ORIGINAL ARTICLE

Results of a Prospective Registry of Patients with Hypertensive Disorders of Pregnancy in a Center of the City of Buenos Aires

Resultados de un registro prospectivo de Pacientes con desórdenes hipertensivos del embarazo en un centro de la Ciudad de Buenos Aires

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ABSTRACT

Background: Hypertensive disorders of pregnancy (HDP) complicate 10% of pregnancies. They are the main cause of maternal mortality and require a multidisciplinary team to address them.
Objectives: The aim of this study was to quantify the prevalence and define the characteristics and outcome of HDP in a center with a program focused on its management.
Methods: This was a continuous and prospective registry from November 2019 to July 2021 that included all patients with HDP [chronic hypertension (CHT), gestational hypertension (GHT), early-onset preeclampsia (EPE), late preeclampsia (LPE), superimposed preeclampsia (SIPE) and eclampsia] who met the inclusion criteria. Patients without medical coverage that prevented long-term outpatient follow-up at the institution were excluded. Baseline characteristics and evolution, treatment and persistent HT after puerperium were evaluated. The incidence of intrauterine growth retardation (IUGR), preterm delivery, maternal mortality and neonatal death within the first 28 days of life was analyzed.
Results: Among a total of 5825 deliveries/caesarean sections, 152 patients with GHT (37.5%), EPE (19.7%), LPE (38.8%), SIPE (3.3%), and eclampsia (0.6%) who met the inclusion criteria were included in the study. Mean age was 36.4±5.6 years. Aspirin was administered to 38.1% of patients. The most commonly used antihypertensive drugs were labetalol (65.8%) and enalapril (44.1%) during pregnancy and puerperium, respectively. There was no maternal mortality, and neonatal mortality was 3.6%. Persistent HT was 20.0%.
Conclusion: Late preeclampsia was the most frequent HDP in the population analyzed. More than half of the patients who developed HDP did not receive preventive treatment with aspirin, showing a deficit in the identification of the population at risk. One in 5 HDP patients remained with CHT after puerperium.

Key words: Pre-Eclampsia - Hypertension, Pregnancy-Induced - Heart Disease Risk Factors

RESUMEN

Introducción: Los desórdenes hipertensivos del embarazo (DHE) complican el 10% de los embarazos. Son la principal causa de mortalidad materna, y requieren un equipo multidisciplinario para su abordaje.
Objetivos: Cuantificar prevalencia y definir características y evolución de los DHE en un centro con un programa dedicado para su abordaje.
Material y métodos: registro continuo y prospectivo desde noviembre 2019 hasta julio 2021 que incluyó todas las pacientes con DHE (Hipertensión arterial crónica - HTAC, hipertensión gestacional - HTg, preeclampsia precoz – PEp, preeclampsia tardía - PEt, preeclampsia sobreimpuesta – PESI, y eclampsia) y que cumplieran los criterios de inclusión. Se excluyeron las pacientes sin cobertura médica que impidiera su seguimiento ambulatorio a largo plazo en la institución. Se evaluaron características basales y evolución, tratamiento y persistencia de HTA luego del puerperio. Se analizó la incidencia de retardo en el crecimiento intrauterino (RCIU), parto pretérmino, mortalidad materna y muerte neonatal dentro de los primeros 28 días de vida.
Resultados: Se realizaron 5825 partos/cesáreas y se incluyeron 152 pacientes que cumplieron criterios de inclusión, con HTg (37,5%), PEp (19,7%), PEt (38,8%), PESI (3,3%)), eclampsia (0,6%). Edad media 36,4 ± 5,6 años. El 38,1% recibió aspirina. Los antihipertensivos más utilizados fueron labetalol (65,8%) y enalapril (44,1 %) en el embarazo y el puerperio respectivamente. No hubo mortalidad materna, y la neonatal fue 3,6%. La persistencia de HTA fue del 20,0%
Conclusión: La preeclampsia tardía fue el DHE más frecuente en la población analizada. Más de la mitad de las pacientes que desarrollaron DHE no recibían tratamiento preventivo con aspirina, evidenciándose un déficit en la identificación de la población de riesgo. Una de cada 5 pacientes con DHE quedó con hipertensión arterial crónica luego del puerperio.

