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Assessment of Cardiovascular Disease after Hypertensive Pregnancy Disorders

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2015

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citation for published version (APA)

Visser, V. S. (2015). *Assessment of Cardiovascular Disease after Hypertensive Pregnancy Disorders*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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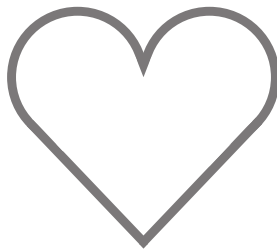
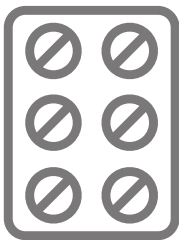
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CHAPTER

Introduction

1



Hypertensive pregnancy disorders are associated with major maternal and neonatal morbidity and mortality worldwide [1, 2]. In the western world it remains the most important cause of maternal mortality [3].

Hypertensive pregnancy disorders are characterized by new onset of hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic, **table 1**) after 20 weeks gestation. Hypertensive pregnancy disorders include pregnancy induced hypertension i.e. hypertension in the absence of proteinuria, and preeclampsia, hypertension in coexistence of new-onset proteinuria [4]. The etiology of hypertensive pregnancy disorders remains partly unraveled. For early hypertensive pregnancy disorders, developed before 34 weeks of pregnancy, impaired placentation is the most important component in pathophysiology [5]. This impaired placentation is known to result in different factors including imbalance in angiogenesis and endothelial dysfunction [6], which in turn further decrease placental development and function. Extensive research shows differences in risk factors for early versus late hypertensive pregnancy disorders, which might indicate different etiologies for both diseases [7,8]. It has been described that late hypertensive pregnancy disorders are more influenced by maternal risk factors including chronic hypertension and positive family history of hypertension whereas in early hypertensive pregnancy disorders placental risk factors are more present.

Over the last decade, more evidence has become available that women with a history of hypertensive pregnancy disorders have a higher risk of *cardiovascular disease later in life* [7]. Higher cardiovascular risk is described for women with hypertensive pregnancy disorders, including pregnancy induced hypertension and preeclampsia [8]. Almost half of the women with a history of early onset preeclampsia (i.e. preeclampsia resulting in delivery before 34 weeks gestation) and 25% of women with a history of late onset preeclampsia have hypertension later in life. Of the women with a history of pregnancy induced hypertension 40% have hypertension later in life [6]. It remains open for discussion if increased cardiovascular risk factors is a consequence of

Table 1. Hypertensive Pregnancy Disorders²²

Pregnancy Induced Hypertension (PIH)	New onset hypertension after 20 weeks' gestation; RR1 diastolic ≥ 90 mmHg and/or RR systolic ≥ 140 mmHg
Preeclampsia (PE)	New onset hypertension after 20 weeks' gestation; RR diastolic ≥ 90 mmHg and/or RR systolic ≥ 140 mmHg In combination with proteinuria $>0.3\text{gr}/24\text{h}$
Early Preeclampsia	Development of Preeclampsia before 34 weeks' gestation
Late Preeclampsia	Development of Preeclampsia after 34 weeks' gestation
Chronic Hypertension	Hypertension before 20 weeks' of gestation; RR diastolic ≥ 90 mmHg and/or RR systolic ≥ 140 mmHg

1RR; Blood Pressure

hypertensive pregnancy disorder or if there is a predisposition on cardiovascular disease before pregnancy which reveals during pregnancy or it is a combination of both [9,10].

Cardiovascular disease is the leading cause of death in women in the western world [11]. Worldwide a third of all death in women is caused by heart disease. Clinical manifestation of cardiovascular disease is different for women as compared with men. Diagnostic tools for cardiovascular disease in women are less sensitive and specific [12]. Therefore it is important to identify women specific risk factors for cardiovascular disease like hypertensive pregnancy disorders at a relative young age. Recent guidelines on diagnosis and management of cardiovascular disease in women are adjusted adding hypertensive pregnancy disorders as a risk factor [13].

