP decrease in the first half of the pregnancy could contribute to masked chronic hypertension.

In the recently published CHAP study, Tita et al [10] showed that the treatment of mild chronic hypertension (office BP 140–160/90–100 mmHg before 20 weeks of gestation) was associated with better pregnancy outcomes without an increase in the risk of low birth weight, highlighting the importance of identifying and early treat pregnant women with chronic hypertension. Regarding women with office BP < 140/90 mmHg, an observational study performed on low-risk pregnant from China shows that women with office BP between 130–140 and/or between 80–90 mmHg (measured before 20 weeks of gestation) had more than 2 times risk of PE, compared with those with lower values of office BP [11]. In this sense, in previously published studies we communicated a high prevalence of masked hypertension in high-risk pregnant women with office normotension [9]. Thus, it could be possible that some of the risks for PE observed in pregnant women without office hypertension could be attributed to masked chronic hypertension.

Furthermore, gestational hypertension is also associated with cardiovascular disease in the long-term follow-up. In a populational study from Sweden including more than 400,000 women, the adjusted

incidence rate ratio for later development of ischemic heart disease was 1.6 (95% CI 1.3–2.0) when the first pregnancy was complicated by gestational hypertension without proteinuria [12]. In a retrospective cohort study, women with gestational hypertension (without PE) showed a higher risk for all-cause and cardiovascular mortality than normotensive women matched by age, year of childbirth, and parity at the time of the index pregnancy [13]. Again, untreated masked hypertension could be a plausible explanation for the relationship between gestational hypertension and long-term cardiovascular disease. Furthermore, in the study by Saudan et al, 70% of women with hypertension gestational had had hypertension at previous gestation, suggesting the possibility that these women had indeed chronic hypertension [6].

Our findings could partially explain the heterogeneity in the risk for PE associated with gestational hypertension. Indeed, our cohort of high-risk pregnant women with gestational hypertension was composed of two subgroups with very different risks of PE development: women without chronic hypertension who developed true gestational hypertension and had low risk of PE (OR 0.72, 95% CI 0.15–3.45) and women who had masked, untreated, hypertension, and had a very high risk for PE (OR 4.47, 95% CI 1.16–12.63). These subgroups could be easily identified by an ABPM performed in the first half of pregnancy.

Remarkably, the risk of PE of pseudo gestational hypertension was higher than that associated with chronic hypertension (OR 4.47 vs 2.81, Table 3). In the general population, a similar phenomenon has been described by Banegas et al [14] for the risk of cardiovascular disease. It has been attributed to the fact that masked hypertension is an undiagnosed and untreated condition. The benefits of treating mild hypertension in pregnant women with chronic hypertension showed in the previously mentioned CHAP study, could support our findings. Indeed, Table 1 shows that the average baseline values BP of office and ABPM were normal in women with hypertension, suggesting that, on average, they were adequately treated. Conversely, although women with pseudo gestational hypertension have average normal office BP, they remain hypertensives as evaluated by ABPM.

Although the results of our study are straightforward, certain limitations must be addressed. First, this study was performed on a cohort of high-risk pregnant women, and therefore, our findings are not necessarily applicable to pregnancies without this condition. Indeed, the high prevalence of PE observed might be explained by selection bias. Second, the diagnosis of hypertension by ABPM was achieved using the same threshold as for the general population. However, a recently published study of pregnant women in a southern Chinese population defined similar ABPM thresholds using a maternal and fetal outcome-derived approach [15]. Third, this is an observational study; consequently, some bias could be not discharged. Thus, the use of low doses of aspirin, calcium supplements, or antihypertensive drugs may influence the results. However, the OR values were not altered by adjustment for covariates. Fourth, no studies showed the benefits of treating masked hypertension in pregnant women. However, the CHAP study showed in the analysis for subgroups that women with chronic hypertension diagnosed and receiving medication previously, had a significantly lower risk than those newly diagnosed and those with chronic hypertension diagnosed but without receiving medication [10]. Finally, the number of events was modest and further studies are necessary to confirm our results.

In conclusion, gestational hypertension seems a heterogeneous condition. More than half of women diagnosed as gestational hypertensives using only office BP really had chronic masked hypertension. These women with pseudo gestational hypertension had a very high risk of PE. Thus, an ABPM performed before 20 weeks of gestation in office normotensives appears necessary to identify this subgroup, at least in high-risk pregnancies.

Declarations

Data Availability Statement

The authors have available the databases and results of the studies that are kept in the Cardiometabolic Diseases Unit of the Hospital San Martin de La Plata.

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Ethical Approval

The study protocol was approved by the medical bioethics committee of the Faculty of Medical Sciences, National University of La Plata (UNLP), Buenos Aires, Argentina (COBIMED 0/27).

Competing Interests

None of the authors declare any conflicts of interest.

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Figures

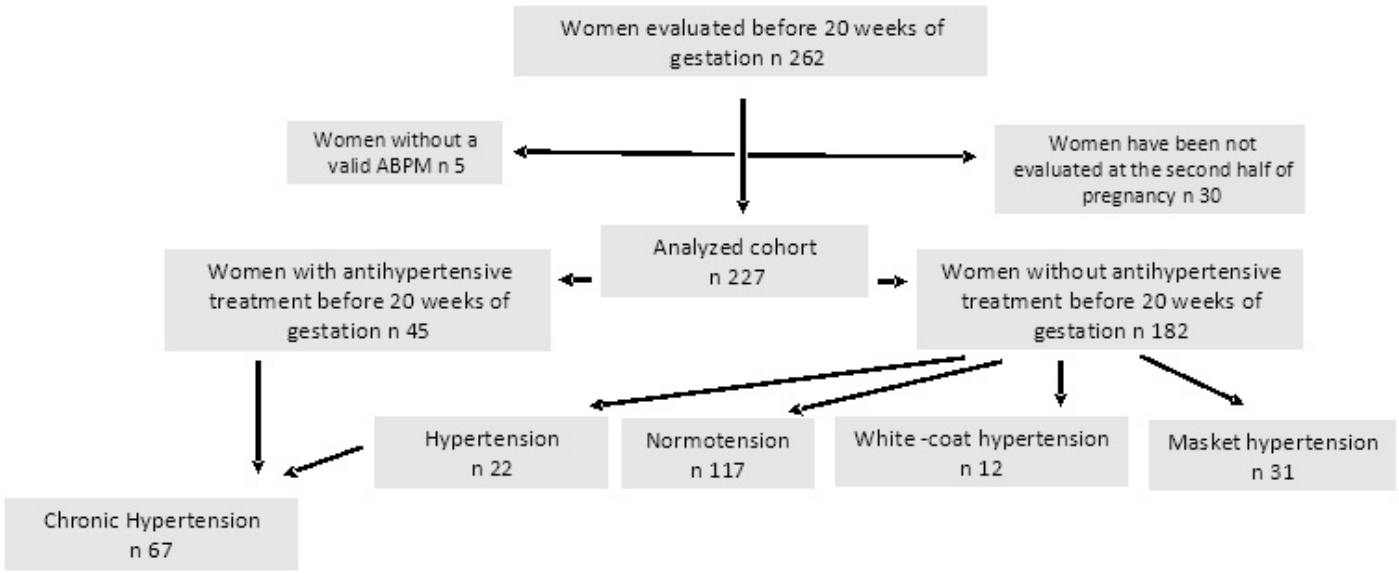

Figure 1

Flow chard of the study including the classification of pregnant women before 20 weeks of gestation using ambulatory blood pressure monitoring.