Palabras clave: Pre-Eclampsia - Hipertensión Inducida en el Embarazo - Factores de riesgo de enfermedades del corazón

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INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are the main cardiovascular complication of pregnancy, with an incidence of 6 to 10% according to the Ibero-American Network of Vascular Alterations in Pregnancy Disorders (RIVATREM), while the World Health Organization estimates that in developing countries the incidence would be 7 times higher. (1-3) According to the classification of the International Society for the Study of Hypertension in Pregnancy (ISSHP), gestational hypertension (GHT), chronic hypertension with superimposed preeclampsia (SIPE), preeclampsia (PE), eclampsia and HELLP syndrome are included in HDP. (4) Its severe forms represent around 4.4% of all births and are the main cause of admission to intensive care during this period. (3,4)

According to the data obtained from the 2018 vital statistics, HDP constituted the first cause of maternal mortality in Argentina, and were also responsible for important severe acute morbidity and chronic disability, both in the mother and in the fetus and neonate. (5). The long-term impact of HDP has recently been considered. In 2011, the American College of Cardiology together with the American Heart Association (ACC/AHA), and later in 2016, the European Society of Cardiology (ESC), incorporated PE as a specific cardiovascular risk factor for women, and there is evidence of its association with adverse cardiovascular events in women who suffer from it in at least one pregnancy. (6-10)

The aim of this registry was to study the prevalence of HDP, describe its epidemiological and clinical characteristics, and evaluate the evolution during hospitalization and puerperium by a dedicated multidisciplinary team in a center of the City of Buenos Aires.

METHODS

A prospective and consecutive registry was carried out in a private center in the City of Buenos Aires from November 2019 to July 2021, including all patients with previous or during hospitalization HDP diagnosis and who met the inclusion criteria (Figure 1). The ISSHP classification was used to define HDP. (4) Preeclampsia was subdivided according to its time of onset into early-onset preeclampsia (EPE), (diagnosed up to week 34) and late preeclampsia (LPE) (diagnosed from week 35 and up to and including puerperium). Blood pressure (BP) was measured following the recommendations of the Hypertension Consensus of the Argentine Society of Cardiology, with the use of validated automatic pressure meters (OMRON®, Kyoto, Japan). Hypertension (HT) was defined when systolic BP (SBP) was ≥140 mmHg and/or diastolic BP (DBP) was ≥90 mmHg and/or the patient was receiving antihypertensive treatment. (11)

According to the ISSHP classification, chronic HT is any HT known prior to pregnancy or which is diagnosed de novo before week 20 of pregnancy, and it is therefore not considered HDP, unless it presents as SIPE. (4)

Those patients who, for reasons of medical coverage, could not have long-term outpatient follow-up at the institution were excluded from the analysis. The information of each patient was recorded in a specially designed database (CCS and AMRG) with access restricted only to the work group responsible for patient follow-up (CCS and HJ). The analyzed data (AMRG) were anonymized in order to preserve the patient identity, following the regulations of Good Clinical Practices and ANMAT. Approval was obtained from the Medical Directorate of the institution to carry out this registry.

Baseline demographic, clinical and laboratory characteristics were evaluated on hospital admission, and they were analyzed during evolution. In addition, treatment was ana-

