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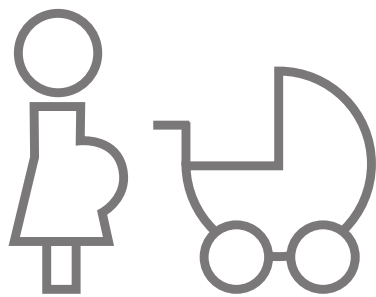
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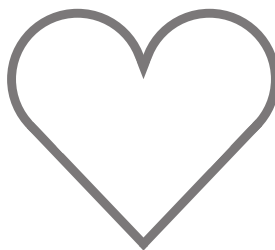
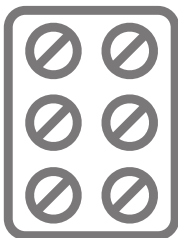
# CHAPTER

# 6

High blood pressure six weeks  
postpartum after hypertensive  
pregnancy disorders at term  
is associated with chronic  
hypertension

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**ABSTRACT**

**Objectives:** Hypertension in pregnancy is associated with cardiovascular disease (CVD) later in life. Blood pressure monitoring in women who experienced hypertension in pregnancy after puerperium has been suggested to be important for early detection and prevention of CVD. The aim of this study is to evaluate if hypertension six weeks postpartum is associated with chronic hypertension in women with a history of term hypertensive pregnancy disorders.

**Study design:** Women with a history of term gestational hypertension or preeclampsia were included in a follow up study of the HYPITAT trial. Blood pressures were measured six weeks and 2.5 years postpartum according to the study protocol.

**Main outcome measures:** Hypertension was defined as a diastolic blood pressure  $\geq 90$  mmHg and/or a systolic blood pressure  $\geq 140$  mmHg or use of antihypertensive medication. Differences in categorical variables between groups were analyzed by Chi-Square tests. Blood pressure was analyzed using unpaired t-tests and Wilcoxon ranked tests.

**Results:** Among 187 women who had term hypertensive pregnancy disorders, 75 (40%) had hypertension at six weeks postpartum. Of these 46 (61%) had hypertension 2.5 years postpartum. In contrast, of 112 women without hypertension at six weeks postpartum, 36 (32%) had hypertension 2.5 years (OR 3.3, 95% CI 1.8–6.2).

**Conclusion:** Among 61% of women who had hypertensive pregnancy disorders at term, high blood pressure at six weeks postpartum indicated chronic hypertension. This warrants the importance of identification of hypertension 6 weeks postpartum for women's future health.

## INTRODUCTION

Cardiovascular disease (CVD) is the most important cause of morbidity and mortality in women in the western world [1]. A recent large review shows the association of hypertensive pregnancy disorders and cardiovascular disease in women later in life [2]. Both case-control and cohort studies indicated higher cardiovascular and cerebrovascular events in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy [3–8]. Hypertensive pregnancy disorders rank among the commonest causes of maternal and perinatal morbidity and mortality worldwide [9]. The prevalence of hypertensive pregnancy disorders is 6–8% [10,11]. The increased risk for the development of cardiovascular disease for women with a history of hypertensive pregnancy disorders has been described in the range of 1.5 till 4-times [2]. Women with a combination of preeclampsia, intrauterine growth restriction and a preterm delivery have an 8-fold higher risk to develop cardiovascular disease in later life compared to women with normotensive pregnancies [6]. These data favor attention for the future cardiovascular health in women who experienced hypertension in pregnancy.

We recently [8] described that women with a history of gestational hypertension or preeclampsia at term had a high prevalence of hypertension (34%) and metabolic syndrome (25%) 2.5 years postpartum. In addition, women with a history of hypertension in pregnancy have higher levels of glucose, insulin, triglycerides, total cholesterol and LDL cholesterol compared to women with a history of a normotensive pregnancy described in a meta-analysis [12].

