Beyond pregnancy: long-term maternal and offspring health implications of pregnancy disorders
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CHAPTER
11
Pregnancy and childbirth have a long-term impact on both maternal and offspring health. Despite increasing knowledge on this topic, healthcare and research to date mostly focus on instant and short-term risks and outcomes, thereby missing opportunities to positively impact long-term maternal and offspring health. This thesis described several long-term consequences of pregnancy disorders for maternal and offspring health, and explored windows of opportunity pregnancy offers. It focused on two aspects: maternal cardiovascular health (part I) and offspring cognitive development (part II).

PART I - PREGNANCY DISORDERS AND MATERNAL CARDIOVASCULAR HEALTH ACROSS ETHNIC GROUPS

The first part of this thesis aimed to provide insight into the association between different pregnancy disorders characterised by uteroplacental dysfunction and cardiovascular risk in multi-ethnic populations and to improve the prediction of pregnancy disorders characterised by uteroplacental dysfunction and CVD after a complicated pregnancy.

In Chapter 2, we summarised current literature on ethnic differences in both HDP and in relative risk of cardiovascular risk factors after HDP. We identified an increased prevalence of chronic hypertension, (superimposed) preeclampsia and eclampsia among Hispanic and non-Hispanic Black women compared to non-Hispanic White women in most studies. However, rates of gestational hypertension and overall HDP were similar or even lower in these ethnic groups. Women from East Asian, Southeast Asian, North African or Middle Eastern origin seemed at decreased risk for HDP compared to non-Hispanic White women. HDP was consistently associated with increased CVD risk across racial and ethnic groups in the reviewed literature, but head-to-head comparisons of different ethnic groups were scarce and evidence contradictory. We concluded that the body of evidence is yet insufficient to draw conclusions on the role of ethnicity in the association between HDP and CVD. Further studies, preferably prospective, on potential differences and their etiology are required.

In Chapter 3, we outlined the ongoing HELIUS-Perined study. The HELIUS-Perined study is a ZonMw funded data-linkage study on the association between pregnancy disorders characterised by uteroplacental dysfunction and cardiovascular disease among women from different ethnic backgrounds. It links data from approximately 11,000 women of Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish and Moroccan origin who participated in the prospective HELIUS study, to national registry data on pregnancy and birth outcomes (Perined). The HELIUS study collected extensive (cardiovascular) health data between 2011 and 2015. Additionally, follow-up data was collected between 2019 and 2022. Multiple research questions have been formulated within the HELIUS-Perined study. Results of two of these research
questions are described in chapter 4 and 5 of this thesis. Further results will be published later.

In Chapter 4, the association between preconception lipid profile and pregnancy disorders characterised by uteroplacental dysfunction in subsequent pregnancies among women of the HELIUS study is described. Additionally, the potential value of lipid profile for the identification of women at high risk for uteroplacental dysfunction in addition to the NICE guideline criteria and EXPECT prediction tool for the prediction of preeclampsia is explored. We included 1177 women of Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish and Moroccan origin who had at least one pregnancy between inclusion in the HELIUS study and 2019. Preconception triglyceride level was associated with increased prevalence of HDP, adjusted for demographic, lifestyle and medical characteristics. Age-adjusted prevalence of HDP was also higher among women with high LDL-C level, high TC/HDL-C ratio or with ≥4 adverse lipid parameters, but most of these findings were not statistically significant after adjustment. Addition of triglyceride level and other lipid parameters to the NICE guideline criteria and to the EXPECT prediction tool did not improve discriminative ability for HDP, preterm birth or fetal growth restriction. We concluded that preconception lipid profile did not aid in the identification of women at high risk for disorders of placental dysfunction. Further studies are needed to improve preconception prediction models for HDP and other pregnancy disorders characterised by uteroplacental dysfunction using serum biomarkers or other easily available measurements.

Finally, in Chapter 5, we described the association of different pregnancy disorders with cardiovascular risk profile up to 15 years after pregnancy, and explore the predictive ability of these pregnancy disorders above traditional risk factors for cardiovascular disease. We included 2455 women of Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish and Moroccan origin who participated in the HELIUS study, and who had at least one pregnancy before inclusion. History of HDP and preterm birth were associated with higher prevalence of chronic hypertension and chronic kidney disease across most groups (PR 1.6-1.9). Gestational diabetes mellitus was associated with increased type 2 diabetes mellitus risk, particularly in ethnic minority groups. While PRs ranged from 4.5 to 7.7, associations did not significantly differ across ethnic groups. The prediction models did not improve substantially after adding pregnancy disorders to traditional eligibility criteria for CVD risk screening. We concluded that addition of pregnancy disorders to traditional eligibility criteria for CVD risk screening does not substantially aid in the prediction of CVD risk factors if uptake of protocolised screening is high. However, pregnancy disorders may function as a red flag for both healthcare professionals and patients to ensure timely screening, specifically if general uptake of screening is low.
PART II – PREGNANCY DISORDERS AND OFFSPRING HEALTH & DEVELOPMENT

The second part of this thesis aimed to provide insight in the association between different pregnancy disorders and offspring cognitive development.

