

Vascular and renal adjustments during and after preeclampsia

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CHAPTER 9

Valorisation

VALORISATION

This chapter addresses the relevance and possible impact of this thesis for society. In this thesis the objective was to provide more insight in maternal adaptation to pregnancy. Thereafter we discuss maladaptation during pregnancy and bring attention to possible long term consequences on vascular endothelial and kidney function as a result of a hypertensive complicated pregnancy.

SOCIETAL RELEVANCE

There are half a million maternal deaths worldwide related to pregnancy, of which 1% occurs in high income countries ¹. Preeclampsia, a hypertensive complicated pregnancy, occurs in 2 - 8% of all pregnancies. Interestingly, the proportion of maternal death directly related to preeclampsia is similar in high income compared to middle and low income countries. In the Netherlands, preeclampsia is the leading cause of maternal mortality ². It impacts maternal health and child's health and wellbeing, especially if the child is born prematurely. For many women, developing preeclampsia is generally an unexpected, difficult and traumatic life experience. This is particularly relevant if they felt ill, gave birth too early, or if their baby died. It is not surprising that preeclampsia, especially with secondary neonatal intensive care necessity, strongly links to post traumatic stress disorder and depression. Moreover, in presence or absence of psychological trauma, women often find difficulties to reintegrate in societal labour after giving birth.

Maternal cardiovascular adaptation during pregnancy can be suboptimal contributing in the development of a hypertensive complicated pregnancy. In conjunction with maternal characteristics, the placenta plays a pivotal role in the development of such a maladaptive pregnancy. During the disease state however, there are currently no curative treatment options available, but only symptomatic treatment to correct the underlying cardiovascular shortcomings, namely optimizing blood-pressure and -flow and protection from possible imminent seizures that can occur as a result of the disease.

Better understanding of the healthy adaptational process during pregnancy may result in future therapies targeted to improve maternal cardiovascular adjustments during the implantation and development of the placenta and possibly reduce penetrance of parallel maternal circulatory maladaptation. Consequently, the risk of later maternal and foetal complications may be reduced.

Adaptational changes supporting physiological pregnancy are not systematically taken into account. In order to facilitate nomogram guided care, we established reference values for both vascular endothelial function, expressed by flow mediated dilation, and kidney

function, expressed by glomerular filtration rate, to describe the normal physiological processes during pregnancy. These reference curves are based on current literature and improve our understanding of the females' adaptive capabilities during pregnancy. In these meta-analyses we highlight the maladaptive response in women with a hypertensive complicated pregnancy. Moreover, we set up an explorative study from which we concluded that women destined to develop a hypertensive complicated pregnancy exhibited a decreased adaptation of both cardiac and kidney function before the occurrence of disease. This indicates the possibility of using maternal haemodynamic maladaptation as an indication for an increased risk of a hypertensive complicated pregnancy. A non-physiological adaptive pattern detailed by serial measurements may therefore open up the possibility to institute tailored preventive measures before disease becomes apparent.

Recently the possible long term consequences of a hypertensive complicated pregnancy have been more in the scientific spotlight. The increased risk of cardiovascular and chronic kidney disease in these affected women have become more apparent, more accepted in medicine and integrated in guidelines. Several meta-analyses show this increased risk. Women with a hypertensive complicated pregnancy are at a 2 – 6 fold increased risk of future cardiovascular disease and a 3 - 7 fold increased risk of future kidney disease, depending on the severity of the disease hypertensive disease during pregnancy^{3,4}. It seems therefore relevant to understand why this increased risk is present and what, if any, the common pathways would be. The understanding of the system-biology towards disease might eventually provide possibilities to develop targeted therapies.

Three chapters in this thesis are dedicated to this particular understanding of possible correlations between a hypertensive complicated disease and cardiovascular and/or chronic kidney disease in later life. We brought attention to long term consequences on both vascular endothelial and kidney function and found that women with a history of preeclampsia have a decreased kidney function, expressed by loss of albumins in their urine. This indicates that a particular subset of woman is at risk of future kidney disease.

We also found that aging women independently of a hypertensive complicated pregnancy have stiffened brachial arteries along with increased vessel diameter, even though endothelial dependent vasodilation capacity remained intact. Age related arterial stiffening primarily seems related to emerging traditional cardiovascular risk factors and only partially to aging itself. This finding sheds a different light on the concept of vascular aging, as aging cannot be influenced, while the occurrence and development of traditional cardiovascular risk factors can.

A major problem in the prevention of cardiovascular disease has been the difficulty to identify individuals at risks at an early enough stage for them to benefit from interventions. Appropriate treatment, aimed at preventing progression of cardiovascular disease and risk factors, is important since blood pressure control, lifestyle advice and exercise can slow down or even reverse progression of cardiovascular disease. The current approach in the follow-up of women with a history of a hypertensive complicated pregnancy is not uniform or even, in most cases, recommended in healthcare communities. However, these women are at an increased risk and should therefore be monitored more closely. Changes in lifestyle and a healthy exercise pattern can be beneficial not only for the women with an increased risk but could also stimulate the whole family to lead a healthier life. A healthy life style is also beneficial for general health and can prevent or reduce the risk of other diseases as well.

A large cross-sectional study is still ongoing (titled Queen of Hearts) with the aim to improve diagnosis of early stages of cardiovascular disease in women, in the particular subset of women with a hypertensive pregnancy in their history. The main goal is to obtain biomarkers, based on pathogenesis of microvascular disease, which improve the early diagnosis of diastolic dysfunction and heart failure in women.

This thesis aimed to highlight the importance of a better understanding of the maternal adaptations during pregnancy and the possible long term effect of a hypertensive complicated pregnancy. By understanding the physiological adaptation to pregnancy we may eventually be able to reduce maladaptation leading to a hypertensive complicated pregnancy and to improve maternal health. More research is needed not only to improve understanding of adaptation but also to evaluate effectiveness and costs of such strategies.

DISSEMINATION AND TARGET

This thesis highlights a patient population that are young women, who are generally in good health except for a hypertensive complicated pregnancy in their history and are curious to know how this disease affects their cardiovascular risk. We have an obligation as physicians to inform women of this increased risk and to provide guidance on how to prevent and/or treat women affected. Recent changes in guidelines do help in the dissemination of this information to physicians and eventually to patients.

We have taken various efforts to ensure that the knowledge gained from our studies is spread across different target groups. Four out of six studies, described in this dissertation, have already been published in several international journals to spread the findings to the international research community. In addition, most findings have been presented at national and international conferences that hosted many researchers from across the globe. The findings discussed in this dissertation are relevant to multiple target groups. Firstly, researchers in the field of obstetrics, nephrology and general practitioners can benefit from the information in this thesis. Secondly, physicians may use nomograms to follow healthy pregnancy adjustments from adverse patterns.

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