Placental syndrome

Valorization

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This chapter describes the (future) valorization of this thesis. Valorization refers to the process of value creation from knowledge. This chapter depicts the potential impact of the research presented in this thesis and its societal and economic value.

Introduction

A healthy pregnancy is often taken for granted. Although most pregnancies indeed progress without complications and result in the delivery of a healthy child, a substantial number of women experience complications of pregnancy of varying clinical presentations and severity. There is a growing body of literature showing that many pregnancy complications are associated with disorders of the development of the placenta. The placenta is the temporary organ that joins the mother and fetus, transferring oxygen and nutrients to the fetus and permitting the release of waste products in the other direction. The different types of complications have been grouped together as 'placental syndrome'.

Placental syndrome is thought to result from defective development of placental villous and vascular structure, that is caused by maladaptation to pregnancy of certain maternal vessels, so-called spiral arteries. However, there still remains much to be elucidated regarding the developmental mechanisms of placental syndrome and how these are linked to the spectrum of clinical presentations.

Relevance

Placental syndrome accounts for roughly 15-25% of pregnancies and is an essential cause of both maternal and perinatal morbidity and mortality. Currently, treatment is targeted on control of maternal symptoms and monitoring fetal wellbeing in order to reduce the risk of obstetric complications associated with the syndrome by appropriate timing of the delivery. To date the only curative treatment is delivery of the placenta, which invariably implies iatrogenic, and frequently premature, delivery. Iatrogenic premature delivery constitutes a huge challenge to modern health economic systems and carries the additional burden of short-term neonatal morbidity and mortality and the long term cardiovascular and metabolic risks for both mother and offspring. By unravelling the pathophysiology of placental syndrome, doctors will be triggered towards earlier detection of symptoms and swifter initiation of treatment to minimize the rate of complications. Subsequently, the duration and scale of hospital admissions can be reduced resulting in decreased costs.

Furthermore, women developing placental syndrome during pregnancy have an increased risk for developing cardiovascular disease in later life. Pregnancy, in this respect, should be regarded as a 'stress test' for cardiovascular risk. When several clinical diseases within

the placental syndrome spectrum occur simultaneously (e.g. preterm birth, fetal growth restriction and preeclampsia) the risk of developing later ischemic heart disease is even seven times greater than in women with a normal pregnancy.

The results in this thesis show that women developing placental syndrome demonstrate increased circulating biomarkers for endothelial dysfunction already in the first half of pregnancy. Endothelial dysfunction represents an early stage of atherosclerosis and is therefore an important prognostic marker for cardiovascular disease. Thus, the results do not only provide directions to detect placental syndrome early in pregnancy, but also emphasize the connection between placental syndrome and (future) cardiovascular disease. In addition, this thesis provides an overview of the current knowledge of the etiology of placental syndrome which connects preexisting endothelial dysfunction to spiral artery maladaptation, and the latter to altered development of fetal vessels in the placenta.

Target group

The target group of this research consists namely of pregnant women with a previous history of placental syndrome, since recurrence risk is up to threefold increased in women with a previous pregnancy complicated by placental syndrome. Yet, the results of this research are also relevant to women who are pregnant for the first time and who, based on their cardiovascular or metabolic risk profile, would be considered as a high-risk population to develop obstetric complications.

The past few years approximately 170,000 babies are born annually in the Netherlands. Of these pregnancies about 25,000-42,000 women (15-25%) develop placental syndrome. Although some of these pregnancy complications are recurrences, it can be estimated that annually at least 25,000 new women develop an increased cardiovascular risk. However, currently our health care does not act upon the increased risk in these women.

Implications for health care

The primary aim of this research is to gain more insight into the pathophysiology of placental syndrome, which remains largely elusive. Placental syndrome consists of many different clinical entities, and even within these separate entities recent studies have implicated different etiologies. In preeclampsia, for example, there is growing conviction among researchers that there are two types: an early-onset and a late-onset type, depending on the timing of clinical disease onset during pregnancy. It is believed that the early-onset type is associated with fetal growth restriction and is caused by spiral artery maladaptation and defective placentation, while the late-onset type runs a milder course and is associated with normal sized babies and no or mild placental dysfunction. In conjunction, we use the term 'early placental syndrome' in parts of this thesis to emphasize the difference between the two types.