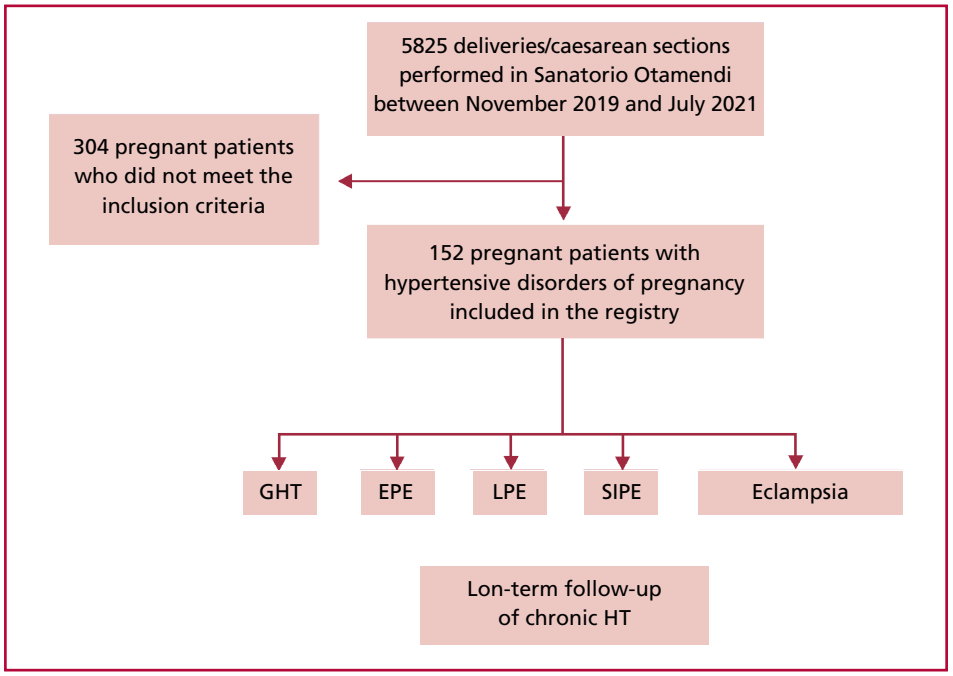


Fig. 1. Registry design

GHT: Gestational hypertension; EPE: Early-onset preeclampsia; LPE: Late preeclampsia; SIPE: Superimposed preeclampsia on chronic hypertension; HT: Hypertension

lyzed at the time of admission and whether this was modified during pregnancy, or later during follow-up. The incidence of intrauterine growth retardation (IUGR), preterm delivery (termination of pregnancy before week 37), maternal mortality and neonatal death defined as that occurring within the first 28 days of life were analyzed as complications. The incidence of persistent HT, defined as that which does not resolve after the third month of puerperium, was studied. The following variables were evaluated as risk factors for the development of HDP: maternal age, body mass index (BMI), smoking and dyslipidemia, nulliparity, twin pregnancy, gestational diabetes, having received fertility treatment, history of previous HDP, history of PE in a first-degree relative, diagnosis of thrombophilia and/or previous autoimmune diseases, and diagnosis of chronic HT. Among patients who developed HDP, we compared the clinical evolution of those who had received aspirin (ASA) as PE prophylaxis with those who had not received it and had developed the same pathology. The characteristics of patients with persistent HT beyond the third month of puerperium were also analyzed, comparing them with those who had resolved the condition.

Statistical analysis

Categorical and continuous variables were used for the descriptive statistical analysis and the $\chi 2$ test was used to compare categorical variables, with Yates correction when appropriate, and one-factor analysis of variance (ANOVA) was applied for continuous variables. A p value <0.05 was considered to be significant. SPSS® 17.0, IBM, United States, statistical package was employed for data analyses.

RESULTS

Among 5825 deliveries/caesarean sections performed in our institution from November 2019 to July 2021, 456 (7.8%) presented HDP. A total of 152 patients with the possibility of long-term follow-up were included in the registry. Mean age was 36.4±5.6 years; 1.3% were diabetic, 7.2% suffered from chronic HT and mean body mass index (BMI) was 28.6±6 kg/m^2. Regarding obstetric history, 34.9% were primigravida. Among multiparous patients, 18.8% had had previous HDP.

As reported in Table 1, 25.6% of patients had received fertility treatment, 30.8% of which were through egg donation.

The most frequent clinical presentation was LPE (38.8%), followed by GHT (37.5%), EPE (19.7%), SIPE (3.3%) and eclampsia (0.6%) (Figure 2).

Table 1 shows the baseline clinical and obstetric characteristics of all the patients in the registry and the most frequent forms of clinical presentation.

