Hemodynamic adjustments during pregnancy

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Impact

This chapter addresses the possible impact and relevance of this thesis for our society. The general aim is to describe hemodynamic adjustments in normotensive and hypertensive pregnancy, and to propose strategies to optimize the use of maternal hemodynamic parameters in the prevention of gestational vascular complications, amongst preeclampsia, HELLP syndrome and foetal growth restriction, as current preventive measures fall short. In this chapter, the financial and social burden of preeclampsia are delineated as well as the potential financial and social gain that preventing this disease can achieve.

Preeclampsia, a hypertensive vascular disorder, complicates 4.6% (95% CI 2.7–8.2%) of all pregnancies worldwide.[1] In the Netherlands, 167.588 women delivered in the year 2019, meaning that over 7700 women recently experienced this gestational complication.[2] Incidences are on the rise, possibly as a consequence of increasing prevalence of cardiovascular risk factors among women in the reproductive age, including elevated BMI (and concurrent dyslipidaemia, glucose handling disorders and high blood pressure) and advanced maternal age at gestation.[2-4] Preeclampsia is a major cause of maternal and neonatal mortality and morbidity.[5] Remotely, it associates with early development of cardiovascular and metabolic diseases in affected women, and in their offspring in case of impaired foetal growth and preterm birth. To date, there is no definite treatment for preeclampsia other than delivery, with associated neonatal risks of iatrogenic preterm birth. In Western world countries, the direct medical care costs of a preeclamptic pregnancy can amount to €22.360 extra compared to an uncomplicated pregnancy.[6] Based on Dutch economic findings in a group of formerly preeclamptic women receiving comparable intensive outpatient follow up throughout gestation (€8047), accounting for the additional costs made for normogram-guided care (€336/pregnancy trajectory) and the reduction in clinical outcome made -preeclampsia (costs €3720), which is also the primary variable together with preterm birth on additional direct costs- this kind of care is estimated to be at least cost effective or even less expensive than current care.[7] On the short term, the primary drivers of the incremental costs are infant costs, especially in preterm and extreme preterm birth when admittance to a neonatal intensive care unit is necessary. These expenses neither include future costs to the healthcare system of preeclampsia-associated health problems for women and offspring, nor indirect costs and costs associated with lost productivity.

Effect on mental health

Pregnancies complicated by preeclampsia have great impact on physical and mental health of the parents, especially for the mother. Many women experience preeclampsia as a traumatic life event, particularly in preeclampsia with severe features necessitating hospital admission to an obstetric high- or intensive-care unit, combined with an

unexpected emergency delivery -often a ceasearean section- and birth of a premature child. This is possibly followed by admission of the neonate to the intensive care unit, or in the most severe cases, offspring handicap or infant loss. High levels of stress following this (severe) illness and/or adverse neonatal outcomes may develop into more severe psychological disorders, including post-traumatic stress disorder and depression, which, in turn affects cognitive functioning and well being.[8, 9] Physical and mental health complaints might interfere with resumption of everyday life, affecting work obligations, leisure activities and family commitments.[10]

In the research agenda of 2020-2023 of the NVOG (Dutch Society of Obstetrics and Gynaecology), the challenges in the development of preventive and treatment options for preeclampsia are outlined. The limited availability of predictors, and limited possibilities of early diagnosis are emphasized. This agenda suggests that future research should focus on unravelling the pathophysiologic pathways leading to preeclampsia and foetal growth restriction, determination of (bio)markers and imaging for early diagnosis, and to evaluate preventive and therapeutic interventions on maternal and offspring outcomes during pregnancy. This thesis is in line with these goals, with deviant hemodynamic adjustments in early pregnancy as contributor and impressionable factor. Deviant hemodynamic adjustments during pregnancy is assessable by monitoring cardiac output next to blood pressure measurements. To date, minimal- and non-invasive techniques are available to assess cardiac output in an outpatient obstetric clinic. We highlighted the USCOM, an efficient non-invasive method to determine cardiac output. Although absolute values of the USCOM are not interchangeable with values measured by transthoracic echocardiography, this 'point-of-care' method is a suitable and attainable option to get an impression of the hemodynamic balance in hypertensive pregnant women. The prospects of the use of the hemodynamic (im)balance to prevent preeclampsia are outlined in this thesis.

