

# Morning Hypertension and Non-dipper Behavior in Pregnant Women with White Coat Syndrome

## *Hipertensión matinal y comportamiento non-dipper en embarazadas con hipertensión de guardapolvo blanco*

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### ABSTRACT

**Background:** White coat syndrome (WCS) is common during pregnancy, although little is known about its clinical outcome during gestation. Morning hypertension and the non-dipper behavior, measured by ambulatory blood pressure monitoring (ABPM), are associated with greater risk of cardiovascular events. However, there are few studies during pregnancy.

**Objectives:** The primary aim of the study was to evaluate morning hypertension and the non-dipper behavior in pregnant women with WCS versus a control normotensive group. A secondary objective was to evaluate whether WCS, morning hypertension and the non-dipper behavior in the second trimester of pregnancy were associated with greater hypertension in the third trimester.

**Methods:** This prospective study included 95 primiparae in the 20th week of gestation, 50 with WCS and 45 as normotensive control group. Routine lab tests, office blood pressure and ABPM at inclusion and in the 32th week of gestation were recorded. Morning hypertension and the non-dipper behavior were evaluated by ABPM.

**Results:** Age, baseline blood glucose level and daytime and nighttime blood pressure by ABPM were similar in both groups. Conversely, patients presenting WCS had significantly higher values of morning hypertension and non-dipper behavior, which were independently associated with sustained hypertension in the third trimester of pregnancy.

**Conclusions:** Pregnant women with WCS in the 20th week of gestation presented greater morning hypertension and non-dipper behavior and progressed more frequently to sustained hypertension than the control normotensive group.

**Key words:** White Coat Hypertension - Sustained Hypertension - Pregnancy - Morning Blood Pressure Surge

### RESUMEN

**Introducción:** La hipertensión de guardapolvo blanco (HGB) es común en el embarazo, aunque su evolución clínica durante la gestación se conoce poco. La hipertensión matinal y el comportamiento non-dipper, medidos por monitoreo ambulatorio de la presión arterial (MAPA), se asocian con mayor riesgo de eventos cardiovasculares; no obstante ello, son escasos los estudios en la gestación.

**Objetivos:** El objetivo primario del estudio fue evaluar la hipertensión matinal y el comportamiento non-dipper en embarazadas con HGB versus un grupo control de normotensas. Se planteó como objetivo secundario evaluar si la HGB, la hipertensión matinal y el comportamiento non-dipper en el segundo trimestre del embarazo se relacionan con mayor hipertensión sostenida en el tercer trimestre.

**Material y métodos:** Estudio prospectivo en el que se incluyeron 95 primigestas en la semana 20 de gestación, 50 con HGB y 45 normotensas como grupo control. Se registraron laboratorio de rutina, presión de consultorio y MAPA en la inclusión y a las 32 semanas de gestación. La hipertensión matinal y el comportamiento non-dipperse evaluaron por MAPA.

**Resultados:** La edad, la glucemia y la presión diurna y nocturna por MAPA fueron similares en el examen basal en ambos grupos. Por el contrario, las pacientes con HGB presentaron valores significativamente superiores de hipertensión matinal y comportamiento non-dipper, lo cual se asoció en forma independiente con hipertensión sostenida en el tercer trimestre del embarazo.

**Conclusiones:** Las gestantes con HGB en la semana 20 de embarazo presentaron mayor hipertensión matinal y comportamiento non-dipper y evolucionaron con más frecuencia a hipertensión sostenida que el grupo control de normotensas.

