Severe early onset preeclampsia

SEVERE EARLY ONSET PREECLAMPSIA

SHORT AND LONG TERM CLINICAL, PSYCHOSOCIAL AND BIOCHEMICAL ASPECTS

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klinische, psychosociale en biochemische aspecten op korte en lange termijn

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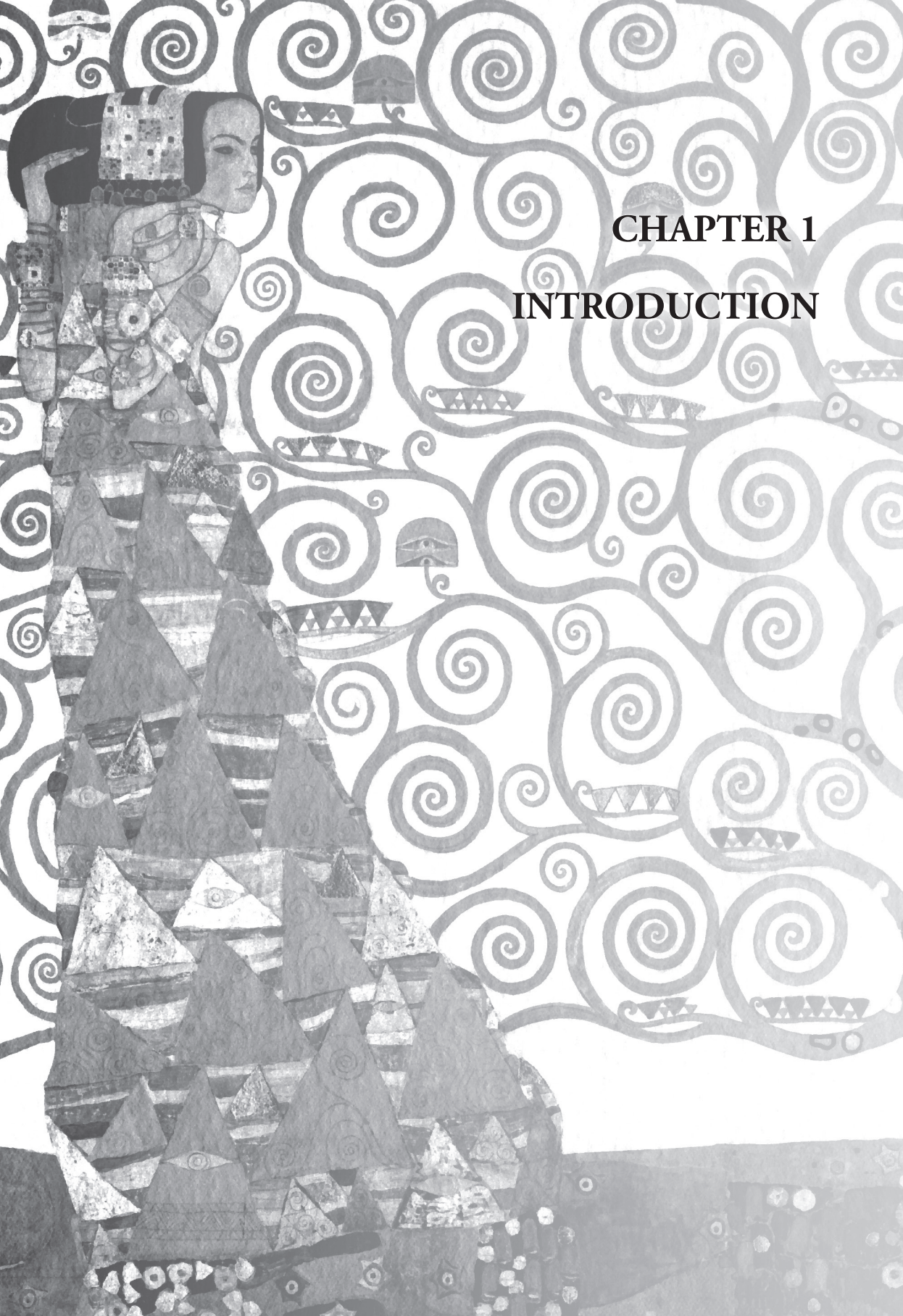
Department of Obstetrics and Gynaecology, Division of Obstetrics and Prenatal Medicine.

To all women with
severe early onset preeclampsia

CONTENTS



CHAPTER 1

INTRODUCTION

Severe early onset preeclampsia
short and long term clinical, psychosocial and biochemical aspects

Introduction

Preeclampsia is a pregnancy specific disorder commonly defined as de novo hypertension and proteinuria after 20 weeks gestational age. It occurs in approximately 3-5% of pregnancies and it is still a major cause of both foetal and maternal morbidity and mortality worldwide[1]. As extensive research has not yet elucidated the aetiology of preeclampsia, there are no rational preventive or therapeutic interventions available. The only rational treatment is delivery, which benefits the mother but is not in the interest of the foetus, if remote from term. Early onset preeclampsia (<32 weeks' gestational age) occurs in less than 1% of pregnancies. It is, however often associated with maternal morbidity as the risk of progression to severe maternal disease is inversely related with gestational age at onset[2]. Resulting prematurity is therefore the main cause of neonatal mortality and morbidity in patients with severe preeclampsia[3]. Although the discussion is ongoing, perinatal survival is suggested to be increased in patients with preterm preeclampsia by expectant, non-interventional management. This temporising treatment option to lengthen pregnancy includes the use of antihypertensive medication to control hypertension, magnesium sulphate to prevent eclampsia and corticosteroids to enhance foetal lung maturity[4]. With optimal maternal haemodynamic status and reassuring foetal condition this results on average in an extension of 2 weeks. Prolongation of these pregnancies is a great challenge for clinicians to balance between potential maternal risks on one the eve hand and possible foetal benefits on the other. Clinical controversies regarding prolongation of preterm preeclamptic pregnancies still exist – also taking into account that preeclampsia is the leading cause of maternal mortality in the Netherlands[5] - a debate which is even more pronounced in very preterm pregnancies with questionable foetal viability[6-9]. Do maternal risks of prolongation of these very early pregnancies outweigh the chances of neonatal survival? Counselling of women with very early onset preeclampsia not only comprises of knowledge of the outcome of those particular pregnancies, but also knowledge of outcomes of future pregnancies of these women is of major clinical importance.

This thesis opens with a review of the literature on identifiable risk factors of preeclampsia. Identification of modifiable risk factors in early pregnancy might

improve antenatal care and subsequent pregnancy outcome. In the following chapter direct maternal and perinatal outcome after severe preeclampsia with a very early onset before 24 weeks' gestation is described. It focuses on prolongation of these very preterm pregnancies against the debate of maternal risks and foetal benefits. In chapter 2.3 outcomes of subsequent pregnancies and long term cardiovascular health of this particular cohort of women and their partners. Knowledge of (subsequent) pregnancy outcome is of major importance to counsel these parents.
Chapter 3 of the thesis describes long term psychosocial effects, on average 7 years after severe early onset preeclampsia before 32 weeks' gestation. The cohort comprises of women diagnosed with severe preeclampsia before 24 weeks' gestation between 1993-2003 as described in chapter 2.3 and all women with severe preeclampsia at 24-32 weeks' gestation between 1999-2004, who were admitted and delivered before 34 weeks' gestation at the department of Obstetrics and Prenatal Medicine of the Erasmus University Medical Center Rotterdam. For most obstetricians direct maternal and perinatal clinical outcome is of course of initial primary concern, whereas in general, little attention is paid to long term psychological and social sequelae. In clinical practice we have observed that some women who had pregnancies complicated by severe early onset preeclampsia seem to suffer from longstanding posttraumatic stress symptoms and depression leading to social isolation. This is confirmed by several studies but follow up is often limited to 2 years[10-13]. However, the evidence with regard to long term effects is lacking. Better insight in the extend of these psychosocial effects will answer the question whether there is necessity and need for structured psychosocial follow up after severe early onset preeclampsia.

Furthermore, hypertensive pregnancy complications share common risk factors with future adult cardiovascular disease. Pregnancy is therefore a challenge test for cardiovascular disease in later life. Modifiable cardiovascular risk factors including hypertension, obesity, dyslipidemia and insulin resistance are therefore also studied as part of the study described in chapter 2.3. In addition, pathophysiological changes in angiogenic biomarkers in women with preeclampsia have been reported recently[14-16]. Increased levels of anti angiogenic factors (sFLT-1 and s-Eng) and lower levels of angiogenic factors (VEGF and PLGF) have been described in women with severe and/or early onset preeclampsia[17-22]. Literature on these novel risk factors focuses mainly on discriminatory and predictive abilities for preeclampsia as altered levels of angiogenic factors are detectable as early as in the first trimester[23-26]. However, knowledge of these factors after preeclamptic pregnancies is scarce. There seems no literature available on the role of these novel risk factors, as vascular or endothelial dysfunctional markers, years after preeclampsia. The presence of these factors may suggest vascular dysfunction after severe preeclampsia. Therefore, women with a history of preeclampsia with

onset before 24 weeks' gestation provide a unique opportunity to investigate angiogenic risk factors of cardiovascular disease. Associations between early preeclampsia, risk factors and future cardiovascular disease may enable us to identify the women at risk and renders the possibility for prevention for cardiovascular morbidity and mortality in later life. In chapter 4.1 the results of angiogenic risk factors in women, ten years after severe early onset preeclampsia before 24 weeks' gestation, are described. Participating women in this study are the same women who participated in the study described in chapter 2.2 and 2.3.
In chapter 4.2 we focus on the association between increased maternal iron status and preeclampsia[27, 28]. In the study of Rayman et al.[28] eighteen percent of women with preeclampsia had transferrin saturation levels in the region associated with iron overload. Iron overload can be caused by genetic hemochromatosis, which is the most common, autosomal recessive disorder in Northern Europe, with a gene frequency of about 5%[29]. The hemochromatosis *(HFE)* gene encodes for the HFE protein, a transmembrane glycoprotein that is implicated in the modulation of iron uptake from the diet. The C282Y mutation in this gene is known to be associated with moderately increased serum iron indices. We hypothesised that this mutation can be found more frequent in women with a history of preeclampsia.
The thesis is accomplished with a general discussion including the new Dutch guideline on neonatal resuscitation in very early preterm delivery and suggestions for future research.

Aims of the thesis:

1) To study maternal and foetal outcome of severe early onset preeclampsia before 24 weeks' gestation after expectant management policy.
2) To study future pregnancy outcome, classic and novel cardiovascular risk factors in women with a history of severe early onset preeclampsia before 24 weeks' gestation.
3) To study psychosocial effects long term after severe early onset preeclampsia before 32 weeks' gestation.

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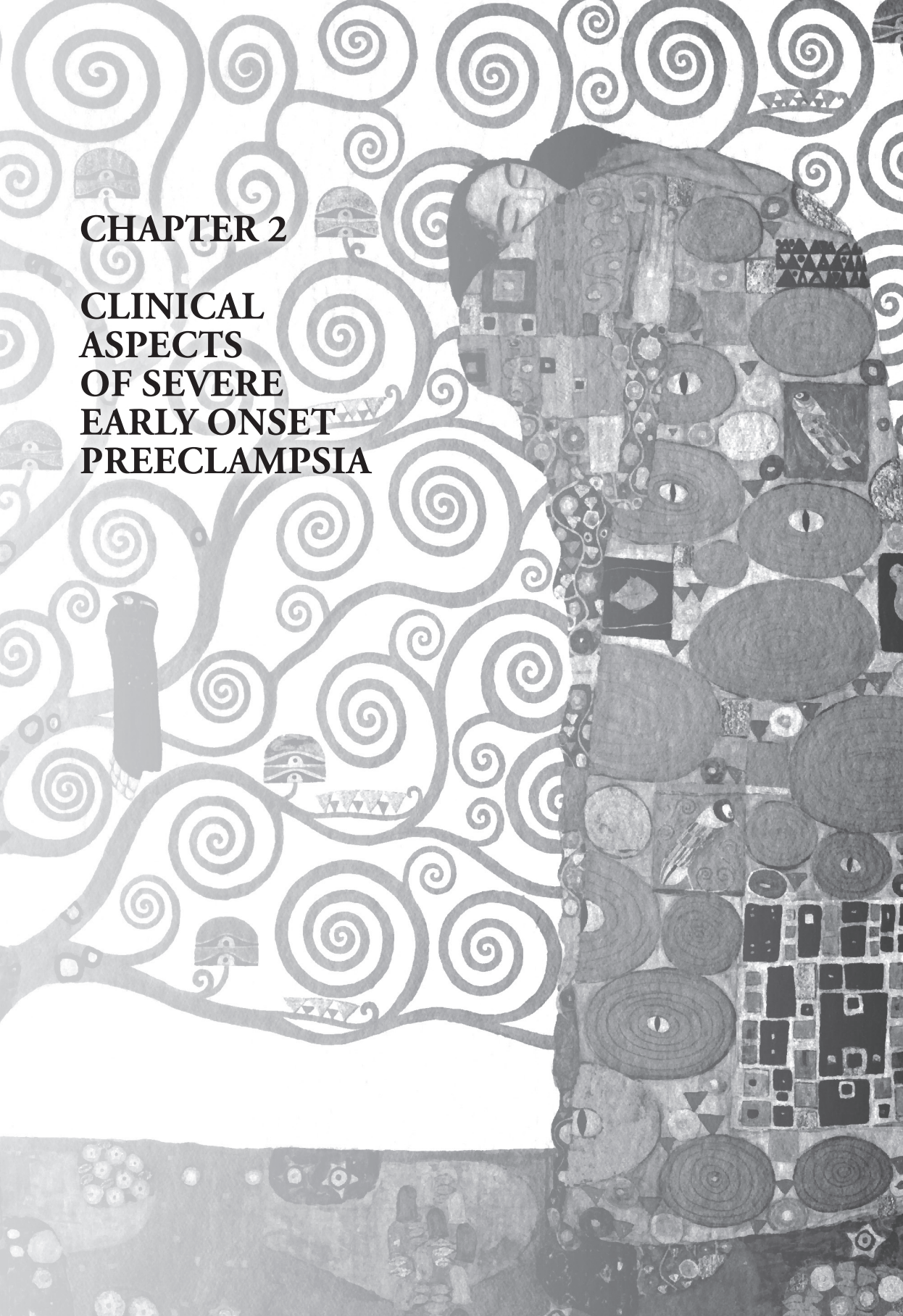
CHAPTER 2

CLINICAL ASPECTS OF SEVERE EARLY ONSET PREECLAMPSIA



CHAPTER 2.1

Clinical risk factors for preeclampsia

Ingrid PM Gaugler-Senden, Eva M Roes, Christianne JM de Groot,
Eric AP Steegers

Abstract

Preeclampsia, diagnosed by increased blood pressure and de novo proteinuria, is a pregnancy- specific disease associated with a high incidence of maternal and foetal morbidity and mortality. Identification of women at risk for this potential life threatening disease might enable the clinician to identify and counsel patients adequately. A major concern by identification of clinical risk factors for the development of preeclampsia is the confusion over the clinical classification of this syndrome which has resulted from using different definitions. For this in-depth review and meta-analysis only well defined reports were selected. Maternal constitutional and environmental factors as well as pregnancy-specific changes as risk factors for the development of preeclampsia were studied.

This review describes both dependent and the following independent risk factors for the development of preeclampsia: chronic hypertension, renal disease, diabetes, nulliparity and long pregnancy interval.

Introduction

Preeclampsia is a pregnancy-specific disease associated with a high incidence of maternal and foetal morbidity and mortality. Preeclampsia is diagnosed by increased blood pressure and de novo proteinuria. Despite intensive research and improved technology in recent decades the cause and pathophysiology of the syndrome remain enigmatic. Therefore its treatment is empirical and controversial. Expedient delivery initiates the resolution of preeclampsia. In the case of prematurity, however, it is a major cause of neonatal morbidity and mortality. Identification of patients at risk for preeclampsia is important for several reasons. Firstly, it enables the clinician to counsel a patient, if possible even before pregnancy. Secondly, it might discriminate preeclampsia, a disorder with life threatening maternal consequences and danger for the foetus, from transient gestational hypertension, medically a generally benign disorder with mild to moderate elevations of blood pressure. A major concern in the identification of the clinical risk factors for women at risk for preeclampsia is the confusion over clinical classification of this syndrome which results in the use of different definitions in recent years. In this in-depth review and meta-analysis of available well defined reports we describe the major clinical characteristics of women at risk for preeclampsia on the basis of a recent hypothesis[1]: the interaction of underlying maternal constitutional and environmental factors interact with pregnancy-specific changes, resulting in a complex of reduced foetal and placental perfusion and maternal endothelium activation. The maternal endothelium activation can cause serious physiological disturbances by creating a multifaceted vicious cycle resulting in acute pathogenic changes of preeclampsia.

Material and Methods

A PubMed search of English-, Dutch-, and German-language publications until 2004 was undertaken. Search terms included pregnancy, preeclampsia and risk factors. Specific known medical and obstetrical conditions which previously have been associated with preeclampsia were used as single search term in combination with preeclampsia. Maternal constitutional and environmental factors were: extremes in age, ethnicity, chronic hypertension, renal disease, urinary tract infection, obesity, glucose intolerance/insulin resistance/gestational diabetes mellitus, diabetes mellitus, systemic lupus erythematosus/antiphospholipid syndrome, hyperthyroidism/hypothyroidism, epilepsy, migraine, polycystic ovary syndrome, thrombophilia, family history of preeclampsia, family history of hypertension, smoking, and working activity. Pregnancy-specific changes were nulliparity, paternity, previous history of abortion, prior preeclampsia, assisted reproduction, twin pregnancy, and molar pregnancy/foetal hydrops. All articles cited were reviewed. Articles were selected if they presented a proper definition of preeclampsia[2]. Data relevant to the purpose of the review were extracted. Only case-control studies and cohort studies were included for calculation of odds ratios (OR) and 95% confidence intervals (CI).

Results

Maternal constitutional factors

Extreme age

An increasing number of women choose to delay pregnancy until their fourth or fifth decades of life. A retrospective study comparing more than 1,400 women aged at least 40 years with controls aged 20-29 years found preeclampsia is more common among older women, regardless of parity (1.8, 95% CI 1.3–2.6)[3-5]. Prepregnancy weight, history of preeclampsia, race, smoking and medical history were controlled for in the comparisons. This association might be related to underlying progressive vascular endothelial damage that occurs with aging.
Older pregnant women are more often highly educated, and pregnant upon assisted reproduction. However, Tuck et al.[6] found no differences in the prevalence of preeclampsia between primigravidae aged over 35 years with no history of involuntary infertility and those with involuntary infertility of at least 1 year. The risk of preeclampsia associated with extremely younger age has been reported as entailing sometimes an increased risk and sometimes no difference in risk[7]. A possible explanation of this inconsistency is that parity is a potential confounder. Younger women are more likely to be nulliparous, and first pregnancies are associated with an increased risk of preeclampsia.

Ethnicity

Reports about the role of ethnicity as risk factor for preeclampsia have been inconsistent. Several authors[8-11] found no differences between black and white women whereas others[7;12;13] found a higher incidence of preeclampsia in blacks. The higher incidence of preeclampsia in blacks may be related to a higher prevalence of chronic hypertension[14]. Secondly, fewer black women smoke, and smoking has been identified as a protective factor for preeclampsia[10;15]. Most studies find socioeconomic conditions are not a risk factor.

Chronic hypertension

Chronic hypertension can be a serious medical condition, complicating 1-5% of pregnancies. Chronic hypertension is defined by hypertension before or in early pregnancy (> 140/90 mmHg) or the use of anti-hypertensive drugs. The most common maternal complication, involving 5-52% of cases,[16;17] is the development of superimposed preeclampsia, defined as worsening of hypertension (a rise of at least 30 mmHg in systolic pressure or at least 15 mmHg in diastolic pressure) together with the development of proteinuria[18]. Women of advanced maternal age (> 40 years), and obese and black women are more likely to develop chronic hypertension during pregnancy[19]. In recent decades an increasing number of women have chosen to delay childbearing to an older age. Because of this the incidence of chronic hypertension during pregnancy has been rising. Sibai et al.[19] studied 763 women with chronic hypertension and reported that hypertension lasting at least 4 years, diastolic blood pressure of at least 100 mmHg early in pregnancy, and the presence of preeclampsia in a previous pregnancy were associated with a higher rate of preeclampsia. Both systolic and diastolic pressures early in pregnancy (before 22 weeks gestation) predict the risk of preeclampsia and may be related to abnormal placentation in the beginning of pregnancy. Mildly elevated blood pressure in the second trimester in normotensive women appears to be a risk factor for preeclampsia[11;20]. Among healthy, chronically hypertensive nulliparous women with a second trimester diastolic pressure below 95 mmHg, 2-3% developed preeclampsia whereas of women with diastolic pressures above 120 mmHg 15% did so[21].
Ideally women with chronic hypertension should be evaluated before pregnancy for end-organ damage such as left ventricular hypertrophy, hypertensive nephropathy and retinopathy. It remains unclear whether early treatment of chronic hypertension in pregnancy prevents preeclampsia. Several randomized controlled trials have found no association between treating chronic hypertension and the incidence of superimposed preeclampsia[19]. On the other hand, women who develop preeclampsia have a higher incidence of subsequent chronic hypertension than parous women with normotensive pregnancies[22].

Renal disease

There is extensive literature on renal disease and pregnancy outcome. However, no accurate risk assessment of renal disease and preeclampsia is available since well defined studies are lacking. As few reports provide a proper definition of (superimposed) preeclampsia, it is therefore not possible to differentiate between symptoms of preeclampsia and those of worsening renal diseases and the presence of chronic hypertension, such as in lupus nephritis. Both renal disease and preeclampsia are characterized clinically by (increase of) hypertension and (increase in severity of) proteinuria. As a consequence the incidence of preeclampsia in patients with renal disease has been reported between 30 and 80%[23-26]. Stettler and Cunningham[26] investigated the risk of preeclampsia in pregnancies with asymptomatic coincidental proteinuria of 500 mg/day or higher at enrolment (n= 65). Among these women 74% had renal insufficiency (serum creatinine >75 µmol/l) and 40% chronic hypertension. Preeclampsia occurred in 65% of cases, 29% in patients with renal insufficiency only (defined as serum creatinine concentration >80 µmol/l), and 77% of patients with both renal insufficiency and chronic hypertension. A comparable high incidence of preeclampsia of 54% was found by Jungers et al.[25] among 38 pregnancies with impaired renal function (defined as serum creatinine concentration of 110-490 µmol/l). Furthermore, Cunningham et al.[23] reported the incidence of preeclampsia in patients with moderate and severe renal impairment, and the presence of chronic hypertension. In normotensive patients with moderate (serum creatinine 125-220 µmol/l) or severe renal impairment (serum creatinine >220 µmol/l) preeclampsia occurred in 58% and 64%, respectively. Superimposed preeclampsia occurred in 79% and 86% of cases of chronic hypertension, respectively. Julkunen found an incidence of preeclampsia of 23% in patients with lupus nephritis, although all but one patient (n=26) had normal range serum creatinine concentrations before onset of pregnancy. Chronic hypertension was not reported. North et al.[27] examined pregnancy outcome in 54 pregnancies with reflux nephropathy, 19% of which patients had proteinuria (>300 mg/24h) early in pregnancy. Preeclampsia occurred in 14% of the patients who were normotensive in the first half of pregnancy (n=35) and in 42% of those who had chronic hypertension.
In conclusion, it appears that the risk of preeclampsia is not determined by the type of renal disease per se, but by the severity of impaired renal function and presence of chronic hypertension.

Urinary tract infection

Several papers have been published on the relationship between urinary tract infection and preeclampsia[9;28;29]. However, a definite conclusion from this literature as to whether urinary tract infection is a risk factor for the development of preeclampsia is not possible due to the varying definitions used for urinary

tract infections and preeclampsia. Stuart et al.[30] reported in a prospective case-control study of 2,713 consecutive pregnancies a positive association of bacteriuria and hypertensive disorders of pregnancy (18.2% of the cases versus 4.5% of the controls). It has been suggested that urinary tract infection during pregnancy is merely a correlate of prior infectious renal damage that may predispose the women to preeclampsia[31]. Detection of urinary tract infection during labour or post partum in preeclamptic patients might be related to the increased use of a urine catheter and to the increased caesarean section rate[32]. Moreover, increased host susceptibility to infection due to proteinuria and hypercatabolism in women with preeclampsia may play a role[33].

Obesity

Numerous studies have been published about obesity and preeclampsia. All but three reports found a two- to fivefold increased risk of preeclampsia in obese patients. Three studies[7;8;34] found no association between obesity and preeclampsia, but this might be due to lack of statistical power and/or relative low body mass index for their definition of obesity. Although the remaining studies comprise almost one million women, more accurate risk assessment of obesity is difficult. The various studies have important differences in their inclusion criteria such as parity, age, race and maternal diseases such as chronic hypertension and diabetes mellitus. In addition, they differ in their definition of obesity, and the body mass index may have been based on self reported prepregnancy weight or been calculated at enrolment at varying gestational ages. Nevertheless, most studies demonstrate a consistently strong association between body mass index, determined either before pregnancy or at enrolment, and the risk of preeclampsia. The risk of preeclampsia rises with increasing categories of body mass index, with a step-up increase in the relative risk of preeclampsia[10;11;35;36]. The studies which used multivariate analysis to adjust for potential confounding factors such as chronic hypertension and diabetes mellitus[11;35-38] observed at least a doubling of the risk of preeclampsia with excess maternal body mass index. Haelterman et al. and Stone et al.[39;40] both observed a 3.5- fold increased risk of severe preeclampsia in women with a body mass index higher than 30 and higher than 32, respectively. Abi-Said et al.[12] found among 66 cases and 264 matched controls, a 2.5-fold increased risk of eclampsia in women with a prepregnancy body mass index higher than 35. The effect of weight gain during pregnancy on the risk of preeclampsia is unclear. Sibai et al.[11] demonstrated that a weight gain of more than 2 pounds per week in the second or third trimester led to a three- or almost fourfold increased risk of preeclampsia in the overall study population. Edwards et al.[41] observed no effect of weight gain during pregnancy in women with a body mass index above 29.
Obesity is a well known risk factor for cardiovascular disease. Obesity is also associated with diabetes, chronic hypertension and hyperlipidemia[42]. Therefore, obe-

sity and preeclampsia may share some of the pathophysiological changes that are responsible for the increased risk of preeclampsia. Both obesity and preeclampsia may be manifestations of the insulin resistance syndrome. Insulin at high levels is associated with insulin resistance or obesity and may regulate intracellular cation pumps that affect vascular tone and blood pressure. It may also stimulate the sympathetic nervous system or induce hypertrophy of vascular smooth muscle. Increased levels of vasoconstrictive peptides that are associated with hyperinsulinemia may contribute to the endothelial cell injury that is characteristic of both preeclampsia and the insulin resistance syndrome. Interestingly, women with a maternal low birth weight (<2500 g) had a twofold higher risk of developing preeclampsia compared to women weighing 2500-2599 g at birth. Those women who are small at birth and who became overweight as adults are particularly at risk for developing preeclampsia[43-45].