Personalized care

Personalized drug treatment in gestational hypertension is likely to improve obstetric outcomes. The study protocol in this thesis outlines a theoretical background of appropriate antihypertensive medication choice based on the hemodynamic parameters that determine blood pressure. Correcting the imbalance between cardiac output and total peripheral vascular resistance with appropriate counteracting drugs normalizing hemodynamic functioning may prevent disease evolvement from mild and moderate hypertension to severe hypertension and preeclampsia. Previous studies showed that improved blood pressure control in pregnancy is achieved when choice of medication is based on cardiac output.[11, 12] As cardiac output assessment is not yet standardly feasible in obstetric clinics, we also developed a treatment algorithm to personalize antihyper-

tensive treatment with readily available parameters (mean arterial pressure and heart rate). Pending the results of our randomized controlled trial with this treatment scheme, obstetricians may in ahead use the presented algorithm in daily clinical practice to make a more substantiated choice of antihypertensive agent in gestational hypertension.

In this thesis, we provide evidence that treatment of hemodynamic imbalances towards healthy, physiological hemodynamic values, even before blood pressure rises, substantially improved recurrence rates of preeclampsia and HELLP syndrome without any disadvantageous offspring effects. In-depth insight in timing and magnitude of physiological adjustments in cardiac output and peripheral vascular resistance is necessary to employ this strategy in daily clinical practice. Therefore, we executed a systematic review and meta-analysis to summarize all available data in current literature on hemodynamic parameters, and we provided reference values of physiological adjustments during pregnancy. We presented both mean difference relative to non-pregnant values and absolute hemodynamic values throughout gestation. The former makes usability in clinical practice method- and device-independent.

The experience of a complicated pregnancy influences couples' decision-making about future family planning. A first pregnancy complicated by preeclampsia results in lower rate of subsequent pregnancies compared to women without preeclampsia, although not in case of perinatal death.[13,14] Reasons for not achieving a subsequent pregnancy are fear of recurrent disease and preterm delivery. To date, available preventive measures, and optimal monitoring and intervention strategies in women at risk for this pregnancy complication are limited. Provided care-as-usual during pregnancy greatly depends on patients' preference and physicians' common practice. As a consequence, health care consumption in the subsequent pregnancy after early onset preeclampsia and/or HELLP syndrome greatly varies between individual cases, ranging between 5 and 37 outpatient visits.[7] Our presented cardiovascular monitoring and modification program during the subsequent pregnancy in formerly preeclamptic women not only reduces the incidence of recurrent preeclampsia, it also make the control frequency more uniform and predictable, and may improve feeling of control of the parents during the next pregnancy.

Dissemination

Various efforts to disseminate the knowledge gained from our studies to different target groups were initiated. All of the studies and the protocol presented in this thesis have been published in diverse international journals, and most of them as open access publications to spread the findings to the international research community and clinical practices. In addition, most findings have been presented at national and international conferences that hosted many physicians and researchers from the Netherlands and

across the globe. The systematic review and meta-analysis on hemodynamic adjustments during pregnancy is part of a designed series of reviews and meta-analyses on physiological adjustments of maternal cardiovascular and cardiometabolic parameters during pregnancy. Results of all review subjects are intended to be published in a reference book for (medical) students and specialists.

A non-pregnant cardiovascular and cardiometabolic risk factor assessment in Maastricht is accessible to all women in the country who experienced a pregnancy complicated by hypertension, preeclampsia and/or associated adverse events. From 2013 onwards, all these women are invited to participate in the -still ongoing- cardiovascular program during their pregnancy with modulation of deviant hemodynamic adjustments, in addition to regular care. More than half of the formerly preeclamptic women participating in this program are referred by physicians from other hospitals. Results of every single evaluation, and advices for pharmacological modulation of abnormal hemodynamic adjustments are explained to the parental couple and the referring physician. Therefore, many obstetricians in the country are informed about this early treatment strategy, and this is likely to enhance implementation of the program in other hospitals. Moreover, one of the women participating in the cardiovascular program during pregnancy was reported for the television program “Dokters van Morgen” (*Physicians of Tomorrow*), which was broadcasted on national television in November 2020. In this program, innovations and new insights in health care are highlighted, and the program was selected for the hypertension episode. Every other year, our research group together with patient support group “Hart voor HELLP” organizes a patient conference, where results of our (ongoing) studies are elucidated. Unfortunately, the planned conference for 2020 could not take place due to the regulations regarding the COVID-19 pandemic.

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