**Palabras clave:** Hipertensión de guardapolvo blanco - Embarazo - Hipertensión sostenida - Hipertensión matinal - Comportamiento non-dipper

### Abbreviations

<b>ABPM</b>	Ambulatory blood pressure monitoring.	<b>HTN</b>	Hypertension
<b>BP</b>	Blood pressure	<b>SHTN</b>	Sustained hypertension
<b>BMI</b>	Body mass index	<b>SBP</b>	Systolic blood pressure.
<b>DBP</b>	Diastolic blood pressure	<b>WCS</b>	White-coat syndrome

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## INTRODUCTION

White-coat syndrome (WCS) is common in pregnancy, with a prevalence ranging between 20-30%. (1) Its clinical evolution during pregnancy has been described as benign and unlikely to evolve to sustained hypertension (SHTN) or preeclampsia. However, this concept has not yet been clearly established. (2, 3)

White coat syndrome is defined as the diagnosis of hypertension in the clinical setting with normal blood pressure (BP) at home or 24-hour ambulatory blood pressure monitoring (ABPM). (4)

In general, WCS is considered an entity of benign clinical evolution; however, this concept has been a matter of debate in recent years. Some authors claim that WCS in the general population is an entity of intermediate risk between normotension and SHTN, (5, 6) and this concept could also be true in WCS during pregnancy.

It has been described that in the overall population and especially in hypertensive patients, altered circadian BP patterns are associated with increased risk of cardiovascular events, such as stroke or myocardial infarction. (7-9) These alterations, mainly represented by elevated morning blood pressure surge and non-dipper behavior can be measured by ABPM. Altered circadian rhythm during pregnancy could also be related with greater morbidity throughout gestation, as well as higher incidence of SHTN. However, there are at present few clinical trials evaluating morning hypertension and non-dipper behavior in pregnant women at risk of preeclampsia and, to our knowledge, none in pregnant women with WCS.

Our initial hypothesis was that patients with WCS may present with different risk patterns in the ABPM at 20 weeks of gestation and evolve more frequently to SHTN compared to normotensive pregnant women.

## METHODS

This is a prospective, longitudinal study with control group, approved by the Ethics Committee of the Hospital General de Agudos Donación Francisco Santojanni. Patients were evaluated at 20 (range 18-22) and 32 (range 32-36) weeks of gestation.

At the beginning of 2011 primiparous patients with early pregnancy evaluated at the obstetric clinic were invited to participate in the study, which ended in 2013. It included 80 patients with WCS and 97 normotensive patients as control group. Inclusion criteria were: first pregnancy in the 20th week of gestation and age between 18-35 years. Exclusion criteria at study entry were: previous disease, including diabetes or hypertension (HTN), antihypertensive medication, presence of alterations in routine laboratory tests, including 24 hour urinary protein >300 mg, abnormal electrocardiogram, and HTN in the ABPM performed at inclusion.

The diagnosis of WCS and normotension was performed according to the results of office systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) plus daytime systolic and/or diastolic blood pressure in the ABPM. (4)

- WCS: office BP  $\geq$  140 and/or 90 mmHg; ABPM  $\leq$  135 and 85 mmHg.
- SHTN: office BP  $\geq$  140 and/or 90 mmHg; ABPM  $\geq$  135 and

85 mmHg.

- Normotension: office blood pressure  $\leq$  140 and/or 90 mmHg; ABPM  $\leq$  135 and 85 mmHg.

The Omron 705 (Tokyo, Japan) device, with bracelets according to the arm circumference of each patient, was used to measure office BP. Three BP recordings on 2 consecutive days were obtained according to the Argentine Society of Cardiology Hypertension Consensus recommendations (10), and during the following week the patients underwent routine lab tests (hematocrit, blood glucose, creatinine, uric acid, coagulation panel and 24-hour urine protein), electrocardiogram and ABPM using a Spacelab 90207ABP monitor (SpaceLabs Medical Inc. Redmond, WA, USA) to measure average daytime and nighttime pressures, and assess morning hypertension and non-dipper behavior. This study was performed to all patients who continued the follow-up period.

Morning hypertension was calculated as:

- *Average mean BP in the first 2 hours after awakening.*
- *Average mean BP of the remaining daytime hours.*

Morning hypertension was considered when the difference between the two measured periods was greater than 10%.

Non-dipper behavior was defined as less than 10% reduction in SBP and/or DBP during sleep.

