GENERAL INTRODUCTION
Chapter 1

BEYOND PREGNANCY

Pregnancy and childbirth are — quite literally — life changing events with an impact for both mother and child reaching far beyond birth and the puerperium. Despite increasing knowledge on the long-term consequences for maternal and offspring health, healthcare and research to date mostly focus on instant and short-term risks and outcomes. Consequently, important opportunities to positively impact long-term maternal and offspring health are overlooked.

This thesis focuses on two aspects of long-term health: maternal cardiovascular health and offspring cognitive development. While inherently linked through pregnancy, they both present with their own pathophysiology, challenges and opportunities. These are discussed separately in this introduction section, in part I and part II of the thesis, respectively, and in the discussion section. Collectively, this thesis aims to contribute to better understanding of the possible long-term consequences of pregnancy disorders for mother and child and to encourage professionals to look beyond pregnancy and embrace the window of opportunity that pregnancy can offer to improve the future health of these women and their children.

PREGNANCY DISORDERS

In this thesis we focus on three different pregnancy disorders: hypertensive disorders of pregnancy (HDP), preterm birth and fetal growth restriction (FGR). These are among the most common pregnancy disorders worldwide.1-4 While clinical presentation evidently differs across these pregnancy disorders, they are thought to at least partly share a common pathophysiology, characterised by uteroplacental dysfunction, secondary to impaired placentation and/or uteroplacental malperfusion.5, 6 It is for that reason that they are collectively referred to in this thesis as disorders of uteroplacental dysfunction.

Hypertensive disorders of pregnancy

Approximately 6-8% of all pregnancies are complicated by HDP.7 HDP include chronic hypertension (predating pregnancy or diagnosed before 20 weeks of pregnancy) and de novo hypertension, either with (i.e. preeclampsia) or without (i.e. gestational hypertension) clinical or biochemical signs of end-organ dysfunction.8 These signs of end-organ dysfunction include proteinuria, acute kidney injury, liver dysfunction, neurological features, haemolysis, thrombocytopenia and placental insufficiency resulting in FGR. Women with HDP are at increased risk of maternal mortality and of being faced with neonatal mortality and morbidity, with highest risks among those that develop preeclampsia early in pregnancy.
The pathophysiology of preeclampsia and other HDP remain poorly understood. Traditionally, preeclampsia has been considered a primary placental disorder, in which placental stress causes the release of soluble factors from the placenta in the maternal circulation. These factors trigger systemic inflammation, endothelial dysfunction, vasoconstriction and multiorgan hypoperfusion, causing what is known as the maternal syndrome of preeclampsia. In early-onset preeclampsia, the placental stress results primarily from impaired trophoblast invasion and spiral artery remodeling. This impaired deep placentation causes uteroplacental malperfusion and oxidative or endoplasmic reticulum stress in the placenta, resulting in secretion of factors in the maternal circulating, causing the maternal symptoms. Additionally, it results in impaired placental function, causing the FGR that is often present in early-onset preeclampsia. In contrast, in late-onset preeclampsia placental stress is thought to result from uteroplacental malperfusion secondary to physical limits on placental growth and age. Recent evidence suggests that, in both early-onset and late-onset preeclampsia, the maternal cardiovascular function and its ability to adapt to the increasing demands of the pregnancy play an important role in the development of the disease.

**Preterm birth**

Preterm birth is defined as delivery before 37 weeks of pregnancy. Incidence varies between population, ranging from 5-18%. Preterm birth is the leading cause of neonatal mortality and morbidity worldwide, with highest risks among those born at earliest gestational ages. Approximately two-thirds of preterm births are spontaneous; one-third is iatrogenic, mainly because of preeclampsia and/or FGR. Spontaneous preterm birth is generally considered a syndrome with multiple causes and phenotypes. Among these are uterine infection and inflammation, uteroplacental ischemia and haemorrhage, uterine overdistension, cervical insufficiency, hormonal disorders and other immunologically mediated processes. Pathology findings of defective deep placentation in spontaneous preterm birth support the theory that uteroplacental dysfunction plays a role in the pathophysiology of spontaneous preterm birth.