Women who experience pregnancy induced hypertension or preeclampsia are considered to 'fail' a stress test; pregnancy can reveal a vulnerability for several diseases including cardiovascular disease [14]. Sattar et al described that women who develop hypertensive disorders in pregnancy have a higher pre-pregnancy vascular risk status described by increased endothelial dysfunction which will first manifest as a clinical syndrome during pregnancy [15]. Subsequently, these women develop cardiovascular disease later in life at a younger age than women with uncomplicated pregnancies. Therefore a hypertensive pregnancy disorder is useful as a diagnostic test for increased risk to develop cardiovascular disease later in life, providing opportunities for strategies to prevent or postpone the (early) development of cardiovascular disease.

One of the steps in linking hypertensive pregnancy disorders to cardiovascular disease is investigation of markers for *endothelial dysfunction*. Biochemical risk markers for cardiovascular disease are known to be elevated in women with a history of preeclampsia [16]. Several markers have been investigated to predict cardiovascular disease after hypertensive pregnancy disorders, including homocysteine. Homocysteine plasma concentration is considered to be an independent risk factor for the development of atherothrombotic and cardiovascular diseases [17]. Women who have or have had preeclampsia are known to have higher homocysteine concentrations than women who have had an uncomplicated pregnancy.

Another marker described in hypertensive disorders is abnormal placentation by *impaired angiogenesis*. In addition, the pathophysiological link between hypertensive pregnancy disorders and cardiovascular disease later in life could be impaired angiogenesis. Impaired angiogenesis is seen in abnormal placentation in case of preeclampsia [19]. Impaired angiogenesis is also seen in diseases concerning neoplasm development. Both placentation and the development of a neoplasm are characterized by angiogenetic invasion: placental invasion in the uterus in pregnancy and tumor stroma invasion in case of neoplasm. Women with impaired angiogenesis might experience abnormalities in placentation (with subsequently pregnancy disorders like preeclampsia) with a possible parallel link to abnormalities in tumor stroma invasion in neoplasm development. Therefore, we tested the hypothesis that women with a history of preeclampsia have a higher incidence of neoplasm with impaired stromal invasion.

The increased risk for cardiovascular disease in women with a history of hypertensive pregnancy disorders is well investigated. In order to prevent or postpone cardiovascular disease in women with a history of hypertensive pregnancy disorders, women should first be aware of their in-

creased risk and possible preventive interventions. This *awareness* in women can be achieved by adequate information provided by gynecologists. To increase awareness on this subject in gynecologist and subsequently information provided by gynecologists, *guidelines* on this subject should be complete and consistent. The increased risk of cardiovascular disease after hypertensive pregnancy disorders is described in national guidelines on hypertensive pregnancy disorders although specific guidelines on follow up after hypertensive pregnancy are still brief and mostly without evidence [19 - 21]. At the end of 2014, the Dutch Association of Obstetrics and Gynecology (NVOG) created a guideline on Cardiovascular Risk after Reproductive Disease including advice on follow up after hypertensive pregnancy disorders [22]. In this guideline for women with a history of hypertensive pregnancy disorders, at age of 50 years a cardiovascular risk assessment is advised. Since the guideline is recently published, it is still unclear in what extend *implementation* will be attained.

In this thesis we will focus on the risk of cardiovascular disease in women after hypertensive pregnancy disorders. The focus of the first part of this thesis is etiology. We investigate risk markers after hypertensive pregnancy disorders as described above. We describe non-traditional cardiovascular risk markers after hypertensive pregnancy disorders as these could give more insight in the parallels in pathogenesis of these diseases including homocysteine after hypertensive pregnancy disorders. Further, we investigate the role of abnormal placentation by abnormal angiogenesis. We tested the hypothesis of the parallel link between hypertensive pregnancy disorders to neoplasm formation by abnormal angiogenesis. For these studies we included women with a history of hypertensive pregnancy disorders. These women participated in a nationwide multicenter trial on induction of labor versus expectant management in women with pregnancy induced hypertension or preeclampsia at term. For the study on neoplasm after hypertensive pregnancy disorders we included women with a history of breast or colon carcinoma from the database of the Leiden University Medical Centre.

