MANUSCRIPT

Postpartum Cardiovascular Risks: Hemodynamic and Endothelial Dysfunction

Cheyenne McBane
Independent Researcher

Pregnancy causes major cardiovascular physiological changes, such as an increase in blood volume and cardiac output, along with a drop in systemic vascular resistance and cardiac remodeling. Though most women experience some level of recovery after birth, a small number of women, especially those who developed gestational hypertension, preeclampsia, or gestational diabetes, show signs of long-term cardiovascular disease. Compared to the rest of the population, those who had these issues are more likely to suffer from cardiovascular disease due to the disruption of the endothelium process, vascular stiffness, and subclinical heart remodeling.

It is my assumption that the reason behind postpartum cardiovascular dysfunction is persistent injury to endothelium combined with oxidative stress and imbalance of pro-and anti-angiogenic agents. Dysregulation of endothelium and stress in blood vessels can be tracked for up to one year after giving birth based on circulating levels of inflammatory agents (IL-6, TNF-α, hs-CRP), parameters of endothelium malfunction (VCAM, ICAM, endothelin), angiogenesis factors (sFlt-1, PlGF), and indicators of oxidative stress (MDA, IMA). To test this hypothesis, I propose the longitudinal cohort study based on the comparison of women with non-complicated and complicated pregnancies using echocardiography for heart function monitoring, vascular tests and biomarker evaluation procedure up to the postpartum period of one year.

Endothelial dysfunction

Oxidative stress

Postpartum cardiovascular risk

Cardiac Remodeling

INTRODUCTION

A pregnant woman's body undergoes substantial hemodynamic adaptation because of the numerous demands that a growing baby will put on her heart. Pregnant women may experience as much as a 50% increase in blood volume, an increase in the amount of blood pumped from their heart (cardiac output), and a decrease in the resistance of their blood vessels to the movement of blood through them (systemic vascular resistance). In order to accommodate these significant increases in cardiac and vascular load, the structure and function of the heart and blood vessels will undergo considerable changes, which includes physiological cardiac hypertrophy and remodelling of the vascular system. It is expected that the majority of these changes will return to normal, or pre-pregnancy, levels through spontaneous regression after childbirth. Cardiovascular function usually returns to pre-pregnancy levels within months after delivery.

Increasing numbers of studies have shown that about 20% of women will not completely recover the cardiovascular function that they had before becoming pregnant, even after delivering. Women who have developed chronic or recurrent conditions such as pre-eclampsia, gestational hypertension or gestational diabetes will often have documented persistent endothelial dysfunction, increased arterial stiffness, and abnormal cardiac remodelling. These are all shown to substantially increase the risk of developing hypertension, coronary artery disease (CAD), heart failure (HF), and multiple other cardiovascular disorders throughout one's lifespan.

The hemodynamic burden associated with pregnancy creates a substantial amount of hemodynamic stress on the female heart and vascular system. For some women, persistent maladaptive responses to the increased haemodynamic burden of pregnancy will be exacerbated by the presence of chronic low-grade inflammation and oxidative stress. The continued development of initial vascular injury and endothelial dysfunction will thus contribute to the ongoing dysregulation of blood pressure and thus maintain cardiovascular homeostasis. Identifying how the above-mentioned mechanisms work is extremely important in identifying potential candidates (women) who may be at risk of developing cardiovascular disease in the future, as well as for developing early-intervention strategies for cardiovascular disease. The current study will utilize a variety of techniques, including non-invasive imaging techniques, vascular functioning tests, and circulating biomarker evaluation, to investigate postpartum recovery from cardiovascular disease by determining whether persistent cardiovascular abnormalities can be identified in postpartum women (new mothers).

THE HYPOTHESIS

Following parturition, cardiovascular parameters typically regress toward baseline. Some physiological adaptations that took place throughout the duration of your pregnancy included increased blood volume, elevated cardiac output, and reduced vascular resistance, including

reversible changes in both the heart muscle and blood vessels (the cardiovascular system). Most of these changes are thought of as normal physiological adaptations that occur during pregnancy.

This research proposes that incomplete regression of pregnancy-related cardiovascular changes can create an "endothelial dysfunction," increase arterial stiffness, and cause maladaptive cardiac remodeling contributing to increased cardiovascular workload during the postpartum phase. Women who experienced complications during pregnancy may have evidence of persistent left ventricular hypertrophy, mild diastolic dysfunction, and compromised endothelial function that will create an increase in cardiovascular workload in the long run. Moreover, ongoing inflammation and oxidative stress may continue to damage the endothelium (the inner lining of blood vessels) and vasculature (blood vessels) postpartum, leading to chronic modifications in the regulation of blood flow. These mechanisms may provide a biological rationale for the established connection between poor outcomes in pregnancy and an increased likelihood of developing cardiovascular disease in the future.

EVOLUTION OF HYPOTHESIS

To test the hypothesis about recovery of cardiovascular function after childbirth in women, we will conduct longitudinal research to evaluate this recovery over time. We will do this through a prospective cohort study comparing women who had pregnancies with complications (i.e., pregnancy-induced hypertension) with those who had otherwise uncomplicated pregnancies. Participants will have serial evaluations of their cardiovascular structural (i.e., heart size) and functional (i.e., how well a woman’s heart is working) characteristics at various time points following childbirth.