Glucose intolerance/insulin resistance/gestational diabetes mellitus

A review of the literature poses difficulties in drawing conclusions about the association of glucose intolerance, insulin resistance, and gestational diabetes mellitus as risk factors for preeclampsia. The major problems are the inconsistency in defining gestational diabetes mellitus and the fact that it is impossible to distinguish between preexisting diabetes and diabetes that is truly provoked by pregnancy (gestational diabetes mellitus). Sibai et al.[11] and Solomon et al.[46] observed no association between gestational diabetes mellitus (defined by an abnormal 1-hour 50-g oral glucose screen) and preeclampsia in almost 4,000 patients. Neither study performed further glucose tolerance tests, and therefore any possible associations between the level of glucose intolerance and preeclampsia could not be determined. Both Joffe et al.[47]and Sermer et al.[48] studied the relation between the glucose levels after a glucose-screening test and/or a glucose tolerance test and preeclampsia. Joffe et al.[47] found, even after adjustment for body mass index, race and clinical center an almost twofold increased risk of preeclampsia in the highest quartile of plasma glucose after a 50-g glucose challenge. Sermer et al.[48] reported increasing incidences of preeclampsia with increasing glucose levels after a 50-g glucose challenge test. They noted a twofold increased risk for preeclampsia in patients with at least one abnormal value in the 100-g oral glucose tolerance test. However, in a full multivariate model glucose values no longer predicted preeclampsia. Lindsay et al.[49] found impaired glucose tolerance, defined as one single abnormal glucose value in a 100-g oral glucose tolerance test, to be a risk factor for preeclampsia among 4,618 women, tested for gestational diabetes (OR 2.51, 95% CI 1.14-5.52). Also after logistic regression modelling for confounding factors (nulliparity, age, morbid obesity, race and multiple gestation) an increased risk for preeclampsia was demonstrated (OR 2.81, 95% CI 1.26-6.28). In contrast, Joffe et al.[47] reported no association between preeclampsia and im-

paired glucose tolerance (defined as an abnormal 50-g glucose challenge test and fewer than 2 abnormal glucose values in the 100-g glucose tolerance test) and preeclampsia.
Looking at gestational diabetes mellitus, a diagnosis based on the criteria of the National Diabetes Data Group, an increased incidence of preeclampsia was found in a large prospective case-controlled study by Garner et al.[50]. Schmidt et al.[51] used two different diagnostic criteria for gestational diabetes (from the World Health Organization and American Diabetes Association). Both sets of criteria were associated with an increased risk of preeclampsia. Logistic regression analysis, controlling for center, age, maternal height, prepregnancy body mass index and weight gain to enrolment, revealed relative risks of 2.28 (95% CI 1.22-4.16) and 1.94 (95% CI 1.22-3.03) using American Diabetes Association and World Health Organisation criteria, respectively.

Diabetes mellitus

Prepregnancy insulin-dependant diabetes mellitus is in general associated with an increased risk of preeclampsia[19;52-64]. In these studies the incidence of preeclampsia varied between 9% and 66%, depending on the selection of patients, with different stages of severity of disease being included. The rate of preeclampsia increases with the severity of diabetes by White's classification. In White's class B-D the incidence of preeclampsia has been reported between 9% and 17%[19;56;59-62]. However, the rate of preeclampsia in women with diabetic nephropathy ranged from 27-66%[19;57-59;61-64]. These discrepancies may be related to the criteria used to define nephropathy and preeclampsia. In addition, there were substantial differences in the sample sizes of the various studies. Hiilesmaa et al [60] showed in their prospective case-control study that nulliparity (OR 2.7, 95% CI 1.7-4.4), retinopathy (OR 2.0, 95% CI 1.2-3.3), duration of diabetes (OR 1.2, 95% CI 1.0-1.5) and poor glycaemic control early in pregnancy (OR 1.6, 95% CI 1.3-2.0) are independent risk factors for preeclampsia in women with type 1 diabetes (White's class B,C,D,R). Improvement of glycaemic control until mid pregnancy reduced the risk of preeclampsia (OR 0.6, 95% CI 0.5-0.8). Combs et al.[54] found three significant risk factors for preeclampsia in type 1 diabetes: early pregnancy proteinuria of more than 190 mg/day (OR 2.6, 95% CI 1.9-3.5), glycohaemoglobin greater than 9% (OR 1.4, 95% CI 1.1-2.0), and nulliparity (OR 1.4, 95% CI 1.0-1.9). Proliferative retinopathy and chronic hypertension were not significantly associated with preeclampsia. However, additional regression analyses showed a significant positive interaction between chronic hypertension and proteinuria, indicating a synergistic effect of these variables on the risk for preeclampsia. In conclusion, nulliparity[53;59;65], poor glycaemic control early in pregnancy[65], chronic hypertension[53;54], microalbuminuria prior to pregnancy[66], minimal proteinuria

before 20 weeks[54], nephropathy[53;57;63], and duration of maternal diabetes[65] are risk factors for preeclampsia in women with type 1 diabetes.

Systemic lupus erythematosus and antiphospholipid syndrome

Systemic lupus erythematosus (SLE) is defined clinically by abnormalities of multiple organ systems and serologically by the presence of autoantibodies[67]. Severe multisystemic SLE seriously complicates pregnancy, primarily through its manifestations of high fever, hypertension, renal failure, and on occasion cardiac and respiratory failure as well as through the treatment administered. The maternal sequelae of pregnancy in SLE have been studied, especially the effect of pregnancy on renal function. The majority of papers have studied the effect of pregnancy on renal function[68-71] and lupus flares in pregnancy [68;70;72;73]. Any renal disease predisposes the patient to preeclampsia. Both maternal and foetal complications seem to be related to recurrence of exacerbations and disease activity at onset of pregnancy. Review of the literature does not improve insight in SLE as potential independent risk factor for preeclampsia since most studies lack proper definition of preeclampsia and they represent a heterogeneous population of SLE patients. Moreover, it is difficult, and in some cases impossible, to distinguish a lupus renal flare from preeclampsia. Buyon et al.[74] found that lack of increase in serum complement 3 and 4 is more characteristic of lupus flare. Lao and Leung[75] found that a fall in serum complement 3 occurs in exacerbation of SLE. They suggest serial determination of these components to distinguish between preeclampsia and exacerbation of SLE.
Patients with antiphospholipid syndrome may have vascular occlusive events, thrombocytopenia, valvular heart disease and recurrent foetal death. Several authors found increased incidences of preeclampsia[76-79]. On the other hand, some authors found increased rates (10-20%) of antiphospholipid antibodies in patients with preeclampsia[80-82], severe preeclampsia[83-85] and eclampsia[86], whereas others could not find increased rates of antiphospholipid antibodies [86-88]. Some authors have found that the presence of antiphospholipid antibodies in unselected obstetric patients was associated with significantly higher incidence of preeclampsia[89-91], whereas others have found no increased risk [92]. The rates of antiphospholipid antibodies reported in these studies were between 2% to 7%, a variation which might be the result of selection bias of the population and differences in laboratory methods. The antiphospholipid antibody status in patients with systemic lupus erythematosus, in patients with recurrent miscarriages (3 or more)[93] and in patients with a history of preeclampsia[94] does not appear to be predictive for the development of preeclampsia. Therefore, antiphospholipid antibodies should be tested only when the antiphospholipid syndrome is suspected.

Hyperthyroidism/hypothyroidism

Hyperthyroidism occurs in about two of every 1,000 pregnancies[95]. About 95% of such cases of hyperthyroidism are due to Graves' disease, an autoimmune disorder associated with circulating thyroid-stimulatory immunoglobulins. The combination of hyperthyroidism and preeclampsia is unusual and difficult to diagnose and treat since hypertension and seizures may complicate hyperthyroidism as well as (pre)eclampsia[96]. Untreated hyperthyroidism substantially increases the risk of preeclampsia, being also higher among women who were hyperthyroid during pregnancy and delivery (OR 4.7 CI 95% 1.14–19.7) than those who are well controlled during pregnancy[97].
Although, pregnancy in hypothyroid women is relatively uncommon due to the frequent ovulatory dysfunction, preeclampsia is a common complication. Leung et al.[98] found that women with overt and subclinical hypothyroidism had an increased risk of pregnancy-induced hypertension, preeclampsia and eclampsia. The mechanism of preeclampsia in hypothyroidism is unclear[99]. Hypothyroidism is a recognized cause of reversible hypertension in nonpregnant women. Furthermore, preeclampsia can affect thyroid function manifested by low triiodothyronine syndrome, reduced total and free thyroxine and elevation in thyroid-stimulating hormone[100-102], mimicking real thyroid disease. Moreover, disturbances in thyroid hormone concentrations appear to reflect the severity of preeclampsia[101]. In conclusion, both hypothyroid and hyperthyroid women should be treated before pregnancy and the goal should be euthyroidism as indicated by normal serum levels of thyroid-stimulating hormone and free thyroxine.

Epilepsy

Epilepsy is one of the most common neurological disorders, and certainly one of the most frequently encountered in pregnancy. Epilepsy is a brain disorder characterized by recurrent seizures. As the result of relatively small, poorly controlled studies there are conflicting data about the association of preeclampsia and epilepsy. Hiilesmaa et al.[103] compared in a group of 150 women with epilepsy to women without epilepsy and found no differences (OR 0.8 95% CI 0.2–2.9), while others[104;105] have reported an increased risk of preeclampsia in women with epilepsy. Confounding factors such as parity, maternal age and relative small sample size were not taken into account. However, women who develop seizures during pregnancy should be treated as eclampsia since eclampsia is the cause of most seizures during pregnancy and puerperium.

Migraine

Migraine is the most common of the vascular headaches and a typically paroxysmal-occurring disorder, with headaches lasting from 2 to 12 hours. Preeclamp-

sia is associated with migraine in only one, well-defined study[106]. The OR rose with the average frequency and duration of migraine attacks. However, data were based on interviews a few days postpartum which might introduce a recall bias. Preeclampsia is often more associated with headaches and therefore it is possible that women who had preeclampsia were more likely to report episodes of headaches before pregnancy. This finding is consistent with the concept that headaches in women with preeclampsia are associated with abnormal cerebral perfusion pressure[107].

Polycystic ovary syndrome

Polycystic ovarian syndrome is a disorder characterized by oligoovulation, hyperandrogenism and hyperinsulinemia. Hyperinsulinemia and insulin resistance are present in 20-50% of both obese and nonobese women with polycystic ovarian syndrome[108;109]. Women with polycystic ovarian syndrome have increased insulin secretion during pregnancy as compared to women with uncomplicated pregnancies. This may also explain the higher risk of preeclampsia in women with polycystic ovarian syndrome than in women without polycystic ovarian syndrome (OR 12.1, 95% CI 1.3–566)[108;110;111]. The association of polycystic ovarian syndrome and preeclampsia is independent of infertility treatment (overproduction of ovarian hormones), maternal age and body mass index[112]. In addition, preeclampsia is more frequent in women with insulin-resistant polycystic ovarian syndrome than in women with non-insulin-resistant polycystic ovarian syndrome[113]. Unfortunately, testing of insulin sensitivity before pregnancy or early in pregnancy is not a good predictor of preeclampsia[113]. In contrast, Mikola et al.[114] found that polycystic ovarian syndrome contributes only slightly to the risk of preeclampsia; parity and multiple pregnancies were found to be important confounding factors. It is important to realize that both diseases, polycystic ovarian syndrome and preeclampsia, share the predisposition for diabetes and hypertension in later life.

Thrombophilia

Thrombophilia[115] includes disorders associated with an increased tendency to develop thrombosis that may be genetically determined, acquired or both. Three inherited risk factors for venous thrombosis were initially reported: antithrombin, protein C, and protein S, all being defects in the anticoagulant pathways. More recently, there have been reports of genetic risk factors associated with resistance to activated protein C (factor V Leiden mutation) and with increased prothrombin (prothrombin 20210A allele or factor II G20210A mutation). They are more prevalent than defects in the anticoagulant pathways. Because the latter two are more prevalent and are single gene mutations, and therefore more easily investigated, most reviews study the association of factor V Leiden mutation and factor II G20210A mutation. A recent meta-analysis of almost 3,000 women who

developed preeclampsia during pregnancy[116] found an association of Factor V Leiden (OR 2.25, 95% CI 1.50–3.38), however, the five largest studies observed no association (OR 1.21, 95% CI 0.84–1.74). Moreover, studies published in 2001 and 2002 show no association, in stark contrast with earlier studies[117], and there is a wide and statistically significant heterogeneity in the results of different studies. A common variant in the gene methylene tetrahydrofolate reductase (677 TT MTHFR), associated with mildly elevated homocysteine levels, showed a slight association of MTHFR C677T homozygosity and severe preeclampsia (OR 2.84, 95% CI 1.95–4.14)[117].

Family history of preeclampsia

There are data supporting that both a maternally transmitted and a paternally transmitted genetic predisposition play a role in the development of preeclampsia. The maternal genetic predisposition is supported by studies reporting that preeclampsia is more likely to develop in women whose mothers had preeclampsia (fourfold increased) than in women whose mothers did not[118;119]. A genome-wide scan was carried out in the Icelandic population including women with proteinuric and non-proteinuric hypertension identified a significant locus on 2p13[120]. The paternal genetic predisposition is supported by studies reporting that a woman who becomes pregnant by a man who has already had a child with a different woman who had preeclampsia has a risk of preeclampsia that is nearly twice as high as that of a woman whose partner does not have such a history[121]. Furthermore, Esplin et al.[122] reported that men who are themselves born of pregnancies complicated by preeclampsia are twice as likely to have a child who is the product of a pregnancy complicated by preeclampsia as are men who were born after a normal pregnancy. Several models of inheritance have been proposed, and specific candidate genes that may account for maternal and paternal susceptibility have been suggested. However, many genes appear to be involved, and there is no simple mode of inheritance

Family history of hypertension

In a recent study Ness et al.[123] found that women who develop preeclampsia are more likely to have two or more first-degree relatives with increased cardiovascular risk (hypertension, heart disease or diabetes)[7;124;125]. In particular, they were more likely to have familial hypertension (OR 2.2, 95% CI 1.1–4.5), hypercholesterolemia, stroke, or familial heart disease. In contrast to women with no parental history of hypertension, women with a history of maternal hypertension had a similar risk of preeclampsia as women with paternal hypertension only (twofold increased risk of preeclampsia). Women with both maternal and paternal history of hypertension had an almost threefold increased risk of preeclampsia[7;124;126]. Familial aggregation represents shared genetic or environmental (risk)

factors, which are carried by women into pregnancy[127]. These studies suggest that women entering pregnancy with an increased risk for cardiovascular disease are more likely to develop preeclampsia. In contrast, Stone et al.[40] found no effect of family hypertension on the prevalence of severe preeclampsia.

Maternal environmental factors

Smoking

In a meta-analysis of 400,000 singleton pregnancies of women who smoked during pregnancy revealed a protective effect on the development of preeclampsia (OR 0.57, 95% CI 0.55-0.59)[10;11;13;128-133]. In nulliparous and multiparous women the OR values were 0.60 (CI 0.57-0.63)[10;11;129;133-135] and 0.38 (CI 0.34-0.43)[13;133], respectively. Smoking appeared to reduce the risk of preeclampsia also after controlling for confounding factors such as maternal age and maternal weight. In the analysis of women who had multiple pregnancies (n= 4,051 women) smoking also had a protective effect (OR 0.82, 95% CI 0.66-1.00)[136-138]. However, the protective effect of smoking was confined to women who continued to smoke, particulary beyond 20 weeks gestation. Stone et al.[40] observed no protective effect of smoking on the risk of severe preeclampsia. Only few studies show figures of the effects of smoking before pregnancy and smoking only in early pregnancy on the risk of preeclampsia. England et al [129] found no evidence that women who smoke but quit before pregnancy were at reduced risk. Sibai et al.[10] found the lowest incidence of preeclampsia in women who quit smoking at the start of the pregnancy. Marcoux et al [139] found a positive dose-respons relationship of smoking on the reduction in risk of preeclampsia, but Martin et al.[137] observed this dose-respons relationship only in multiparous women. However, none of the other studies that include the effect of dose of smoking showed a further reduction in the risk of preeclampsia by increase in dose of smoking[38;128;131;132].
The mechanism of this protective effect on the manifestation of preeclampsia remains unknown. Smoking may augment the production of a protective factor or induce chronic changes that desensitize the endothelium, which reduces its response to the triggers of preeclampsia. It is also possible that smoking is associated with earlier delivery in women who would be otherwise be destined to develop preeclampsia[13].
Although, maternal smoking is associated with a decreased risk of preeclampsia, the net detrimental effect of smoking on pregnancy outcome is unquestionable[140]. In spite of the protective effect of smoking against the risk of preeclampsia smoking during pregnancy is associated with an increased risk of perinatal mortality and morbidity.

Working activity

Women with high life stress scores are no more prone to preeclampsia than women with low stress scores. Life stress scores are based upon their social network, education, employment, household conditions and traumatic experiences scored in the first trimester[141]. However, other authors report that maternal work, particularly if continued into the third trimester, is associated with an increased incidence of preeclampsia[7]. Recently, Higgins et al.[142] reported in a prospective study of 933 healthy primigravidas a significant association of maternal work and the development of preeclampsia (OR 4.1, 95% CI 1.1–15.2) even after controlling for possible confounding factors including maternal age, smoking, body mass index and marital status. Especially women exposed to a high psychological demand and low decision attitude at work are at a higher risk of developing preeclampsia[143;144]. A meta-analysis found physically demanding work to be associated with preeclampsia[145]. In addition, preeclampsia is reported to be more common in physicians pregnant during residency than in the wives of their male classmates[146]. The explanation for the association between work and preeclampsia is unknown. It has been suggested that the stress of work results in increased release of catecholamines and a day-long sympathetic response that increases blood pressure. Moreover, women at work have higher mean daytime systolic and diastolic blood pressures than those not working. Also, women who performed regularly leisure time physical activity during the first 20 weeks gestation have a reduced risk of preeclampsia (OR 0.67, 95% CI 0.46–0.96)[143;147]. Although the data were collected from cases and controls a few days postpartum, a bias of the cases on (increased) frequency and duration of activities, would result in the underestimation of the protective effect of leisure time physical activity on preeclampsia.

Pregnancy related factors

Nulliparity

Preeclampsia is a disease of nulliparous women. The reported incidence of nulliparity is 2.8 –14.1%[10]. Nulliparity is associated with a three- to ninefold increase in the risk of preeclampsia[7;148]. Covariates including low prepregnancy weight, low weight gain and low maternal age are related to nulliparity. Failure to control for these variables may result in underestimating the increased risk of nullipartity and preeclampsia[148]. In contrast, Stone et al.[40] found nulliparity not to be a risk factor for severe preeclampsia.

Paternity

Several studies have suggested that the risk of preeclampsia decreases with a second pregnancy only if the mother's partner is the same[149-152]. The hypothesis is that the risk of preeclampsia is reduced with repeated maternal exposure and adaptation to specific foreign antigens of the partner. The duration of sexual cohabitation (< 6 months) or primipaternity has shown to be associated with preeclampsia[153;154]. According to this hypothesis, a new partner presents new antigens, which results in a risk of preeclampsia that is similar to the risk during the first pregnancy. Thus changed paternity has been considered a significant risk factor for preeclampsia in multiparas, which could be explained by a foetal genotypic influence[155]. However, recent studies question the primipaternity theory of preeclampsia since the increased risk in women who change partner disappears when controlling for the time since previous birth[156;157]. Skjaerven et al.[158] found that multiparous women who become pregnant 10 years or longer after their previous pregnancy are as likely to have preeclampsia as nulliparous women. Even after controlling for smoking, prepregnancy weight, and maternal age, a long interpregnancy period is an independent risk factor for preeclampsia[156;159]. The long interpregnancy period may reflect difficulty in conception or implantation and is thus associated with preeclampsia[159], although the causal mechanism has not been determined. In contrast to these findings, recent epidemiological studies suggest an independent contribution of paternal genes to the risk of preeclampsia supporting an immunological component of the disease[122;160]. In conclusion, the observation of changing partner and increased risk of preeclampsia is likely to be confounded by the effect of interbirth period. This interpretation may also apply to the association of miscarriage and reduced risk of preeclampsia in a subsequent pregnancy. The fact that the average period between pregnancies is shorter after a miscarriage than after a live birth suggests a shorter interbirth period and reduced risk of preeclampsia[158]. A short interbirth period, however, should not be recommended preconceptionally as other adverse outcomes such as preterm delivery are more likely to occur. [161;161]

Previous history of abortion (spontaneous and/or induced)

A meta-analysis of almost 60,000 women suggests a protective effect of one (OR 0.85, 95% CI 0.75–0.96)[8;10;11;162] or more abortions (OR 0.81, 95% CI 0.67–0.99)[8;10;11;162] on the risk of preeclampsia. In this analysis selected several characteristics of abortion such as gestational age, number of previous abortions and abortion type were not taken into account. The effect of an induced abortion on the risk of preeclampsia is unclear[8]. In the analyses of two large multicenter cohorts of expectant women, Sibai et al.[10;11] found a trend of decreasing incidence of preeclampsia with increasing number of previous abortions (also after controlling for confounding effects such as maternal age, ethnic origin, and

smoking). Although abortion of any type yields some degree of protection against preeclampsia in a second pregnancy, this protection is not as great as a first term pregnancy (≥ 37 weeks gestation)[162].

Previous preeclampsia

A history of preeclampsia represents one of the highest risk factors for preeclampsia in the second pregnancy (overall, OR 8.1 CI 95% 6.5–9.9) in a population-based study[7;13]. The risk is inversely proportional to gestational age at delivery and severity of the first pregnancy[163;164]. Sibai et al.[165] reported a recurrence rate of women who had preeclampsia in the second trimester of about 20% in the second of third trimester in their subsequent pregnancy. Because the onset of preeclampsia usually precedes delivery, gestational age at delivery may underestimate the relationship of "onset" of preeclampsia and recurrence. Other risk factors for preeclampsia in a second pregnancy were generally consistent with the finding of previous studies including longer interbirth period, previous preterm delivery or small for gestational age newborn, obesity and race. Gestational diabetes is strongly associated with the recurrence of preeclampsia in a second pregnancy[163]. When preeclampsia did not recur in a subsequent pregnancy, the overall obstetric outcome was favourable, although more women developed pregnancy-induced hypertension than in the general obstetric population[166].
Women who have had preeclampsia remote from term are at increased risk of chronic hypertension and undiagnosed underlying renal disease[16]. This is an important issue in counselling women with a history of preeclampsia for their recurrence rate as well as their increased risk of cardiovascular disease later in life[167].

Assisted reproduction

Only a few studies have suggested an association between subfecundity and preeclampsia. In a recent study Basso et al.[159] found a higher risk of preeclampsia (50%) in those with longer times to pregnancy (> 6 months to conceive). It is well-known that the increased utilization of assisted reproduction has resulted in an increased number of multiple gestations, which in turn have an increased risk of preeclampsia. Also oocyte donation pregnancies are more often complicated by preeclampsia (16-40%) than age- and parity-matched controls and controlling for multiple pregnancies[168]. Three studies report a higher than expected incidence of preeclampsia in pregnancies conceived by donor insemination[169]. These findings suggest that pregnancies achieved from oocyte, sperm or embryo donation are unique since they result from donor gametes that are immunologically foreign to the mother.

Twin pregnancy

Preeclampsia in twins has a reported rate of 13-37%[170]. In a meta-analysis of five studies (180,000 women) twin pregnancies had a threefold higher risk for preeclampsia than singleton pregnancies[136;171-174] . The disease is reported as more severe and occurring at earlier onset[172] which is even more evident in triplets[161;170]. A small study observed that triplets had a higher incidence of preeclampsia than pregnancies with first-trimester triplets with subsequent twins due to spontaneous pregnancy loss or multifoetal reduction[161]. This observation points at the importance of both successful implantation and placenta mass. Risk factors in singleton pregnancies act similarly in twin pregnancies[136]. Furthermore, women who received assisted reproductive technologies were twice as likely to develop preeclampsia than spontaneous conceived twins[175]. Women conceiving with assisted reproductive technologies are more often nulliparous and have a more advanced maternal age but even after controlling for these variables the use of assisted reproductive technologies remains an independent risk factor for preeclampsia. Furthermore, some studies reported no difference in the incidence in preeclampsia between monozygous twins and dizygous twins[176;177]. These results do not support the theory of quantitative immunohistocompatibility in the pathogenesis of preeclampsia[178]. Other studies, however, have found higher rates of preeclampsia associated with monozygotic twins than dizygotic twins[179] or visa versa[180].

Molar pregnancy and foetal hydrops

In 1892 Ballantyne first reported that maternal oedema is more common in severe foetal and/or placental hydrops than in normal pregnancies. Over the years several case reports and case series have described the association of preeclampsia (or preeclampsia-like symptoms) in pregnancies with severe foetal and/or placental hydrops. Various terms have been used for this maternal syndrome: Ballantyne's syndrome[181-184], triple oedema[182;184], mirror syndrome[185;186], pseudotoxemia[187;188], triploidy syndrome[187], maternal syndrome[189;190], and maternal hydrops syndrome[189;191;192].

It is difficult to assess the prevalence of preeclampsia due to lack of proper definition. Rijhsinghani et al.[193] has published the only well-defined study assessing the risk of preeclampsia in second-trimester triploid pregnancies associated with foetal hydrops: in which 5 of 17 (29%) patients developed preeclampsia. These patients had significantly higher levels of human chorionic gonadotropin than those who did not develop preeclampsia. Moreover, triploid pregnancies (partial molar pregnancies), commonly clinically complicated by foetal hydrops, are usually genetically determined by an overrepresentation of paternal genes[194-196]. This may be a clue in the pathogenesis of preeclampsia: an overload of foetal (foreign/paternal) antigens may be responsible for the maternal disease; the recipient

(mother) receives foetal immunogenic cells, and these cells recognize maternal tissue as "foreign" with finally activation of the maternal vascular endothelium. The maternal vascular endothelium is strategically positioned lining each organ. Activation of maternal vascular endothelial is clinically manifested by systemic disease affecting various maternal organs and the placenta with potentially adverse effects on both mother and child.

However, some authors suggest that molar pregnancies are a different entity: low haematocrit is observed in patients with maternal hydrops syndrome[192;197] in contrast to women with preeclampsia[198]. Quagliarello et al.[183] reported absence of glomerular endotheliosis, which is the characteristic glomerular lesion of preeclampsia, while Akhtar et al.[197] found glomerular endotheliosis in a patient with preeclampsia secondary to a partial molar pregnancy.

Nevertheless, since early pregnancy ultrasound scanning and highly sensitive radioimmunoassays for human chorionic gonadotropin have become readily available in recent years, the traditional presenting features of (partial) molar pregnancies, including early preeclampsia have become rare[199]. Also, foetal hydrops due to rhesus isoimmunization has become less frequent as a result of the introduction of anti-D rhesus immunoprophylaxis. These improvements in health care have resulted in reducing the frequency of the maternal hydrops syndrome and therefore that of early, severe preeclampsia in the mother[192;197;200].

Conclusion

Determination of risk factors is complicated by the lack of uniformity of criteria used to classify hypertensive disorders of pregnancy and difference in the study populations used. In judging whether a variable is really predictive of preeclampsia, there are several considerations. Firstly, the variable is a predictor a priori. Secondly, the variable appears to be a predictor in several well-defined studies and tested as an independent risk factor. For example, advanced maternal age is associated in some studies with preeclampsia but older women have more often chronic hypertension, which is also a risk factor for preeclampsia. Independent risk factors are chronic hypertension, renal disease, diabetes, nulliparity and pregnancy interval. These risk factors are important in order to determine fetal and maternal morbidity and mortality. Moreover, the extent and risk factors may provide an early window into further diseases: hypertensive diseases during pregnancy are associated with cardiovascular diseases in later life. If greater awareness of this association leads to earlier diagnosis, improved management by reducing risk factors might reduce pregnancy complications as well as cardiovascular risks later in life. Interventions such as decreasing insulin sensitivity by weight reduction will reduce pregnancy complications and cardiovascular disease in later life. Pre-pregnancy counselling is therefore warranted.