These data suggest that biochemical cardiovascular risk factors are potential indicators for cardiovascular disease later in life. These data support the hypothesis of hypertensive pregnancy disorders as a stress test for cardiovascular disease in later life and provide an opportunity for screening and primary prevention of cardiovascular disease. This raises the question whether blood pressure measurement after hypertensive pregnancy disorders at the routine six weeks postpartum visit predicts development of hypertension later. Up to now authoritative guidelines for prevention of cardiovascular disease in women and for hypertensive disorders of pregnancy do not include specific recommendations on blood pressure measurements after pregnancy [13–15].

In this study we analyzed whether hypertension at six weeks postpartum is associated with hypertension at 2.5 years postpartum (chronic hypertension) in women with a history of term hypertensive pregnancy disorders.

## METHODS

### Participants

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 expectant management in women with gestational hypertension or preeclampsia at term [16]. 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.

In the HYPITAT study gestational hypertension was defined as a diastolic blood pressure of 95 mmHg or higher, measured on two occasions at least six hours apart. Preeclampsia was defined as diastolic blood pressure of 90 mmHg or higher measured on two occasions at least six hours apart, combined with proteinuria (two or more occurrences of protein on a dipstick, >300 mg total protein within a 24 h urine collection, or ratio of protein to creatinine >30 mg/mmol). Patients were excluded if they had severe gestational hypertension or severe preeclampsia before randomization, defined as systolic blood pressure of 170 mmHg or higher, diastolic blood pressure of 110 mmHg or higher, or proteinuria of 5 g or higher in 24 h. Other exclusion criteria were antihypertensive medication use for chronic hypertension, diabetes mellitus, gestational diabetes treated with insulin, renal disease,

heart disease, previous cesarean section, hemolysis elevated liver enzymes and low platelets syndrome (HELLP syndrome), oliguria of less than 500 mL per 24 h, pulmonary edema or cyanosis, human immunodeficiency virus (HIV) seropositivity, use of intravenous antihypertensive medication, fetal anomalies, suspected intrauterine growth restriction (IUGR), and abnormalities detected during fetal – heart rate monitoring. Progression to severe disease was defined as the occurrence of any of the following: eclampsia, HELLP syndrome (platelet count <100 x 10<sup>9</sup>/L and ASAT >70 U/L or ALT >70 U/L), maternal mortality, diastolic blood pressure ≥110 mmHg, systolic blood pressure ≥170 mmHg and/or proteinuria ≥5 g in 24 h. At randomization women consented to be contacted 2.5 years postpartum to participate in the follow-up study, the Hypertension Risk Assessment Study (HyRAS study) [18].

The HYPITAT study protocol included a six week postpartum visit with a blood pressure measurement. Blood pressure was measured manually according to a local protocol of the hospital. For missing data in the medical, obstetrical records on blood pressure measurement in the postpartum period we contacted general practitioners. We called the practices three times. In case of no response we faxed the general practitioners. Blood pressure was included in this study if it was measured manually within the period of six to eight weeks postpartum either by gynecologist or general practitioner.

The HyRAS study, follow up study of the HYPITAT, found place between June 2008 and November 2010. Women who had participated in the HYPITAT trial were invited for participation in the HyRAS study. The aim of the HyRAS study was to assess cardiovascular risk factors at least 2 years postpartum in women with a history of term hypertensive pregnancy disorders. For the HyRAS trial we used a follow-up period of at least 2 years as this time interval allows using pregnancy as a stress test to identify young women who are at high risk for cardiovascular disease in later life. Furthermore, 2.5 years is long enough to ensure that pregnancy and lactation have no major influence on biochemical cardiovascular risk factor levels. Three academic hospitals and 17 non-academic hospitals across four geographical regions in the Netherlands (Leiden, Groningen, Amsterdam, Brabant) participated. The methods, and results of the HyRAS study are described in detail and published elsewhere [17,18]. In short, women who experienced gestational hypertension or preeclampsia at term exhibit significantly more cardiovascular risk factors 2.5 years postpartum, including systolic and diastolic blood pressure, body mass index, glucose, HbA1c, insulin and total cholesterol compared to women with a history of uncomplicated pregnancy. Furthermore, they appear to have higher prevalence of chronic hypertension and metabolic syndrome

compared to women with a history of normotensive pregnancies. Blood pressure measurement 2.5 years postpartum was done according to the HyRAS study protocol [18]; blood pressure measurement manually in the sitting position at the right upper arm. Information on antihypertensive medication use was obtained by a questionnaire and from the nationwide pharmacies' databank.