**Fetal growth restriction**

FGR complicates 3-9% of all pregnancies in high-income countries, and up to 25% of pregnancies in low- and middle-income countries. It is characterised by the inability of the fetus to reach its intrinsic growth potential as a result of impaired placental function. FGR is associated with increased risk of stillbirth, neonatal morbidity, poor neurodevelopment and metabolic and cardiovascular disease (CVD) in adult life. Therefore, it is important to correctly identify those fetuses that are suffering from growth restriction. FGR is often defined by deviation of fetal size from a population-based reference. A much-used example is small for gestational age (SGA), defined as a birthweight below the 10th birthweight percentile. However, such definitions are problematic as they do not distinguish between fetuses that are constitutionally small, and those that are small due to impaired placental function, while only the latter are at
increased risk of adverse outcomes. Additionally, growth restricted fetuses with a size considered normal but that do not meet their biological growth potential, are not being recognised when size-based definitions are used. A consensus-based definition for FGR including both size and functional parameters was published in 2016 to address some of these issues.17

In early-onset FGR, pathophysiology comprises impaired trophoblast invasion and spiral artery remodelling, as described in preeclampsia, resulting mainly in maternal vascular malperfusion and impaired uteroplacental function. In late-onset FGR, multiple factors contribute to development of uteroplacental dysfunction and subsequent FGR.16

PREGNANCY AND MATERNAL CARDIOVASCULAR HEALTH

Over the last two decades, multiple studies have shown convincingly that women with a history of different pregnancy disorders, including HDP, preterm birth and FGR, are at increased risk of CVD later in life.20-28 At highest risk of future CVD are those after the early-onset of disease, and with severe and/or recurrent disease.29 The increased CVD risk may be present immediately after pregnancy and persist for more than 20 years.30, 31

Increasingly, evidence suggests that in many of these women the strain of pregnancy unmasks a pre-existing unfavourable cardiovascular profile. While often subclinical prior to pregnancy, this suboptimal maternal cardiovascular health status restrains the physiological cardiovascular and hemodynamic adaptations necessary to accommodate pregnancy and for optimal placental development, resulting in pregnancy disorders, such as preeclampsia and FGR. As such, pregnancy is often considered to be a cardiometabolic stress-test with pregnancy disorders as the first indicator, relatively early in life, of an increased risk for CVD. Alternatively, some hypothesise that pregnancy disorders themselves contribute to the increased cardiovascular risk later in life through persistent endothelial damage, dysregulation of the renin-angiotensin-aldosterone system, or an enduring high inflammatory state.29, 32

Role of ethnicity

Most of the research on the association between HDP and CVD has been conducted in white majority populations, and there is limited and heterogeneous reporting of ethnicity in published studies.33 This is potentially problematic, as there is substantial heterogeneity in the burden of HDP and CVD across different ethnic (sub)populations, with some groups being disproportionally affected compared to others.33-35 Few studies have been conducted in multi-ethnic populations, with some showing evidence of interaction between pregnancy disorders and ethnicity for the CVD risk after pregnancy, while others do not find this.36-38 This highlights the need for more research on the
association between pregnancy disorders and maternal cardiovascular health in multi-
ethnic populations and the potential influence of ethnicity.