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CHAPTER 2.2

Maternal and perinatal outcome of preeclampsia with an onset before 24 weeks' gestation. Audit in a tertiary referral center

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Abstract

Objective: Preeclampsia, with an onset before 24 weeks' gestation is a rare but severe condition in pregnancy with little data of maternal and perinatal outcome, particularly after expectant management. We therefore, evaluated pregnancy outcome in these women at our department where temporizing management was introduced as the standard policy in early onset preeclampsia.
Study design: We analysed retrospectively all consecutive women with preeclampsia, with an onset before 24 weeks' gestation, between 1 January 1993 and 31 December 2002 at a tertiary university referral center.
*Results***:** Twenty-six pregnancies, of which two were twin pregnancies, resulted in 65% of the women in at least one major maternal complication: maternal death (n=1), HELLP syndrome (n=16), eclampsia (n=5) and pulmonary edema (n=4). Thirty percent of these women presented already with serious morbidity at admission. The median prolongation of the pregnancy was 24 days (range 3-46 days). The overall perinatal mortality was 82%: 19 fetal deaths and 4 neonatal deaths.
*Conclusion***:** Early onset preeclampsia, with an onset before 24 weeks' gestation, results in considerable maternal and perinatal morbidity and mortality. Therefore, expectant management should not be considered as a routine treatment option in these patients.

1. Introduction

Severe, very early onset preeclampsia is associated with high mortality and morbidity for both mother and child. Although the etiology of preeclampsia is unknown[1], delivery of the fetus and placenta is the only way of arresting this serious disease. Delivery may benefit the mother but is not in the interest of the fetus, if remote from term. The main cause of neonatal mortality and morbidity in patients with severe preeclampsia is prematurity[2]. Therefore, expectant or "conservative" management with temporizing treatment was introduced in order to lengthen gestation, which may be associated with enhanced perinatal survival. Expectant management of preeclampsia includes variable periods of using pharmacological agents for controlling hypertension with accurate, maternal hemodynamic monitoring and the prophylaxis of eclampsia by magnesium sulphate. Corticosteroids are administered to enhance fetal lung maturity. Maternal and fetal surveillance is conducted at regular intervals and delivery is indicated for worsening maternal and fetal conditions. Prolongation of pregnancy has been described with an average of 2 weeks[3,4] with longer periods gained at earlier gestation[5,6]. However, the number of reported patients with very early onset preeclampsia treated expectantly is very small[3,4,6,7]. Therefore, data remain limited on the maternal morbidity and mortality and on how many of these pregnancies will result in a take home baby. At our department a protocol of temporizing management of severe, early onset preeclampsia was instituted in 1985, consisting of volume expansion and vasodilatation guided by Swan Ganz catheter for continuous blood pressure measurements[4]. Since 1993 temporizing treatment was guided by a central venous line instead of a Swan Ganz catheter. In the present study all women with preeclampsia with an onset before 24 weeks' gestation, admitted between 1993 and 2003, were evaluated for their maternal and perinatal outcome.

2. Material and methods

From 1 January 1993 until 31 December 2002 information of all 26 consecutive women who had preeclampsia with an onset before 24 weeks' gestation at the Erasmus Medical Center Rotterdam were recruited from a computer database and patient charts. Data were collected from 1993 since an automated database was available.

Preeclampsia was defined as blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic measured on at least two occasions in women normotensive before 20 weeks' gestation and proteinuria ≥300 mg/24h (or ≥2+ on dipstick of voided specimen). Superimposed preeclampsia was defined as a rise of blood pressure ≥30 mm Hg systolic or ≥15 mm Hg diastolic over values in the first 20 weeks and proteinuria ≥300 mg/24 h (or ≥2+ (1 g/l) on a voided specimen or ≥1+ (0.3 g/l) on a catheterized specimen (ISSHP)[8]. Severe preeclampsia was defined as

an absolute diastolic blood pressure of ≥110 mm Hg and proteinuria (≥2+ (1 g/l)) on a catheterized specimen on admission, or the occurrence of preeclampsia described above in combination with eclampsia or HELLP syndrome. HELLP (hemolysis, elevated liver enzymes, and low platelets) was defined as thrombocytes <100x10^9/l, and both aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) >70 U/l and lactate dehydrogenase > 600 U/L[8].
All patients were admitted to the obstetrical high care unit or intensive care unit. Of the 26 women who met the criteria of preeclampsia with an onset before 24 weeks' gestation, 20 patients were referrals for maternal-fetal indications. Eleven patients were referred immediately, whereas nine patients received initial treatment after onset of disease in the referral hospital (mean of 5 days, range 1-11 days). Gestational age was defined by last menstrual period confirmed by first trimester ultrasound. Expectant management consisted of bed rest and correction of the maternal circulation by means of pharmacological vasodilatation (dihydralazine, ketanserin and labetalol and/or oral medication: methyldopa, nifidipine or a combination) and plasma volume expansion under hemodynamic monitoring using an intra-arterial catheter and a central venous catheter in the brachial vein. The target value of diastolic intra-arterial blood pressure was 90 - 100 mmHg[9]. Magnesium sulphate prophylaxis was not considered unless the women developed imminent eclampsia. Intravenous fluids and urinary output were monitored daily and a full blood count was performed at least twice weekly. Initially, fetal viability was set at gestation of ≥ 27 weeks and a minimum estimated (by ultrasound) fetal weight of ≥ 650 g. From January 2001 till December 2002 fetal viability was set at 26 weeks' gestation with the same (≥ 650 g) estimated fetal weight (11 of the 26 women). When the estimated fetal weight was <650 g, women were counseled by the obstetric and paediatric staff before delivery, regarding their desires for intervention by caesarean section and/or maximal neonatal resuscitation in case of fetal distress. When fetal viability was reached or the parents had the desire for active intervention, betamethazone (12 mg) was given, and repeated after 24 h. The fetus was then monitored daily by cardiotocography (CTG) and ultrasound evaluation of growth and amniotic fluid index every second week.
Failure to control blood pressure, defined by a diastolic blood pressure ≥ 110 mmHg despite combined intravenous antihypertensive treatment on maximal dose, or the development of major maternal complications (cerebral or hepatic haematoma, severe edema/ascites) at any gestation were indications for delivery by the attending obstetrician. A non-reassuring CTG was the fetal indication for delivery. A member of the neonatology staff evaluated live born infants at birth. The decision to resuscitate or to render hospice care was based on birth weight and gestational age at delivery.

2.1. Maternal outcome data.

Peripartum maternal complications including maternal mortality, HELLP syndrome, eclampsia, pulmonary edema, intracerebral haemorrhage, hepatic haematoma, renal failure, sepsis, and abruptio placentae were abstracted from the charts. Pulmonary edema was defined as respiratory failure with an arterial *p*O2 <10 kPa, confirmed by typical findings on chest X-ray. Intracerebral haemorrhage was diagnosed by computerized tomography performed on clinical suspicion. In case of severe upper quadrant abdominal pain ultrasound examination was performed to exclude hepatic haematoma. Renal failure was defined as the necessity of dialysis because of renal insufficiency. Sepsis was defined as bacteremia and septic shock symptoms with necessity of vasoactive drug therapy. The diagnosis abruptio placentae was based on clinical work-up. Maternal demographic data were abstracted included gestational age on admission, maternal age, parity, race, medical history including previous hypertensive disease, proteinuria in the first trimester, diabetes, systemic lupus erythematosus and thrombosis. Information regarding blood pressure, laboratory tests, mode and indication of delivery, and medication was collected.

Neonatal outcome data included gestational age at delivery, birth weight, Apgar scores, cord blood gases, and complications before admission to the neonatal intensive care unit. Subsequent data on neonatal survivors were obtained from the records of the neonatal intensive care unit including number of days of stay on the unit, number of days of ventilation, intraventricular haemorrhage, necrotizing enterocolitis, sepsis, patent ductus arteriosus, bronchopulmonary dysplasia and retinopathy of prematurity. Placental insufficiency was based on histopathologic findings.

2.2. Analysis

Blood pressure is reported in median (range). Maternal clinical parameters at admission, and neonatal survival were analyzed using univariate regression analysis. Gestational age at delivery, birth weight, and neonatal parameters were analyzed using multiple regression analysis.

3. Results

During the 10-year study period, 14,212 women were delivered in the Erasmus Medical Center Rotterdam. Twenty-six women were admitted because of preeclampsia with an onset before 24 weeks' gestation and therefore, eligible for the study. None of the patients was offered termination of pregnancy. The median prolongation of pregnancy was 24 days (range 3-46 days).

3.1. Maternal outcome data

Maternal mortality and major morbidity of preeclampsia and superimposed preeclampsia are presented in Table 1. None of the women had an intracerebral haemorrhage, hepatic haematoma and/or sepsis. Sixty-five percent (17/26) of the women had at least one other major complication.
One maternal death occurred of 21-year-old African women in her third pregnancy. Her medical and obstetric history was unremarkable. Prenatal care was uneventfully until 23 weeks' gestation when she had eclampsia at home. On admission she had several eclamptic fits, severe hypertension (blood pressure 200/150 mmHg) and HELLP syndrome. She was treated with intravenous antihypertensive medication, plasma volume expansion and anti convulsive medication. One day after admission she developed progressive respiratory insufficiency and subsequently renal insufficiency. Because of her threatened condition she was referred to our hospital (gestational age 23 2/7 weeks). Intrauterine death occurred at 23 2/7 weeks and at 24 weeks she delivered spontaneously a deceased girl of 425 g. Severe adult respiratory distress syndrome and multiorgan failure resulted in maternal death 8 days after delivery.

Tabel 1. Major maternal morbidity and mortality

	Preeclampsia: N=17	Superimposed pre-eclampsia: N=9	Total: N=26 (%)
Maternal mortality	1	0	1 (4)
HELLP	10	6	16 (62)
Eclampsia	5	0	5 (19)
Pulmonary edema	4	0	4 (15)
Renal failure	0	0	0
Abruptio placentae	0	0	0
Uncontrolled hypertension	2	0	2 (8)

At admission the median (range) systolic and diastolic blood pressures were 170 mmHg (130-220) and 100 mmHg (75-150), respectively for women who had not been treated before admission. One patient in the untreated group had a diastolic blood pressure of 75 mmHg. She was admitted because of HELLP syndrome and proteinuria. She developed hypertension one day after admission. Median systolic and diastolic blood pressures were 180 mmHg (180-200) and 100 mmHg (100-135), respectively for women who were using antihypertensive medication. All women had significant proteinuria (median 5.5 g/24 h, range 0.5-27). The most frequent maternal complication was HELLP syndrome occurring in 16 patients of which eight patients developed HELLP syndrome after admission (mean 9 days, range 1-32 days). Six of the nine patients with superimposed preeclampsia had HELLP syndrome, of which four patients developed this complication after initiation (6-39 days) of temporizing management. All five women who had eclampsia were ante partum. Three patients had eclampsia before or shortly after admission, two patients had eclampsia after initiation of temporizing management. All four patients with pulmonary edema developed this complication during expectant management.

The median gestational age at admission was 22 6/7 weeks (range 21 3/7 – 23 5/7). The median maternal age was 31 years (range 18-40). Most women were nulliparous (62%). Sixteen women were Caucasian, eight women were African, and two Asian women. Eleven women (42%) had a complicated medical history before the index pregnancy consisting of chronic hypertension (*n*=9) of whom three were receiving antihypertensive medication, renal disease (*n*=1), and a history of thromboembolism not related to pregnancy (*n*=1). None of the patients had proteinuria before 20 weeks' gestation. Four women had a previous pregnancy complicated by preeclampsia, and one woman had a history of poor perinatal outcome (four fetal deaths between 18-20 weeks' gestation) due to antiphospholipid syndrome.

3.1.1. Neonatal outcome

Of the 26 pregnancies, 18 (68%) pregnancies, including one twin pregnancy had a fetal death at a median of 16 days (range 2-42) after admission. Median gestational at birth 26 3/7 weeks (range 22 5/7 – 29 4/7 weeks), median birth weight 455 g (range 300 – 710 g). Reasons of intrauterine fetal death were placental insufficiency (*n*=18, one twin included) and parvo virus infection (*n*=1). Of these 18 pregnancies, two were terminated before viability (at 24 3/7 and 25 3/7 weeks) by administration of intravenous prostaglandins, because of uncontrolled hypertension.

The nine live-born infants (eight pregnancies including one twin) were evaluated by the neonatology staff. Eight infants were born by caesarean section for fetal reasons in five cases (including one twin), and for maternal reasons in two

cases. One child was born vaginally after spontaneous onset of premature labor. Hospice care was given to two of the nine infants because of extreme prematurity. The remaining seven infants were admitted to the neonatal intensive care unit, where they were treated. The median (range) gestational age of these infants was 28 weeks (26 2/7 – 29 6/7) with a median (range) birth weight of 670 g (520 – 775). Of these seven infants two babies died after 4 and 10 days after admission at the neonatal intensive care unit (one sepsis, one respiratory failure). The overall perinatal mortality was 82%. The five surviving infants are described in Table 2. Univariate regression analysis showed that none of the maternal clinical parameters at admission including gestational age, blood pressure, HELLP syndrome, eclampsia, or history of hypertension was associated with neonatal survival. There is a positive trend for gestational age and birth weight, and neonatal survival (odds ratio 1.2, 95% CI (0.97-7.2) and 1.02, 95% CI (0.99-7.0), respectively). No differences in intrauterine complications at admission (intrauterine growth restriction, oligohydramnion and Doppler findings) and neonatal survival were observed between women who had antenatal care in our tertiary center, women who were referred immediately and women who were treated before referral (odds ratio 0.55, 95% CI 0.01-22.8).

Table 2. Neonatal outcome of the surviving neonates

Gestational age at delivery (weeks) (prolongation in days)	Hospital stay (days)	Ventilation (days)	Morbidity	Follow up interval (months)	Maternal disease At admission
28 0/7 (37)	71	12	Sepsis, PDA, IVH gr I	22 no disabilities[a]	Preeclampsia
28 0/7 (37)	78	14	Sepsis, PDA, BPD	22 no disabilities	Preeclampsia
28 0/7 (33)	89	19	PDA,BPD	23 no disabilities	Preeclampsia + HELLP
27 2/7 (40)	75	21	PDA, BPD, ROP grI-II	72 no disabilities	Superimposed preeclampsia[b]
29 5/7 (46)	53	1	None	9 no disabilities	Preeclampsia

PDA = patent ductus arteriosus, BPD = bronchopulmonary dysplasia, ROP = retinopathy of prematurity, IVH=intraventricular haemorrhage. wks = weeks.
[a] no cerebral palsy, no visual/hearing disability
[b] this patient developed HELLP syndrome 39 days after admission

4. Discussion

We describe 26 pregnancies complicated by preeclampsia, admitted before 24 weeks' gestation, managed expectantly. One maternal death occurred. This patient was actually not eligible for temporizing management because of her poor clinical condition at admission. At admission eight patients presented with severe morbidity (eight HELLP syndrome of which three in combination with eclampsia). After initiation of temporizing management another nine patients developed severe morbidity; eight patients with HELLP syndrome of which four in combination with pulmonary edema, and one patient had eclampsia. Very early onset of preeclampsia therefore, resulted in overall major maternal morbidity, including one maternal mortality, in 65% of the women. These women delivered 28 babies with an overall perinatal mortality of 82%. Five babies were taken home.

The clinical course of early onset preeclampsia is often associated with progressive deterioration in both maternal and fetal conditions. In our study 30% of the patients present already with serious morbidity at admission. During expectant management another 35% of the patients develop serious morbidity. Of course, it is difficult to differ between morbidity due to the disease as such, and the morbidity as a result of temporizing management. However, the actual course and pace with which the disease progresses in the individual patient is unpredictable. This is illustrated in our study by the lack of association of clinical parameters at admission including gestational age, blood pressure, HELLP syndrome, eclampsia, or history of hypertension and neonatal survival. Previously, no association could be found between either increases in protein excretion or the presence of heavy proteinuria and perinatal outcome[10].

The maternal morbidity rate of 65% in the present study is higher than that reported previously[3,6] possibly as a result of the fact that there was no other treatment option than expectant management. It is difficult to explain the differing maternal complications between the studies: Sibai et al.[3] reported 60 women with severe preeclampsia in the midtrimester (18-27 weeks) treated with expectant management with a higher number of abruptio placentae (22%), similar number of women with eclampsia (17%). The lower number of women with HELLP syndrome (17%) in the study of Sibai et al. could be explained by exclusion for temporizing management of patients who had HELLP syndrome at admission. In their second study on the same subject, Sibai et al.[6] noted an improved maternal outcome with an overall maternal morbidity of 27%. They suggest that the improved maternal morbidity might be due to earlier, more intensive maternal monitoring and immediate referral from local hospitals before the onset of complications. This study and our study had a similar length of prolongation of pregnancy. In contrast, we report a high rate of maternal complications, which can only partially be explained by late referral. In our study nine women (35%) were referred after expectant management had been initiated in the local hospi-

tal. Only in half of the cases (*n*=4) patients were referred after onset of maternal complications. No differences in maternal complications were observed between women who had antenatal care in our tertiary center, women who were referred immediately and women who were treated before referral (odds ratio 0.51, 95% CI 0.10-2.44). Nevertheless, since early onset preeclampsia is rare expectant management should only be considered in experienced hands.
Moodley et al.[11] reported a maternal complication rate of 31% in 50 women with preeclampsia presenting before 32 weeks' gestation. Twelve of these women were admitted before 26 weeks gestation. They reported one maternal mortality, one woman had an eclampsia, and two women had pulmonary edema. Table 3 presents perinatal mortality and maternal morbidity in expectant management of severe, very early onset preeclampsia by several authors. However, most studies report maternal complications of severe preeclampsia with gestational ages beyond 24 weeks[5-7].
The overall neonatal survival rate of 18% in this study is very low and should be interpreted in the context of our policy regarding defining fetal viability. We defined fetal viability as 27 weeks of gestation with a minimum estimated fetal mass of 650 g (in our study *n*= 8/28). Several authors have demonstrated an increase in perinatal survival as gestation increases[4,12,13]. Odendaal et al.[14] showed increased

Table 3. Maternal and neonatal outcome in very early onset preeclampsia and expectant management

Author	Gestational age at onset (wks)	Patients (n)	Perinatal mortality (%)	Severe maternal complications (%)
Sibai[4]	18-27 18-25	60 31	87 74[a]	35[b] not stated
Pattinson[7]	<28 <24	45 11	71 100	9 not stated
Sibai[5]	≤24	15	93	27
Moodley[11]	<32 <24	50 8	62 100	31 not stated
Present study	<24	26	82	65

severe complications: maternal death, abruptio placentae, eclampsia, HELLP syndrome, coagulopathy, renal failure, intracerebral haemorrhage, hepatic haematoma, hypertensive encephalopathy, pulmonary oedema
[a] foetal death
[b] number of severe complications

perinatal survival as birth weight increased. We report women presenting at a severe premature gestational age, whose pregnancy is complicated in most cases by intrauterine growth restriction (16/28 fetuses at admission and 23/28 neonates were below the 10th percentile)[15]. Only a few studies report neonatal morbidity and mortality of extreme prematurity due to preeclampsia and thus most often complicated by intrauterine growth restriction. Moodley et al.[11] reported 12 pregnancies complicated by preeclampsia presenting before 26 weeks gestation without any neonatal survival. Pattinson et al.[7] described favorable results with expectant management in 45 patients developing preeclampsia before 28 weeks. Eleven patients were less than 24 weeks pregnant and all suffered perinatal deaths. The prolongation of these pregnancies was not mentioned. Sibai et al.[3] reported 74% fetal death when preeclampsia developed at 25 weeks or before. In their subsequent study[6] on the same subject, they noted not only an improved maternal outcome but also neonatal outcome. However, the fifteen women with preeclampsia with an onset before 24 weeks, and expectant management resulted in only one neonatal survival. Moreover, preeclampsia per se does not have a beneficial effect on the postnatal course of infants born at 24-35 weeks' gestation[16]. Despite the improved treatment regiments at the neonatal intensive care units, which lead to 50% neonatal survivors as early as 24 weeks' gestation as reported by some centers, the likelihood of occurrence of major reversible and irreversible morbidity remains dependent on gestational age. These findings have led to the assumption that prolongation of pregnancy may improve neonatal survival. One should realize, however, that in severely ill preeclamptic patients temporizing treatment is attempted in a potentially hostile intrauterine environment. Prolongation of pregnancy therefore, does not necessarily result in better neonatal outcome. In our study 13 of the 26 pregnancies presented at admission with a growth restricted fetus (below the 10th percentile). Even after prolongation of pregnancy by 2 weeks none of these fetuses did meet the criteria for fetal viability. This resulted in a high percentage of intrauterine deaths (68%). Moreover, we need to realize that only eight of the 28 fetus reached the defined gestational age of viability of which five survived. Therefore, the minimal improvement that might occur in neonatal outcome is not balanced against the serious maternal risks.

In summary, prolongation of pregnancies complicated by preeclampsia with an onset before 24 weeks' gestation is associated with very high perinatal mortality and serious maternal morbidity. These maternal complications outweigh improved chances of a take home baby. Therefore, expectant management of women with very early onset, preeclampsia should only be considered as an exception management option in tertiary referral centers and only after thorough counseling of these women. Since the results of this audit have become available, patients will be counseled in our department towards termination of pregnancy

with the knowledge that although the recurrence risk is relatively high[17-19], perinatal outcome in a subsequent pregnancy can be expected to be much better[20].

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CHAPTER 2.3

Severe, very early onset preeclampsia: subsequent pregnancies and future parental cardiovascular health

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Abstract

Objective: To study subsequent pregnancy outcome in women with severe, very early onset preeclampsia (onset before 24 weeks' gestation) and to analyze cardiovascular risk profiles of these women and their partners.
Study design: Twenty women with preeclampsia with an onset before 24 weeks' gestation, admitted between 1 January 1993 and 31 December 2002 at a tertiary university referral center, were enrolled in the study. Data on subsequent pregnancies were obtained from medical records. Their cardiovascular risk profiles and those of their partners (n=15) were compared with those of 20 control women after uncomplicated pregnancies only, matched for age and parity, and those of their partners (n=13). Body weight, height, waist and hip circumference, blood pressure and intima media thickness (IMT) of the common carotid artery were measured. Fasted blood samples were drawn for detection of metabolic cardiovascular risk factors.
Results: Of the 20 case women 17 women had 24 subsequent pregnancies, of which 12 (50%) were complicated by preeclampsia. Severe preeclampsia developed in 5 (21%) pregnancies. No perinatal deaths occurred. Case women had significantly more often chronic hypertension as compared to controls (55% vs. 10%, P=0.002). IMT of the common carotid artery was increased in a subset of case women using antihypertensive medication (P=0.03). Case women showed increased microalbuminuria (P<0.05). No differences were found in cardiovascular risk profiles between partners of cases and controls.
Conclusions: Women with severe, very early onset preeclampsia have an increased risk of preeclampsia in future pregnancies, yet neonatal outcome is, in general, favourable. Regarding cardiovascular health, women after severe, very early onset preeclampsia exhibit more risk factors compared to controls whereas men who fathered these pregnancies do not.

1. Introduction

Severe, very early onset preeclampsia before 24 weeks' gestation is a rare complication in pregnancy. Small series have described high maternal morbidity and very poor perinatal outcome[1,2]. However, we could locate no reports on the outcome of subsequent pregnancies and future health parameters of these women with very early onset preeclampsia. Women with preeclampsia in general, especially complicated by HELLP syndrome, are at increased risk for all forms of hypertension related complications in subsequent pregnancies [3-6].

In addition to offering advice about family planning, these women may have to be counselled in the future regarding their long-term cardiovascular prognosis. Several epidemiological studies have suggested an association of hypertensive disorders in pregnancy and increased risk of cardiovascular disease later in life[7]. These studies suggest a more pronounced effect in women with preeclampsia, premature delivery <37 weeks' gestational age and low birth weight offspring[7-9]. It is hypothesized that common risk factors predispose to both hypertensive pregnancy disorders as well as cardiovascular disease[10,11]. Knowledge of the pathophysiological determinants involved is indispensable when it comes to patient counselling and future preventive strategies in order to reduce the risk of cardiovascular disease in this specific group of women.

Genetic factors that increase the risk of cardiovascular disease may also be involved in the development of preeclampsia. Such genes may also be paternally derived, since it has been suggested that paternal genes, as expressed in the placenta and foetus, contribute to the risk of preeclampsia[12-14]. Consequently, it can be hypothesized that men who fathered preeclamptic pregnancies have an increased risk of cardiovascular disease themselves.

In the present study we investigated the recurrence risks of hypertension related pregnancy complications and the cardiovascular risk profiles of women, as well as of their partners, who had experienced a pregnancy complicated by severe, early onset preeclampsia before 24 weeks' gestation, in a case control study design.

2. Material and methods

2.1. Participants

All consecutive women (*N*=26), who had been admitted to the University Medical Center Rotterdam between 1993 and 2003, with the diagnosis severe, early onset preeclampsia before 24 weeks' gestation were selected for participation in the study. Maternal and perinatal outcome data of this cohort have been published previously[1]. Severe preeclampsia was defined as an absolute diastolic blood pressure of ≥110 mm Hg and proteinuria (≥2+ [1 g/l]) on a catheterized specimen on admission, or the occurrence of preeclampsia (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic measured on at least two occasions in women

normotensive before 20 weeks' gestation and proteinuria ≥300 mg/24h (or ≥2+ on dipstick of voided specimen) in combination with eclampsia or HELLP syndrome. HELLP (hemolysis, elevated liver enzymes, and low platelets) was defined as thrombocytes <100x10^9/l, and both aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) >70 U/l and lactate dehydrogenase > 600 U/L. Superimposed-preeclampsia was defined as a rise of blood pressure ≥30 mm Hg systolic or ≥15 mm Hg diastolic over values in the first 20 weeks and proteinuria ≥300 mg/24 h (or ≥2+ (1 g/l) on a voided specimen or ≥1+ (0.3 g/l) on a catheterized specimen. Gestational hypertension was defined as a blood pressure of >140/90 mmHg after 20 weeks' gestational age in formerly normotensive women, measured on two separate occasions with an interval of at least 4h.
Twenty women (80%) consented to participation. There was 1 maternal death. Four women refrained from participation because of psycho-emotional distress due to traumatic memories of their hospital admission and poor perinatal outcomes, as all experienced intrauterine foetal death. One patient declined participation because of language difficulties. These five women did not differ from the participating women with regard to parity, presence of chronic hypertension or neonatal survival. There was no difference in occurrence of severe complications (HELLP syndrome, eclampsia, pulmonary oedema) between the refraining and participating group (5/5 versus 18/20). The characteristics of the 20 participating women are described in Table 1. After consent of the woman, partners were approached for participation. Fifteen men (75%) consented to participation, four men declined and one man had died due to a violence offence. All participants provided informed written consent. The study was approved by the Medical Ethics Committee of the University Medical Center Rotterdam.
Healthy control patients after uncomplicated term pregnancies only, with healthy, appropriate for gestational age weight babies, matched for age, parity, race and year of delivery were selected by the computerized hospital database. Two control patients declined participation and two did not respond to our mailing. Each participating case was matched with one control patient (*N*=20). Thirteen partners (65%) of these control patients consented participation, of which one declined blood sampling.

