Assessment of Cardiovascular Disease after Hypertensive Pregnancy Disorders

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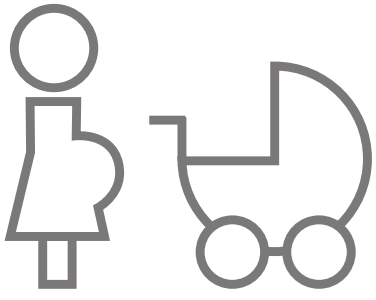

CHAPTER 5

Prognostic model for chronic hypertension in women with a history of hypertensive pregnancy disorders at term

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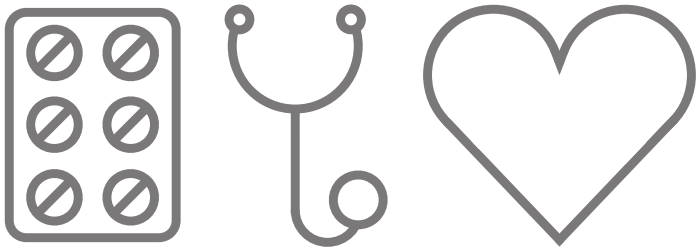

ABSTRACT

Introduction: The association between hypertensive pregnancy disorders and cardiovascular disease later in life is well described. In this study we aim to develop a prognostic model from patients characteristics known *before*, *early in*, *during* and *after* pregnancy to identify women at increased risk of cardiovascular disease e.g. chronic hypertension years after pregnancy complicated by hypertension at term.

Methods: We included women with a history of singleton pregnancy complicated by hypertension at term. Women using antihypertensive medication before pregnancy were excluded. We measured hypertension in these women more than 2 years postpartum. The following patients characteristics *before*, *early in*, *during* and *after* pregnancy were considered to develop a prognostic model of chronic hypertension at 2-years: maternal age, ethnicity, education, parity, smoking, family history for hypertension, cardiac event or stroke and hypertensive pregnancy disorder, BMI, blood pressure at pregnancy intake, highest systolic and diastolic blood pressure during pregnancy, development of preeclampsia or pregnancy induced hypertension, small for gestational age neonate, progression to severe disease and blood pressure six weeks post-partum. Univariable analyses followed by a multivariable logistic regression analysis was performed to determine which combination of predictors best predicted chronic hypertension. Model performance was assessed by calibration (graphical plot) and discrimination (area under the receiver operating characteristic (AUC)).

Results: Of the 305 women in who blood pressure 2.5 years after pregnancy was assessed, 105 women (34%) had chronic hypertension. Higher maternal age, lower education, negative family history on hypertensive pregnancy disorders, higher BMI at booking, higher diastolic and systolic blood pressure during pregnancy and higher diastolic blood pressure at six weeks post-partum were included in the prognostic model for chronic hypertension. Model performance was good as indicated by good calibration and good discrimination (AUC; 0.83 (95% CI 0.75 – 0.92).

Conclusion*:* Chronic hypertension can be expected from patient characteristics *before*, *early in*, *during* and *after* pregnancy. These data underline the importance and awareness of detectable risk factors both for increased risk of complicated pregnancy as well as increased risk of cardiovascular disease later in life.

INTRODUCTION

Cardiovascular disease is the leading cause of death in women in the western world [1]. Worldwide a third of all death in women is caused by heart disease. Hypertensive pregnancy disorders are associated with a higher cardiovascular disease risk later in life [2-5]. Epidemiologic studies showed that ischemic heart disease is more common among women with a history of hypertensive pregnancy disorders than in the general population; women with a history of hypertension have a 2-fold risk of maternal ischemic heart disease admission or death [6,7]. In addition, women with a history of hypertensive pregnancy disorders experience elevated cardiovascular risk markers as soon as 2.5 years after pregnancy including chronic hypertension [8].

Hypertensive disorders in pregnancy are hypothesized to act as a "stress test" for cardiovascular disease later in life; women who fail this 'stress test' by developing hypertensive pregnancy disorders are suggested to have an increased cardiovascular risk [9]. Since pregnancy is a relative early event in women's life, failure of this stress test or early manifestation of cardiovascular disease, opens opportunities for early diagnosis and preventive measurements in cardiovascular disease at a relative young age.