Prediction and prevention of pregnancy disorders
The theory of cardiovascular maladaptation as an important factor in development of uteroplacental dysfunction and subsequently preeclampsia and other disorders characterised by uteroplacental dysfunction potentially provides opportunities for better and earlier prediction or detection of these pregnancy disorders before, or during, early pregnancy.\(^4\) Better prediction of those at highest risk is important, as it would allow targeted use of preventive strategies (e.g. aspirin for the prevention of preeclampsia) and intensified monitoring. Examples of screening tools that incorporate known cardiovascular risk factors are The Fetal Medicine Foundation (FMF) algorithm and the EXPECT prediction tool.\(^39,40\) Both models perform substantially better than the traditional NICE guideline criteria for the prediction of preeclampsia.\(^40-42\) It would be interesting to investigate whether other cardiovascular risk factors or known markers for reduced cardiovascular function can further improve the prediction of pregnancy disorders before or during early pregnancy.

Prediction and prevention of cardiovascular disease
Another important opportunity to improve health outcomes, is through better identification, monitoring and potentially treatment of those that fail the stress-test of pregnancy and thus are at increased risk for CVD later in life. Based on the evidence of increased cardiovascular risk among women with a history of pregnancy disorders, most professional bodies of obstetricians, general practitioners and cardiologists nowadays emphasise the need for systematic follow-up in these women after pregnancy. However, uniform recommendations are lacking.\(^43-46\) Underlying this lack of uniform recommendations is the paucity of evidence on optimal timing and method of follow-up, and on effective CVD risk reduction programmes. Specifically, the potential value of obstetric history as predictor of CVD risk above and beyond conventional predictors is being debated, with some recent studies showing no or only small improvements to CVD risk prediction.\(^47-49\) Further research is needed on whether and how obstetric history should be incorporated into cardiovascular risk management (CVRM) for women alongside other risk factors.
COGNITIVE DEVELOPMENT OF THE OFFSPRING

Beside the impact on maternal long-term health, pregnancy disorders have also been associated with a large range of long-term health and development problems in the offspring, including increased risks of respiratory, neurological and behavioural problems. A considerable part of these are thought to be mediated through gestational age at delivery: it is the (relative) immaturity at birth as a result of the underlying condition that causes many of the known problems, including in neurocognitive development. Additionally, deprivation in utero as a result of placental insufficiency is thought to influence brain development and induce cardio-metabolic changes, contributing to decreased neurocognitive development and increased cardiovascular risk later in life, respectively.¹⁸, ⁵⁰

Over the past two decades, extensive research has been conducted on the association between preterm birth and neurocognitive development of the offspring. As the brain continues to grow and develop in utero until full gestation, increasing gestational age at birth has been associated with higher academic achievement. The impact is largest among those born early preterm, but the association persists until 40-41 weeks.⁵¹-⁵³ This is interesting in light of the recent trend towards more and earlier induction of labour, leading to more (relative) prematurity, including among relatively uncomplicated pregnancies. Yet, long-term outcomes of labour induction have rarely been studied. Additionally, many biological and environmental factors, such as parental education level and socioeconomic status, have an important influence on school performance, and the interaction between gestational age and these factors for neurocognitive development are understudied.⁵⁴

The association between FGR and neurocognitive development has been studied considerably less than that of preterm birth. Previous research showed reduced academic achievement in children that were born SGA.⁵⁵-⁵⁷ However, FGR is not confined to those below the 10th birthweight centile and further research is needed to get a better understanding of the potential impact of FGR on academic achievement.

AIMS OF THE THESIS

This thesis focuses on two aspects of health beyond pregnancy: maternal cardiovascular health in multi-ethnic populations (part I) and offspring cognitive development (part II).

Part I explores the association between pregnancy disorders and maternal cardiovascular health in multi-ethnic populations. It aims:
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- to provide insight into the association between pregnancy disorders and cardiovascular risk across ethnic groups, and to explore the potential role of ethnicity in this association;
- to improve prediction of pregnancy disorders, before conception or during early pregnancy, based on cardiovascular profile within multi-ethnic populations; and
- to improve prediction of cardiovascular risk within multi-ethnic populations based on history of pregnancy disorders.