### Statistics

We used SPSS (version 17) to analyze the data. Differences in baseline characteristics were analyzed with Chi-Square tests. The unpaired Student's t-test and Wilcoxon signed ranks test were used to compare blood pressures between women with a history of gestational hypertension and women with preeclampsia. The predictive value of blood pressure measurements at six weeks postpartum on hypertension at 2.5 years postpartum was analyzed by logistic regression and described by odds ratios and their 95% confidential intervals. P-values <0.05 were considered to indicate statistical significances.

## RESULTS

In short, of the 751 eligible women from the HYPITAT trial, women with a history of hypertensive pregnancy disorders, 168 women refused participation, 175 women were lost to follow-up and 101 pregnant or lactating women were excluded. One woman died in a car accident. In the follow up study, HyRAS study, 306 women were included from three academic hospitals and 17 non-academic

hospitals across four geographical regions in the Netherlands (Leiden, Groningen, Amsterdam, Brabant) [18]. In this study we included 187 women (61%) of the total of 306 women with a history of term hypertensive pregnancy disorders who had their blood pressure measured at six weeks postpartum. In 119 women (49%), blood pressure was not measured at six weeks postpartum (**figure 1**).

Women with hypertension at six weeks postpartum were older, more often multiparous and more often had progression to severe disease than women without hypertension at six weeks postpartum (resp.  $p < 0.01$ ;  $p = 0.03$ ;  $p = 0.04$ ). There were no significant differences in ethnicity, smoking, body mass index at start pregnancy, blood pressure at start pregnancy and hypertensive pregnancy disorder (gestational hypertension or preeclampsia) between women with hypertension at six weeks postpartum compared to **table 1**.

More women who had hypertension at six weeks postpartum, had also hypertension at 2.5 years postpartum compared to women who were normotensive at six weeks postpartum ( $p < 0.01$ ; OR 3.3 (95% CI 1.8–6.2)). When we adjusted for age and parity the odds ratio of hypertension at six weeks postpartum to hypertension at 2.5 years postpartum is 2.9 ( $p < 0.01$ ; 95% CI 1.5–5.8). The positive predictive value of hypertension at six weeks postpartum for hypertension at 2.5 years postpartum was 61% and the negative predictive value was 67%.

The predictive value of hypertension at six weeks postpartum on hypertension at 2.5 years after pregnancy did not depend on whether pregnancy was complicated by either gestational hypertension or preeclampsia.

**Table 1.** Baseline Characteristics

	Hypertensive 6 weeks postpartum (n = 75)	Normotensive 6 weeks post- partum (n = 112)	p-value	BP not mea- sured 6 weeks postpartum (n = 119)	p-value**
Maternal age at start pregnancy Mean (SD)	32 (5.8)	30 (4.8)	<b>&lt;0.01</b>	32 (4.6)	0.16
Parity; primiparous N (%)	48 (64%)	88 (78%)	<b>0.03</b>	75 (63%)	0.07
Ethnicity; Caucasian N (%)	64 (91%)	94 (94%)	0.84	92 (84%)	<b>0.01</b>
Smoking; smoking N (%)	10 (13%)	14 (13%)	1.00	14 (13%)	0.96
Body mass index at start pregnancy; BMI $\geq$ 25kg/m <sup>2</sup> N (%)	12 (16%)	20 (18%)	0.69	50 (47%)	0.31
Gestational hypertension or preeclampsia; preeclampsia N (%)	15 (20%)	23 (21%)	1.00	38 (32%)	<b>0.02</b>
Diastolic blood pressure at start pregnancy, mmHg Mean (SD)	74 (9.3)	72 (9.0)	0.10	72 (8.7)	0.61
Systolic blood pressure at start pregnancy, mmHg Mean (SD)	122 (13)	119 (10)	0.16	120 (12.2)	0.47
Progression to severe disease* N (%)	35 (47%)	35 (31%)	<b>0.04</b>	24 (20%)	<b>&lt;0.01</b>