In Chapter 6, we described the trends in spontaneous and iatrogenic preterm birth in relation to perinatal mortality rates in singleton pregnancies. We conducted a consecutive cross-sectional study among 811 534 women with a singleton pregnancy who gave birth at ≥20 weeks of pregnancy in Victoria, Australia, between 2007 and 2017, inclusive. Total preterm birth rate increased from 5.9% to 6.4% due to an increase in iatrogenic preterm birth from 2.5% to 3.6%. Comparable trends were seen in pregnancies complicated by SGA and hypertension and in pregnancies not complicated by SGA, hypertension, pre-eclampsia or prelabour rupture of membranes (PROM). In pregnancies complicated by SGA, hypertension, preeclampsia or PROM the perinatal mortality rate from 20 weeks of gestation significantly declined (13 to 12 per 1000 births). In pregnancies not complicated by SGA, hypertension, (pre)eclampsia or PROM, there was no significant change in the perinatal mortality from 28 weeks and no decrease in the preterm weekly prospective stillbirth risk. These results stress the need for an ongoing debate and research on optimal timing of delivery, including in singleton pregnancies not complicated by SGA, hypertension, (pre)eclampsia or PROM.

In Chapter 7, we described the trends in spontaneous and iatrogenic preterm birth in relation to perinatal mortality rates in twin pregnancies. We included 12 757 women with a twin pregnancy who delivered at ≥20 weeks of gestation in the state of Victoria, Australia between 2007 and 2017. The preterm birth rate increased from 52% to 69% between 2007 and 2017, mainly due to an increase in iatrogenic preterm birth from 28% to 49%. This was irrespective of the presence of pregnancy disorders. Our study showed neither a decrease in perinatal mortality from 28 weeks of gestation nor in preterm average weekly prospective stillbirth risk. These results are in line with findings among uncomplicated singleton pregnancies, and highlight the need for further research and dialogue on optimal timing of delivery for complicated and non-complicated twin pregnancies.

In Chapter 8, we explored the association between gestational age, sociodemographic factors and school performance at the age of 12 years among 860 332 liveborn singletons born in the Netherlands between 1999 and 2006 at 25-42 weeks’ gestation. Pregnancy data were collected from the national Dutch perinatal registry (Perined); school performance data was obtained from the national education registry (Statistics Netherlands). School performance increased with gestational age up to 40 weeks. This pattern was evident across sociodemographic strata. Children born at 25 weeks had 0.57 SD (95% CI 0.79, 0.35) lower school performance z-scores and lower secondary
school level compared to 40 weeks. Low maternal education, low maternal age and non-European origin were strongly associated with lower school performance. Being born third or later and low socioeconomic status (SES) were also associated with lower school performance, but differences were smaller than among other factors. When born preterm, children in socially or economically disadvantaged situations were at higher risk for lower school performance compared to children in more affluent situations (evidence of interaction), making them more vulnerable to the negative impact of preterm birth.

In **Chapter 9**, we studied the association between elective induction of labour and school performance at the age of 12 years among 226,684 liveborn children from uncomplicated singleton pregnancies (no hypertensive disorders, diabetes or birthweight ≤p5), born from 37\(^0\) to 42\(^0\) weeks of gestation in cephalic presentation in 2003-2008 in the Netherlands. Birth records from the national Dutch perinatal registry (Perined) were linked with national data on school achievement. For each gestational age up to 41 weeks, induction of labour was associated with decreased school performance scores compared with non-intervention (at 37 weeks 0.05 SD, 95% CI 0.10 to 0.01 SD; adjusted for confounding factors). After induction of labour, fewer children reached higher secondary school level (at 38 weeks 48% vs 54%; adjusted OR 0.88, 95% CI 0.82-0.94). Although analyses were adjusted for the most important confounders, residual confounding may remain. While the effect on the individual child is admittedly subtle, the societal impact due to the large number of early term labour inductions could be large. Clinicians should incorporate these long-term effects in counselling and decision making around elective induction of labour.

Finally, in **Chapter 10**, we described the association between birthweight for gestational age and school performance at the age of 12 years among 266,440 liveborn singletons from uncomplicated pregnancies, delivered between 36 and 42 weeks of gestation in 2003-2008. Mean school performance score (range 501-550) increased gradually with increasing birthweight centile, from 533.6 in the 1\(^{st}\)-5\(^{th}\) birthweight centile group to 536.8 in the 81\(^{st}\)-85\(^{th}\) birthweight centile group. Likewise, the proportion of children at higher secondary school level increased with birthweight centile from 43% to 57%. Compared with the 81\(^{st}\)-85\(^{th}\) birthweight centile group, mean school performance score and proportion of children at higher secondary school level were significantly lower in all birthweight centile groups below the 80\(^{th}\) centile, after adjusting for confounding factors. We concluded that birthweight centile is associated positively with school performance at 12 years of age across the entire birthweight spectrum, well beyond the conventional and arbitrary cut-offs for suspected fetal growth restriction. This underlines the importance of developing better tools to diagnose fetal growth restriction and reduced placental function, and to identify those at risk for associated short- and long-term consequences.