Vascular dysfunction in preeclampsia
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Chapter 1

General introduction
and aims of this thesis
Chapter 1

History

Eclampsia was described for the first time almost 2000 years ago by Celsus, who presented an account of seizures in pregnant women that abated with delivery. This abnormality was named eclampsia, the Greek word for “lighting”, indicating the rapid and unexpected appearance. For hundreds of years eclampsia was considered a seizure disorder unique to pregnancy. It was not until 1827 that Lever and Bright recognized the similarity of the edematous patient with eclampsia to the dropsic individual with “Bright’s disease” (acute glomerulonephritis), which resulted in the examination of urine of women with eclampsia for protein. It was found that most women with eclamptic seizures had proteinuria and that proteinuria could antedate seizures. The hard bounding pulse of eclamptic women had already suggested arterial hypertension to the old-time clinicians, but it was not until 1896, when the invention of the sphygmomanometer enabled the measurement of blood pressure, that the hypertension in women with eclampsia was actually measured - again frequently antedating seizures. Over the next several decades, it was recognized that pregnant women who have proteinuria and hypertension - this condition now being called preeclampsia - and their infants were at risk for mortality and morbidity even if the disorder did not progress into convulsions. Thus, eclampsia was no longer considered a seizure disorder, but part of a continuum of a pregnancy-specific fetal-maternal disorder [3,4].

Disease characteristics

Nowadays, preeclampsia occurs in about 4-5% of all human pregnancies. As mentioned previously, hypertensive disorders of pregnancy are major risk factors for maternal and fetal morbidity and mortality in pregnancy. Although medical care has improved tremendously in the past centuries, resulting in reduction of the complication rates, still in The Netherlands 35% of the maternal mortality is related to eclampsia or preeclampsia [5]. Preeclampsia can result in eclampsia, when convulsions develop, or manifest itself as the HELLP syndrome, a severe form of preeclampsia with multiple organ involvement, characterized by Hemolysis, Elevated Liver enzymes and Low Platelet count (HELLP). Severe complications of preeclampsia are cerebral hemorrhage, lung edema or liver hemorrhage and rupture. Intrauterine growth restriction and iatrogenic preterm birth of the fetus, associated with preeclampsia, result in a high risk of intruterine or early neonatal death and infant mortality or morbidity, mainly due to respiratory disease and long term neurological morbidity [6]. Moreover, women with preeclampsia are at increased risk for ischemic heart disease later in life [7,8] as are children that were born with a low birthweight [9].
**Pathogenosis**

The mechanisms causing preeclampsia are still unclear. Much insight has developed in the past decades. It has become clear that preeclampsia is a complex disease, with many factors involved in its pathogenesis. A suboptimal placentation seems to be central in the early stage of the disease, while a generalized vascular dysfunction is central in the late stage of the disease, when the clinical symptoms develop. The missing link between the suboptimal placentation and the generalized vascular dysfunction is believed to be a factor, released from the placenta into the maternal blood. Thus far, this factor has not been identified. Evidence starts to accumulate that microparticles, fragments of blood and vascular wall cells that are released upon cell activation or apoptosis, are involved in the pathogenesis of cardiovascular diseases. Many parallels exist between the pathogenesis of cardiovascular diseases and preeclampsia. Therefore, we hypothesized that microparticles may be the unknown circulating factor that causes vascular dysfunction in preeclampsia. Investigation of this hypothesis was the first aim of this thesis.

The second aim of this thesis was to investigate the nature of the vascular dysfunction in preeclampsia. Many studies have described the presence of endothelial dysfunction in preeclampsia. However, vascular smooth muscle cells form the final link in the generation of vascular tone. There is very limited information on the role of vascular smooth muscle cells in preeclampsia. Therefore, we aimed to investigate their role in preeclampsia and to explore possibilities for improvement of vascular function in this disease.

**Aims of this thesis**

The main objectives of this thesis were:

1. to determine the role of circulating microparticles in the pathogenesis of preeclampsia.

2. to investigate vascular dysfunction in the resistance vasculature in preeclampsia, and whether this is endothelium and/or vascular smooth muscle related. We also attempted to identify mechanisms that could improve vascular function in this disease.
Outline of this thesis

Part I
In part I an extensive overview of the literature on vascular dysfunction in preeclampsia and on the current opinion on the pathogenesis of this disease is presented (Chapter 2). Furthermore, an overview of the literature on microparticles, and in particular the evidence for a role of microparticles in the pathogenesis of cardiovascular diseases is presented (Chapter 3).

Part II
The studies performed in order to fulfill our first aim are described in part II. We started to investigate whether syncytiotrophoblast-derived microparticles can cause vascular dysfunction in isolated myometrial arteries (Chapter 4). We broadened this investigation to all cell-derived microparticles circulating in the maternal blood. We characterized the circulating microparticles in pregnancy and preeclampsia (Chapter 5), investigated whether they can cause vascular dysfunction in isolated bioassay arteries (Chapter 6 and 7), investigated whether the phospholipid composition of microparticles is important in inducing vascular dysfunction (Chapter 7), and investigated the role of microparticles in the enhanced coagulation activation that is observed in preeclampsia (Chapter 8).

Part III
The studies performed in order to fulfill our second aim are described in part III. We determined contractile behavior and vascular smooth muscle calcium sensitivity in isolated subcutaneous arteries from nonpregnant, normal pregnant and preeclamptic women (Chapter 9). Furthermore, we investigated whether there is remodeling in the subcutaneous resistance vasculature in preeclampsia (Chapter 10). Finally, we investigated whether estrogens are a useful therapy for improvement of vascular dysfunction in preeclampsia (Chapter 11).

Part IV
In part IV the results of the studies described in this thesis are discussed and the main conclusions are drawn. In combination with the literature the findings of the studies in this thesis are translated into a hypothesis regarding the role of microparticles in the pathogenesis of preeclampsia. Furthermore, directions for future research and preliminary results of a pilot study are discussed.