2.2. Data collection

All participants were invited for examination at our hospital. Information on medical and obstetrical history, medication use and smoking habits was obtained by means of interviews by the research physician. Any statement of hypertensive complications of subsequent pregnancies were confirmed by review of their medical records. Participants were classified as non- or current smokers. Current smoking was defined as smoking more than one cigarette daily. Family history of

hypertension and diabetes was defined by the use of antihypertensive drugs and/ or the use of blood glucose lowering drugs by first or second degree relatives.
Subsequently, cardiovascular health was described in cases and controls by means of the following variables. Body mass index (kg/m2) was calculated from height and weight. Waist and hip circumference were measured using a tape measure with the participant in upright position. Waist circumference was measured halfway between the rib cage and the pelvic bone. Hip circumference was measured at the maximal circumference of the hips. Waist-to-hip ratio was calculated from these measurements. Blood pressure was measured twice with the participant in the sitting position at the right upper arm using a sphygmanometer. The mean of these two measurements was used in the analyses. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg and/ or a diastolic blood pressure ≥ 90 mmHg and/or use of anti-hypertensive medication. Intima media thickness (IMT) of the common carotid artery was assessed by duplex scan ultrasonography using a 12-5 MHz linear-array transducer (Philips iU22). IMT was measured offline from frozen images over an average distance of 10 mm of the common carotid arteries[15]. The mean was calculated of the maximum IMT of the near and far wall measurements of both left and right arteries. In presence of a plaque at the 10 mm site, IMT was measured in the region adjacent to the plaque.
Fasting blood samples were drawn for measurements of biochemical parameters. Routine biochemical parameters were performed on a Hitachi 917 chemistry analyzer (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid, glucose, albumin, and urinary micro-albumin (Roche Diagnostics)). Apolipoprotein A, apolipoprotein B and lipoprotein(a) were measured by immunonephelometry on an Immage 800 nephelometer analyzer. HbA1c was measured using a colorimeter (Menarini HA-8160). Liquid chromatography mass spectrometry was used for measurement of homocystein and flowcytometry (HST 302) was used for measurement of leucocytes.

2.3. Statistical analyses

Continuous variables are expressed as medians with ranges. General characteristics were compared between groups using T-test, $\chi 2$ statistics and Fisher's exact test where appropriate. Differences in cardiovascular risk parameters were analyzed using analysis of variance. Variables with skewed distribution were normalized using (natural) logarithm transformation. All analyses on cardiovascular risk factors were adjusted for smoking and body mass index except for anthropometric variables, which were solely adjusted for smoking. A p-value <0.05 was considered statistically significant. For all statistical analyses we used SPSS for Windows, version 11.0.1.

Table 1. General characteristics of women with a history of severe, early onset preeclampsia and men who fathered these preeclamptic pregnancies compared to controls

	Women		**Men**	
	Preeclampsia (n=20)	Controls (n=20)	Preeclampsia (n=15)	Controls (n=13)
Index pregnancy				
Age (years)	32.2 (18.1-40.6)	31.6 (18.8-40.1)	33.5 (22.1-53.2)	34.5 (25.8-50)
Caucasian	12 (60)	12 (60)	10 (66.7)	8 (61.5)
Primiparous	12 (60)	12 (60)	NA	NA
Gestational age (weeks)	26 (22-29)*	40 (36-42)	NA	NA
Birth weight (g)	561 (300-775)*	3435 (2303-5200)	NA	NA
HELLP syndrome	10 (50)*	0	NA	NA
Eclampsia	4 (20)	0	NA	NA
Live Infant[a]	4 (18)*	22 (100)	NA	NA
Hypertension[b]	7 (35)†	0	NA	NA

Current study				
Age (years)	38.8 (22.1-47.7)	37.7 (23.8-41.9)	39.9 (26.2-60.4)	38.8 (31.6-57.8)
Time since index pregnancy (years)	5.5 (4-10)	5.9 (4.4-10.9)	NA	NA
Parity	3 (1-4)	2 (1-4)	NA	NA
Anti-hypertensive drugs	7 (35)[†]	0	1 (6.7)	0
Lipid-lowering drugs	0	0	2 (13.3)	0
Diabetes mellitus	0	0	1 (6.7)	0
Current smoking	2 (10)	3(15)	8 (53.3)	5 (38.5)
Family history				
Family hypertension	15 (75)	12(60)	5 (33.3)	7 (53.8)
Family diabetes	13 (65)	7 (35)	5 (33.3)[§]	10 (76.9)
Family preeclampsia	3 (15)	2 (10)	1 (6.7)	0

Data are presented as medians (min-max) or absolute number (%). NA: not applicable

[a]Two twin pregnancies included

[b]Hypertension defined as systolic blood pressure ≥140 mm Hg and/or diastolic ≥90 mmHg in the first trimester of pregnancy

*p value <0.001, [†]p value <0.01, [§] p value <0.05

3. Results

General characteristics of participants are depicted in Table 1. Seven (35%) of the women with a history of severe, early onset preeclampsia exhibited hypertension in the first trimester of the index pregnancy, but none of them had been treated with medication prior to pregnancy. At time of study, 5.5 years (range 4 to 10 years) after index pregnancy, five of those 7 women used antihypertensive medication. Overall, women with a history of preeclampsia used significantly more often antihypertensive medication as compared to controls ($p<0.01$).
Men who fathered preeclamptic pregnancies did not differ significantly from control men with respect to paternal age and medical history. Diabetes mellitus was significantly more common in families of men who fathered uncomplicated pregnancies as compared to men who fathered preeclamptic pregnancies.

3.1. Subsequent pregnancies

Of the 20 women with severe, early onset preeclampsia in their index pregnancies 17 women had in total 24 subsequent pregnancies. Out of the 17 first subsequent pregnancies, 9 were complicated by preeclampsia, 7 by gestational hypertension and one by IUGR. Out of the seven second subsequent pregnancies, three were complicated by preeclampsia, three by gestational hypertension and one by IUGR. The median birth weight (range) was 2950 (720-3860) g and gestational age 38 (27-41) weeks. This was significantly different from the median birth weight of 3500 (2960-3980) g and gestational age of 40 (38-42) weeks in the 15 subsequent pregnancies of the 20 control women ($p=0.001$ and $p=0.01$, respectively). There were no perinatal deaths in any of the 39 subsequent pregnancies. No hypertensive complications or foetal growth restriction occurred in the control group. Fig. 1 summarizes the outcome of subsequent pregnancies of women with severe early onset preeclampsia in the index pregnancy. In 92% of the subsequent pregnancies some form of hypertensive complication occurred. Preeclampsia developed in 12 of the 24 subsequent pregnancies (50%), of which 5 developed severe preeclampsia (3 patients with HELLP syndrome and 2 women with uncontrolled severe hypertension). Recurrence of preeclampsia before 36 weeks' gestation was found in 5 pregnancies. Ten pregnancies (42%) were complicated by pregnancy induced hypertension. Only two (8%) pregnancies were not complicated by hypertensive disease, although two mildly growth retarded foetuses were born with birth weights between the 5th and 10th percentile. The 10 women who had HELLP syndrome in their index pregnancy had 11 subsequent pregnancies of which 3 (27%) were complicated by recurrence of HELLP syndrome.
Next, we compared women with recurrent and non-recurrent preeclampsia with regard to various parameters of the index pregnancy (HELPP syndrome, eclamp-

sia, gestational age and birth weight) and their family history of hypertensive disease, yet no significant differences were found.

3.2. Cardiovascular health

Cardiovascular risk variables of participants are depicted in Table 2. Anthropometric parameters (body mass index and waist-to-hip ratio) were not significantly different between women with a history of preeclampsia as compared to controls, although there was a tendency to greater body mass index in women with a history of preeclampsia. Regarding the vascular variables, women with a history of preeclampsia were found to have higher diastolic blood pressures than controls. Although the median value for diastolic blood pressure did not pass the threshold of 90 mmHg, which was used in the definition of hypertension, women with preeclampsia were more often diagnosed with chronic hypertension. This could be explained by the fact that diagnosis of chronic hypertension was not solely based on blood pressure measurements but also on the use of antihypertensive medication. No differences were observed in IMT of the common carotid artery between groups. However, when we included only women with a history of preeclampsia using antihypertensive medication, we found that women with a history of preeclampsia with medication had significantly increased IMT (0.71, 0.58-0.80 mm, p=0.03) as compared to controls (0.59, 0.52-0.70 mm). With respect to metabolic variables associated with insulin insensitivity, no significant differences were observed between groups. Fasting lipid concentrations did not differ between cases and controls. Lipoprotein(a) levels was not significantly different (p=0.05) in women with previous preeclampsia as compared to controls. Micro-albuminuria was significantly higher in women with a history of preeclampsia (p<0.05).
Subsequently, we compared the cardiovascular risk parameters between women who had recurrent preeclamptic pregnancies and women with only one preeclamptic pregnancy. No significant differences were observed between the groups. None of the above-mentioned variables were significantly different between men who fathered preeclamptic pregnancies as compared to control men (Table 2).

4. Comment

4.1. Subsequent pregnancies

We found a 50% recurrence rate of preeclampsia in women with a history of severe, early onset preeclampsia before 24 weeks' gestation. Neonatal survival was 100% in contrast to 18% in the index pregnancy consistent with higher gestational age (on average +12 weeks) and higher birth weight (on average +2400 g) compared to the index pregnancy.

Table 2. Cardiovascular risk variables of women with a history of severe, early onset preeclampsia and men who fathered these preeclamptic pregnancies compared to controls

	Women			Men		
	Preeclampsia (*n*=20)	Controls (*n*=20)	*P*	Preeclampsia (*n*=15)	Controls (*n*=13[a])	*P*
Body mass index (kg/m^2)	25.7 (20.2-37.1)	22.7 (17.8-43.1)	0.2	25.4 (18.9-32.2)	25.3 (20.8-29.7)	0.5
Waist-hip ratio	0.80 (0.71-0.90)	0.78 (0.7-0.9)	0.3	0.86 (0.72-0.98)	0.84 (0.8-0.94)	0.7
Systolic blood pressure (mmHg)	130 (95-155)	115 (100-170)	0.1	120 (105-170)	120 (105-150)	>0.9
Diastolic blood pressure (mmHg)	83 (65-110)	75 (55-110)	0.02	75 (55-90)	80 (65-105)	0.3
IMT common carotid artery (mm)	0.6 (0.46-0.92)	0.59(0.46-0.85)	0.4	0.59 (0.52-0.87)	0.64 (0.52-0.88)	0.5
Hypertension	11 (55)	2 (10)	0.002	1 (6.7)	4 (30.8)	0.2
HbA1c (%)	5.2 (4.4-5.8)	4.9 (4.4-5.7)	0.4	5.0 (4.7-6.4)[b]	5.1 (4.4-5.6)	0.8
Fasting glucose (mmol/L)	3.7 (2.5-5.6)	4.0 (2.9-4.8)	0.3	3.8 (2.7-5.1)[b]	4.0 (3.4- 4.7)	0.7
Insulin (mmol/L)	37 (14-121)	32 (14-120)	>0.9	29 (14-111)[b]	31 (14-92)	>0.9
HOMA	159 (50-296)	179 (52-312)	>0.9	210 (49-316)[b]	193 (62-286)	0.8
Cholesterol (mmol/L)	5.0 (4.1-7.1)	4.9 (3.1-5.9)	0.08	4.8 (3.8-6.2)	5.5 (4.3-6.0)	0.08
LDL-cholesterol (mmol/L)	2.9 (2.1-5.2)	2.7 (1.5-4.1)	0.09	3.1 (1.3-4.3)	3.4 (2.0-4.5)	0.1
HDL-cholesterol (mmol/L)	1.6 (1.3-2.9)	1.6 (1.1-2.9)	0.6	1.3 (0.84-1.8)	1.3 (0.98-2.3)	0.4
Triglycerides (mmol/L)	0.86 (0.47-1.7)	0.76 (0.44-6.1)	0.8	1.1 (0.35-11.2)	0.88 (0.71-1.8)	0.4

ApoA (g/L)	1.6 (1.3-2.6)	1.5 (1.2-2.8)	0.2	1.4 (1.1-1.6)	1.5 (1.1-2.0)	0.1
ApoB (g/L)	0.85 (0.65-1.5)	0.88 (0.46-1.4)	0.1	0.96 (0.7-1.3)	1.0 (0.7- 1.4)	0.2
Lipoprotein(a) (g /L)	0.27 (0.02-1.2)	0.08 (0.02-1.1)	0.05	0.16 (0.02-0.77)	0.15 (0.02-0.59)	0.9
Leucocytes ($x10^9$/L)	5.7 (1.6-10)	6.3 (3.4-11.1)	0.3	6.1 (3.6-17.9)	5.2 (4.4-7.3)	0.4
CRP (mg/L)	2.0 (1.0-11.0)	1.5 (1.0-11.0)	0.3	1.0 (1.0-4.0)	1.0 (1.0-4.0)	0.9
Homocysteine (µmol/L)	9.4 (6.3-21.4)	9.8 (6.3-15.4)	>0.9	12.9 (8.8-17.3)	12.7 (8.6-20.2)	0.9
Micro-albuminuria (g/mol)	0.008 (0.001-0.2)	0.006 (0.002-0.01)	<0.05	0.005 (0.003-0.03)	0.004 (0.002-0.04)	0.8
Uric acid (mmol/L)	0.28 (0.17-0.37)	0.26 (0.13-0.37)	0.2	0.34 (0.24-0.48)	0.37 (0.27-0.45)	0.4

Values are presented as medians (min-max) or as absolute number (%).
[a] *n*=12 for parameters obtained from blood samples
[b] *n*=14, one participant with type 1 diabetes was excluded

The described recurrence rate of preeclampsia of 50% is similar to that described by Sibai et al.[3] after second trimester severe preeclampsia. Regarding the recurrence of HELLP syndrome we observed a recurrence rate of 27%, whereas previous reports found different rates of 2-5%[16-18]. Sullivan et al [19] found a recurrence rate of 19%; however, gestational age at disease was not studied in relation with risks of recurrence. Differences in recurrence rates might be explained by differences in study population and sample size. In addition, management of the disorder may have been different; women in our study with recurrent preeclampsia at < 32 weeks' gestation were treated with intention to extend their gestational age. The higher incidence of HELLP syndrome may therefore be explained by a longer time interval between diagnosis of preeclampsia and delivery. We were not able to predict which women would experience recurrence of preeclampsia as neither clinical nor biochemical parameters were different between women who experienced recurrence and those who did not.

4.2. Cardiovascular health

The present study was conducted in view of the expectation that women with severe, very early onset disease in co-occurrence with low birth weight offspring and preterm delivery would exhibit more risk factor or more pronounced cardiovascular risk profiles compared to controls with uncomplicated obstetric outcome[7-9]. We are aware that the small sample size is a limitation of our study, as it is therefore underpowered to detect small differences between groups. It could, however, be calculated that our study had sufficient power (80%) to detect larger differences, for example differences in blood pressure >7 mmHg or glucose concentrations >0.3 mmol/L.

In the present study women with such a history had more often chronic hypertension and increased microalbuminuria but no differences in features of the metabolic syndrome. These findings are interesting for speculations about differences in origin in early and late-onset preeclampsia. Increased prevalence of chronic hypertension (about 20% in most studies) is the common finding of nearly all reports evaluating women with a past history of preeclampsia, even though time intervals between pregnancy and study varied from 3-25 years in the different studies[20-23]. Lipoprotein(a) levels were not significantly different between women with a history of severe, early onset preeclampsia and controls in our study. However, our data might suggest a trend towards higher lipoprotein(a) in these women since the *p*-value was 0.05. The one other study we are aware of, that focused on lipoprotein(a) levels in severe, early preeclampsia reported higher levels in women with preeclampsia as compared to controls[24.] In contrast, Leerink et al. could not detect any differences in lipoprotein(a) in a population with both early and late-onset disease[25]. Possibly higher lipoprotein(a) levels are more specifically associated with early onset disease. With respect to micro-

albuminuria, increased levels were also reported in previous studies in women with a past history of preeclampsia as compared to women with uncomplicated pregnancies[26, 27]. Hypertension[28, 29], lipoprotein(a)[30] and microalbuminuria[31, 32] are well established as independent risk factors of atherosclerotic disease. Microalbuminuria is a particularly strong predictor of ischemic heart disease among subjects with hypertension[32]. In addition, lipoprotein(a) levels are reported to be higher in subjects with renal dysfunction[33]. Therefore, our findings may be a reflection of underlying, early onset atherosclerotic disease in women with a history of severe very early onset preeclampsia. Remarkably, in contrast to previous studies with heterogeneous groups of preeclamptic women,[21, 22, 34], no indication for insulin insensitivity was found. This may be explained either by the fact that not all studies controlled for body mass index [21] or by differences in time interval between pregnancy and study[20]. Another explanation could be that metabolic disturbances associated with insulin insensitivity are a more specific feature of late-onset preeclampsia whereas vascular pathology is more specific for early onset preeclampsia, suggesting different pathogeneses. Recent data on HOMA-IR values in the first trimester of pregnancy, showing significantly higher values in late-onset preeclampsia, but not in early onset preeclampsia when compared to controls support this hypothesis[35].

In addition, cardiovascular profiles of men who fathered preeclamptic pregnancies were assessed as possible indirect evidence for involvement of paternal cardiovascular susceptibility genes, in the development of preeclampsia. We could, however, not detect any differences in profiles between men who fathered preeclamptic pregnancies compared to controls. This is in accordance with the findings of a large epidemiological study that did not observe higher mortality in men who fathered preeclamptic pregnancies[9].

In conclusion, very, early onset preeclampsia is related to some kind of hypertensive disease in almost all subsequent pregnancies. Although the recurrence rate of preeclampsia is as high as 50%, of which half of the cases develop severe preeclampsia mostly before 36 weeks' gestation, neonatal outcome in these subsequent pregnancies was favourable.

The cardiovascular risk profiles after 5.5 years of women who experienced severe, early onset preeclampsia showed more often chronic hypertension and increased micro-albuminuria. These data suggest a more hypertension related vascular aetiology rather than a metabolic syndrome origin in severe, early onset preeclampsia, however, specific biochemical markers for counselling women to discriminate those with minor complications in future pregnancies are lacking. Specific markers of endothelial dysfunction, e.g. brachial artery dilatation following transient forearm ischemia should be evaluated[23].

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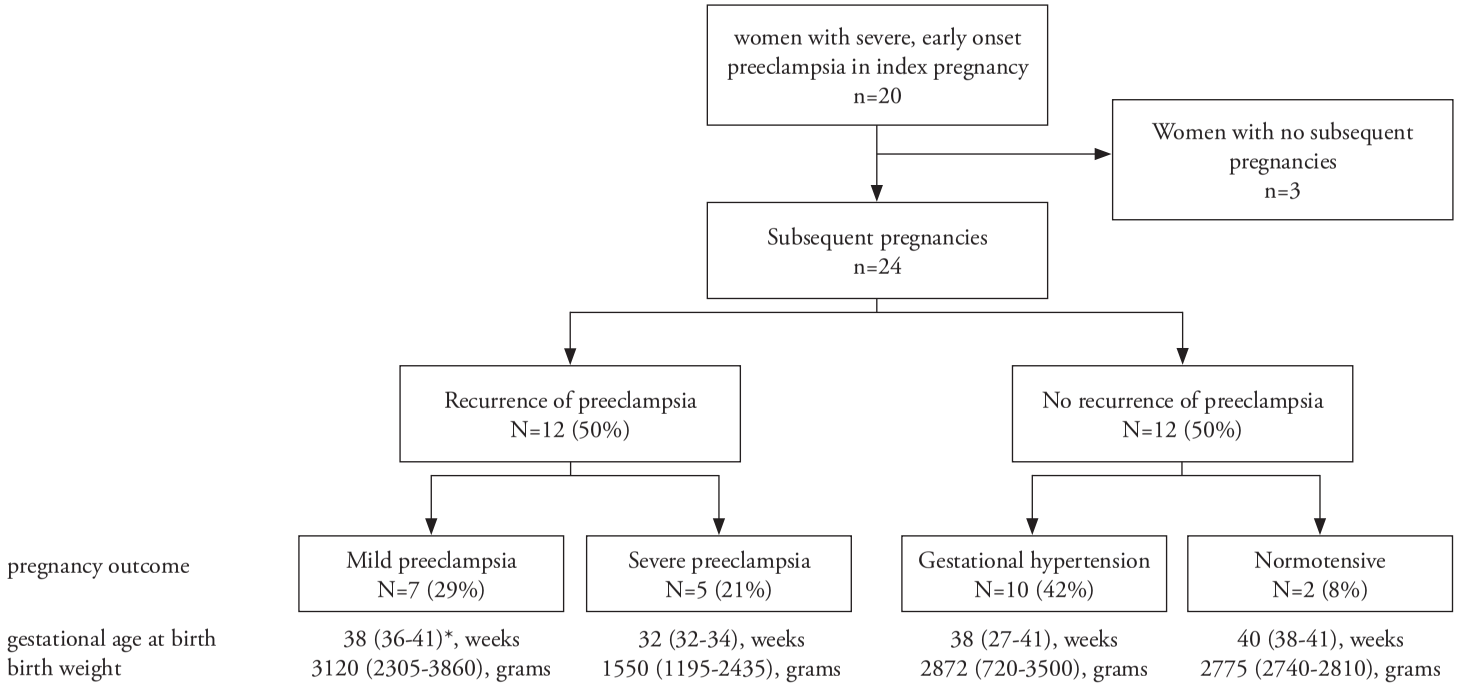
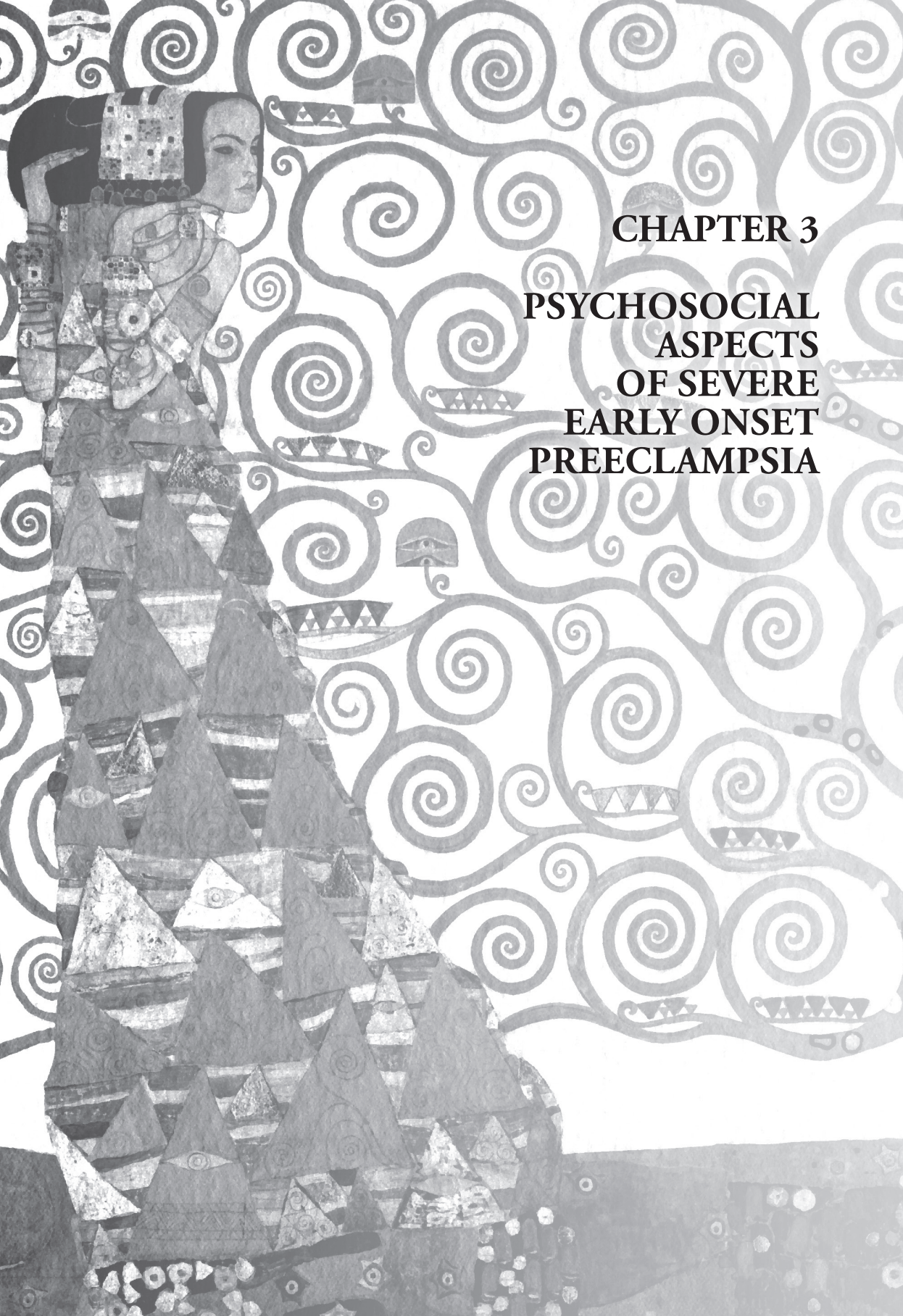
Figure 1. Outcome of subsequent pregnancies after severe, early onset preeclampsia in index pregnancy



* median (range)



CHAPTER 3

PSYCHOSOCIAL ASPECTS OF SEVERE EARLY ONSET PREECLAMPSIA

CHAPTER 3.1

Maternal psychosocial outcome after early onset preeclampsia and preterm birth

Ingrid PM Gaugler-Senden, Hugo J Duivenvoorden, Anika Filius,
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Abstract

Objective: To evaluate the impact of severe, early onset preeclampsia on long term maternal psychosocial outcome after preterm birth.
Methods: Women with severe, early onset preeclampsia before 32 weeks' gestation (cases) admitted in a tertiary university referral center between 1993-2004, and women with preterm delivery without preeclampsia (controls), matched for age, parity, gestational age at delivery, ethnicity and year of delivery. Women who consented to participation received 3 questionnaires in 2008 concerning depression (Zung Depression Scale: score range 0-20; 20 items with 2-point frequency scale: no=0 and yes=1), posttraumatic stress symptoms (Impact of Event Scale: score range 0-75; 15 items with 4-point frequency scale: not at all=0, rarely=1, sometimes=3 and often=5. Scores >19 are regarded as high symptom levels) and social aspects (Social Readjustment Rating Scale: selection of six items concerning relational aspects with husband/partner, employer or future family planning).
*Results***:** Included in the study were 104 cases and 78 controls (response rate 79% and 58% respectively). There was no difference in depression scores between cases (5.4±4.0) and controls (5.4±4.3). Patients with severe, early onset preeclampsia had significantly higher scores of posttraumatic stress symptoms (28.7±8.6 vs 25.7±7.9). The majority of women among both cases and controls had high posttraumatic stress symptom levels (88% vs 79%) No differences could be found in relational aspects.
*Conclusion***:** Women with preterm birth due to severe, early onset preeclampsia experience more often posttraumatic stress symptoms on average 7 years after the pregnancy compared to women with preterm birth without preeclampsia.