Risk indicators for development of preeclampsia, one of the hypertensive pregnancy disorders, are well investigated. A model by North et al [10] shows that at 14-16 weeks' gestation, amongst others, advanced maternal age, elevated mean arterial blood pressure, high body mass index (BMI), positive family history of pre-eclampsia and positive family history of coronary heart disease were predictive for development of preeclampsia.

Tuuk et al [11] developed a predictive model for the development of severe hypertensive disease in pregnancy for women diagnosed with pregnancy induced hypertension or mild pre-eclampsia. Factors strongly associated with progression to a high-risk situation were, amongst others; null parity, maternal age, ethnicity and higher blood pressures during pregnancy.

Various risk factors for chronic hypertension after hypertensive pregnancy disorders have been reported, but no prognostic model was developed on this subject. We focus on chronic hypertension in this study, since several previous studies have shown that, in women, cardiovascular disease the main determinator is hypertension [12]. In this study, we aim to develop a prognostic model for chronic hypertension at 2.5 years post-partum after hypertensive pregnancy disorders by using family history, blood pressure measurements and maternal weight at the start of pregnancy, and indicators developed in pregnancy.

MATERIAL AND METHODS

Definitions

We included women initially selected from the HYPITAT trail [13]. Between October 2005 and March 2008 the HYpertension and Preeclampsia Intervention Trial At Term, the HYPITAT study (trial registration: ISRCTN08132825) was conducted nationwide in the Netherlands. This was a multicenter, parallel, open-label randomized controlled trial of induction of labor versus expect-

ant management in women with gestational hypertension or preeclampsia at term. The HYPITAT study included women with gestational hypertension or preeclampsia, with a singleton pregnancy and a fetus in cephalic presentation at a gestational age between 36+0 and 41+0 weeks. These patients with a history of hypertensive pregnancy disorder were invited for our follow up study, the HyRAS study [8]. Between June 2008 and November 2010 women who participated in this follow-up study were assessed for cardiovascular risk factors at least two years after index pregnancy. All women in the HyRAS study have been included. A description of the inclusion and exclusion criteria of the study participants and the results of the study are described and published elsewhere (HyRAS study) [8,13].

In summary, for the HyRAS follow up study cardiovascular risk factor assessment was conducted by blood pressure measurement, weight and height at least two years after post partum. Furthermore, all participants were asked to complete a questionnaire including obstetric and family history, current use of medication e.g. antihypertensive medication, and smoking [8].

Indicators

The information analyzed in this study was information known *before* pregnancy that included maternal age, ethnicity (Caucasian or non-caucasian), education (high education or low education), parity, smoking (smoking at start of pregnancy), family history of hypertension, cardiac event or stroke and hypertensive pregnancy disorder (included first degree family). High education was defined as higher professional school or university. Further we included information known *early in* pregnancy that included BMI and blood pressure at pregnancy intake. In addition, we analyzed information *during* pregnancy that included highest blood pressure during pregnancy, existence of preeclampsia or pregnancy induced hypertension, small for gestational age neonates and progression to severe disease. Small for gestational age was defined as a birth weight below tenth percentile for gestational age [14]. Progression to severe disease was defined as any of the following: a diastolic BP > 110 mmHg, a systolic BP > 170 mmHg and/or proteinuria > 5 g in 24 h, maternal complications: eclampsia, HELLP syndrome (platelet count (<100 · 109/L and AST >70U/L or ALT>70U/L) and mortality. Finally we included information *after* pregnancy, which was a blood pressure measurement at six weeks post-partum control, for its predictive value on chronic hypertension after hypertensive pregnancy disorders.

To define if women had chronic hypertension, blood pressure was measured 2.5 years after pregnancy for all cases, according to the HYRAS study protocol. The cases all filled in a questionnaire on family history and further information important for this study was gathered from the HYPITAT database.

Outcome - Chronic hypertension

For this study we evaluate hypertension at 2.5 years after pregnancy in women with a history of hypertensive pregnancy disorders. Chronic hypertension is defined as a diastolic blood pressure ≥ 90mmHg and/ or the systolic blood pressure ≥ 140mmHg at 2.5 years post partum or use of antihypertensive medication.

Statistics

Baseline characteristics were determined separately for patients with chronic hypertension and the patients who were normotensive at 2.5 year post-partum. Means and standard deviations were calculated for continuous variables and numbers and proportions were presented for categorical variables.

