General introduction, aims and outline
GENERAL INTRODUCTION

Preeclampsia (PE) is a severe placenta-related pregnancy disorder, that complicates around 5-8% of pregnancies.1 PE can have detrimental consequences during pregnancy for the mother, as it increases the risk of for example stroke, liver rupture, and lung edema. It also contributes significantly to perinatal morbidity, as approximately 12% of PE cases is complicated by fetal growth restriction, and around 20% results in preterm birth.2 Besides these short term consequences, PE is also associated with health risks later in life for both mother and child. Women who have suffered from PE have a 2-4 times higher risk of developing cardiovascular diseases.3,4 Furthermore, prematurity and low birth weight increase the risk of cardiopulmonary and neurological impairment in children.5,6

Nowadays PE is defined as de novo hypertension after the 20th week of gestation, along with evidence of maternal organ damage and/or fetal growth restriction.7 However, as early as 400 BC, Hippocrates already wrote that ‘a headache accompanied by heaviness and convulsions during pregnancy is considered bad’.8 In that time it was thought that all female diseases resulted from an imbalance in body fluids, and therefore treatments existed of dietary changes, purging and blood-letting.9 In the 17th century, the word ‘eclampsia’ arose and the disease was systematically described for the first time. In an attempt to prevent convulsions, phlebotomies during pregnancy were recommended.10 In the 19th century, the disease was called ‘toxemia’, as it was thought that it resulted from the inability to eliminate an increase in waste products.11 Treatment still mainly existed of bleeding and purging, in order to eliminate the excess of toxic elements. It was not until the 20th century that the pathophysiology of PE was linked to the abnormal placentation in early pregnancy.12 Although still not fully elucidated, it is now known that increased placental vascular resistance leads to an imbalance in pro- and antiangiogenic factors, causing generalized endothelial dysfunction.13,14 The latter is characterized by disturbances in different vascular pathways, e.g. decreased activity of the nitric oxide pathway and increased activity of the endothelin system.15,16 Furthermore, there is an imbalance in the immune system response, with a shift towards pro-inflammatory conditions.17,18

To date, still no cure is available for PE, except for delivery of the placenta. Patients are often stabilized with antihypertensive drugs, such as methyldopa and/or calcium antagonists, and magnesium sulfate to prevent further complications and prolong pregnancy as long as possible. Targeting the vascular endothelial dysfunction in PE is a promising strategy in developing new therapeutic options.
The ex vivo placental perfusion system

For the research described in this thesis we used dual-sided ex vivo placental perfusion of isolated cotyledons, an established experimental model to study the transfer of drugs across the human placenta, their subsequent effects and placental metabolism. It is the only reliable method to predict in vivo fetal exposure to maternally administered compounds without imposing risks on mother or child.\textsuperscript{19,20} The model was first described in 1967 by Panigel et al.\textsuperscript{21} and later modified by Schneider et al. in 1972.\textsuperscript{22} The model used for the studies in this thesis has been adapted from the model described by Schalkwijk et al.\textsuperscript{23} It consists of a plastic perfusion chamber and two peristaltic roller pumps. Heating devices and a water bath keep the temperature in the setup at 37 °C. Maternal and fetal perfusion media are aerated continuously with 95% O\textsubscript{2} – 5% CO\textsubscript{2}. After arrival at the lab directly after birth, an intact cotyledon is selected and the corresponding chorionic artery and vein pair is cannulated to establish the fetal circulation. Subsequently, the cotyledon is cut from the rest of the placenta and placed inside the perfusion chamber. Maternal circulation is created by placing four blunt cannulas in the intervillous space and outflow from the intervillous space is collected in a reservoir. Changes in fetoplacental pressure and pH are recorded using acquisition software. A schematic overview of our placental perfusion model is shown in Figure 1.

![Figure 1. Schematic overview of the placental perfusion model in our lab.](image)

AIMS AND OUTLINE OF THE THESIS

In this thesis new treatment strategies for PE are discussed, targeting the placental vascular dysfunction that plays a key role in the pathogenesis of this disease. By using ex vivo techniques, such as perfusion of the isolated cotyledon and wire-myography, the human placenta is studied without the risk of harming either mother or fetus.
The aims of this thesis are:
1. To understand placental vascular reactivity in health and disease
2. To evaluate possible new treatment options for PE, using *ex vivo* placental perfusion

**Chapter 2** provides an extensive overview of the vascular reactivity profile of the human placenta. It summarizes the most important pathways and factors that are involved in the regulation of (placental) vascular function during healthy pregnancy and changes associated with PE. Furthermore, potential treatment strategies interfering with these changes are discussed. **Chapters 3-6** focus on experimental therapeutic strategies targeting the vascular dysfunction seen in PE. In **Chapter 3** we study the transfer and effect of the phosphodiesterase-5 inhibitor sildenafil in placentas from healthy and PE pregnancies. In **Chapter 4** we try to elucidate the vasodilator mechanism of pentoxifylline by studying its effect in porcine coronary arteries and human chorionic plate arteries. **Chapter 5** discusses the possibility of using endothelin receptor antagonists for PE treatment. It includes an overview of all cases reported in literature of women who were exposed to these drugs during pregnancy. Following this, in **Chapter 6** we examine the transfer and effects of the endothelin receptor antagonists macitentan, sitaxentan and ambrisentan in the human placenta. **Chapter 7** explores the associations between first-trimester *in vivo* placental vascular parameters and *ex vivo* placental vascular function at term. **Chapter 8** provides a general discussion and suggestions for future research, and in **Chapter 9** this thesis is summarized.
REFERENCES

9. Green MH. The transmission of ancient theories of female physiology and disease through the early middle ages. 1985