Introduction

Severe, early onset preeclampsia followed by delivery of a preterm infant is a major trauma. Although severe, early onset preeclampsia before 32 weeks' gestational age occurs in less then 1% of pregnancies, this clinical condition is of major concern in high-risk obstetrics because of its effect on maternal and foetal morbidity and mortality[1,2].

Many patients experience severe physical symptoms such as extreme headache, severe upper abdominal pain and excessive weight gain as a result of massive fluid retention. For the patients this as an unexpected attack on their physical integrity. It is not only a personal threatening experience but also severe preeclampsia is the most common cause of maternal death in the Netherlands[3]. The severity of early disease necessitates admission to a tertiary referral obstetric high care or intensive care unit, for haemodynamic stabilization and close monitoring, including intraarterial blood pressure monitoring and in some cases insertion of a central venous catheter. The obstertic high care unit in our center offers the same quality of monitoring as an intensive care unit apart from the possibility of mechanical ventilation. For most patients admission in a tertiarry care center means referral to a hospital remote from home, thus away from the support structure of family and friends. In very preterm pregnancies prolongation of the pregnancy might improve neonatal outcome, so these patients will be admitted for days or weeks in the high/intensive care unit. Obstetric care for these patients faces a major challenge to balance between maternal risks on one side and possible foetal benefits on the other side. For the women involved this situation has major psychological impact. Besides worries about their own health, these women worry about the prospects for their very preterm baby. In a substantial number of cases deterioration of the foetal condition necessitates emergency delivery usually by caesarean section remote from term. The neonate requires admission to the neonatal intensive care unit, which may be extraordinary stressful for the parents. These stressful circumstances induce psychological responses, which subsequently might lead to depression and posttraumatic stress symptoms.

Symptoms of posttraumatic stress are categorized into three clusters: *intrusion* (re-experiencing: nightmares, flashbacks), a*voidance* (amnesia, avoiding reminders) and *increased arousal* (irritability, sleeping disturbances, concentration problems)[4].

The sequelae of maternal psychological health following preterm childbirth have been described in several publications[5-9]. Yet, reports on these effects after preterm birth due to severe preeclampsia are scarce[10-13] and information on long term maternal psychosocial outcome seems to be lacking. In clinical practice we have observed that some women who had pregnancies complicated by severe, early onset preeclampsia seem to suffer from posttraumatic stress symptoms and depression leading to social isolation. Most obstetricians and family physicians

focus on the pregnancy outcome but not on consequences later in life. This aspect has often been overlooked. To study the extent of long term psychosocial sequelae of preterm birth due to severe, early onset preeclampsia, we investigated women with such a history and matched subjects.

Material and methods

Participants

Women diagnosed with severe preeclampsia before 24 weeks' gestation between 1993-2003 (clinical outcome of this cohort has been published[2]) and all women with severe preeclampsia at 24-32 weeks' gestation between 1999-2004, who were admitted and delivered before 34 weeks' gestation at the Erasmus University Medical Center Rotterdam, were identified from the hospital database. Severe preeclampsia was defined as an absolute diastolic blood pressure of ≥110 mm Hg and proteinuria (≥2+ [1 g/l]) on a catheterized specimen on admission, or the occurrence of preeclampsia described above in combination with eclampsia or HELLP syndrome. HELLP (haemolysis, elevated liver enzymes, and low platelets) was defined as thrombocytes <100x10^9/l, and both ASAT (aspartate aminotransferase) and ALAT (alanine aminotransferase) >70 U/l and lactate dehydrogenase >600 U/L[14]. Each case was matched with a control selected through the hospital database. Controls were healthy women who had spontaneous preterm delivery, matched for age, parity, gestational age at delivery, ethnicity, and year of delivery. Major congenital anomalies were excluded. Addresses were checked through the last known data from the hospital database or information by the general practitioner. Patient information forms were sent by post and after signed consent women were included for participation. During the period 1993 – 2004 the treatment of patients with severe, early onset preeclampsia was based on temporizing management, a treatment program that aims for haemodynamic stabilization of the mother thus enabling a continuation of the pregnancy in order to improve fetal outcome[15,16]. Because of the severity of the disease all patients were admitted to the obstetric high care or intensive care unit for intravenous antihypertensive therapy and plasma volume expansion. During the study period there were no major changes in the treatment protocol for patients with severe early onset preeclampsia.

Assessment

To safeguard that women were not retraumatized by being confronted with memories of their experience, the Medical Ethics Committee advised to interview 18 patients with the diagnosis severe preeclampsia before 24 weeks' gestation and controls by one of the authors (I G-S). As none of these participants experienced emotional stress in such an extent that they needed psychological support, ap-

proval was given for further investigation by sending the questionnaires by post to patients with the diagnosis severe preeclampsia between 24-32 weeks' gestation and their controls.

Participants were requested in 2008 to answer three questionnaires with respect to depressive and posttraumatic stress symptoms and impact on relational and social aspects: Zung Depression Scale[17], Impact of Event Scale[18] and a modified version of the Social Readjustment Rating Scale[19]. To study the development of depression and posttraumatic stress symptoms over time, Zung Depression Scale and Impact of Event Scale asked both for current symptoms and recall of symptoms shortly after delivery. The Zung Depression Scale is a 20-item well-validated screening tool for depression symptoms. It has a 2-point frequency scale (0=no, 1=yes), therefore a possible score range of 0 to 20. The Impact of Event Scale is a 15-item questionnaire and one of the most widely used global self-report instrument to assess intrusive and avoidance symptoms of posttraumatic stress reactions. This scale uses a 4-point frequency scale (0=not at all, 1=rarely, 3=sometimes, 5=often) with a possible range of 0-75. Of the Social Readjustment Rating Scale six items were selected to investigate social impact on relational aspects with husband/partner, relatives/friends and employer.

Statistical analyses

Questionnaires were considered for analysis when 7 out of 10 questions of the Zung Depression Scale were answered and 12 out of 15 questions of the Impact of Event Scale (IES). Scores of >19 in the Impact of Event Scale are regarded as "high" symptom levels of posttraumatic stress[18]. The scores were adjusted for the number of missing data. Continuous variables are expressed as medians and ranges. In addition to the continuous level of IES, analyses were performed at the clinical cut-off score (dichotomized at ≤19 and >19, respectively). Statistical analyses included t-test, Chi square and Mann-Whitney test for bivariate analyses, where appropriate. Analyses of covariance (ANCOVA) was applied to compare adjusted values of IES for cases and controls. The method of multiple regression analysis was performed to identify and estimate posttraumatic stress and depression symptoms across time. The standardized regression coefficient (ß), which varies between -1 and +1 was considered as measure of individual performance. Differences with $p<0.05$ (two tailed) were regarded significant. For statistical analyses SPSS for Windows, version 15.0 (SPSS Inc. Chicago, Illinois, USA) and Mplus, version 5.12 (Mplus software, Leeuwarden, The Netherlands) was used.

Results

During the observation period, 202 women had the diagnosis of severe, early onset preeclampsia before 32 completed weeks' gestation (26 subjects before 24 weeks' gestational age and 176 subjects at or after 24 weeks' gestational age). There were five maternal deaths (referral cases in deteriorated clinical condition), leaving 197 cases. Current addresses were available of 173 women with severe preeclampsia. Of the matched 197 control patients addresses could be traced for 179. Eighty-five percent of unknown addresses concerned patients of African or Caribbean origin, with an equal distribution among cases and controls.

The response rate was 79% (n=136) for the cases and 58% (n=103) for the controls ($p<0.001$). Non-responders did not differ from responders with regard to age, parity, gestational age at delivery, prolongation of pregnancy, or year of delivery. Thirty-two cases and 25 controls responded but refused to participate; of them 22 cases (69%) and 10 controls (40%) stated that their memories of that pregnancy were too traumatic ($p=0.04$). These refraining women did not differ from the participants with respect to age, gestational age at delivery, prolongation of pregnancy, year of delivery, or neonatal survival. Analyses could be performed on 104 cases and 78 controls, almost exclusively Caucasian participants. Relevant baseline characteristics are depicted in Table 1. In total, 79% of the women with preeclampsia and preterm birth delivered by caesarean section. All but one of the other women of the case group who deliverd vaginally experienced intrauterine fetal death. The caesarean section rate among the women with preterm birth without preeclampsia was 23%. All women with vaginal delivery in this group delivered alive babies.

As indicated in Table 2, depression scores currently or as recalled postpartum did not differ significantly and depression improvements were similar for both cases and controls. Regarding posttraumatic stress symptoms, the women with severe preeclampsia and preterm birth reported significantly more current stress then the women with preterm birth only. For both groups of women there was no significant change of overall posttraumatic stress scores over time.

Table 3 presents differentiation in high posttraumatic stress scores (>19) and low-moderate scores (≤19) currently and as recalled postpartum. Shortly after delivery, high scores occurred in 76 of 103 cases versus 47 of 77 controls, whereas high scores at time of the survey occurred in 91 of 103 and 60 of 76 of cases and controls, respectively. In both groups there were increased number of women with high scores of posttraumatic stress symptoms over time ($p=0.001$ and 0.02 for cases and controls, respectively).

Table 1. Relevant baseline characteristics.

	Cases		Controls		p
	n=104		n=78		
Maternal age (yrs)	30	(18-40)	30	(20-39)	0.84
Nulliparity	86	(83)	62	(80)	0.71
Gestational age (wks)	29.5	(22-33)	29	(24-34)	0.14
Interval delivery-study (yrs)	7.0	(5-12)	7.5	(4-11)	0.04
Neonatal survival	77	(75.5)	64	(82.1)	0.37
Caucasians	96	(92)	74	(95)	0.70

Values expressed as median (range) or numbers (%) as appropriate

Table 3. Postpartum and current high (>19) vs. low-medium (≤19) posttraumatic stress scores

		PTS score Current ≤19		PTS score Current >19		p
		n	%	n	%	
Cases	PTS postpartum					
n=103	≤19	10	9.7	17	16.5	0.001
	>19	2	1.9	74	71.9	
Controls	PTS postpartum					
n=77	≤19	12	15.6	18	23.4	0.02
	>19	5	6.5	42	54.5	

McNemar's test for related samples (twotailed)

Table 2. Depression and posttraumatic stress scores recalled postpartum and at current time

	Cases[1]		Controls[1]		p	Cases[2]		Controls[2]		p
	mean	sd	mean	sd		mean	sd	mean	sd	
Depression Scores (Zung)										
Postpartum	11.83	4.11	11.21	4.67	0.37	11.78	4.51	11.37	4.58	0.59
Current	5.39	3.97	5.42	4.31	0.97	5.40	4.28	5.51	4.33	0.87
Posttraumatic stress Scores (IES)										
Postpartum	29.79	16.70	27.53	19.30	0.41	29.72	18.3	28.17	18.52	0.60
Current	28.66	8.58	25.69	7.90	0.02	28.64	8.74	25.85	8.80	0.05

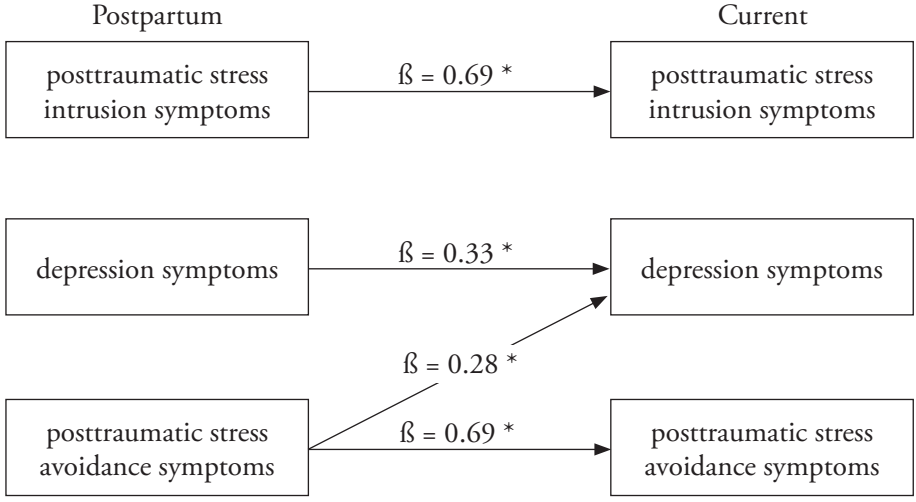
[1]T-test for independent observations

[2]ANCOVA adjustments for maternal age, parity, gestational age at delivery, prolongation of pregnancy, neonatal survival, time interval index pregnancy-study and future procreation.

Figure 1 depicts the relationship between recalled postpartum scores and scores currently for both posttraumatic stress (IES intrusion and IES avoidance) and depression (Zung). In both groups there was a highly significant association between postpartum and current depression scores and between postpartum and current posttraumatic stress ($p<0.001$). Besides, there was a highly significant association between IES avoidance symptoms postpartum and current depression scores ($p<0.001$).

There were no significant differences between women with preterm birth due to severe, early preeclampsia and women with preterm birth without preeclampsia regarding the effect on the quality of the relationship with husband/partner ($p=0.18$), relatives ($p=0.89$), and employer ($p=0.42$). Cases and controls reported a change in conflicts with their husbands or partners in 42% and 33% respectively, of which two-third in both groups state a negative change ($p=0.06$). One third of participants who experienced a change in conflicts with their husband or partner attributed these conflicts to their physical or mental health state ($p=0.94$). Divorce/separation occurs in 12% and 17% of cases and controls respectively ($p=0.32$). Both groups present more than half of patients (58% of women with preterm birth and preeclampsia and 55% of women with preterm birth without preeclampsia) with a change in future family planning, of which the vast majority states a very negative change. At the time of this study 55% of women who men-

Figure 1. Path analyses of postpartum and current depression, intrusion and avoidance symptoms



* $p< 0.001$

tioned this change had at least one more successful pregnancy. Half of the women in each group described a change in their relation with relatives and friends, of which 50% note a positive change. Ninety percent of the women with severe preeclampsia and 82% of the women with spontaneous preterm birth intended to resume work after their pregnancy (p=0.76) Thirty percent of cases and 40% of controls reported problems with their employer, which led to dismissal in one in three patients in both groups (p=0.86).

Discussion

Our observation suggests that both severe, early onset preeclampsia and preterm birth can exert influence on maternal psychosocial status up to seven years after delivery. Women with preterm birth due to preeclampsia do not differ in depression symptoms or in long term impact on relations from women with preterm birth without preeclampsia. High overall posttraumatic stress scores were found in both women with severe early onset preeclampsia and in women with spontaneous preterm birth. At time of the survey, women with severe, early onset preeclampsia had significantly more high posttraumatic stress scores. As there was no significant difference in neonatal survival between cases and controls, the difference in posttraumatic stress scores could reflect the fact that patients with severe, early onset preeclampsia were admitted to the obstetric high care or intensive care unit and had been critically ill.

The selection of the two participating groups of women in our study, consisting of women with severe early preeclampsia and preterm birth and women with preterm birth only, needs further comment. Looking at the literature one sees quite clearly the dilemma that mood disorders after normal pregnancies and childbirth are still being lumped together with the severe mental health sequelae of dramatic events in pregnancy such as severe, early preeclampsia, preterm birth or experience of natural disasters[20,21]. To compare experiences of women with term births of healthy babies with experiences of women with dramatic events in their pregnancy would not do justice to either group of patients. Maybe DSM V will re-phrase the present "one size fits all" classification of postpartum mental health disorders[22].

Comparison with previous reports on depression or post traumatic stress symptoms is difficult as these earlier studies included often different study populations, different questionnaires, and shorter follow up, which is most often less than two years. Although some publications described depression after prematurity[5,23], we could not identify studies on depression in patients with early onset preeclampsia. In a study of posttraumatic stress symptoms after preeclampsia and preterm birth Engelhard et al[11] analyzed 18 primiparas with live births and a recent hospitalization (<2 years) because of preterm preeclampsia. The median gestational age at admission in their study was 32 weeks, although the severity of preeclamp-

sia was not mentioned. They did not find any difference in posttraumatic stress symptoms between patients with preterm preeclampsia and patients with preterm delivery. Nonetheless, patients with preeclampsia stated significantly more often a threat to life and physical integrity. Rep et al[13] studied the psychosocial effect in women with early onset hypertensive disorders in pregnancy, using the 90-item Symptom Check List (SCL-90) comprising 8 subscales to assess general pathology. A substantial amount of these women had severe early disease, however part of their population had not severe disease and were not admitted in the hospital. Over time, they found a significant improvement of the psychosocial condition. Even so, the median scores over time are high and after one year 25% of women were still in a poor psychosocial condition. Comparable to our findings, a relevant percentage of women did not resume work because of sick leave (9%) or of health problems (7%).

Some limitations of our study need to be taken into account. We collected information on postpartum symptoms that rely on the memories of a life event of years ago, which might be biased. However, it is generally known that exact recall of even very recent experiences can be extremely unreliable, especially when circumstances were very emotional or stressing. The questionnaires used in our study do not propose to reproduce actual facts but represent the personal experiences of the women. Moreover, with the selected classic questionnaires we did not aim for diagnostic purposes to classify mental disease in our participants but used these instruments to have an impression of the extend of mental and physical symptoms after their major life event.

Post partum depression is associated with previous history of depression[20] and previous psychosocial or marital problems[24,25]. We do not know the psychosocial health status of our participants before the index pregnancy, so the relevance of preexisting psychological or social problems on long term outcome is unknown. Fetal demise was not a predictor of poor depression scores or poor posttraumatic stress scores.. No information of the current medical condition of the surviving neonates was available for both groups of participating women. The effect of physical or mental impairment of the child on maternal psychosocial outcome is therefore unknown. Noumerous researchers have reported increased stress and mental health problems among parents of disabled children, however many parents adapt succesfully to the demands of raising a child with disabilities and they recognize the positive contribution made to their life by this child[26]. It is likely that others factors than the severity of the disability of the child determine maternal psychosocial outcome. Suggested factors are familial support, social class, marital status and preexisting psychological problems, however literature on this specific issue is lacking. We matched for ethnicity but it appeared that the vast majority of mainly non-Caucasian immigrants could not be traced or did not respond to our mailing. As this group of women is particularly vulnerable, comprising of asylum seekers and patients of low socio-economic class, high psycho-

social effects of severe, early preeclampsia and preterm delivery may be expected. Lastly, the difference in the response rate may have biased our results. Women with preterm birth and preeclampsia had a significantly higher respons rate compared to controls, suggesting that women with severe, early onset preeclampsia more likely feel the need to share their experience, possibly in the hope for more attention and better understanding, underlined by several personal remarks in their questionnaires. In contrast, due to traumatic memories significantly more women with preterm birth due to severe preeclampsia refrained from participation most likely underestimates the psychosocial impact and subsequently masks possible differences in impact between cases and controls.

The findings in our study imply the need for obstetricians to be aware of long term psychosocial impact of preterm birth. Posttraumatic stress symptoms occur extremely frequent, especially in patients with preterm birth due to severe, early onset preeclampsia. The women in our study were offered psychosocial support during their tertiary care admission. Prolongation of support was possible for women with a baby admitted in the neonatal intensive care unit. After discharge to peripheral hospitals patients often stated abrupt discontinuation of support. Therefore, we strongly recommend a structured follow up program for these patients. Collaboration with neonatologists is of great value because of their intensive and prolonged contact with the parents. Mishina and Takayama underline this paediatric contribution suggesting routine screening for maternal depression[27]. Both obstetricians and paediatricians pay most attention to physical recovery of their patients, whereas aspects of mood and mental condition is often overlooked. With structured attention for psychosocial aspects of preterm birth and early onset preeclampsia symptoms of depression and posttraumatic stress will be recognized, which enables professional support for specific patients.

Acknowledgments

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Declaration of Interest

The authors report no declarations of interest

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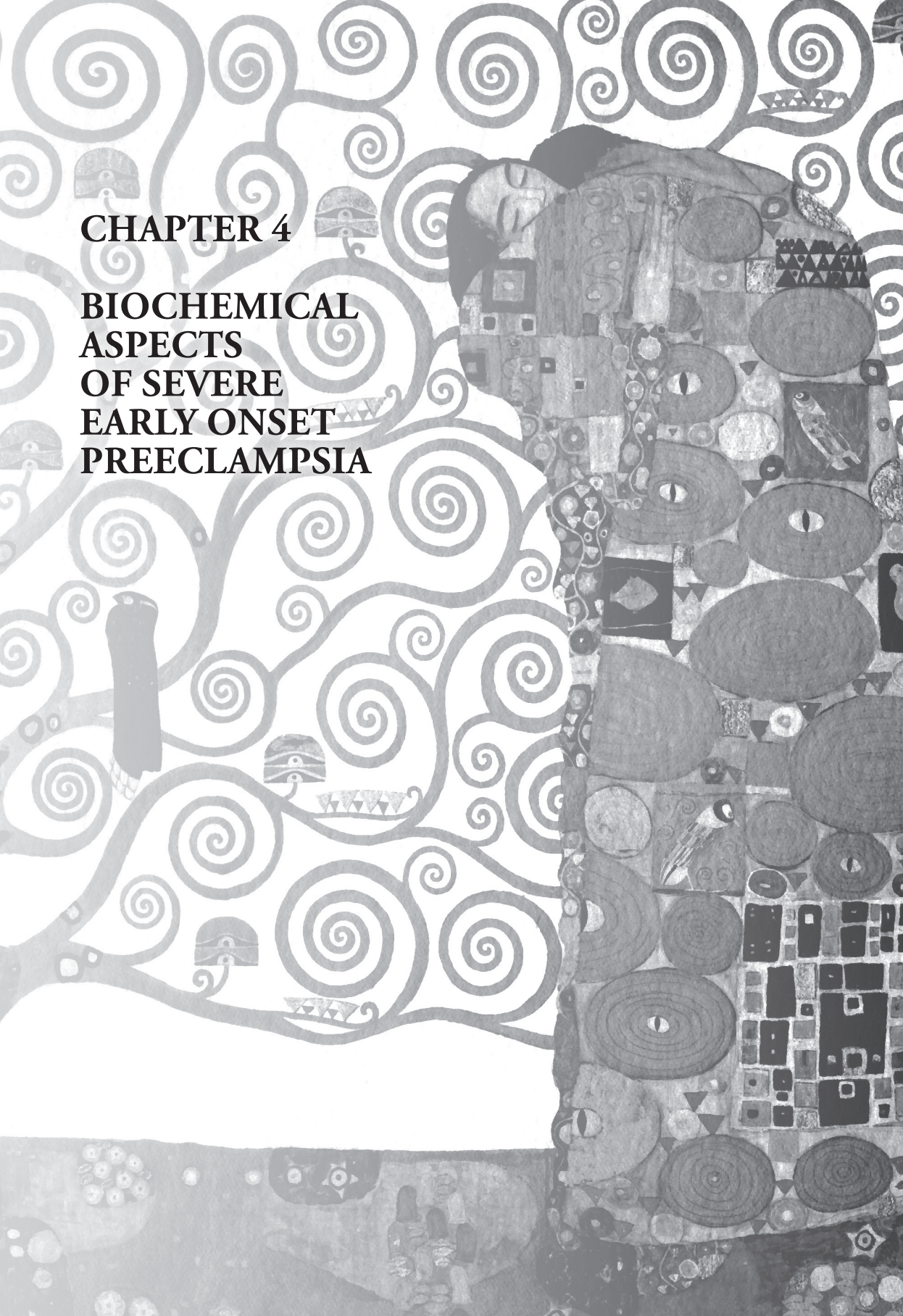
CHAPTER 4

BIOCHEMICAL ASPECTS OF SEVERE EARLY ONSET PREECLAMPSIA



CHAPTER 4.1

Angiogenic risk factors in women ten years after severe very early onset preeclampsia

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Abstract

Objective: Women with a history of preeclampsia, mainly after severe early onset disease, have an increased risk of future cardiovascular disease. Recently, it has been described that women with preeclampsia have increased levels of anti-angiogenic factors. We hypothesize that these angiogenic risk factors in women who had preeclampsia are associated with future cardiovascular disease.
Design: Case-control study.
Setting: Tertiary referral centre.
Population: Twenty women with severe early onset preeclampsia before 24 weeks' gestation, who delivered between 1993-2003 and twenty matched controls with uncomplicated pregnancies and healthy term infants were addressed for participation in the study.
Methods: Venous plasma samples were analyzed for basic fibroblast growth factor (bFGF), placental growth factor (PLGF), soluble fms-like tyrosine kinase-1 (sFlt-1), vascular endothelial growth factor (VEGF), E- and P-selectin, soluble intercellular adhesion molecule-3 (sICAM-3) and thrombomodulin by ELISA.
Main outcome measures: levels of angiogenic factors.
Results: 16 case subjects and 18 control subjects consented participation. The median time interval index pregnancy to study was 9.4 and 9.7 years for cases and controls, respectively. Median levels for cases-controls (p-value) were not different; bFGF: 17.43-11.11 pg/mL (0.33), sFlt-1: 102.98-101.92 pg/ml (0.84), PLGF: 3.57-4.20 pg/mL (0.38), VEGF: 64.05-45.72 pg/mL (0.73), E-selectin: 5.11-4.68 ng/mL (0.20), P-selectin: 85.35-71.69 ng/mL (0.69), sICAM-3: 0.42-0.63 ng/mL (0.41) and Thrombomodulin: 0.92-0.93 ng/mL (0.59).
Conclusion: There were no differences in the angiogenic factors between women who had severe early onset preeclampsia vs uncomplicated pregnancy suggesting that these angiogenic factors do not have an important role in (secondary) detection and prevention of future cardiovascular disease.

Introduction

Preeclampsia occurs in 3-5% of pregnancies and is a major cause of both fetal and maternal morbidity and mortality worldwide[1, 2]. The clinical features of the maternal syndrome, hypertension and proteinuria, are based on widespread maternal endothelial dysfunction and microangiopathy[3]. Although, the cause of preeclampsia is unknown, shallow invasion of the trophoblast into the spiral arteries of the placental bed appear to play a key role[4]. Increasing numbers of studies focus on altered expression of angiogenic and anti-angiogenic factors as a result of this impaired cytotrophoblast invasion leading to hypoxia. Current evidence suggests that excess of anti-angiogenic factors mediates symptoms and signs of preeclampsia[5-7].

Preeclampsia reflects not only impact on pregnancy itself, epidemiological studies have demonstrated an association between preeclampsia and maternal cardiovascular disease in later life[8-11]. Cardiovascular disease (CVD) and preeclampsia share many risk factors and pathophysiological abnormalities like hypertension, insulin resistance and increased systemic inflammatory response. Classic risk factors for CVD are hypertension, hyperlipidemia, insulin resistance, and obesity. In the last decade several papers have been published regarding other biomarkers as risk factor for CVD. These novel factors comprise of angiogenic factors such as vascular endothelial growth factor (VEGF), placental growth factor (PLGF) and basic fibroblast growth factor (bFGF), anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (s-Eng) and adhesion molecules such as intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), soluble P-selectin and soluble E-selectin. We hypothesize that because of the shared mechanism of hypertensive disorders in pregnancy and CVD later in life, distinct levels of angiogenic and anti- angiogenic factors are expressed in women who had preeclampsia and women who had an uncomplicated pregnancy[5, 12]. In addition, women with a history of severe, early onset preeclampsia are at the highest risk of CVD and might express distinguished angiogenic risk factors which could be used as markers for secondary preventive measures[13]. Therefore, we studied angiogenic novel risk factors in women with a history of severe preeclampsia with an onset before 24 weeks' gestation (cases) and healthy women who had an uncomplicated pregnancy (controls).