\*eclampsia, HELLP syndrome, maternal mortality, diastolic BP $\geq$ 110mmHg, systolic BP $\geq$ 170mmHg, proteinuria $\geq$ 5gr/24h

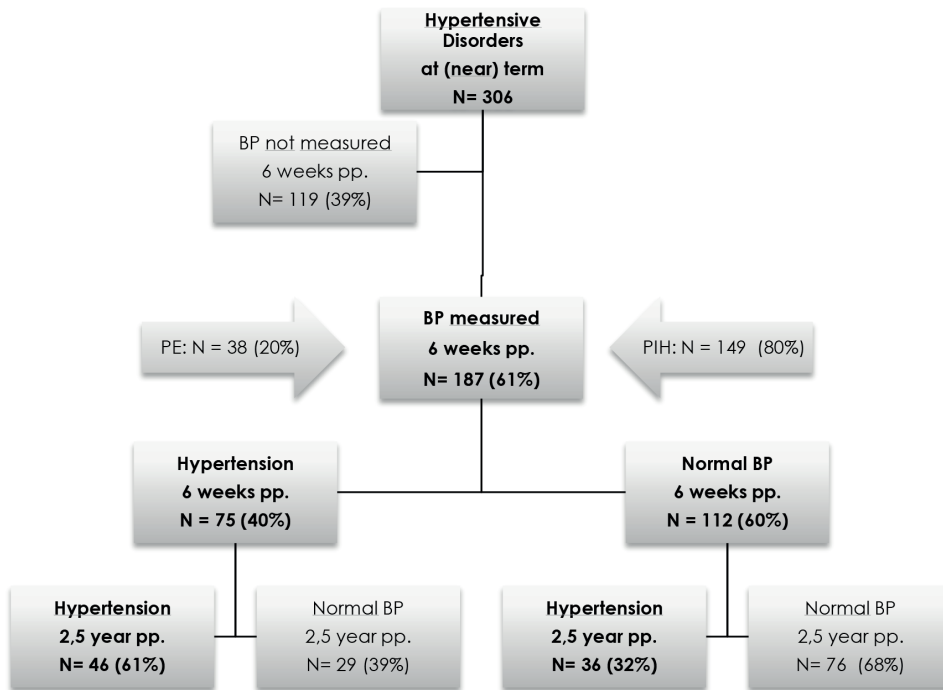
\*\* women in whom blood pressure was **not** measures versus women in whom blood pressure was measured

### Subanalyses

The high prevalence of hypertension postpartum in the study group might partially be explained by inclusion in the HYPITAT study of some women with hypertension before pregnancy, which was initially masked by the physiological fall of blood pressure in early pregnancy. Therefore, we analyzed women with a blood pressure of <120/ 70 mmHg at booking (n = 24). Six women had hypertension at six weeks postpartum, and all these women had hypertension at 2.5 years postpartum. Among the 18 normotensive women at six weeks postpartum, four women had hypertension at 2.5 years after pregnancy. In this subgroup, more women who had hypertension at six weeks postpartum, also had hypertension at 2.5 years postpartum compared to women who were normotensive at six weeks postpartum (OR 2.5 (95% CI 1.3–4.8)).

There were no significant differences in maternal age, parity, smoking, body mass index at start





**Figure 1.** Hypertension six weeks and 2,5 years after pregnancy

(BP = Blood Pressure; pp = post partum; PE = preeclampsia; PIH = pregnancy induced hypertension)

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pregnancy and blood pressure at start pregnancy between women of whom the blood pressure was not measured compared to the women of whom the blood pressure was measured at six weeks postpartum. Women of whom the blood pressure was not measured at six weeks postpartum were less often Caucasian, more often had a pregnancy complicated by preeclampsia and had less often progression to severe disease (resp.  $p = 0.01$ ;  $p = 0.02$ ;  $p < 0.01$ ).

## DISCUSSION

We found that in women who suffered hypertensive pregnancy disorders at term, hypertension at six weeks postpartum was associated with a threefold increased risk of chronic hypertension, resulting in a positive predictive value of 60%. In contrast, among women without hypertension at six weeks postpartum the risk of chronic hypertension was 30%.