After these procedures 12 patients were excluded due to high glucose level, 28 for poor quality nighttime sleep and 26 for unsatisfactory amount of ABPM readings (<80%); and 16 patients did not attend the second assessment at 32 weeks of gestation. For the final analysis, 50 patients with WCS and 45 with normotension were considered.

At week 32 of gestation office blood pressure, ABPM for the diagnosis of SHTN, and routine lab tests were assessed in all patients in follow-up; normotensive patients also underwent ABPM to rule out masked hypertension and to ensure the diagnosis of normotension.

Preeclampsia was diagnosed when the patients had office SBP  $\geq$  140 mmHg and/or DBP  $\geq$  90 mmHg plus 24-hour urinary protein >300 mg.

## Statistical analysis

Quantitative variables are expressed as mean and standard deviation and qualitative variables as percentage. Student's t test was used for the analysis and comparison of mean quantitative variables with normal distribution, established according to the Kolmogorov-Smirnov test and homocedasticity. For variables not meeting this condition the nonparametric Kruskal-Wallis test was used. The chi square test (statistical significance  $p < 0.05$ ) was used for qualitative variables. The percentage of patients with normotension and WCS at week 12 of gestation who evolved to SHTN at 32 weeks of gestation was recorded.

A stepwise multivariate analysis was used to assess the relationship between variables; the significant ones were included in logistic regression models to determine which predicted SHTN.

Since morning hypertension and non-dipper behavior variables were strongly related to the presence of WCS, two logistic regression models were constructed in order to avoid colinearity between these variables; in both, SHTN (at 32 weeks of gestation) was the dependent variable and the independent variables (evaluated at 20 weeks of gestation) in the first model were: office SBP and DBP, daytime and nighttime SBP and DBP, and WCS. In the second logistic regres-

sion model the independent variables were: office SBP and DBP, daytime and nighttime SBP and DBP, morning hypertension and non-dipper behavior. Both models were adjusted for body mass index (BMI), age and blood glucose level. A  $p$  value  $<0.05$  was considered as statistically significant.

Statistical analyses were performed using the SPSS version 17.0 for Windows (SPSS Inc., Chicago, Ill, USA) software package.

### Ethical considerations

The protocol was reviewed and approved by the Ethics Committee of the Hospital General de Agudos Donación Francisco Santojanni.

### RESULTS

Patients with WCS at baseline examination presented with similar values of age, blood glucose level, creatinine and 24-hour urinary protein compared to normotensive patients. Body mass index was higher in WCS; however it was not a predictor of SHTN in the study population.

Office BP values were higher in WCS patients, whereas those of ABPM did not differ between the two study groups, as expected according to the definition of WCS and normotension used for inclusion. (Table 1)

Twenty-one patients (42%) with WCS and 10 (22%) with normotension presented with morning hypertension, while 23 patients (46%) with WCS and 8 (17%) with normotension, presented with non-dipper behavior. These differences were statistically significant, thus supporting our original hypothesis.

Interestingly, 9 patients presented with preeclampsia between the 34th and 39th week of gestation, 7 of which were WCH and 2 were normotensive in the second trimester of pregnancy. Although this group of patients had higher office BP and ABPM on inclusion, the percentage of patients with this event was low, and therefore no conclusions could be drawn.

To determine SHTN evolution, office BP and ABPM were recorded in the third trimester of pregnancy, except in 11 patients considered as sustained hypertensive, who were receiving antihypertensive drugs (6 patients with 2 g of alpha-methyldopa every 24 hours and 5 with 2 g of alpha-methyldopa plus 30 mg of extended-release nifedipine, administered orally every 24 hours).

The percentage of progression to SHTN was higher in patients with WCS: 46% ( $n=25$ ) compared with 13% ( $n=6$ ) normotensive patients, a percentage which was statistically significant by chi-square test ( $p=0.01$ ) (Table 2). Sustained hypertension predictors by logistic regression analysis in the third trimester of pregnancy were WCS (OR: 3. 95% CI 2.3-11), morning hypertension (OR: 2.6; 95% CI 1.8-15) and non-dipper behavior (OR: 8, 95% CI 2-9) diagnosed in the 20th week of pregnancy. (Table 3).