During pregnancy, the most used antihypertensive agents were labetalol (65.8%), nifedipine (23.7%) and alpha methyldopa (17.1%). In 63.1% of cases, patients required a drug to control hypertension and the remaining 34.5% more than one. During puerperium, the most used drug was enalapril in 44.1% of cases.

During pregnancy, 38.1% of patients used aspirin as prophylaxis for PE. Among patients who developed EPE, 50% received aspirin while those who developed LPE received aspirin in 33 % of cases. (p=0.02).

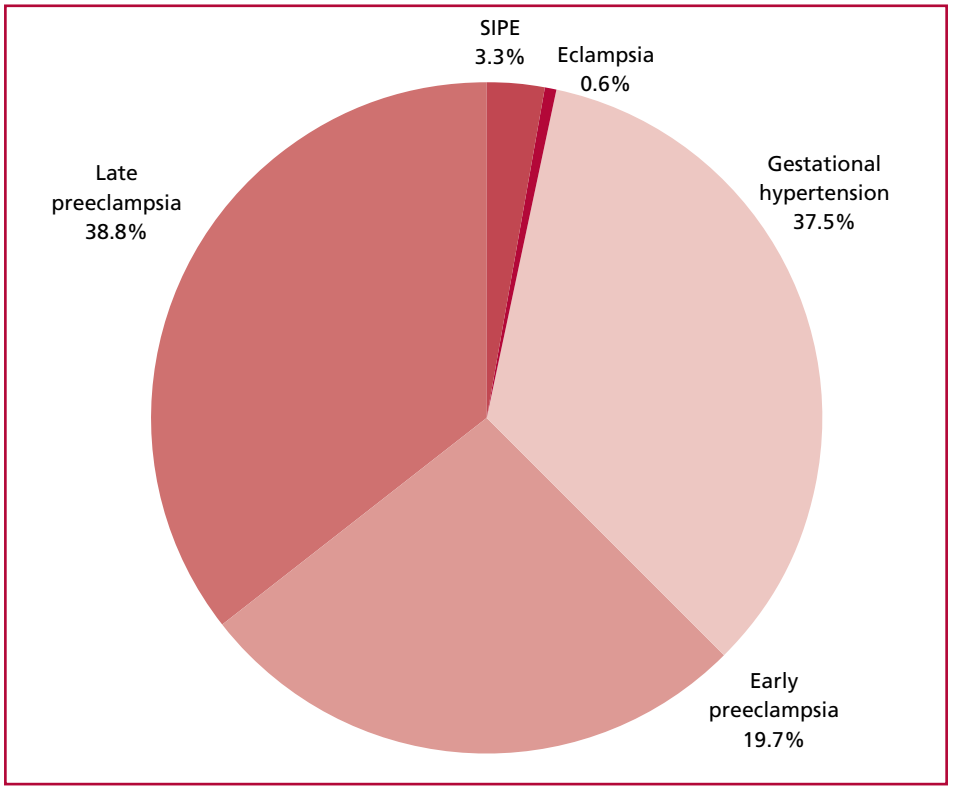
The incidence of intrauterine growth retardation (IUGR) occurred in 25% of patients and increased pulsatility index was recorded in 24.3% of cases. There was no evidence of maternal mortality and neonatal mortality was 3.3%.

The incidence of persistent HT after puerperium was 19.1% (in those patients who completed 3 months of postpartum follow-up and who did not have a diagnosis of chronic HT); Table 2 shows the baseline characteristics of patients who developed chronic HT after HDP. When compared with normotensive patients, the former were aged 37.1 ± 5.6 years vs. 36 ± 5.5 years,

Table 1. Baseline clinical and obstetric characteristics in the total registry population*