The focus of the second part of this thesis is prognosis. We aim to identify predictive information for cardiovascular disease in women with a history of hypertensive pregnancy disorders. We investigate which clinical and demographic data in women with a history of pregnancy complicated by hypertension are predictive for cardiovascular disease later in life. We investigate in how far blood pressure measurement is performed in clinical practice at the traditional postpartum visit six weeks after delivery in women who experienced a hypertensive pregnancy disorder and what the prognostic value is of this measurement for later cardiovascular disease. Next we assess the awareness of gynecologists on their patient's higher cardiovascular risk and examine the implementation of guidelines on the follow up after hypertensive pregnancy disorders. Further, we obtain the recommendations on follow up from the local protocols on hypertensive pregnancy disorders and analyze the awareness of gynecologists of the higher risk for cardiovascular disease in women with a history of hypertensive pregnancy disorders. Finally we assess if women who are informed on a higher risk status of cardiovascular disease after hypertensive pregnancy disorders change their lifestyle in favor of prevention (**figure 1**).

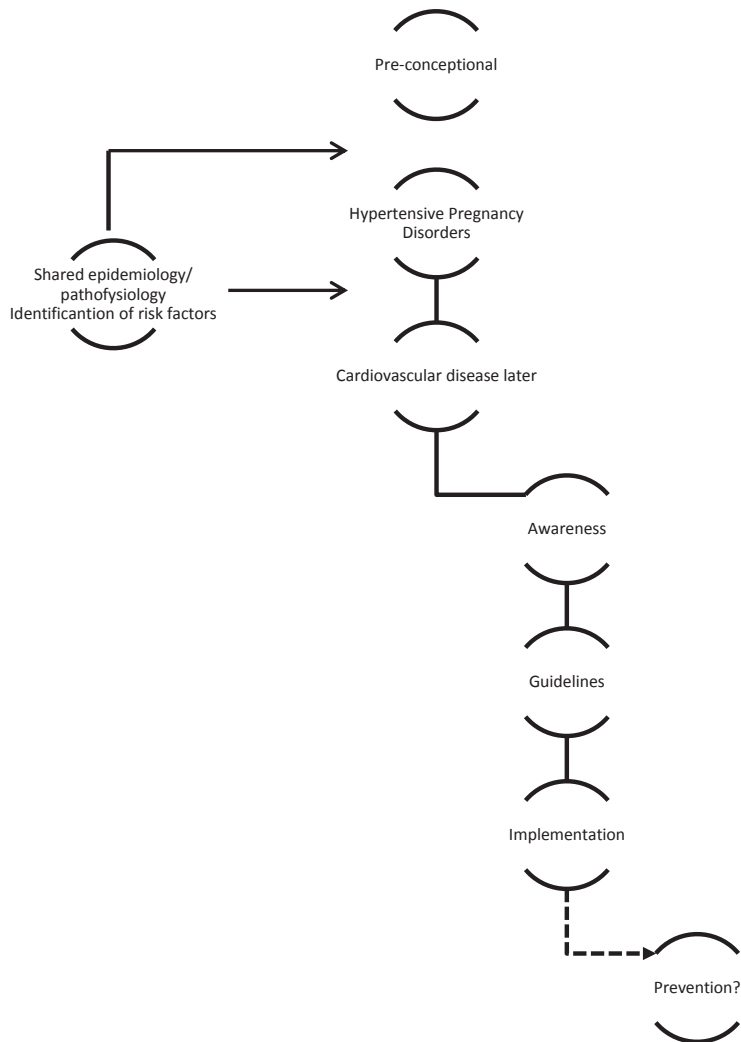


Figure 1.

Aims

The first aim of the research presented in this thesis is to identify (endothelium) markers after hypertensive pregnancy disorders. Initial we focus on classic and less known cardiovascular markers after complicated pregnancies by hypertension in order to find indications of shared pathogenesis of hypertensive pregnancy disorders and cardiovascular disease later in life. In order to gain more insight in the shared pathophysiology of pregnancy and later development of cancer, focusing on angiogenesis in both diseases, we analyzed the association of hypertensive pregnancy disorders and oncologic tumors specifically on angiogenesis and impaired stroma invasion.