### DISCUSSION

White coat syndrome is common in pregnancy. (11,

**Table 1.** Population characteristics at 20 weeks of gestation

	WCS (n=50)	N (n=45)	p
Age, years	29±3.3	29±4	ns
BMI, kg/m <sup>2</sup>	27.3±3.4	25±3.4	0.05
Blood glucose, g/L	73±8	68±5	ns
Smoking, n	7	9	ns
OSBP, mmHg	151±10	113±9	0.01
ODBP, mmHg	96±6	67±6.5	0.01
ABPM daytime SBP, mmHg	112±9	110±8	ns
ABPM daytime DBP, mmHg	66±9	65±7	ns
ABPM nighttime SBP, mmHg	100±6	97±5.8	ns
ABPM nighttime DBP, mmHg	62±5	57±5	ns

The table shows the results of the studied variables in the first evaluation at baseline inclusion. Values are expressed as mean±standard deviation. The  $p$  value  $<0.05$  was obtained with Student's  $t$  test or the Kruskal-Wallis test.

WCS: White-coat syndrome. N: Normotension. n: Number of patients. BMI: Body mass index, OSBP: Office systolic blood pressure. ODBP: Office diastolic blood pressure. SBP: Systolic blood pressure. DBP: diastolic blood pressure. ns: Not significant

**Table 2.** Characteristics at 20 weeks of gestation of patients who progressed to sustained hypertension

	SHTN (n=31)	N (n=64)	p
WCS at 20 weeks of gestation, n (%)	25 (80%)	20 (31%)	0.01
BMI, kg/m <sup>2</sup>	27.3±3.4	27±3.4	ns
Blood glucose, g/L	78±8	69±5	ns
OSBP, mmHg	146±10	119±9	0.01
ODBP, mmHg	94.5±6	68±7	0.01
ABPM daytime SBP, mmHg	112.8±9	110±7	ns
ABPM daytime DBP, mmHg	66.5±9	64.2±7	ns
ABPM nighttime SBP, mmHg	99.4±6	97.2±5.8	ns
ABPM nighttime DBP, mHg	63±5	56±5	0.05
MH, n (%)	19 (61%)	12 (18.7%)	0.01
NDB, n (%)	21 (67.7 %)	10 (15.6%)	0.001

The table shows the results of the studied variables in the first evaluation at baseline inclusion of patients who progressed to sustained hypertension during the third trimester of pregnancy vs. those who remained normotensive. Values are expressed as mean±standard deviation. The  $p$  value  $<0.05$  was obtained with Student's  $t$  test or the Kruskal-Wallis test.

SHTN: Patients with sustained hypertension. N: Normotensive patients. n: Number of patients. WCS: White-coat syndrome. BMI: Body mass index, OSBP: Office systolic blood pressure. ODBP: Office diastolic blood pressure SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MH: Morning hypertension. NDB: Non-dipper behavior. ns: Not significant

12) The benign nature which characterizes this entity is because most of the time patients with WCS present with normotension, except in the doctor's office, where in those minutes of evaluation BP is high.

Antihypertensive treatment is risky in this popula-

Independent variables	B	Standard error	Wald chi square	p	OR
WCS	2.2	0.6	12	0.001	3 (2.3-11)
Morning hypertension	2.1	0.5	7.6	0.03	2.6 (1.8-15)
Non-dipper behavior	2.0	0.6	11	0.01	8 (2-9)

The table shows the variables that were predictors of sustained hypertension in the third trimester of pregnancy, according to the logistic regression models described in the text.

B: Regression coefficient. OR: Odds ratio. WCS: White-coat syndrome.

**Table 3.** Determinants of sustained hypertension by logistic regression

tion since the resulting hypotension decreases fetoplacental irrigation and compromises fetal growth. (13)

In the general population presenting with WCS without target organ damage, antihypertensive treatment is also contraindicated (14).