Several women (n = 207 (67%)) had missing values for one or more of the potential predictors.

Univariable logistic regression analyses were performed to analyze the relationship between the occurrence of the endpoint (chronic hypertension) and each of the patient variables. For both dichotomous and continuous variables, odds ratios, 95% confidential intervals and p-values, were calculated. For continuous variables we assessed whether the association was linear, and if not, variables were dichotomized according to commonly used cut-offs described in the scientific literature.

Although generally not recommended, only those predictors were included for multivariable analysis that had a p-value ≤ 0.20 in univariable analysis to retain a reasonable number of events per variable [15,16].

Subsequently a multivariable logistic regression analysis with a stepwise backward selection procedure of the variables was preformed based on p-value (<0.2 for inclusion) to construct a prediction model for chronic hypertension. Internal validation was assessed by bootstrapping, in which 1000 samples of equal size as the study population were drawn with replacement from the study population.

Model performance was assessed using calibration and discrimination. Calibration refers to the agreement between predicted probabilities and observed proportions and was assessed graphically using a calibration plot [15, 16]. Discrimination refers to the ability of the model to distinguish those women with chronic hypertension from those without and was assessed by the area under the Receiver Operating Characteristic (AUC). Analyses were performed using SPSS Statistics 22.0.

RESULTS

Indicators

From 306 cases included in HyRAS study, we included 305 women who had a pregnancy complicated by hypertension. Of one woman no blood pressure was available at 2.5 years post partum, she was excluded from this study. 105 women (34%) had chronic hypertension, hypertension 2.5 years post partum.

Baseline characteristics

Baseline characteristics are displayed in **table 1**.

Women with chronic hypertension were significantly less often Caucasian (resp. 84% vs 92%) were less often nulliparous at index pregnancy (resp. 54% vs 77%), had less often preeclampsia (resp. 18% vs 28%) and had a higher diastolic blood pressure six weeks post-partum (resp. 90mmHg vs 80mmHg) compared to normotensive women. No significant differences were found is maternal age, education, smoking, family history on hypertension, on cardiac event or stroke

and on hypertensive pregnancy disorders, BMI, blood pressure at booking, highest blood pressure in pregnancy, small for gestational age neonates, progression to severe disease and systolic blood pressure six weeks post-partum.

Of all women with a history of pregnancy complicated by hypertension, 75 had a history of preeclampsia and 230 had a history of pregnancy induced hypertension.

Of all women with a history of preeclampsia (n = 75), 18 women (24%) had chronic hypertension. Of all women with a history of pregnancy induced hypertension (n = 230), 87 women (37%) had chronic hypertension. Significantly more women with a history of pregnancy induced hypertension experienced chronic hypertension defined as hypertension 2.5 years post partum compared to women with a history of preeclampsia (p = 0.01).

Prognostic model

In the univariable analyses, the following patient characteristics were found to significantly increase the risk of chronic hypertension: advanced maternal age, non-Caucasian ethnicity, nulliparity at time of the index pregnancy, a positive family history for hypertension and for cardiac event or stroke, higher BMI at booking, higher blood pressure at booking, higher highest blood pressure during pregnancy, small for gestational age neonate, progression to severe disease and higher blood pressure post-partum **(table 2).** Characteristics that reduced the risk of chronic hypertension were higher education, smoking, positive family history on hypertensive pregnancy disorders and the preeclampsia (compared to the existence pregnancy induced hypertension) **(table 2)**.

For all continuous variables we found a linear association. In a multivariable regression model there were seven variables associated with chronic hypertension; higher maternal age, lower education, negative family history on hypertensive pregnancy disorders, higher BMI at booking, higher diastolic blood pressure at pregnancy intake, higher systolic blood pressure during pregnancy and higher diastolic blood pressure at six weeks post-partum **(table 2).** De variables that were significantly associated with chronic hypertension were lower education, higher diastolic blood pressure at booking and higher systolic blood pressure during pregnancy**.**

The model showed good discriminative ability with an AUC of 0.83 (95% CI 0.75 – 0.92). Predicted probabilities and observed proportions showed good agreement, indicating good calibration of the model (**Figure 1**).