The second aim is to investigate prediction of cardiovascular disease after hypertensive preg-

nancy disorders in order to identify women at a relatively young age who are at increased risk for cardiovascular disease later. Once women are identified, knowledge of information is essential from caregiver to patient therefore we analyzed the awareness of gynecologist and advise in guidelines of the association of hypertensive pregnancy disorders and later cardiovascular disease. Finally we assess the lifestyle changes women performed after they were informed on a higher risk of cardiovascular disease.

REFERENCES

1. Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. *Semin Perinatol*. 2012 Feb;36(1):56-9.
2. Schutte JM, Schuitemaker NW, Van RJ et al. Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands.[see comment]. *BJOG: an International Journal of Obstetrics and Gynaecology* 2008; 115:(6)732-6.
3. A.L. Tranquilli, G. Dekker, L. Magee, J. Roberts, B.M. Sibai, W. Steyn, G.G. Zeeman, M.A. Brown. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Hypertension Pregnancy* 2014, Received: November 4, 2013; Published Online February 17, 2014.
4. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet*. 2005 Feb 26-Mar 4;365(9461):785-99.
5. Chaiworapongsa T, Chaemsaihong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol*. 2014 Aug;10(8):466-80.
6. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. *Obstet Gynecol Surv*. 2011 Aug;66(8):497-506.
7. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol*. 2013 Dec;209(6):544.e1-544.e12.
8. Veerbeek JH, Hermes W, Breimer AY, van Rijn BB, Koenen SV, Mol BW, Franx A, de Groot CJ, Koster MP. Cardiovascular Disease Risk Factors After Early-Onset Preeclampsia, Late-Onset Preeclampsia, and Pregnancy-Induced Hypertension. *Hypertension*. 2015 Jan 5.
9. Hermes W, Tamsma JT, Grootendorst DC, Franx A, van der Post J, van Pampus MG, Bloemenkamp KW, Porath M, Mol BW, de Groot CJ. Cardiovascular risk estimation in women with a history of hypertensive pregnancy disorders at term: a longitudinal follow-up study. *BMC Pregnancy Childbirth*. 2013 Jun 4;13:126.
10. Osol G, Bernstein I. Preeclampsia and maternal cardiovascular disease: consequence or predisposition? *J Vasc Res*. 2014;51(4):290-304.
11. Magnussen EB, Vatten LJ, Lund-Nilsen TI, Salvesen KA, Davey Smith G, Romundstad PR. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. *BMJ*. 2007 Nov 10;335(7627):978.
12. Burell G, Granlund B. Women's hearts need special treatment. *Int J Behav Med* 2002;9(3):228-42.

13. Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. *Eur Heart J* 2006; 27(8):994-1005.
14. Mosca, L., E.J. Benjamin, K. Berra, et al., Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *Circulation*, 2011. 123(11): p. 1243-62.
15. Williams D. Pregnancy: a stress test for life. *Curr Opin Obstet Gynecol*. 2003 Dec;15(6):465-71.
16. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? *BMJ*. 2002 Jul 20;325(7356):157-60.
17. Hermes W, Ket JC, van Pampus MG, Franx A, Veenendaal MV, Kolster C, Tamsma JT, Bloemkamp KW, Ponjee G, van der Hout E, Ten Horn H, Loix S, Mol BW, de Groot CJ. Biochemical cardiovascular risk factors after hypertensive pregnancy disorders: a systematic review and meta-analysis. *Obstet Gynecol Surv*. 2012 Dec;67(12):793-809.
18. Castro R, Rivera I, Blom HJ, Jakobs C, Tavares de Almeida I. Homocysteine metabolism, hyperhomocysteinaemia and vascular disease: an overview. *J Inher Metab Dis*. 2006 Feb;29(1):3-20.
19. Jardim LL, Rios DR, Perucci LO, de Souza LP, Gomes KB, Dusse LM. Is the imbalance between pro-angiogenic and anti-angiogenic factors associated with preeclampsia? *Clin Chim Acta*. 2015 May 13.
20. www.nvog.nl guideline on Hypertensive Disorders in Pregnancy Disorders.
21. www.nice.org.uk guideline on Hypertension in Pregnancy
22. www.acog.org guideline on Hypertensive Disorders in Pregnancy
23. www.nvog.nl guideline on Cardiovascular Risk Management after Reproductive Disease