To our knowledge this is the first study that shows the relation between blood pressure at six weeks postpartum on chronic hypertension. Previous studies demonstrated that women with a history of hypertensive pregnancy disorders have a higher risk at cardiovascular disease later in life [2]. It is still unraveled if hypertensive pregnancy disorders cause cardiovascular disease or if hypertensive pregnancy disorders reveal underlying higher risk at cardiovascular disease [3]; however detection at relatively young age opens opportunities for preventive measurements.

Although the pathogenesis of both hypertensive pregnancy disorders and cardiovascular disease later in life is not unraveled nowadays [19], results of this study suggest a shared pathophysiologic pathway.

In addition we found in only 60% of women with a history of term hypertensive pregnancy disorders the blood pressure was measured at six weeks postpartum. It is imaginable from clinical perspective that women with a history of severe hypertensive pregnancy disorders are monitored more carefully than women with a history of mild disease. This is supported by the finding in this study that blood pressure measurement at six weeks postpartum is more often performed in women with progression to severe disease. A previous study [20] comparing women with a history of preeclampsia and women with a history of uncomplicated pregnancy showed blood pressure measurement was more often checked in women with a history of preeclampsia (57% versus 12%). In their study, no women with a history of gestational hypertension were included explaining the higher blood pressure measurement rate.

In most clinics, women are visiting routinely outpatient clinics at six weeks postpartum. The NICE guideline by the National Institute for Health and Clinical Excellence [15] states that women with a history of gestational hypertension or preeclampsia should be offered a medical review at the postnatal review six to eight weeks after birth. However, no specific recommendations about the medical review are made. In the Netherlands, the national obstetric guideline on hypertension in pregnancy pays attention to the risk of cardiovascular disease after pregnancy although no specific recommendations on follow up or prevention of this disease are made [14].

### **Strengths and weaknesses**

This study is performed in a large cohort of women with a history of hypertensive pregnancy disorders, therefore significant differences and statements on predictive value can be proven in this study. Although we found an evident association between the blood pressure at six weeks postpartum and the later risk of hypertension, women with a normal blood pressure at six weeks postpartum after a pregnancy complicated by hypertension, are still at higher risk of developing cardiovascular disease later in life illustrated by a negative predictive value of 67%. Blood pressure measurements in this study are performed at six weeks postpartum as part of routine postpartum care, but this time point might not be ideal.

Although studies show that microvascular changes in cerebral arteries resolve spontaneously before six weeks postpartum [21], it is supposed that in most women with a history of hypertensive pregnancy disorders, hypertension will resolve within 12 weeks postpartum or the diagnosis of chronic hypertension should be stated [22].

For this study we only used the blood pressure for prediction of cardiovascular disease because it is an easy, noninvasive, reliable, reproducible and cheap test to perform. It is suggestive to be an important first indicator of developing cardiovascular disease later in life. Hypertension is one of the most important risk factors for the development of cardiovascular disease [23] and is part of the risk scores for cardiovascular disease like the Framingham Risk Score [24]. However, cardiovascular disease is a multifactorial entity including hypertension, inflammation, dyslipidemia and atherosclerosis and disturbs glucose metabolism [25].

Since baseline criteria maternal age and multiparous were different between women with hypertension at six weeks postpartum compared to normotensive women at six weeks postpartum, this could imply an effect of higher prevalence of increased blood pressure before pregnancy [3]. As is seen in the subanalyses in this study, when we excluded women with a possible chronic hypertension, the association of hypertension at six weeks after pregnancy with hypertension at 2.5 years postpartum still remains. Unfortunately this is only a small subgroup. Missing values in this study were that no prepregnancy blood pressures could be analyzed in these women.

### **Recommendations**

This study supports the urgency for improvement of guidelines by adequate follow up after hypertension at (near) term pregnancies. Blood pressure measurement at six weeks postpartum is important in patients who suffered from hypertensive pregnancy disorders since it could be an indicator for blood pressure later in life and opens a window of preventive opportunities.

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