Part II explores the association between different pregnancy disorders and offspring academic performance. It aims:

- to provide insight into trends in spontaneous and iatrogenic preterm birth in a high-income country and the association between absolute or relative preterm birth and school performance at age 12, in itself and in relation to sociodemographic factors; and
- to provide insight into the association between birthweight for gestational age — as a proxy for fetal growth and placental function — and school performance at age 12.

DATA USED IN THE THESIS

For part I of this thesis, we use data from the prospective Healthy Life in an Urban Setting (HELIUS) study and data from the national Dutch perinatal registry (Perined). The HELIUS study is a multi-ethnic prospective cohort study conducted in Amsterdam, the Netherlands.\(^58\) Aim of the HELIUS study is to investigate the causes of (the unequal burden of) diseases across ethnic groups. Baseline data collection took place between 2011 and 2015 and included 24,789 persons aged 18-70 years from six ethnic groups (Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish and Moroccan origin). Data of the female participants that provided permission for data linkage were linked in the secure research environment of Statistics Netherlands to data on pregnancies between 2000 and 2019 as registered by Perined. Perined registers data on pregnancy, delivery and neonatal outcomes; 97% of deliveries in the Netherlands are included.\(^59\) The linkage between data from the HELIUS study and Perined data resulted in two (partly overlapping) cohorts that were used in this thesis: a cohort of 3034 women with ≥1 pregnancy of ≥24 weeks of gestation between 2000 and 2019 as registered by Perined, and a cohort of 1208 women with ≥1 pregnancy of ≥24 weeks of gestation between inclusion in the HELIUS study and 2019.
For part II of this thesis, we use perinatal registry data from the Australian Victorian Perinatal Data Collection (VPDC; 2007-2017), Perined (1999-2008) and Statistics Netherlands (2006-2019). The VPDC collects data on all births in the state of Victoria, Australia, at ≥20 or weeks of gestation or, if gestation is unknown, with a birthweight of ≥400 grams. Statistics Netherlands stores all registry data collected by the Dutch government and many public bodies, including data on school performance. Data from Perined was linked to data on school performance in the secure research environment of Statistics Netherlands using deterministic linkage. Further details of the (linked) datasets are described in the relevant chapters.

OUTLINE OF THE THESIS

Part I – Pregnancy disorders and maternal cardiovascular health across ethnic groups
The first part of the thesis focuses on maternal cardiovascular health in multi-ethnic populations and consists of four chapters, each describing a different aspect of the interaction between pregnancy and maternal cardiovascular health. Chapter 2 provides an overview on current literature on ethnic differences in both HDP and in relative risk of cardiovascular risk factors after HDP. Chapter 3 describes the protocol of the HELIUS-Perined study, the data-linkage study that is the basis of chapter 4 and 5 of this thesis. Chapter 4 describes the association between preconception lipid profile and the prevalence of pregnancy disorders in subsequent pregnancies among women of the HELIUS-Perined study. Finally, in Chapter 5, the association of different pregnancy disorders with cardiovascular risk profile up to 15 years after pregnancy is studied among women of the HELIUS-Perined study from different ethnic groups, and the predictive ability of these pregnancy disorders above traditional risk factors for CVD is explored.

Part II – Pregnancy disorders and offspring cognitive development
The second part of the thesis, consisting of five chapters, focuses on offspring cognitive development. Chapter 6 and Chapter 7 describe trends in spontaneous and iatrogenic preterm birth in relation to perinatal mortality rates in singleton and twin pregnancies between 2007 and 2017 in Victoria, Australia. In Chapter 8 the association between gestational age, sociodemographic factors and school performance at the age of 12 years is explored. Chapter 9 studies the association between induction of labour and school performance at the age of 12 years among uncomplicated near-term and term pregnancies. Finally, Chapter 10 describes the association between birthweight for gestational age and school performance at the age of 12 years.
REFERENCES


General introduction
PART I

PREGNANCY DISORDERS AND MATERNAL CARDIOVASCULAR HEALTH ACROSS ETHNIC GROUPS