Table 1. Baseline characteristics for women with chronic hypertension vs normotensive women

	Chronic hypertension women n = 105		**Normotensive women** n = 200		**Total population** n = 305
	Value*	Data available n (%)	Value*	Data available n (%)	
Characteristics *before* pregnancy					
Maternal age (year)	32.7 (4.5)	104 (99%)	30.4 (5.2)	199 (99%)	31.2 (5.1)
Caucasian	83 (84%)	98 (93%)	166 (92%)	180 (90%)	250 (81%)
High Education	22 (21%)	64 (61%)	54 (27%)	128 (64%)	76 (24%)
Nulliparous	57 (54%)	105 (100%)	154 (77%)	200 (100%)	211 (69%)
Smoking	10 (10%)	97 (92%)	28 (15%)	189 (94%)	38 (12%)
Positive family history on hypertension	82 (80%)	102 (97%)	134 (70%)	190 (95%)	216 (70%)
Positive family history on cardiac event or stroke	56 (54%)	102 (97%)	96 (50%)	190 (95%)	153 (50%)
Positive family history on hypertensive pregnancy disorders	16 (16%)	101 (96%)	42 (22%)	190 (95%)	58 (19%)
Characteristics *early in* pregnancy					
BMI at booking	26.8 (5.0)	95 (90%)	25.8 (4.8)	173 (86%)	26.4 (4.8)
BP[1] at booking (mmHg)					
BP[1] diastolic	75 (8.1)	100 (95%)	71 (8.9)	196 (98%)	72 (8.9)
BP[1] systolic	123 (11.7)	100 (95%)	119 (11.8)	196 (98%)	120 (12.0)
Characteristics *during* pregnancy					
Highest BP[1] (mmHg)					
BP[1] diastolic	102 (8.9)	104 (99%)	100 (8.4)	199 (99%)	101 (8.5)
BP[1] systolic	158 (18.2)	104 (99%)	152 (14.1)	199 (99%)	154 (15.8)
PE[2] or PIH[3] (PE)	19 (18%)	105 (100%)	57 (28%)	199 (99%)	67 (24%)
Neonate SGA[4] (SGA)	9 (8%)	105 (100%)	11 (5%)	199 (99%)	20 (6%)
Progression to severe disease (severe disease)	37 (35%)	105 (100%)	57 (28%)	199 (99%)	94 (30%)
Characteristics *after* pregnancy					
BP[1] six weeks post-partum					
BP[1] diastolic	87 (9.4)	60 (57%)	79 (9.5)	98 (49%)	82 (10.1)
BP[1] systolic	133 (14.1)	60 (57%)	124 (11.2)	98 (49%)	127 (13.3)

[1]BP = Blood Pressure, [2]PE = Preeclampsia, [3]PIH = Pregnancy Induced Hypertension, [4]SGA = Small for Gestational Age.

Value given in mean (standard deviation) or n (percentage)

Table 2. Univariable and Multivariable analyses for women with chronic hypertension vs normotensive women

	Univariable analyses			Multivariable analyses			
	OR	95% CI	P value	Regression-coefficient	OR	95% CI	P value
Characteristics *before* pregnancy							
Maternal age	2.11	1.29 – 3.46	**<0.01**	0.06	1.06	0.99 – 1.13	0.06
Ethnicity (Caucasian)	2.14	0.98 – 4.64	**0.05**	1.00	2.73	0.97 – 7.70	0.05
Education (high)	0.71	0.38 – 1.33	0.29				
Parity (nulliparous)	2.81	1.70 – 4.67	**<0.01**	0.88	2.41	**1.24 – 4.69**	**<0.01**
Smoking	0.66	0.30 – 1.42	0.29				
Positive family history on hypertension	1.71	0.96 – 3.06	**0.06**	0.68	1.97	0.96 – 4.04	0.06
Positive family history on cardiac event or stroke	1.19	0.73 – 1.93	0.47				
Positive family history on hypertensive pregnancy disorders	0.66	0.35 – 1.25	0.20				
Characteristics *early in* pregnancy							
BMI at booking	1.52	0.92 – 2.52	**0.10**				
BP[1] at booking (mmHg)							
BP[1] diastolic (>70mmHg)	2.66	1.60 – 4.41	**<0.01**	0.05	1.05	**1.01 – 1.09**	**<0.01**
BP[1] systolic (>120mmHg)	1.57	0.95 – 2.57	**0.07**				
Characteristics *during* pregnancy							
Highest BP[1] (mmHg)							
BP[1] diastolic	1.46	0.84 – 2.55	**0.17**				
BP[1] systolic	1.74	0.97 – 3.11	**0.06**	0.03	1.03	1 .05	<0.01
PE[2] or PIH[3] (PE)	0.55	0.30 – 0.98	**0.04**				
Neonate SGA[4] (SGA)	1.60	0.64 – 3.99	0.31				
Progression to severe disease (severe disease)	1.35	0.81 – 2.24	0.23				
Characteristics *after* pregnancy							
BP[1] six weeks post-partum							
BP[1] diastolic (≥90mmHg)	4.16	2.05 – 8.44	**<0.01**				
BP[1] systolic (≥140mmHg)	3.52	1.60 – 7.74	**<0.01**				
Intercept				-12.38			