	Total (n=152)	GHT (n=57)	EPE (n=30)	LPE (n=59)	SIPE (n=5)
Age in years (m±SD)	36.4 ± 5.6	36.4 ± 4.8	38.1 ± 6.4	35.4 ± 6.0	36.8 ± 3.1
Chronic HT, %	7.2	1.7	9.7	1.7	100
Diabetes, %	1.3	1.7	0.0	1.7	0.0
BMI (m±SD)	28.6 ± 6	26.7 ± 5.9	28.9 ± 6.4	29.0 ± 4.6	29.7 ± 6.4
Smoking, %	1.3	0.0	0.0	3.4	0.0
Hypothyroidism, %	24.3	21.0	36.6	18.6	40.0
Thrombophilia, %	6.6	8.8	3.3	6.8	0.0
Family history of PE, %	3.3	0.0	3.3	5.1	20.0
Primigravida, %	34.9	31.6	23.3	45.7	0.0
HDP in previous pregnancies, %	18.8	17.9	33.3	12.5	80.0
Fertility treatment, %	25.6	19.3	36.6	26.6	20.0
Proteinuria, %	44.1	14.0	66.7	59.3	60.0
PI, %	24.3	12.3	56.7	18.6	40.0
Prior ASA, %	38.1	36.8	50.0	32.2	60.0

m: Mean; SD: Standard deviation; GHT: Gestational hypertension; EPE: Early-onset preeclampsia; LPE Late preeclampsia; HT: Hypertension; BMI: Body mass index; HDP: Hypertensive disorders of preganacy; PI: Pulsatility index; ASA: Aspirin.
*The table does not show the baseline characteristics of the only patient with eclampsia



SIPE: Superimposed preeclampsia on chronic hypertension

Fig. 2. Clinical presentation of hypertensive disorders of pregnancy in patients with complete follow-up (n=152)

p=0.33), with a significantly higher BMI (29.5±5 kg/m² vs. 28±4 kg/m², p=0.04). Among the subgroup of patients with previous pregnancies and HDP, 33% had persistent HT, while the incidence in those without previous HDP it was 18.5% (p=0.16).

DISCUSSION

The most frequent HDP in the analyzed population was LPE (38.8%), with data similar to the results of the Ibero-American Network of Vascular Alterations in Pregnancy Disorders (RIVATREM) report. (2)

Hypertensive disorders of pregnancy have been identified as an independent risk factor for cardiovascular disease, after short, medium and long-term puerperium. (6,8-10) Various studies have evaluated this association and currently there are two pathophysiological mechanisms that are postulated as the most probable; the first is related to pregnancy as an event that causes an "unmasking" of preexisting cardiovascular disease in women with previous risk factors that until then were unknown or had not been manifested; and the second is linked to a process of systemic placental- endothelial dysfunction, both as an indicator of future cardiovascular risk as well as subclinical cardiovascular risk that is aggravated during pregnancy. (12,13) It is the subject of current debate whether all HDP are the continuum of the same pathology, whether the pathophysiological mechanism is common to all of them, and whether the long-term impact of each one is the same. (8)

Arnott et al. estimated the risk of suffering a major cardiovascular event at 10 and 15 years in women from a retrospective registry that included more than 500 000 patients, among which 54 000 presented HDP in their first pregnancy. Early preeclampsia was identified as the main factor of cardiovascular risk within HDP. The authors estimated that the risk of suffering a cardiovascular event at 10 years in women diagnosed with EPE is 15.9 ‰ and 24.5‰ at 15 years compared with those without HDP, whose risk was estimated at 2.1‰ at 10 years and 4.7‰ at 15 years. In addition, they identified smoking and diabetes as factors that increase cardiovascular risk at 10 years in women who had suffered from HDP (9.0 and 10.9‰, respectively). (8) In this same registry, LPE was an independent risk factor, of greater magnitude than smoking.