Methods

Participants

Twenty women (as described previously[14]) who had been admitted to the University Medical Center Rotterdam between 1993 and 2003, with the diagnosis severe, early onset preeclampsia before 24 weeks' gestation were included. Healthy control patients after uncomplicated term pregnancies, matched for age, parity, race and year of delivery were selected by the computerized hospital database. As all participants provided informed written consent for future research, this cohort of women was addressed for participation in the current study on novel cardiovascular risk factors. Sixteen of 20 cases and 18 of 20 controls consented to participate. Two cases and two controls did not respond to our mailing and two cases refrained from participation as they stated difficulties in blood sampling. All non-participants were of Afro-Caribbean origin. These women did not differ in maternal complications or fetal outcome at time of the index pregnancy from the participating women. The study was approved by the Medical Ethics Committee of the University Medical Center Rotterdam.
Severe preeclampsia was defined as an absolute diastolic blood pressure of ≥110 mm Hg and proteinuria (≥2+ [1 g/l]) on a catheterized specimen on admission, or the occurrence of preeclampsia (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic measured on at least two occasions in women normotensive before 20 weeks gestation and proteinuria ≥300 mg/24h (or ≥2+ on dipstick of voided specimen) in combination with eclampsia or HELLP syndrome. HELLP (hemolysis, elevated liver enzymes, and low platelets) was defined as thrombocytes $<100x10^9$/l, and both ASAT (aspartate aminotransferase) and ALAT (alanine aminotransferase) >70 U/l and lactate dehydrogenase > 600 U/L.

Data collection

Venous blood samples were obtained in EDTA collection tubes. A standard laboratory procedure was implemented for the centrifugation, aliquoting and storage of samples at –70°C until assay. Plasma was assayed for bFGF, PLGF, sFlt-1, VEGF, E- and P-selectin, sICAM-3 and thrombomodulin by ELISA (MSD® 96-Well MULTI-SPOT® Vascular Injury Panel I Assay and MSD® MULTI-SPOT® Human Growth Factor I Assay). Samples below detection level were excluded from analyzes (bFGF: 2 cases and 1 control, PLGF in 7 cases and 10 controls) Besides, a history of general health, current use of medication and menstrual cycle was noted.

Statistical analyses

Continuous variables are expressed as medians with ranges. General characteristics were compared between groups using independent T-test and $\chi 2$ statistics test where appropriate.
The statistical package used was SPSS 18.0 (Chicago, Illinois). A p-value of <0.05 was considered significant.

Results

General characteristics of participants are demonstrated in Table 1. As expected no differences between women who had preeclampsia and uncomplicated pregnancies were found for maternal age, parity, race and time since index pregnancy (9.4 years vs. 9.7 years in cases and controls, respectively). With regard to the index pregnancy cases delivered significantly earlier and delivered neonates with

Table 1. General characteristics of women with severe very early onset preeclampsia and controls

	Cases n=16		Controls n=18		p<0.05
Index pregnancy† data					
Age, years	32.5	(29.1-36.2)	31.7	(28.2-35.2)	
Parity					
Nulliparous, n (%)	10	(63)	11	(61)	
Race, n (%)					
Caucasian	12	(75)	12	(67)	
African (-Caribbean)	2	(12.5)	4	(22)	
Asian	2	(12.5)	2	(11)	
Gestational age at delivery, weeks	22.8	(22.3-23.3)	40.2	(38.6-41.1)	*
Birth weight, grams	520	(415-600)	3373	(2873-3648)	*
Data at present study					
Age, years	42.9	(38.8-45.1)	41.6	(38.8-45.7)	
Time since index pregnancy, years	9.4	(9.2-10.3)	9.7	(9.3-10.9)	
Antihypertensive medication, n (%)	6	(38)	0		*

Data are expressed as median (interquartile range)
† pregnancy complicated by severe early onset preeclampsia before 24 weeks' gestation

significantly lower birth weights. In the current study, almost ten years after the index pregnancy, six women (38%) used antihypertensive medication of whom five patients had chronic hypertension at time of their (index) pregnancy complicated with severe, early onset preeclampsia before 24 weeks' gestation. None of the controls used anti hypertensive medication.
The results of angiogenic risk factors are depicted in table 2. None of the angiogenic factors were significantly different between cases and controls.

Discussion

We found no differences in novel angiogenic risk factors in women with a history of severe preeclampsia (cases) with an onset before 24 weeks' gestation and healthy women who had an uncomplicated pregnancy (controls) ten years after their pregnancy. Although, hypertension, one of the classic risk factors for cardiovascular disease, was found more prevalent amongst cases, antihypertensive drug use was not associated with angiogenic risk factors.
Angiogenic and anti-angiogenic factors have been studied during normal and preeclamptic pregnancies. In normal pregnancy there is a steady increase of PLGF during the first two trimesters, a peak at 30 weeks, and a consistent decline thereafter. Soluble Flt-1 is steady throughout the first two trimesters and increases slowly in the third trimester. In women with preeclampsia higher levels of sFlt-1 weeks before onset of preeclampsia and lower levels of PLGF have been

Table2. Angiogenic risk factors in women with severe very early onset preeclampsia and controls

	Cases N=16		Controls N=18		p-value
bFGF, pg/mL	18.85	(12.35- 35.23)	11.45	(5.93-30.33)	0.33
sFLT-1, pg/ml	102.98	(89.43-109.64)	101.92	(77.63-123.62)	0.84
PLGF, pg/mL	3.57	(3.01-3.92)	4.20	(2.33-5.48)	0.38
VEGF, pg/mL	64.05	(50.45-101.87)	45.72	(32.39-78.76)	0.73
E-selectin, ng/mL	5.11	(2.89-7.74)	4.68	(3.27-7.82)	0.20
P-selectin, ng/mL	85.35	(41.94-102.20)	71.69	(58.13-108.00)	0.69
sICAM-3, ng/mL	0.42	(0.42-0.73)	0.63	(0.43- 0.73)	0.41
Thrombomodulin, ng/mL	0.92	(0.72-1.23)	0.93	(0.75-1.09)	0.59

Data are expressed as median (interquartile range)

described[5]. Recently, changes have been reported compatible with the notion that the balance between angiogenic and anti-angiogenic factors is altered in women with preeclampsia[6, 15, 16]. More specific, increased levels of anti-angiogenic factors (sFlt-1 and s-Eng) and lower levels of angiogenic factors (VEGF and PLGF) have been described in women with severe and/or early onset preeclampsia[5, 17-21]. Literature on these novel risk factors focuses mainly on discriminatory and predictive abilities for preeclampsia as altered levels of angiogenic factors are detectable as early as in the first trimester[12, 22-24]. However, knowledge of angiogenic factors after preeclamptic pregnancies is scarce. Noori et al.[25] studied angiogenic factors and maternal vascular function prospectively in 159 women during pregnancy until 12 weeks post partum. Levels of, PLGF, sFlt-1 and s-Eng showed a 50-fold, 25-fold and 2,5-fold fall respectively, from their highest level in the third trimester to the lowest level 12 weeks post partum in women with uncomplicated pregnancies. However, post partum PLGF levels in patients with preeclampsia and gestational hypertension were significantly higher compared to women who had been normotensive during pregnancy. The delta PLGF (difference 3rd trimester and postpartum) in normotensive women is higher compared to the delta PLGF in women with hypertensive pregnancies. They suggest that persistence of increased levels of PLGF is responsible for the increased risk of cardiovascular disease in later life. We were unable to trace papers with longer follow up of PLGF after pregnancies complicated by preeclampsia. Placental growth factor is expressed not only in placental cells but also many nonplacental cells including endothelial cells. PLGF promotes angiogenesis, as is of major importance in pregnancy, but also stimulates atherosclerotic intimal thickening[26]. Elevated PLGF levels were associated with an increased risk of coronary heart disease in the Nurses' Health Study[27] more then ten years after a baseline test in asymptomatic women. Data regarding their pregnancies were not reported. In our study PLGF was below the detection limit of the assay in almost half of the samples. It may be speculated that the younger age and premenopausal state of most of our participants explain the low levels.

Sattar et al. studied angiogenic risk factors in women with a history of preeclampsia, 15-25 years after the index pregnancy[13]. Forty women with preeclampsia and matched controls were analyzed for ICAM-1, VCAM-1 and E-selectin. In this study the median gestational age at delivery was near term, in contrast to our study, in which all patients had severe preeclampsia and delivery at 23 weeks. They found an increased concentration of ICAM-1, which is an adhesion molecule involved in monocyte attachment and transformation to macrophages in the vascular wall and appears an independent predictor of coronary heart disease[28]. To our knowledge, there are no other studies on follow up after preeclampsia with respect to bFGF, VEGF, soluble P- and E-selectin and thrombomodulin. However, VEGF and sFlt-1 is described to be associated with cardiovascular disease[29, 30] and sFlt-1 correlates with severity of disease[31]. Although, these findings are not

consistent, VEGF seems not to be an independent risk factor for cardiovascular disease when adjusted for gender, age, smoking and diabetes[32]. With respect to adhesion molecules E- and P-selectin an association with coronary heart disease seems likely[33], however measurements in a prospective study and meta analyses add no further predictive information to that provided by more established risk factors[34].

It has previously been hypothesized that persistent endothelial dysfunction caused by damaged endothelium during preeclampsia, possibly secondary to exposure to anti- angiogenic factors, may be responsible for these long term cardiovascular outcomes. However, the results of our study on angiogenic risk factors, which are most likely associated with severe and early preeclampsia, could not be found at long term follow up in this particular subset of patients. We speculate that the imbalance of angiogenic factors as found in preeclamptic pregnancies arise at the moment when the cardiovascular system is stressed by that pregnancy. Similar to the phenomenon of recovery of hypertension and proteinuria after preeclampsia, which may take up to two years in some women[35], the angiogenic imbalance recovers as well. In later life the highest associations of angiogenic factors with cardiovascular disease seem to be found in patients with manifest and severe disease, and may be a reflection of metabolic alterations, endothelial activation and low grade inflammation known to be present in that situation. Future studies could address this subject by for instance challenge formerly preeclamptic women with metabolic stress factors such as glucose tolerance tests or vaccination and measure the release of angiogenic factors thereafter.

In summary, we found no differences in novel angiogenic risk factors between women with a history of severe preeclampsia and control women ten years after pregnancy. In predisposed women, pregnancy may trigger processes leading to a disbalance between angiogenic and anti-angiogenic factors, pathophysiologically contributing to preeclampsia. Later in life, the same predisposition and mechanisms may aggravate organ damage due to hypertension as well as the process of atherosclerosis. This however, is a hypothesis to be proven. In this view, pregnancy can be seen as a stress test for a (genetic) predisposition to hypertension, obesity and insulin resistance as a cause of CVD in later life.

Disclosure of interest

The authors have no conflicts of interest.

Contribution to authorship

I.G.-S. has carried the main responsibility for acquiring the data and drafting this manuscript. All authors have collaborated in the conceptualization and the design of the study, revised and approved the final manuscript.

Details of ethics approval

The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center Rotterdam (MEC 2005-185).

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CHAPTER 4.2

Preeclampsia and the C282Y Mutation in the Hemochromatosis (HFE) Gene

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To the Editor

The hemochromatosis *(HFE)* gene encodes the HFE protein, a transmembrane glycoprotein that is implicated in the modulation of iron uptake from the diet[1]. The C282Y mutation in this gene is known to be associated with moderately increased serum iron indices. Recently, several studies have described an association between increased maternal iron status and an unfavorable pregnancy outcome[2, 3]. Preeclampsia is one of the most common pregnancy-related syndromes as well as a major cause of fetal and maternal morbidity and mortality. Preeclampsia is defined by de novo hypertension and proteinuria in pregnancy. The etiology of preeclampsia is complex and not fully understood, but abnormal placentation and endothelial dysfunction may play an important role in its pathogenesis. Abnormal placentation may lead to a malperfused placenta with release of toxic iron through hemoglobin or heme, which finally may contribute to generalized endothelial dysfunction[2]. In the present study, we analyzed the association between the C282Y allele and the presence of preeclampsia in a case–control study described previously[4]. The analysis was restricted to those patients and their controls who fulfilled recent criteria for preeclampsia (157 women in each group).

The *HFE* C282Y genotype was determined by an automated method using minor-groove-binding DNA oligonucleotides (MGB probes) as described previously[5]. The presence of a C282Y allele was confirmed by conventional PCR with restriction fragment length polymorphism analysis.

A Fisher exact test with a 0.050 one-sided significance level showed 90% power to detect the difference between a C282Y allele frequency of 10% (estimated population frequency) and a case frequency of 22.5% (odds ratio = 2.8) when the sample size in each group was 157.

The observed frequency for the *HFE* C282Y allele was similar for women with preeclampsia and controls (0.070). In addition, there was no significant difference between cases and controls in the frequency of the three genotypes [wild type (wt)/wt, wt/C282Y, and C282Y/C282Y] or the presence of the C282Y allele (wt/C282Y and C282Y/C282Y; Table 1). Furthermore, we found that adjustment for clinical indices previously positively (familial hypertension and body mass index) and negatively (smoking) associated with preeclampsia in a logistic model had no significant effect on the distribution of the various C282Y genotypes among women who developed preeclampsia and controls.

The finding of no differences in the C282Y allele distribution or the frequency of the C282Y allele between women with pregnancies complicated by preeclampsia and controls with uncomplicated pregnancies suggests that the C282Y polymorphism is not predominantly involved in the development of endothelial cell dysfunction as a result of increased iron caused by this mutation in women with preeclampsia.

In the total group of cases and controls we found a high frequency (1 of 63) of women who were homozygous for the C282Y allele, whereas 1 in 9 were heterozygous for this allele. The proportion of pregnant women in the present study who had the C282Y/C282Y genotype (1.6%), however, did not differ significantly from the frequency of 0.3–0.5% reported previously for individuals of Northern European descent[1].

In conclusion, our data do not support the hypothesis that the C282Y allele of the hemochromatosis *(HFE)* gene is a clinically important marker of an increased risk for the development of preeclampsia.

Table 1. Genotype frequencies in women with preeclampsia and control women.

	Women with preeclampsia (n = 157)		Controls (n = 157)		Odds ratio[a] (95% confidence interval)
Genotype	n	%	n	%	
wt/wt	137	87.2	138	87.9	1.0
wt/C282Y	18	11.5	16	10.2	1.13 (0.56–4.27)
C282Y/C282Y	2	1.3	3	1.9	0.67 (0.11–3.12)
wt/C282Y or C282Y/C282Y	20	12.8	19	12.1	1.06 (0.54–4.08)
fC282Y[b]		0.067		0.070	

[a] Odds ratios were determined by multiple logistic regression analysis.

[b] Frequency of the C282Y allele. For women with preeclampsia and controls, the observed vs expected allele frequencies are 1.27% (95% confidence interval, 0.15–4.5%) and 1.91% (0.4–5.5%), respectively.

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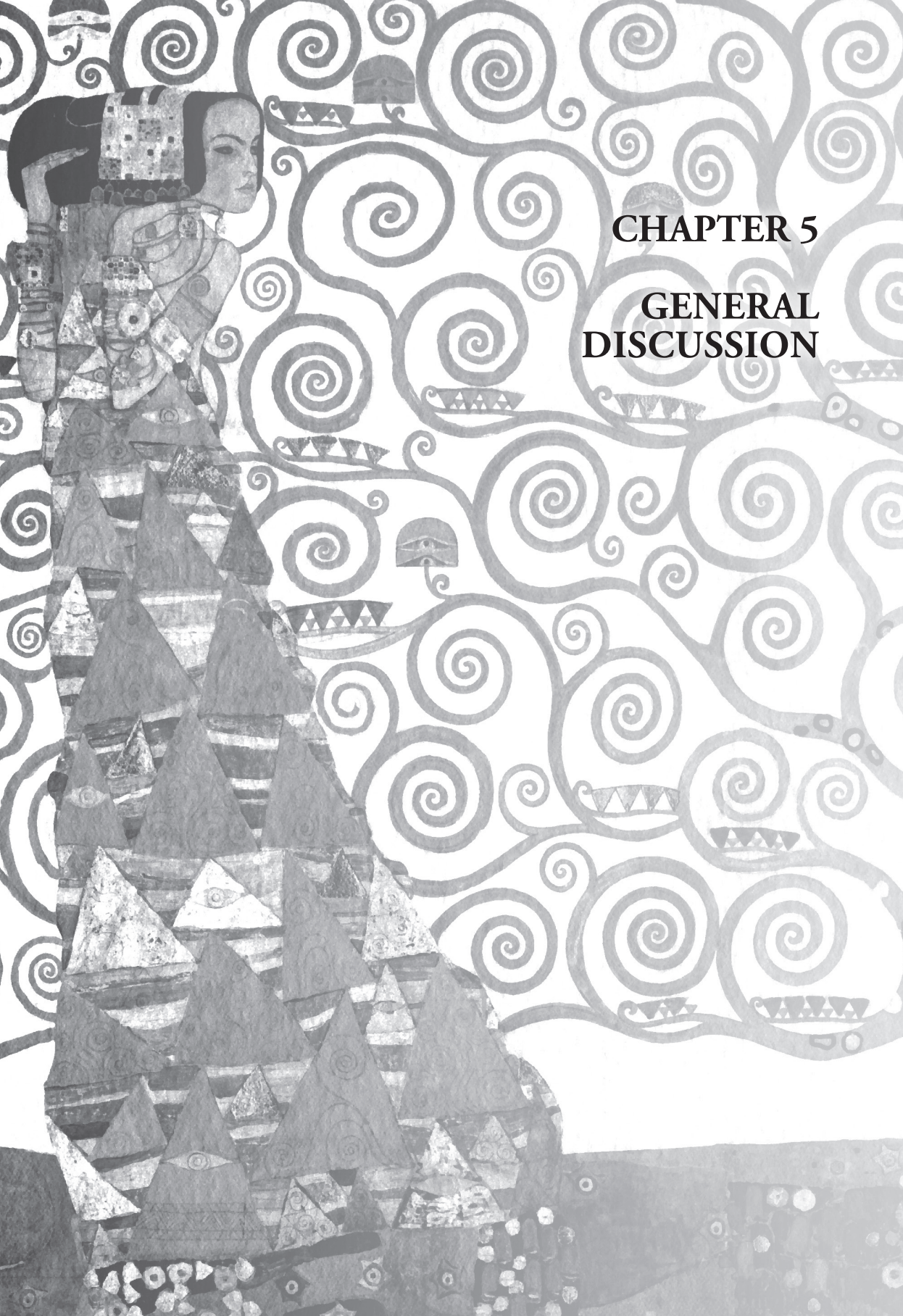


CHAPTER 5

GENERAL DISCUSSION

General discussion

The work presented in this thesis aimed at increasing our knowledge of both short and long term clinical, psychosocial and biochemical outcome of severe early onset preeclampsia. We studied a relatively rare subset of patients, who developed severe preeclampsia before 24 weeks' gestation for their clinical outcome of the index pregnancy (chapter 2.2) and their future pregnancy outcome (chapter 2.3). In addition, long term classical (chapter 2.3) and novel (chapter 4.2) cardiovascular risk factors were studied in these patients. Besides, as the number of patients with onset of disease before 24 weeks' gestation is very small, psychosocial effects of early onset preeclampsia were also studied in patients with onset of severe disease before 32 completed weeks of gestation (chapter 3).
In this final chapter we focus on the main findings and discuss implications for future clinical care for these women.

1.
Severe early onset preeclampsia before 24 weeks' gestation: clinical outcomes of the index and future pregnancies

Implications for conservative management and counselling

In our audit, addressing maternal and foetal outcome of severe early onset preeclampsia before 24 week's gestation we presented a high percentage of maternal morbidity and poor neonatal outcome. Using a temporizing treatment regime, based on prolongation of the pregnancy in order to improve foetal outcome, we found 65% of women with at least one major complication including HELLP syndrome, pulmonary oedema and eclampsia, whereas neonatal survival was only 18%. We were not able to identify clinical parameters, at time of admission to the hospital of these women, to predict neonatal survival. However, HELLP syndrome, intrauterine growth restriction and abnormal Doppler findings of the umbilical artery at time of admission were associated with foetal death. We concluded in this study that expectant management should not be considered as a routine management option for women with severe preeclampsia manifest before 24 weeks gestation.
However, the results of this study should be placed in the context of the time, in which these patients had been treated. Patients were treated and delivered between 1993 and 2003 and at that time expectant management in the Erasmus Medical Center Rotterdam was based on antihypertensive drug treatment, concomitant plasma volume expansion and prolongation of pregnancy, in order to improve neonatal survival. The amount of fluid administration was based on central venous pressure measurements. Four of 26 patients (15%) developed pul-

monary oedema, which is high compared to 1.6-2.6% reported by others[1-3]. This is likely the result of treatment very early in pregnancy and as a consequence long prolongation of the pregnancies in our cohort (median 24 days), during which plasma volume expansion was administered. Ganzevoort et al[4] randomly allocated one hundred and eleven patients with severe preeclampsia or severe foetal growth restriction and pregnancy induced hypertension between 24 and 34 completed weeks to the treatment group (plasma volume expansion and diastolic blood pressure target of 85-95 mmHg) and one hundred and five patients to the control group (intravenous fluid restriction and diastolic blood pressure target 95-105 mmHg). They found an association with administration of high volume levels and pulmonary oedema. There is lack of evidence that mother or foetus benefit from plasma volume expansion, so a more restricted policy of fluid administration may lower the risk of pulmonary oedema in women with severe very early onset preeclampsia. Nevertheless, similar to Ganzevoort et al[5] it seemed hardly possible to predict adverse maternal outcome in women undergoing conservative management of preeclampsia. The development of eclampsia, HELLP syndrome and other major maternal morbidity after initiation of conservative management reflects the unpredictable and changeable character of the disease. Von Dadelszen et al.[6] described recently the development of the fullPIERS (Preeclampsia Integrated Estimated Risk) model. This model aims to select women with preeclampsia at increased risk of adverse maternal outcome such as maternal death and severe renal, hepatic, pulmonary or cerebral dysfunction within 48 hours after admission. The model does not predict adverse outcome in each individual woman, however it identifies women at lowest risk of adverse outcome, who consequently, may be offered expectant management when remote from term. Application of this risk model on our cohort of women with severe early onset preeclampsia before 24 weeks' gestation results in a median risk score of 0.041 (range 0.003-0.63). All patients in our cohort with a score >0.30, the highest risk score category (N=4, 15%), had adverse maternal outcome, in contrast to adverse outcome in 59% of the participants in their cohort (N=74, 4%). The remaining 85% of patients with adverse maternal outcome in our cohort developed complications both within and after 48 hours after admission, however there seems no relation between the calculated risk category and time of onset of adverse maternal outcome. It can be concluded that this model, which has been developed on the results of a rather heterogeneous group of patients, at later gestational age, with a broad definition of preeclampsia (proteinuric and non-proteinuric), is not simply applicable on this small sized rare cohort of women with severe very early onset preeclampsia. Besides, what clinical consequence would this model have on patients with preeclampsia remote from term in the highest risk category? To prevent severe adverse maternal outcome within 48 hours one would suggest to terminate pregnancy immediately (after stabilizing the maternal condition), without awaiting the effect of corticosteroids for foetal lung maturation.

However, according to the fullPIERS model 41% of women in the highest risk category will not have severe adverse maternal outcome within 48 hours, so their foetuses would not benefit from the proven effect of steroids in case of immediate termination of the pregnancy. Besides, immediate termination of pregnancy in patients with severe early onset preeclampsia is still associated with high maternal morbidity, so prompt intervention to deliver the foetus in these early pregnancies in the highest risk category of the fullPIERS model is not recommended[7].
At the time of our study, foetal viability was initially nationally agreed on 27 weeks (15 women) and after 2001 at 26 weeks gestational age (11 women). In addition, the estimated foetal weight had to be more than 650 g before obstetrical intervention on foetal indication was initiated e.g. on suspicion of asphyxia. In our cohort this policy resulted in 68% foetal deaths. In the last few years, foetal viability was set at 25 weeks gestational age in The Netherlands but recently (September 2010), active management of the premature neonate is proposed from 24 completed weeks onwards. This new guideline[8] applies for spontaneous preterm births of foetuses with a birth weight of more than 500 g. In severe preeclampsia before 24 weeks' gestation a substantial part of the foetuses is already growth restricted at admission. In case we introduce this new policy of active management (minimal 24 completed weeks of gestation and birth weight >500 grams) and we would intend to perform a caesarean section at this early stage of pregnancy, we would have had theoretically 13 live births in our cohort. The one-year neonatal survival rate in live born infants between 24 and 25 weeks' gestation is 82%[9] for those who are admitted in the neonatal intensive care unit, resulting in maximal 10 potential survivors in our cohort. However, one must take into account that these survival rates are Swedish figures, where active management of the extreme premature infant is routine since several years. Extrapolation of their figures to the Dutch situation is questionable. Besides, the rate of at least one major handicap at one year in this Swedish cohort is 45%, which is important knowledge to counsel parents in decision-making to perform a caesarean section, which is not included in the new Dutch guideline at this early stage of pregnancy. Therefore, for the present prolongation of pregnancies complicated with severe early onset preeclampsia before 24 weeks' gestation as a routine management option is still not recommended. Only in exceptional cases with severe preeclampsia close to 24 weeks' gestation prolongation of pregnancy may be considered under strict criteria, in a tertiary referral centre[10]. Prognostic factors for improved neonatal outcome, such as black race and foetal female sex, may be taken into account when counselling these women[11,12]. In addition, knowledge of future pregnancy outcome of these women is crucial in decision-making, which treatment strategy would be the best option for each individual patient. The recurrence rate of preeclampsia in our study (described in chapter 2.2) was as high as 50%, similar to the findings of Sibai[13] after second trimester preeclampsia. Almost half of the patients

with recurrence of preeclampsia developed severe disease with preterm deliveries between 32 and 36 weeks gestation resulting in 100% neonatal survival.