[1]BP = Blood Pressure, [2]PE = Preeclampsia, [3]PIH = Pregnancy Induced Hypertension, [4]SGA = Small for Gestational Age

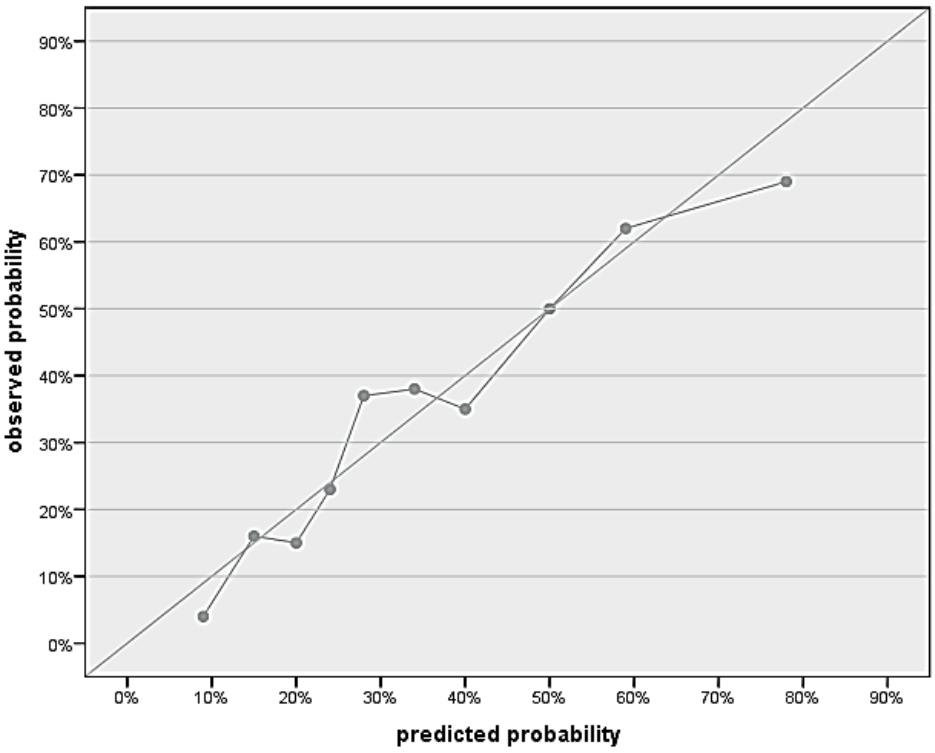

Figure 1. Calibration plot demonstrating predicted probabilities against observed proportions for chronic hypertension. The dots indicate deciles of the total study population.

DISCUSSION

We developed a prognostic model for chronic hypertension after a pregnancy complicated by hypertensive pregnancy disorders. In the prognostic model we found that the variables that were associated with chronic hypertension later were higher maternal age, lower education, negative family history on hypertensive pregnancy disorders, higher BMI at booking, higher diastolic blood pressure at pregnancy intake, higher systolic blood pressure during pregnancy and higher diastolic blood pressure at six weeks post-partum. These data open opportunities for awareness and possibility for prevention of chronic hypertension and therefore cardiovascular disease later.