We hypothesize that the difference in clinical entities can be largely explained by a combination of the severity of spiral artery maladaptation and subsequent defective placentation with pre-existing maternal cardiovascular risk factors. Interestingly, spiral artery maladaptation predisposes to a lesion called acute atherosis, which is histologically similar to early atherosclerotic lesions. After a pregnancy complicated by (early) placental syndrome, the cardiovascular risk increases and leads to earlier development of cardiovascular disease years after this pregnancy. In this way, pregnancy is a women-specific cardiovascular stress-test. Currently, more women than men die of cardiovascular disease. In fact, cardiovascular diseases are the leading cause of death for women, being responsible for more deaths than cancer (including breast cancer), chronic respiratory disease, Alzheimer disease, and accidents combined. The primary cause of cardiovascular disease in women is coronary artery disease, in which the formation of atherosclerotic plaques in the coronary system of the heart is the principal manifestation. It starts with asymptomatic plaques that progress over the years to form symptomatic plaques, eventually leading to coronary occlusion. Disturbingly, most women who die suddenly of coronary artery disease have no previous symptoms. We find it regretful that in current practice, obstetric history is generally not taken into consideration when assessing women's cardiovascular risk, and we hope that our research will encourage health professionals to do so in the future.

Future implications for health care: PEARLS study

The insight gained from our current research into the relationship between placental syndrome and cardiovascular risk has led to the conception of the "PEARLS" (**P**lac**E**ntal **A**cute atherosis **R**ef**L**ecting **S**ubclinical atherosclerosis) study. This study received medical ethical approval has already been provided (NL52556.068.15/METC152019) and is funded with an amount of €73,840 by means of crowd funding supported by the Dutch heart association ("hartstichting"). This study is scheduled to start end of 2018 and aims to recruit 246 women over a period of 36 months at Maastricht University Medical Center+ (MUMC+) to evaluate the possibilities of the placenta as an accurate women-specific cardiovascular screening tool.

We hypothesize that acute atherosis in women mirrors atherosclerosis in other vascular beds and therefore the placenta is a valuable organ to examine histologically to assess the clinical status of her cardiovascular system and her personalized risk for cardiovascular disease later in life. Women who develop preeclampsia will be prospectively included to the study and compared to healthy pregnant women. At delivery, the placenta will be collected and histologically examined for the presence of acute atherosis in the maternal vessels. One year after delivery, women will undergo vascular assessments to assess early stages of atherosclerosis. We will investigate whether the presence of acute atherosis is an accurate screening tool for the presence of early atherosclerosis. In this way, tailored screening and preventive strategies can be developed.

The novel aspect of this project is that examining the vasculature of the placenta to determine a women's risk for coronary artery disease later in life has, to our knowledge, not been carried out before. The placenta is a relatively easy to investigate organ, which is often discarded after delivery and its examination imposes no further burden for the woman. Therefore, the PEARLS study will enable us to make a critical step towards studying the link between clinical pregnancy outcome and cardiovascular risk, and will add significantly to the current cardiovascular screening programs in women.

If our study demonstrates positive results, the evidence will drastically change classical cardiovascular risk assessment in women. In case the placental histological findings correlate with systemic plaque formations as an early marker of atherosclerosis, this finding will not only affect individuals' awareness (both for patient and doctor), but also fortify individual's motivation towards healthier lifestyle. In women's health, shallow awareness has been proven to negatively affect cardiac disease prognosis. As such, this study will tremendously affect clinical practice if the hypothesized relation exists. Examining placentas histologically post-partum may become the next community-based screening method for women and make the large step in early detection and prevention in cardiovascular disease as has been made in the 90's for breast cancer. Furthermore, this study will be a solid base for future grant applications such as the Netherlands Organization for Scientific Research (NOW) or local initiatives of MUMC+.