2.
Severe early onset preeclampsia before 24 week's gestation: classic and novel cardiovascular risk factors

Implications for selection of patients at risk of (severe) preeclampsia and future cardiovascular disease

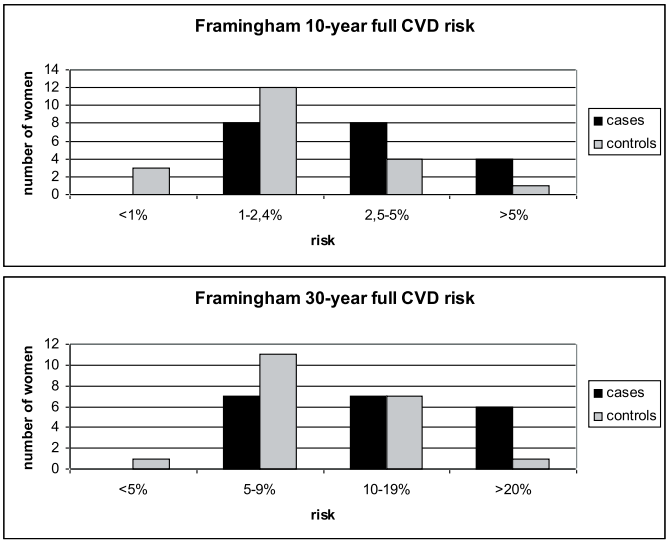
In the review, described in chapter 2.1 we identified chronic hypertension, diabetes, renal disease, nulliparity and long inter-pregnancy interval as independent risk factors for development of preeclampsia. Of the twenty six patients with severe early onset preeclampsia before 24 weeks' gestation, the cohort described in paragraph 2.2, sixteen patients were nulliparous. The high percentage of multiparous women in our cohort may imply an important contribution of other pathophysiological mechanisms such as chronic renal disease[14] and hypertension. Four of the ten multiparous women studied had identifiable risk factors; 3 women showed chronic hypertension and one woman was known with systemic lupus erythematosus. Overall, at time of the index pregnancy nine patients had a history of chronic hypertension and one patient had renal disease. One patient was diagnosed with systemic lupus erythematosus and another patient was diagnosed with antiphospholipid syndrome after their pregnancy had been complicated by severe, early onset preeclampsia. Resulting in almost half of the cohort presenting with underlying medical problems at risk for preeclampsia. Apart from these clinical risk factors as pre-pregnancy risk factors many biomarkers have been assessed early in pregnancy for their predictive value. However, Conde-Agudelo et al.[15] concluded in their systematic review that none of any single biomarker met the clinical standards for a predictive test. None of the patients with chronic hypertension in our cohort were treated with antihypertensive medication in the first trimester. Several randomised controlled trials did not find an association of treated chronic hypertension and the incidence of superimposed preeclampsia[16], however treatment of hypertension seems to prevent complications of preeclampsia[17] although it remains unclear at what level of hypertension early treatment is indicated. An international randomized controlled trail is currently ongoing on this issue (CHIPS http://www.controlled-trials.com/ISRCTN71416914). At our first follow-up study (chapter 2.2), on average 6 years after the index pregnancy, classic risk factors for cardiovascular disease were investigated. Patients with a history of severe early onset preeclampsia had significantly more often hypertension and micro-albuminuria. Hypertension was found in 55% of the cases and in 10% of the controls. There was also a trend towards a higher lipoprotein(a)

and higher body mass index in cases. These parameters are all well established risk factors for cardiovascular disease[18-23]. In contrast to other investigators[24] we did not find an association between chronic hypertension and recurrence of preeclampsia in our patient group. The small sample size of our cohort may have explained this finding. Furthermore, we speculate that other, so far unrecognised (or underdeveloped) cardiovascular risk factors may play a role in the high recurrence rate of preeclampsia in these women with very early onset disease.

In the second follow-up study (chapter 4.1), ten years after the index pregnancy, we investigated the presence of novel angiogenic risk factors in women with severe early onset preeclampsia. None of the investigated factors (bFGF, PLGF, sFlt-1, VEGF, E- and P-selectin, sICAM-3 and thrombomodulin) were different between cases and controls. Literature on these novel risk factors has focused mainly on discriminatory and predictive abilities for preeclampsia as altered levels of angiogenic factors are detectable as early as in the first trimester[25-28]. These angiogenic factors appear to play an important role during pregnancies complicated by preeclampsia, however at long term follow up the results of our study do not confirm an association of these factors with the increased risk of cardiovascular disease in these women. We speculate that the investigated angiogenic factors appear in the circulation in higher concentrations under circumstances with distinct endothelial damage as in preeclamptic pregnancies and in manifest cardiovascular disease. Long term after this pregnancy complication, when the endothelium has (clinically) recovered, the investigated angiogenic factors are present in lower and sometimes undetectable low concentrations. The finding of the association between angiogenic risk factors and manifest cardiovascular disease and disease severity supports this theory. The concept of a threshold for vascular disease has been proposed by Sattar and Greer[29]. Women with a history of preeclampsia are located at a higher level of vascular risk and at time of pregnancy they cross this threshold and develop preeclampsia. In later life they pass this threshold again but at an earlier age compared to women with normal pregnancy outcome. Angiogenic risk factors, which were analysed in our study may follow the same pattern described in this concept. At times when the threshold is passed they appear in the circulation.

Next to our investigated angiogenic risk factors, several other angiogenic risk factors, such as adiponectin[30] (associated with early onset preeclampsia), and angiopoietin-2[31] (associated with severe preeclampsia), have been investigated for their association with cardiovascular disease in later life. Data for the reliability of all these markers are however inconsistent and both their sensitivity and specificity are too low for routine use in clinical practice[32-34]. So, these factors do not seem to add relevant adjuvant information in the cardiovascular risk analyses above classical risk factors, such as hypertension, dyslipidemia, obesity and smoking.

To illustrate the future cardiovascular risk, based on classic risk factors, of the women with severe very early onset preeclampsia in this thesis, compared to their matched controls, we calculated both the Framingham 10-year and a 30-year cardiovascular risk estimate (http://www.framinghamheartstudy.org/risk/index.html) at time of the first follow-up study six years after the index pregnancy.



The first figure presents the estimated risk of general cardiovascular disease (coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, haemorrhagic stroke, transient ischemic attack, peripheral artery disease and heart failure) within 10 years after calculation. Individuals with an estimated risk >5% are recommended to receive intensive medical risk factor modification. Four of the twenty women with a history of severe very early onset preeclampsia versus one woman of the matched controls have a calculated risk in this clinically relevant risk category. The second figure shows the 30-year risk of general cardiovascular disease. Intensive medical risk factor modification in this analyses is recommended for individuals with a risk estimate of >20%. Almost one third of the case women versus one control woman have this relevant a risk score.

So, as pregnancy can be seen as a natural stress test of maternal carbohydrate, lipid pathways and vascular function, indicating an increased risk of these functions in later life, women with a history of preeclampsia should be provided an opportunity for lifestyle advice and risk factor modification[29]. However, randomized controlled trials are needed to evaluate the effect of such preventive intervention strategies in these women. Many challenges still remain to predict and to prevent long term adverse outcome in the individual women after severe early onset preeclampsia.

3.
Severe early onset preeclampsia before 32 week's gestation: long term maternal psychosocial outcome

Implications for future psychosocial care

In chapter 3 we describe the results of long term maternal psychosocial outcome in women on average seven years after severe early onset preeclampsia before 32 weeks' gestation. Patients were compared with matched controls; women with preterm delivery without preeclampsia. The most striking finding of the study is the very high percentage of women with posttraumatic stress symptoms, which seems to worsen over time. Both cases and controls present high symptom levels (score >19), however patients with preeclampsia have significant higher post-traumatic stress scores. As there was no significant difference in neonatal survival between cases and controls, we consider the difference in posttraumatic stress scores as the contribution of maternal illness to these symptoms.
Some aspects of the study are challenging for deeper reflection:
Participants of the study. Of the identified 197 cases and controls current addresses were unavailable in about 10% of each group, of which the majority concerned patients of non-Caucasian immigrants. The response rate was 79% and 58% for the cases and controls, respectively. Most women of African or Caribbean origin did not respond, resulting in almost exclusively Caucasian participants. Language difficulties may be expected in African immigrants, however this does not account for patients from Surinam, Aruba and the Dutch Antilles. In the study of Wendler et al.[35] little differences were found in the willingness of African-Americans and Hispanics in the US, to participate in health research studies. It is not known whether non-Caucasians are more reluctant in participating in psychological studies. Ethnic disparity in depression in persons with physical disabilities was found recently[36]. The importance of stress exposure, coping resources and shame are well underlined in this study to understand the differences. However, no differences in post traumatic stress disorder could be detected between African-American and white American Vietnam veterans[37].
As the group of non-participating women is particularly vulnerable, comprising of asylum seekers and patients of low socio-economic class, more negative psychosocial effects of severe early preeclampsia and preterm delivery may be expected as this group is often traumatized before pregnancy.
Choice of control patients. Severe early onset preeclampsia before 32 weeks' gestational age generally, necessitates admission in obstetric high care or intensive care unites. Many patients experience severe physical symptoms such as extreme headaches, weakness, excessive weight gain and upper abdominal pain. They describe their condition as extremely threatening, the "worst possible health condition they can imagine" and some patients think that they are going to die. Besides,

patients worry about the prospects for their very premature foetus and patients are well aware that in case of extreme premature pregnancies there are little or no chances for neonatal survival yet. To study the effect of maternal disease of preeclampsia we choose women with premature delivery as controls since both share similar worries with respect to foetal outcome. Negative experiences of labour and delivery can provoke psychological responses in about 3-5% of patients, which usually improve within six months[38]. Both maternal and foetal aspects are all in sharp contrast to the prospects of the majority of parturients, who are healthy with good prognosis of their term born foetuses. Comparison of patients in unusual situations with fear for owns life or that of their child and patients with normal healthy pregnancies, would anyhow not justify the circumstances and experiences the former group has witnessed.

Choice of questionnaires. The classic (1979) Impact of Event Scale of Horowitz was elected because this scale is world wide the most used and validated scale in selecting patients at risk for posttraumatic stress disorder (PTSD). The scale rates symptoms and was not designed to diagnose PTSD. To diagnose PTSD, Horowitz and colleagues interviewed patients personally, so the diagnosis was based on clinical judgement. The cut-off level of >19 in the original Impact of Event Scale, referring to a high symptom level of posttraumatic stress, was therefore based on a qualitative judgement of symptoms. Horowitz suggests that investigators may develop their own cut-off scores, by relating scale scores to their own clinical judgement of symptom levels. The analysis of the results of the women participating in our study was performed according to the original paper of Horowitz. It is disputable whether a score of >19 in our cohort should be classified as a high symptom level and therefore, we recommend to take caution in classifying these women as patients suffering from PTSD. Stramrood et al.[39] underline the conflicting results in diagnosing PTSD when using different self-reporting instruments. Apart from difficulties in diagnosing PTSD, it is interesting to see the gradual changes in the diagnostic criteria for PTSD. According to DSM-III (1980)[40] posttraumatic stress disorder was listed as an anxiety disorder encompassing symptoms subsequent to exposure to extreme events that were outside the range of usual human experience. In the next version of DSM (1994)[41] the stressor criterion had been adjusted to stressful situations in which a person had experienced, witnessed, or was confronted with an event that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others. Human childbirth, an experience for at least once in almost half of the entire population of the world, could never fulfil the criteria for PTSD in 1980, however following "softening" the criteria, certain experiences after normal childbirth can be categorised as PTSD. Patients with severe early preeclampsia with the earlier mentioned severe threatening complaints would rather fit in the diagnostic criteria of DSM-III. Changing diagnostic criteria will change prevalence of disorders[42], resulting in difficulties to review the literature.

Severe very early onset preeclampsia

Advice for future care:

As severe early onset preeclampsia can not be predicted in the individual pregnant woman the following recommendations, concluded from the studies described in this thesis, can be phrased once the diagnosis severe early onset preeclampsia before 24 week's gestation has been made. Patients should be referred to a tertiary referral centre for treatment and counselling. Conservative management to prolong pregnancy with the intention to improve neonatal outcome should not be considered as a routine management option. Despite improved treatment and outcome of the very preterm infant, foetuses of pregnancies with severe very early onset preeclampsia are often severely growth restricted. Therefore their prospects at this moment are still very poor and do not justify caesarean section on foetal indication. For patients with severe early onset preeclampsia at later gestational age the national TOTEM study (http://www.studies-obsgyn.nl/home/page.asp?page_id=922) is still ongoing to investigate neonatal outcome after temporising versus terminating policy in severe preeclamptic pregnancies between 28 and 34 weeks' gestation.

The care of future pregnancies of women with a history of severe very early onset preeclampsia is recommended under close surveillance of a perinatologist. The recurrence risk in our study of preeclampsia is 50%, so these women have to be classified as high risk. Half of the women who develop preeclampsia in their future pregnancy will have severe disease again. The high percentage of HELLP syndrome among this group, well after the diagnosis preeclampsia has been made and the fact that some women develop severe disease after 40 weeks' gestation warrants a more aggressive treatment option. This is supported by the findings of the HYPITAT-I study: patients with non-severe hypertensive disease in pregnancy beyond 36 weeks' gestation, induction of labour is associated with less maternal complications compared to expectant management[43]. Currently, this policy is investigated in women with mild-moderate hypertensive disease between 34 and 37 weeks' gestation in the national HYPITAT-II trial (http://www.studies-obsgyn.nl/hypitat2/page.asp?page_id=641).

Post partum women should be screened for underlying disease such as thrombophilia, hyperhomocysteinemia, lupus erythematosus, antiphospholipid syndrome and renal disease. Low dose Aspirin, vitamin supplements (hyperhomocysteinemia) and low molecular weight heparin (antiphospholipid syndrome) can be prescribed in a future pregnancy as indicated. Recently, the data of the FRUIT-study (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=337) have come available and have been presented at the 58th Annual Meeting of the Society of Gynecologic Investigation, March 2011 Miami, USA (poster S-199). Women with a history of early onset preeclampsia and/or foetal growth restric-

tion with an inheritable thrombophilia were randomized in their next pregnancy to treatment with low dose Aspirin or low dose Aspirin combined with prophylactic dose low molecular weight heparin (LMWH). Women in the latter group did not have recurrence of preeclampsia before 34 weeks' gestation
The participants of our study had no structured psychosocial follow up after their complicated pregnancies. Few patients had temporary mental support when admitted in the obstetrical ward or consulted parental psychosocial services when their baby was admitted in the neonatal care unit. Dismissal of themselves or their child was an abrupt discontinuation of support, which several patients experienced as "being left alone". Structured follow up, including obtaining standardized questionnaires regarding posttraumatic stress and depression symptoms are recommended. Additionally, our study shows that every one in six women who intended to resume work after delivery, faces serious problems with the employer after preterm delivery before 34 weeks' gestation, regardless the cause of preterm birth. In The Netherlands, maternity leave amounts to 16 weeks. For most women after very preterm birth this means that they are supposed to resume work when their babies have been discharged from the hospital shortly before. No literature on this specific issue is available, however, a study on return-to-work after childbirth in general is currently ongoing[44]. So far, there is little knowledge of the problems these women face among company medical officers, who are in charge of assignment of sick leave, if necessary. Perinatologists should aim for improvement of interest in the psychosocial effects of preterm birth. Further research, lecturing and publication will increase the general knowledge of specific problems after preterm birth, which may ensure introduction of appropriate facilities for mothers to resume work.

Future Research

Currently, we are able to identify risk groups for preeclampsia however, the identification of the individual patient at risk for development of severe early disease is still a major challenge. The known risk factors as such, are not sensitive and specific enough to be introduced in clinical practice. Future research should focus on the development of a risk model with input of individual clinical, biochemical and genetic factors to predict preeclampsia with both high sensitivity and specificity. Genetic contributions to the risk of preeclampsia have been recognised previously, however the pathophysiological explanations remain unclear. Priority should be given to elucidate interactions between the involved (maternal and paternal) genes mutually and the interaction of these genes with the uterine environment[10]. Proper insight in these mechanisms may contribute to distinguish between several phenotypes of preeclampsia and other placental complications resulting in isolated severe growth restriction.

Recent insight in the contribution of altered VEGF, sFLT-1 and PLGF concentrations in patients with preeclampsia may introduce new therapeutic options. Statins by example block the production of anti angiogenic proteins and induces the production of the angiogenic protein PLGF in laboratory experiments[45] and VEGF121 alleviates hypertension with proteinuria and glomerular endotheliosis in sFlt-1 overexpressed rats[46] Future development of medication suitable for human use, interfering with these angiogenic factors, such as neutralising antibodies against sFlt-1 or sEng, may improve our possibilities not only for treatment of manifest preeclampsia but may also be used for prevention in the individual woman at risk. However, great caution should be considered with the introduction of such new medication in pregnant women, with the potential risk of over treatment. VEGF antagonistic treatment in human cancer trials showed proteinuria, hypertension and loss of glomerular endothelial fenestrae[47,48]. Conversely, potential adverse effects may be expected of VEGF agonistic treatment related to excessive vascular growth in malignant tumors. Although, patients with coronary heart disease and intracoronary VEGF gene transfer did not show an increased risk of malignancies on average eight years after treatment[49], there are no data on safety of these drugs in pregnancy.

What is already known on this topic

- ✓ Mid trimester severe preeclampsia is associated with poor neonatal outcomes and increased risks of maternal complications.
- ✓ The recurrence risk of preeclampsia is increased in early onset preeclampsia.
- ✓ Women with a history of preeclampsia have an increased risk of future cardiovascular disease and express more often features of the metabolic syndrome.
- ✓ Knowledge of long term psychosocial effects of severe early onset preeclampsia is scarce.

What this thesis adds

- ✓ Temporising management to improve neonatal outcome in patients with severe early onset preeclampsia before 24 weeks' gestation should not be considered as a routine treatment option.
- ✓ Despite a recurrence risk of preeclampsia of 50%, neonatal outcome of these pregnancies is in general favourable.
- ✓ Compared to healthy women with uncomplicated pregnancies the women presented in this thesis with severe very early onset preeclampsia have more often pre-existing cardiovascular disease and show significantly more often classic risk factors for cardiovascular disease several years after the index pregnancy. However, they do not differ in glucose intolerance or angiogenic risk factors.
- ✓ At long term follow up a substantial number of women with a history of severe early onset preeclampsia before 32 week's gestation and preterm birth present increased levels of posttraumatic stress symptoms and the social impact on mainly occupational relations appears relatively high.

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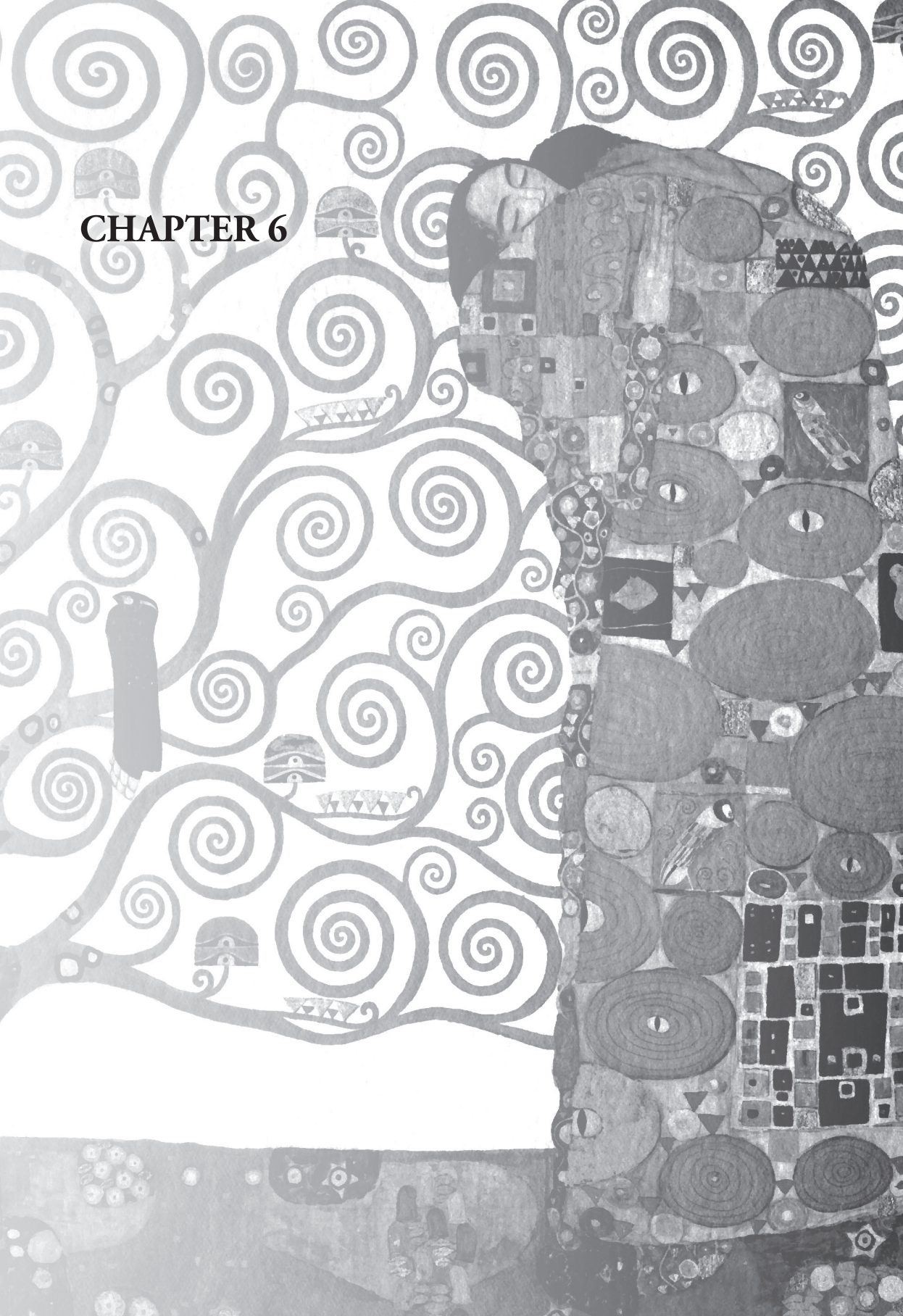
CHAPTER 6



Summary

Severe early onset preeclampsia before 32 weeks' gestational age occurs in less than 1% of pregnancies. However, this obstetric complication is of major concern leading to significant maternal and foetal morbidity and mortality worldwide. The only rational treatment is delivery of the foetus, resulting in very preterm birth. Prolongation of these early pregnancies to improve foetal prospects has been introduced some decades ago. A treatment option (expectant management) which balances between maternal risks and foetal benefits. In case of preeclampsia before 24 weeks' gestation (very early onset preeclampsia), prolongation of pregnancy is however disputable as foetal viability is questionable, even after prolongation. In view of counselling these women with severe preeclampsia at a gestational age with no or little chance of neonatal survival, it is important to have knowledge of the outcome after expectant management. Knowledge of the outcome of future pregnancies of this rare subset of women is an important part of this counselling, as it may influence clinical decision making.

At time of hospitalisation, women with severe early onset preeclampsia may suffer from extreme emotional stress. The majority of women experience severe physical symptoms, which will sometimes be experienced as life threatening. Besides, they worry about the prospects of their very preterm child, who faces substantial risks of mortality and morbidity. In clinical practice we have observed that some women who had pregnancies complicated by severe early onset preeclampsia seem to suffer from posttraumatic stress symptoms and depression leading to social isolation. However, the extend of long term maternal psychosocial effects of severe early onset preeclampsia is unknown.

Compared to women with uncomplicated pregnancies, patients with preeclampsia have an increased risk of future cardiovascular disease. Both preeclampsia and cardiovascular disease share many classic risk factors, such as hypertension, dyslipidemia, and impaired glucose tolerance. Novel angiogenic risk factors, which appear to play an important role during pregnancies complicated by mainly early preeclampsia, have been linked to manifest cardiovascular disease. The presence of these novel and classic risk factors years after a pregnancy complicated by severe very early onset preeclampsia is largely unknown. Identification of these risk factors would enable the clinician to select the patient at risk and the possibility to introduce preventive strategies.

The studies presented in this thesis aim to enhance our knowledge of pregnancy outcome of women with severe very early onset preeclampsia, future pregnancy outcome of these women (chapter 2) and long term maternal psychosocial effects of severe early onset preeclampsia (chapter 3). Additionally, long term classic (chapter 2) and novel (chapter 4) cardiovascular risk factors were investigated in women after severe very early onset preeclampsia. Increased knowledge is neces-

sary for improvement of clinical care of these patients, not only at time of their complicated pregnancy but also long term after.

Chapter 1 provides a general introduction to this thesis.
In chapter 2.1 an in depth review of clinical risk factors of preeclampsia is described. Chronic hypertension, diabetes, renal disease, nulliparity and long interpregnancy interval were identified as independent risk factors.
Chapter 2.2 presents the results of the audit of maternal and perinatal outcome of severe early onset preeclampsia before 24 weeks' gestational age. Twenty six patients, who fulfilled the selection criteria, delivered between 1993 and 2003 in the Erasmus Medical Center Rotterdam. Using a temporising treatment regime, based on prolongation of the pregnancy in order to improve foetal outcome, we found 65% of women with at least one major complication including HELLP syndrome, pulmonary oedema and eclampsia, whereas neonatal survival was only 18%. There was 1 maternal death. We were not able to identify clinical parameters, at time of admission of these women, to predict neonatal survival. However, HELLP syndrome, intrauterine growth restriction and abnormal Doppler findings of the umbilical artery at time of admission were associated with foetal death.
Chapter 2.3 comprises the first follow up study of the women and their partners described in chapter 2.2. Twenty of 25 patients and 15 of their partners consented participation in the study. Both future pregnancy outcome and cardiovascular health (classic risk factors: hypertension, lipid profiles and glucose intolerance) were studied on average 5.5 years after the pregnancy complicated by severe very onset preeclampsia. The recurrence rate of preeclampsia was as high as 50%. Almost half of the patients with recurrence of preeclampsia developed severe disease with preterm deliveries between 32 and 36 weeks gestation, resulting in 100% neonatal survival. The relatively positive prospect of a future pregnancy, especially regarding neonatal outcome, is relevant information in counselling women with severe very early onset preeclampsia. At time of their index pregnancy 35% of the participating women had chronic hypertension, at time of the follow up study the percentage was 55%. Women with a history of severe very early onset preeclampsia showed increased microalbuminuria compared to matched control women with uneventful pregnancy outcome. Moreover, the intima media thickness of the common carotid artery was significantly increased in case women using antihypertensive medication. There were no differences in glucose intolerance between cases and controls, suggesting that the relation between impaired glucose tolerance and preeclampsia, as found by other authors might be more related to preeclampsia with a later onset during gestation. No differences were found in cardiovascular risk profiles between male partners of cases and controls.
Chapter 3 describes the results of the study on long term psychosocial effects of severe early onset preeclampsia. Included in the study were 104 women with severe preeclampsia with onset before 32 weeks' gestation and 78 matched healthy

women with preterm birth without preeclampsia (response rate 79% and 58% respectively). They were on average 7 years after their index pregnancy. There was no difference in depression scores between cases and controls. Women with severe early onset preeclampsia had significantly higher scores of posttraumatic stress symptoms. The majority of women among both cases and controls had high posttraumatic stress symptom levels (88% vs 79%). No differences could be found in social effects with respect to their relation with their partner, relatives, friends and employer. However, women who intend to resume work after their pregnancy experience in 30-40% problems with employers/collegues, leading to dismissal in one third of these problematic relations.

Chapter 4 deals with biochemical aspects of preeclampsia.

Chapter 4.1 comprises the second follow up study in the cohort described in chapter 2.2. In this study we hypothesized that angiogenic risk factors, which seem to play an important role during preeclamptic pregnancies, are associated with future cardiovascular disease and could be used as marker of secondary prevention in women with severe very early onset preeclampsia. On average ten years after their index pregnancy venous plasma samples were analyzed for basic fibroblast growth factor (bFGF), placental growth factor (PLGF), soluble fms-like tyrosine kinase-1 (sFlt-1), vascular endothelial growth factor (VEGF), E- and P-selectin, soluble intercellular adhesion molecule-3 (sICAM-3) and thrombomodulin by ELISA. There were no differences in concentrations of these angiogenic factors between women who had had severe early onset preeclampsia versus those with an uncomplicated pregnancy suggesting that these angiogenic factors will not play an important role in the early detection and secondary prevention of future cardiovascular disease.