Risk of cardiovascular disease is usually established by risk score profiles based on cohort studies like the Framingham Heart Study [17]. Framingham predictive factors for 30 year cardiovascular risk are male sex, age, systolic blood pressure, use of antihypertensive treatment, smoking, diabetes mellitus and body mass index or lipids. The Framingham risk score was derived from data within a middle-class middle-aged Caucasian population and may therefore not be predictive in young adults. Therefore the coronary artery risk development in young adults (CARDIA) was performed and concluded that the Framingham risk score is better than prehypertension in pre-

dicting hypertension and may be a useful tool for identifying young adults with a high risk for developing hypertension [18]. A study on cardiovascular risk factors for young women indicates that auto-immune processes, high lipoprotein(a), and environmental exposure to tobacco smoke and traffic exhaust may play a role in early atherogenesis [19]. This study did not include pregnancy or pregnancy complications in the risk prediction, despite the fact that pregnancy is seen as a vascular stress test [20]. Smith et al state that there are three times during a woman's life that she accesses the health care system, as an infant, for pregnancy and postpartum care, and when she develops a chronic disease [21]. Since cardiovascular disease usually develops over a long period of time, pregnancy and the postpartum period provide a new early window of opportunity to identify risk factors of reproductive age and to improve their long-term health.

The Maternal Health Clinic by Smith el al described an approach to health maintenance and disease prevention by a follow up program after pregnancy. They propose identification for followed up postpartum and included screening opportunities in order to indicate better which women should be closer monitored because of a higher cardiovascular disease risk. For the program, they gathered information that could indicate cardiovascular risk, e.g. age, family history, history of smoking and history of hypertension. Further they included information from general physical examination, e.g. height, eight, body mass index and blood pressure.

Risk indicators for development of preeclampsia or for development if severe disease in women with preeclampsia or pregnancy induced hypertension or mild preeclampsia by North et al [10] and Tuuk et al [11] included beside the risk factor we found in our study (an advanced maternal age), an elevated blood pressure early in pregnancy, a positive family history on cardiovascular disease and a higher BMI. All of these factors did show a positive relation with chronic hypertension in the univariable analyses and a higher blood pressure early in pregnancy was found to be a significant predictive value for chronic hypertension after a pregnancy complicated by hypertensive disease. Surprisingly we found a higher risk on chronic hypertension for women with a negative family history on hypertensive pregnancy disorders. This dispute with the indicators in predictive models for preeclampsia, in which a positive family history on hypertensive pregnancy disorders is a predictive factor for preeclampsia [22].

Strengths and Weakness

Hypertensive pregnancy disorders are still a major pregnancy complication [23]. Chronic hypertension is an important general health problem with high morbidity and mortality in women [24]. Strength of this study is the large study group in a longitudinal, prospective follow up setting of women who had a pregnancy complicated by hypertension at term. Although hypertension after a hypertensive pregnancy disorder can take up months to dissolve [25], we assumed that the influence of the index pregnancy would be (mostly) disappeared at time of blood pressure measurement post-partum for this study. Therefore, we labeled hypertension 2.5 years after pregnancy chronic hypertension.

For clinical convenience we evaluated the prognostic value of indicators which can be assessed by simple noninvasive tests and (short) medical history. The physical exams at pregnancy booking for gathering of information include weighing the patient and blood pressure measurement.

During pregnancy and post-partum only blood pressure measurements were taken into account. These simple tests can be easily performed by most health care workers. If there is more need on prediction of chronic hypertension after hypertensive pregnancy disorders, possible addition serum and plasma markers can even add more information to this prognostic model [26, 27].

Recommendation

Results of this study contribute in more awareness in women and obstetric care workers on the prevalence and risk factors of chronic hypertension after hypertensive pregnancy disorders. Because of a lack of awareness in obstetric care providers, women with hypertensive pregnancy disorders are not well informed on the higher risk of cardiovascular disease later in life [28].

Preventive measurements could reduce the adverse outcome of this disease with high morbidity and mortality [29, 30]. Previous study by Hermes et al showed that 34% of women who had experienced pregnancy related hypertensive complications had hypertension 2.5 years postpartum of which > 80% is (medically) untreated.

We suggest that CVD risk and modifiable risk factors in women with a history of hypertensive pregnancy disorders can be reduced by a multifaceted strategy of intensive lifestyle interventions, and, if indicated, pharmacological interventions. These data justify a randomized controlled trial on follow up management in these women with a complicated pregnancy and a higher risk on cardiovascular disease.

CONCLUSION

We developed a prognostic model for chronic hypertension after hypertensive pregnancy disorders which included different factors *before*, *early in*, *during* and *after* pregnancy. This information is important to be collected in pregnant and post-partum women to predict the cardiovascular risk factors later in life.

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