Although WCS is considered an innocent entity, the risk of progression to SHTN which presents this population is higher than that of normotensive patients (15). This risk could also be present during shorter periods of evolution, such as pregnancy, in which hemodynamic and hormonal changes that occur in a short period of time can precipitate WCS progression in the first half of pregnancy to SHTN during the rest of its course.

In our study, it was shown that SHTN in the third trimester of pregnancy was significantly higher in patients with WCS than in normotensive pregnant women.

The circadian alterations of BP in ABPM are associated with increased cardiovascular morbidity in the hypertensive population; therefore, our original hypothesis was that the presence of these alterations in the second trimester of pregnancy could be predictors of SHTN in the third trimester. Given that SHTN in pregnant women occurs most frequently at 32 weeks of gestation, it is important to identify abnormal patterns during the first half of gestation, both clinical as WCS or by complementary methods such as ABPM, which are associated to increased progression to SHTN in the third trimester of pregnancy.

Normally, BP decreases during nighttime rest and increases in the hours of awakening. Alteration of this circadian pattern in the general population and especially in hypertensive patients is associated with increased risk of cardiovascular events. (16-18) Disruption of the circadian BP rhythm can be evaluated by morning hypertension and non-dipper behavior. (19)

It has been shown that non-dipper behavior is associated with the presence of preeclampsia. (20) Therefore, lack of nocturnal fall in BP indicates increased risk of hypertensive complications in pregnancy. However, there are no studies of non-dipper behavior in pregnant women with WCS in the first half of gestation, in whom there is increased risk of SHTN.

The diagnosis of morning hypertension has been made with different formulas and so far, that proposed by Kario (21) has been the most studied and widespread; however, it is not easy to implement it in

our environment. The choice of the formula used in this work originates from two concepts:

- The normal BP variability during wakefulness and sleep does not exceed 10%, therefore the normal cutoff level was chosen from this concept.
- It was decided not to include nighttime BP within the formula, thus avoiding false positive results in the diagnosis of morning hypertension as in the case of "hyper-dipper" patients.

The results obtained in this study suggest that the presence of WCS, morning hypertension and non-dipper behavior measured at 20 weeks of gestation were SHTN predictors.

The causes predisposing to morning hypertension and non-dipper behavior, have been related to various mechanisms, such as the decrease in arterial compliance and the increase in sympathetic activity; alterations also described in WCS. (22-25)

White coat hypertension is characterized by increased BP reactivity especially during its measurement; this reactivity could be also increased in the immediate hours after awakening as a response to an increased sympathetic activity, which is a characteristic of patients with WCS.

White coat hypertension in the assessed study population may then be considered as a clinical entity for high risk of SHTN, especially in the presence of circadian rhythm alterations, diagnosed through the existence of morning hypertension and non-dipper behavior.

Patients at high risk for preeclampsia, have altered arterial compliance at an early stage of pregnancy, even before SHTN onset (26, 27). In our study, 9 patients were diagnosed with preeclampsia; 7 had WCS at 20 weeks of pregnancy, while only 2 were normotensive during this period. The total number of patients with this event in the analyzed population was too small to determine significant differences between the two studied groups

We excluded patients with previous pregnancies, extreme age and diabetes or chronic HTN, factors that strongly influence the progression to SHTN; therefore, the results of this study should not be extended to the general population of pregnant women.

## CONCLUSIONS

Pregnant women with WCS had higher morning hypertension and non-dipper behavior at 20 weeks of

pregnancy compared with normotensive pregnant women. Also, patients with WCS presented with higher incidence of SHTN in the third trimester of pregnancy compared to the control group.

In this population, the diagnosis of WCS, morning hypertension and non-dipper behavior in the second trimester of pregnancy allowed identifying patients at high risk of SHTN in the third trimester.

#### Conflicts of interest

None Declared

(See author's conflicts of interest forms in the web / Supplementary Material)

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