In chapter 4.2 we investigated the association of C282Y mutation of the hemochromatosis gene (HFE) and preeclampsia. Women with preeclampsia appear to have transferrin saturation levels in the region associated with iron overload in a substantial amount of cases. Iron overload can be caused by genetic hemochromatosis, which is the most common, autosomal recessive disorder in Northern Europe. Our data do not support the hypothesis that the C282Y allele is a clinically important marker of an increased risk for the development of preeclampsia.

Chapter 5 provides a general discussion on the main findings of the presented studies, placed in a broader context and added with suggestions for further research. In summary, despite changed insights in expectant management treatment (restricted fluid administration) with less maternal risk and recently, changed intervention criteria for neonatal resuscitation of the very preterm infant, expectant management should not be considered as a routine management option for women with severe preeclampsia manifest before 24 weeks gestation. Identification of the individual woman at risk for preeclampsia or recurrence of preeclampsia as well as the estimation of her future cardiovascular risk is difficult as so far, we are only able to categorise risk groups. Future research should focus

on the development of a risk model with input of individual clinical, biochemical and genetic factors to predict both preeclampsia and future cardiovascular and metabolic risks with both high sensitivity and specificity. Finally, the high percentage of women with so far, under-appreciated long term psychosocial effects after early onset preeclampsia and preterm birth require structured attention for symptoms of depression and posttraumatic stress as part of routine obstetric care.

Samenvatting

Ernstige vroege pre-eclampsie bij een zwangerschapsduur onder 32 weken komt in minder dan 1% van de zwangerschappen voor. Deze obstetrische complicatie leidt wereldwijd echter tot aanzienlijke maternale en foetale morbiditeit en mortaliteit. De enige rationele behandeling is beëindiging van de zwangerschap, met extreme prematuriteit als gevolg. Ter verbetering van de foetale prognose werd enkele jaren geleden een behandeloptie geïntroduceerd met als doel de zwangerschapsduur te rekken. Deze behandeling, ook conservatief, expectatief of temporiserend beleid genoemd, balanceert tussen maternale risico's enerzijds en foetale voordelen anderzijds. Het rekken van de zwangerschapsduur in geval van ernstige pre-eclampsie onder 24 weken (ernstige zeer vroege pre-eclampsie) is echter discutabel aangezien de foetale levensvatbaarheid twijfelachtig is, zelfs na verlenging van de zwangerschapsduur. In het kader van voorlichting van vrouwen met ernstige vroege pre-eclampsie bij een zwangerschapsduur zonder of met geringe neonatale overlevingskansen, is kennis van de uitkomsten van deze zwangerschappen na conservatief beleid van wezenlijk belang. Daarnaast is kennis van de uitkomsten van toekomstige zwangerschappen van deze zeldzame groep vrouwen van belang, daar dit een belangrijk onderdeel van deze voorlichting betreft en van invloed zou kunnen zijn op de klinische besluitvorming.

Ten tijde van de opname wegens ernstige zeer vroege pre-eclampsie, kunnen vrouwen extreme emotionele stress ervaren. De meerderheid van deze vrouwen hebben zeer ernstige lichamelijke klachten, zodanig dat ze soms als levensbedreigend ervaren worden. Daarnaast zijn ze zeer bezorgd over de vooruitzichten van hun extreem premature kind, met substantiële risico's op morbiditeit en mortaliteit. Uit klinische ervaring is bekend dat een aantal vrouwen met een ernstige vroege pre-eclampsie in de anamnese, posttraumatische stress symptomen en depressies lijken te hebben, die tot sociale isolatie leiden. Echter, de omvang van deze psychosociale gevolgen op lange termijn zijn onbekend.

In vergelijking met vrouwen na ongecompliceerde zwangerschappen, hebben vrouwen met pre-eclampsie in de voorgeschiedenis een verhoogd risico op voortijdig cardiovasculaire aandoeningen. Zowel pre-eclampsie als cardiovasculaire ziekten hebben vele gemeenschappelijke klassieke risicofactoren, zoals hypertensie, dyslipidemie en glucose-intolerantie. Nieuwe angiogene risicofactoren, die voornamelijk bij ernstige vroege pre-eclampsie een belangrijke rol lijken te spelen, zijn eveneens geassocieerd met manifeste cardiovasculaire ziekte op latere leeftijd. De aanwezigheid van zowel klassieke als nieuwe risicofactoren bij vrouwen met een ernstige zeer vroege preeclampsie in de anamnese is merendeels onbekend. Identificatie van deze risicofactoren zou de clinicus in staat stellen om de individuele patiënt met een verhoogd risico te herkennen en de mogelijkheid bieden om preventieve behandelopties aan te bieden.

De beschreven studies in dit proefschrift hebben als doel onze kennis te verruimen met betrekking tot de zwangerschapsuitkomsten van vrouwen met een ernstige zeer vroege pre-eclampsie, de uitkomsten van hun toekomstige zwangerschappen (hoofdstuk 2) en de psychosociale gevolgen van ernstige vroege preeclampsie op lange termijn (hoofdstuk 3). Daarnaast werden klassieke (hoofdstuk 2) en nieuwe (hoofdstuk 4) cardiovasculaire risicofactoren bestudeerd bij deze vrouwen op lange termijn na ernstige, zeer vroege pre-eclampsie. Toename van onze kennis is noodzakelijk om de klinische zorg voor deze vrouwen te verbeteren, niet alleen ten tijde van hun ernstig gecompliceerde zwangerschap maar ook later in hun leven.

Hoofdstuk 1 voorziet in een algemene introductie in dit proefschrift.
In hoofdstuk 2.1 wordt een grondig review met betrekking tot klinische risicofactoren voor pre-eclampsie beschreven. Chronische hypertensie, diabetes, nierziekten, nulliparitеit en lang interval tussen zwangerschappen konden als onafhankelijke risicofactor geduid worden. Hoofdstuk 2.2 beschrijft de uitkomsten van de audit van de maternale en neonatale uitkomsten van ernstige vroege preeclampsie voor de 24^{e} zwangerschapsweek. Zesentwintig patiënten, die aan de selectiecriteria voldeden, bevielen tussen 1993 en 2003 in het Erasmus Medisch Centrum te Rotterdam. Tegen de achtergrond van een conservatief beleid, met als doel de zwangerschap te rekken en daarmee de foetale prognose te verbeteren, werd in 65% van de vrouwen minstens 1 ernstige complicatie gevonden, waaronder HELLP syndroom, longoedeem en eclampsie. Er was 1 maternale sterfte. Het neonatale overlevingspercentage was slechts 18%. Het bleek niet mogelijk om bij opname klinische parameters, voorspellend voor neonatale overleving te identificeren. Anderzijds bleken HELLP syndroom, foetale groeivertraging en afwijkende Doppler profielen van de arteria umbilicalis bij opname geassocieerd met intra-uteriene sterfte.
Hoofdstuk 2.3 bevat de eerste follow-up studie van de groep vrouwen, zoals beschreven in hoofdstuk 2.2 en hun partners (vaders van de indexzwangerschap). Twintig van de 25 vrouwen en 15 van hun partners verleenden toestemming aan deelname. Zowel de uitkomsten van eventuele volgende zwangerschappen als de cardiovasculaire gezondheid (klassieke risicofactoren: hypertensie, lipidenprofiel en glucose-intolerantie) werden gemiddeld 5,5 jaar na de zwangerschap, gecompliceerd door ernstige zeer vroege preeclampsie bestudeerd. Het herhalingsrisico op pre-eclampsie bedroeg liefst 50%. De helft van de vrouwen met recidief preeclampsie ontwikkelde wederom ernstige pre-eclampsie met de geboorte van hun kind tussen 32 en 36 weken zwangerschapsduur. De foetale overleving was 100%. Deze relatief gunstige vooruitzichten van een volgende zwangerschap, met name ten aanzien van de foetale overleving, is relevante informatie voor vrouwen met een zwangerschap met ernstige zeer vroege pre-eclampsie. Ten tijde van de indexzwangerschap had 35% van de vrouwen chronische hypertensie, bij de

follow-up studie bedroeg dit percentage 55%. Vrouwen met ernstige zeer vroege pre-eclampsie hadden een verhoogd microalbumine gehalte in vergelijking met gematchte controle vrouwen met ongecompliceerde zwangerschapsuitkomsten. Daarnaast bleken vrouwen met gebruik van antihypertensiva een significant dikkere intima-media dikte van de arteria carotis communis te hebben. Er was geen verschil in glucose-intolerantie tussen cases en controles, wat suggereert dat de door andere auteurs eerder beschreven verminderde glucose tolerantie bij vrouwen met pre-eclampsie eerder een relatie zou kunnen hebben met pre-eclampsie die later in de zwangerschap ontstaat. Er werden geen verschillen gevonden in de cardiovasculaire risicoprofielen tussen mannen van cases en controles.
Hoofdstuk 3 beschrijft de resultaten van het onderzoek naar de lange termijn psychosociale gevolgen van ernstige vroege pre-eclampsie. Er konden 104 vrouwen met ernstige vroege pre-eclampsie voor 32 weken zwangerschapsduur en 78 gematchte gezonde vrouwen met vroeggeboorte zonder pre-eclampsie voor analyse geïncludeerd worden (respons respectievelijk 79% en 58%). Gemiddeld waren zij 7 jaar na de indexzwangerschap. Er was geen verschil in depressie scores tussen cases en controles. Vrouwen met ernstige vroege pre-eclampsie hebben significant hogere scores met betrekking tot posttraumatische stress symptomen. Echter de meerderheid van zowel cases als controles hebben hoge posttraumatische stress symptoom niveaus (88% versus 79%). Er konden geen verschillen aangetoond worden in sociale gevolgen met betrekking tot de relatie met hun partners, familie, vrienden en werkgever. Niettemin, 30-40% van de vrouwen die voornemens waren na hun zwangerschap weer te gaan werken, ondervonden problemen met hun werkgever en/of collega's, die bij iedere derde vrouw tot ontslag leidden.
Hoofdstuk 4 behandelt een aantal biochemische aspecten van pre-eclampsie.
In hoofdstuk 4.1 wordt de tweede follow-up studie beschreven van het cohort vrouwen uit hoofdstuk 2.2. In deze studie werd verondersteld dat angiogene risicofactoren, die een belangrijke rol lijken te spelen in zwangerschappen gecompliceerd door pre-eclampsie, geassocieerd zijn met cardiovasculaire aandoeningen op latere leeftijd en gebruikt zouden kunnen worden als markers voor secundaire preventie bij vrouwen met ernstige vroege pre-eclampsie in de anamnese. Hiertoe werden, gemiddeld 10 jaar na de indexzwangerschap, veneuze bloedmonsters middels ELISA geanalyseerd betreffende basic fibroblast growth factor (bFGF), placental growth factor (PLGF), soluble fms-like tyrosine kinase-1 (sFlt-1), vascular endothelial growth factor (VEGF), E- and P-selectine, soluble intercellular adhesion molecule-3 (sICAM-3) en thrombomoduline. Er werden geen verschillen in deze factoren gevonden tussen vrouwen met ernstige zeer vroege pre-eclampsie in de voorgeschiedenis en gematchte vrouwen met ongecompliceerde zwangerschapsuitkomsten. Deze bevindingen suggereren dat de angiogene factoren, die in deze studie bepaald werden, geen belangrijke rol spelen in de vroege detectie en daarmee secundaire preventie van toekomstige cardiovasculaire aandoeningen.

In hoofdstuk 4.2 wordt de relatie tussen C282Y mutatie van het hemochromatosegen (HFE) en pre-eclampsie bestudeerd. Bij vrouwen met pre-eclampsie blijkt in een aanzienlijk percentage transferrine saturaties gevonden te worden, vergelijkbaar met waarden die gevonden worden bij patiënten met ijzerstapeling. IJzerstapeling kan onder andere veroorzaakt worden door genetische hemochromatose, het meest voorkomende autosomaal recessieve gendefect in Noord-Europa. De resultaten van ons onderzoek steunen de hypothese dat het C282Y allel een belangrijke klinische rol speelt bij het ontstaan van pre-eclampsie niet.
Hoofdstuk 5 behandelt de resultaten van de diverse studies van dit proefschrift, waarbij deze in een bredere context geplaatst worden en worden aanbevelingen voor toekomstig onderzoek geformuleerd. Samenvattend, ondanks veranderde inzichten in conservatief beleid (restrictievere vochttoediening) waarbij minder maternale complicaties gezien worden en recent veranderde criteria voor actieve resuscitatie van de extreem te vroeg geborene wordt routinematige toepassing van conservatief beleid bij vroege pre-eclampsie onder 24 weken zwangerschapsduur ontraden. Het blijkt niet mogelijk de individuele vrouw voor noch het ontwikkelen van pre-eclampsie, noch het ontwikkelen van een recidief pre-eclampsie, noch voor haar toekomstige cardiovasculaire ziekte te identificeren. Tot dusverre kunnen alleen groepen vrouwen in risicocategorieën geïdentificeerd worden. Toekomstig onderzoek zou zich moeten richten op het ontwikkelen van een risicomodel, waarin individuele klinische, biochemische en genetische parameters het risico op pre-eclampsie en het risico op cardiovasculaire aandoeningen op latere leeftijd met hoge sensitiviteit en specificiteit voorpellen. Tot slot, het hoge percentage van vrouwen met tot op heden ondergewaardeerde psychosociale gevolgen na ernstige vroege pre-eclampsie en vroeggeboorte noopt tot invoering van structurele aandacht voor symptomen van depressie en posttraumatische stress in de routine medische zorg voor deze vrouwen.

Zusammenfassung

Eine schwere, vor der 32.SSW beginnende Präeklampsie tritt in weniger als einem Prozent aller Schwangerschaften auf. Dennoch bekommt diese seltene geburtshilfliche Komplikation sehr viel Aufmerksamkeit, da sie weltweit zu ganz erheblicher fetaler und mütterlicher Morbidität und Mortalität führt. Die einzige erfolgversprechende Behandlung bestand lange Zeit in der zügigen Entbindung der Frau, was zwangsläufig zu einer sehr kleinen Frühgeburt führt. Vor einigen Jahren wurde versucht, derartige Schwangerschaften zu verlängern, um die Überlebens- und Entwicklungschancen des Kindes zu verbessern. Dieses „expektative Management" versucht den optimalen Punkt zwischen Vorteilen für den Fötus und möglichst geringen Nachteilen für die Mutter zu finden. In den Fällen von Präeklampsie, die vor der 24.SSW auftreten (sehr frühe Präeklampsie), ist der Versuch der Schwangerschaftsverlängerung von fragwürdigem Nutzen, da die extrauterine Lebensfähigkeit des Kindes zweifelhaft ist, selbst dann, wenn es gelingt, die Schwangerschaft um einige Tage zu verlängern. Will man Frauen mit schwerer Präeklampsie die in einem Schwangerschaftsalter sind, in dem noch keine oder nur eine geringe Chance auf ein Überleben des Kindes besteht, richtig beraten, muss man über die Ergebnisse des expektativen Managements Bescheid wissen. Ärzte müssen selbst eine klare Vorstellung haben, wie solche expektativ gemanagten Schwangerschaften ausgehen, denn dies kann die Art ihrer Beratung und ihre klinischen Entscheidungen beeinflussen.
Zum Zeitpunkt der Aufnahme im Krankenhaus leiden Frauen mit schwerer früher Präeklampsie unter massivem emotionalem Stress. Der Großteil der Frauen hat deutliche körperliche Symptome, die meist als lebensbedrohlich wahrgenommen werden. Dazu kommen die Sorgen um die Überlebens- und Entwicklungschancen ihres Kindes, welches noch sehr unreif ist und welches ein deutliches Risiko auf Morbidität und Mortalität hat. In vielen Jahren, in denen wir diese Patientinnen betreut haben, haben wir festgestellt, dass manche Frauen, die schwere frühe Präeklampsie hatten, danach an posttraumatischer Stress-Symptomatik und Depression leiden, die sie in die soziale Isolation führt. Wie viele Frauen dies betrifft und wie die psychosozialen Langzeiteffekte von schwerer früher Präeklampsie sind, ist unbekannt. Vergleicht man Frauen mit Präeklampsie mit Frauen, welche komplikationsfreie Schwangerschaften hatten, so zeigt sich, dass die Präeklampsie-Frauen ein deutlich erhöhtes Risiko haben, im späteren Leben an kardiovaskulären Erkrankungen zu leiden. Die Präeklampsie und kardiovaskuläre Erkrankungen teilen sich viele typische Risikofaktoren wie Hochdruck, Dyslipidämie und beeinträchtigte Glukosetoleranz. In den letzten Jahren sind neue angiogenetische Faktoren hinzugekommen, welche offenbar eine wichtige Rolle vor allem bei der früh auftretenden Präeklampsie spielen und die man auch bei kardiovaskulären Erkrankungen findet. Inwieweit diese neu entdeckten Risikofaktoren und die seit langem bekannten Risikofaktoren sich bei Frauen

Jahre nach einer frühen schweren Präeklampsie auswirken, ist großteils unbekannt. Eine bessere Identifikation dieser Risikofaktoren würde den Klinikern die Möglichkeit geben, die Patientinnen nach Risikoprofil zu behandeln und auch mögliche Präventionsstrategien anzuwenden.

In den Arbeiten, die in diesem Band zusammengefasst sind, wird versucht, das Wissen über den Schwangerschafts-Outcome bei Frauen mit schwerer, früh auftretender Präeklampsie sowie den Schwangerschaftsausgang in folgenden Schwangerschaften und die psychosozialen Langzeiteffekte von schwerer, früher Präeklampsie zu beschreiben. Zusätzlich werden bekannte und neue kardiovaskuläre Risikofaktoren bei Frauen mit schwerer früher Präeklampsie untersucht. Frauen müssen nicht nur während ihrer durch Präeklampsie komplizierten Schwangerschaft betreut werden, sondern auch in den Jahren danach, hierzu ist eine Vertiefung des Wissens über die Zusammenhänge notwendig.

In Kapitel 1 wird eine allgemeine Einführung zu dem Thema gegeben. In Kapitel 2.1 wird eine gründliche Beschreibung der klinischen Risikofaktoren für Präeklampsie versucht: Chronischer Hochdruck, Diabetes, Nierenerkrankungen, Nulliparität und lange Intervalle zwischen Schwangerschaften wurden jeweils als unabhängige Risikofaktoren identifiziert. In Kapitel 2.2 werden die Ergebnisse des Audit zum mütterlichen und perinatalen Outcome von schwerer früher Präeklampsie vor der 24 SSW präsentiert. 26 Patientinnen, welche die Kriterien erfüllten, wurden zwischen 1993 und 2003 in der Frauenklinik des Erasmus-Medical-Center Rotterdam entbunden. In einem auf Zeitgewinn ausgelegten, expektativen Behandlungsprotokoll, welches das Ziel hatte, die Schwangerschaft zu verlängern, um den Outcome für das Kind zu verbessern, trat bei 65 % der Frauen zumindest eine schwerwiegende Komplikation auf – Hellp-Syndrom, Lungenödem und Präeklampsie – wobei nur 18 % der Neugeborenen überlebten. Es kam zu einem mütterlichen Todesfall. Wir waren bei der Analyse nicht in der Lage, klinische Parameter festzulegen, die zum Zeitpunkt der stationären Aufnahme dieser Frauen verlässlich das Outcome für das Neugeborene vorhersagen konnte. Allerdings waren Hellp-Syndrom, intrauterine Wachstumsretardierung und abnormale Dopplerbefunde der Nabelarterie zum Zeitpunkt der Aufnahme deutlich mit intrauterinem Tod des Kindes in den folgenden Tagen assoziiert.

In Kapitel 2.3 wird die erste Follow-up-Studie über die Frauen und ihre Partner, welche in Studie 2 beschrieben wurden, präsentiert. 20 der 25 Patientinnen und 15 ihrer Partner erklärten sich bereit, an der Studie mitzuwirken. Im Mittel 5 ½ Jahre nach der Schwangerschaft, die durch schwere frühe Präeklampsie kompliziert wurde, wurden Verlauf und Outcome weiterer Schwangerschaften und die kardiovaskuläre Gesundheit der Frauen (Hochdruck, Lipidprofil und Glukosetoleranz) untersucht. Die Rate des Wiederauftretens einer Präeklampsie bei einer

Folgeschwangerschaft lag bei 50 %. Fast die Hälfte der Patientinnen mit erneuter Präeklampsie entwickelte eine schwere Ausprägung der Krankheit mit Frühgeburt zwischen der 32. und 36.SSW. Allerdings überlebten 100 % der Neugeborenen. Diese relativ positive Prognose einer zukünftigen Schwangerschaft, vor allem was den neonatalen Outcome betrifft, ist eine relevante Information, die man Frauen, die man wegen einer Erstmanifestation von schwerer früher Präeklampsie berät, unbedingt geben muss. Zum Zeitpunkt der ersten Schwangerschaft, die zur schweren Präeklampsie führte, hatten 35 % der Frauen einen chronischen Bluthochdruck, zum Zeitpunkt der Folgeschwangerschaft waren dies 55 %.

Frauen mit einer Vorgeschichte von schwerer früher Präeklampsie zeigten vermehrte Proteinurie verglichen mit Frauen, die eine normale Schwangerschaft hinter sich hatten. Weiters war die Intima-Dicke der Arteria Carotis communis bei den Präeklampsie-Frauen deutlich erhöht, vor allem wenn sie über längere Zeit Antihypertensiva eingenommen hatten. Zwischen der Studiengruppe und der Vergleichsgruppe fanden sich keine Unterschiede betreffend der Glukoseintoleranz. Dies könnte ein Hinweis darauf sein, dass der Konnex zwischen Glukoseintoleranz und Präeklampsie, wie er von anderen Autoren beschrieben wurde, vermutlich nur bei Formen der Präeklampsie, die zu einem späteren Zeitpunkt der Schwangerschaft eintreten, relevant ist. Das kardiovaskuläre Risikoprofil der Partner der Frauen war in beiden Gruppen gleich.

In Kapitel 3 werden die Ergebnisse der Studie zum psychosozialen Langzeiteffekt der frühen schweren Präeklampsie präsentiert. In dieser Studie waren 104 Frauen mit schwerer Präeklampsie, die vor der 32.SSW begonnen hatte und 78 gesunde Frauen, die eine Frühgeburt ohne Präeklampsie hinter sich hatten . Die Rücklaufquote betrug dabei 79 % bei den Präeklampsie-Patientinnen und 58 % bei den Frühgeburts-Patientinnen. Die Befragung fand im Mittel sieben Jahre nach der betreffenden Schwangerschaft statt. Es gab keinen Unterschied in Depressions-Scores zwischen Studienpatientinnen (nach Präeklampsie) und Kontrollpatientinnen (nach Frühgeburt ohne Präeklampsie). Die große Mehrheit der Frauen in beiden Gruppen hatte einen hohen Level von posttraumatischen Stress (88 % zu 79 %). Zwischen den beiden Gruppen konnten wir keine Unterschiede im Sozialverhalten wie etwa der Partnerbeziehung, der Beziehung zu Verwandten, Freunden und am Arbeitsplatz finden. Allerdings zeigte sich, dass Frauen, die nach der Schwangerschaft wieder arbeiten gehen wollten, in 30-40 % der Fälle erhebliche Probleme mit Arbeitgebern und Kollegen mitgemacht hatten, was in über einem Drittel der Fälle zur Entlassung bzw. zur Selbstkündigung führte.

Im Kapitel 4 werden die biochemischen Aspekte der Präeklampsie behandelt. In Kapitel 4.1 wird die zweite Langzeit-Follow-up-Studie der in Kapitel 2.2. beschriebenen Kohorte präsentiert. Bei der Planung dieser Studie vermuteten wir, dass angiogene Risikofaktoren, die eine wichtige Rolle bei der Entwicklung von präeklamptischen Schwangerschaften zu spielen scheinen, mit zukünftigen kardiovaskulären Erkrankungen im Zusammenhang stehen. Dies würde bedeuten, dass man sie

als Marker für die Sekundärprävention bei Frauen mit schwerer früher Präeklampsie verwenden könnte. Im Mittel zehn Jahre nach der entsprechenden Schwangerschaft wurden Blutproben der Frauen auf *Basic Fibroplast Growth Factor*(bFGF), *Placental Growth Factor* (PLGF), *Soluble fms-like Tyrosine-Kinase-1* (sFlt-1), *Vascular Endothelial Growth Factor* (VEGF), *E- und P-Selectin, Soluble Intercellular adhesion molecule-3* (sICAM-3) und *Thrombomodulin* mittels ELISA untersucht. Es zeigten sich keine Unterschiede in der Konzentration dieser angiogenen Faktoren zwischen Frauen, die eine schwere frühe Präeklampsie hinter sich hatten und Frauen die eine unkomplizierte Schwangerschaft hatten. Dies deutet darauf hin, dass die Analyse der angiogenen Faktoren keine wichtige Rolle bei der Detektion und der Sekundärprävention zukünftiger kardiovaskulärer Erkrankungen haben wird.
In Kapitel 4.2 untersuchen wird die Assoziation der C282Y-Mutation des Hämochromatosegens (HFE) mit dem Auftreten von Präeklampsie. Frauen mit Präeklampsie scheinen Transferrin-Sättigungsspiegel zu haben, die sonst mit Eisen-Überladung wie bei Eisenspeichererkrankungen assoziiert sind. Eisen-Überladung kann durch genetische Hämochromatose verursacht werden, welches die häufigste autosomal rezessive Störung in Nordeuropa ist. Unsere Daten geben aber keinen Hinweis, dass das C282Y-Allel ein klinisch wichtiger Marker für ein erhöhtes Risiko für Präeklampsie ist.
In Kapitel 5 werden die Ergebnisse der Studien im weiteren Kontext einschließlich der Zielrichtung zukünftiger Studien diskutiert. Zusammenfassend lässt sich sagen, dass trotz Modifikationen beim Protokoll des expektativen Management derPräeklampsie (Zurückhaltung bei der Flüssigkeitszufuhr), welches zu einer Reduktion des mütterlichen Risikos geführt hat, sowie Veränderungen bei den Interventionskriterien für die Reanimation sehr kleiner Frühgeborener in den letzten Jahren, das expektative Management doch nicht als Routineoption für Frauen mit schwerer Präeklampsie, die sich vor der 24.SSW manifestiert, in Betracht kommt. Die Identifizierung der einzelnen Frau, die ein Risiko auf Präeklampsie hat, aber auch die Einschätzung des Risikos eines erneuten Auftretens von Präeklampsie in einer Folgeschwangerschaft und schließlich die Einschätzung der kardiovaskulären Risiken jenseits der reproduktiven Lebensphase sind deshalb so schwierig, weil wir bisher nicht in der Lage waren, die Risikogruppen zu kategorisieren. Zukünftige Forschungen sollten sich auf die Entwicklung von Risikomodellen konzentrieren, wobei klinische, biochemische und genetische Faktoren hineingenommen werden müssen, um sowohl Präeklampsie als auch zukünftige kardiovaskuläre und Stoffwechselrisiken mit hoher Sensitivität und Spezifität vorhersagen zu können. Schließlich wird es nötig sein, den hohen Anteil an Frauen, die nach früher schwerer Präeklampsie - aber auch nach Frühgeburt - erheblichem psychosozialen Langzeit-Stress ausgesetzt sind, entsprechend wahrzunehmen und zu erfassen und die Behandlung dieser Depressions-Symptome und posttraumatischen Stress-Symptome zu einem Teil der geburtshilflichen Nachsorge zu machen.

CURRICULUM VITAE

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