When comparing our results with those presented in the 2010 Diagnosis and Treatment of Hypertension in Pregnancy Guideline of the Ministry of Health of Argentina, we found a similar incidence of HDP in the analyzed population, and similar associated variables, such as thrombophilia, history of HDP in previous pregnancy, maternal age, chronic HT and BMI. (14)

The use of aspirin to prevent preeclampsia in high-risk pregnancies began to be investigated more than 30 years ago. (15) It is currently recommended in patients with increased risk of PE, evaluated in the first-trimester screening. (16-18) Current screening methods poorly identify women at risk for HDP; par-

Table 2. Comparison of baseline clinical characteristics and hypertensive disorders of pregnancy between patients developing and not developing chronic hypertension

	Non HT (n=123)	Persistent HT (n=29)	p value
Age, years (m±SD)	36.2 ± 5.6	37.3 ± 5.7	0.33
Diabetes, %	0.8	3.4	0.83
BMI, Kg/m2 (m±SD)	27.4 ± 5.4	30.4 ± 6.4	0.04
Smoking, %	0.8	3.4	0.83
Hypothyroidism, %	21.9	34.5	0.15
Thrombophilia, %	5.7	10.3	0.36
Family history of PE, %	2.4	6.9	0.52
Primigravida, %	36.8	27.6	0.36
HDP in previous pregnancies, %	9.7	20.7	0.10
Fertility treatment, %	25.2	27.6	0.79
Proteinuria, %	42.3	51.7	0.35
PI, %	25.2	20.7	0.61
Prior ASA, %	36.6	44.8	0.41
HDP events			
GHT, %	39.8	27.6	0.22
Early PE, %	20.3	17.2	0.70
Late PE, %	39.9	41.4	0.81

m: Mean; SD: Standard deviation; HT: Hypertension; BMI: Body mass index; HDP: Hypertensive disorders of pregnancy; PI: Pulsatility index; ASA: Aspirin; GHT: Gestational hypertension; PE: Preeclampsia

ticularly those who will develop LPE. For EPE, the detection index is 82%, and 53% for LPE (obstetric ultrasound with nuchal translucency plus) (17,18). In our registry, 38.1% of the patients who developed HDP had this drug prescribed as prophylaxis; that is only 33.3% of the women who developed LPE, 50% of those who developed EPE, and 60% of those who developed SIPE. (see Table 1). These results demonstrate the need to implement new methods to identify patients at risk.

Hypothyroidism is recognized as a frequent pathology in women, which can occur in between 0.3% and 2.5% during pregnancy. (19) In our registry, 24.3% of patients suffered from hypothyroidism, which allows assuming a relationship between both pathologies, and a future hypothesis to evaluate more accurate screening methods (17,18).

The most used antihypertensive drug during pregnancy was labetalol, and enalapril during puerperium, which coincides with what is dictated by the hypertension guidelines of the Argentine Society of Cardiology. (11)

Our registry has several limitations. Firstly, as it comes from a clinic with a maternity specialized in high-risk pregnancy, there may be a selection bias. Secondly, according to the type of population admitted to the institution, maternal age and the incidence of fertility treatment are high compared with other parts of the country, and both characteristics are related to HDP. Thirdly, not all pregnant women were evaluated, but only those who developed HDP, so we were unable to determine predictor variables. Finally, not all patients with HDP were followed up, but only those who had a coverage that allowed their outpatient follow-up in our institution.

As strengths of the registry, we found that, although our population was small, information about this group of disorders is scarce in our setting. As it is a closed group of patients, long-term follow-up is possible, which will allow us to know if our population will have adverse cardiovascular outcomes similar to international registries. In our country there are not enough case studies, so we believe that this registry is a starting point in developing research and policies, both public and private, in this area.

In our population there was no maternal mortality and neonatal mortality was low. These results may be due to the management of this group of patients in our center by a team formed by obstetricians, neonatologists, clinicians, and cardiologists.

The incidence of persistent HT after puerperium was 20%; these results should be taken into account when discharging this group of patients, who are often left without clinical-cardiological controls.

Currently we are facing a change in the paradigm of pregnant women and their associated pathologies. This arises from pregnant women at an older age, with greater comorbidities and in many cases subjected to countless fertility treatments, variables that individually and as a whole confer an increased cardiovascular risk per se.

CONCLUSIONS

Late preeclampsia was the most frequent HDP in the analyzed population and 1 out of 5 patients with HDP was diagnosed with CHT after puerperium. Among all

patients who suffered from HDP, 61.9% did not receive preventive treatment with aspirin, including those patients with CHT. These results suggest the need to find new ways to identify risk groups.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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