Non-invasive imaging techniques (e.g., echocardiography) will be used to appraise the remodeling of a woman’s heart and how well it is pumping (i.e., ventricular performance), and testing will be done to evaluate the functioning of the vascular system (e.g., how healthy a person’s blood vessels are; how stiff a person’s arteries are) through testing of the endothelial cells and arteries, while serum samples will also be evaluated for circulating biomarkers associated with inflammation, oxidative stress, and vascular injury. By integrating these three sets of outcomes, we will be able to assess for continued deviations from normal cardiovascular recovery after childbirth. The vascular function will be evaluated through the evaluation of the endothelial's status and evaluation of arterial stiffness; meanwhile blood will be collected and analyzed to evaluate a variety of circulating biomarkers providing information on the body's inflammatory response, contribution from oxidative stress, disruption of the angiogenic balance and evidence of vascular injury.

As such, it has been suggested that the inflammatory biomarkers interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a) and high-sensitivity C-reactive protein (hs-CRP) are associated with the activation of endothelial cells and progression of cardiovascular disease. Markers of endothelial cell dysfunction include vascular cell adhesion molecule-1 (VCAM-1),

intercellular adhesion molecule-1 (ICAM-1) and endothelin-1, which provide evidence to support the presence of vascular inflammation and the dysfunction of endothelium. In order to determine the status of the angiogenic balance, circulating levels of soluble fms-like tyr-ousine kinase-1 (sFlt-1) and placental growth factor (PIGF) will be assessed. Alterations in sFlt-1/PIGF ratio have been associated with endothelial dysfunction in women with preeclampsia. For the assessment of oxidative stress and the presence of oxidative damage/lipid peroxidation, biomarkers reflecting this condition include malondialdehyde (MDA) and ischemia-modified albumin (IMA). Together, proper measurement of vascular function, the presence of inflammatory biomarkers, and oxidative stress markers will provide insight into the biological mechanisms behind the continuation in a subset of women following childbirth.

In addition, we will conduct experimental studies using animal models with pregnancy-related hypertension to understand possible mechanisms that contribute to prolonged cardiovascular dysfunction following childbirth. These models will allow us to differentiate between reversible physiologic adaptations versus long-lasting structural and functional changes caused by pregnancy complications. Together, both the human studies and the animal studies will provide complementary support for the pathways linking pregnancy-related cardiovascular stress to the long-term risk of developing cardiovascular disease. These biomarkers were selected based on prior evidence linking them to endothelial dysfunction and long-term cardiovascular risk following hypertensive pregnancy disorders. Primary endpoints will focus on endothelial dysfunction (VCAM-1, ICAM-1), angiogenic imbalance (sFlt-1/PlGF ratio), and vascular function metrics, with inflammatory and oxidative stress markers serving as secondary mechanistic correlates.

HYPOTHESIS TESTING

Combining longitudinal human assessments with animal mechanistic studies, this research will explore postpartum cardiovascular risk. Cardiovascular assessments will take place throughout the postpartum period, which allows researchers to examine the progression and resolution of endothelial dysfunction, arterial stiffness, and cardiac remodeling. Persistent abnormalities may present opportunities for early intervention through lifestyle changes, clinical follow-up, or pharmacotherapy. The research will combine imaging, vascular function, and biochemical measurement of cardiovascular recovery to identify early maladaptive recovery markers. Concurrent animal studies will provide mechanistic explanations for the human findings of the study and create opportunities to investigate therapeutic strategies to improve postpartum cardiovascular outcomes.

There are a number of potential limitations to consider. Variability in individual postpartum recovery will make it more difficult to establish the universal markers of dysfunction. Other confounding factors such as medications, breastfeeding, body mass index, and lifestyle and socio-economic factors can introduce variability and may even have an impact on

cardiovascular outcome. Another source of variability in the study is the technical limitations of non-invasive vascular imaging and echocardiographic strain measurements. In addition to these sources of variability, while animal studies provide important mechanistic insights, there are physiological differences between rodents and humans during pregnancy that limit the usefulness of the animal study data to predict human outcomes. In summary, observational studies allow us to find association as well as possible pathways but the true causal links in humans require additional interventional studies to establish.

The analysis of biochemical markers will provide evidence as to whether or not there is an ongoing process of inflammation, oxidative stress, activation of the endothelium and/or disruption of angiogenesis associated with continued cardiac dysfunction. The presence of elevated levels of IL-6, TNF-α and hs-CRP can support the occurrence of chronic low level inflammation within the body. The presence of elevated levels of VCAM-1, ICAM-1 and endothelin-1 can indicate that there is ongoing injury to the endothelium and disruption of the vascular endothelium. Abnormal sFlt-1/PlGF ratios would also suggest that there is continued disruption of cellular signalling pathways related to angiogenesis that have previously been associated with preeclampsia and/or vascular disease. The presence of elevated MDA and/or IMA levels will support the occurrence of oxidative stress and could help to explain the ongoing endothelial dysfunction and maladaptive remodeling of the cardiovascular system in some women postpartum.

Despite their limitations, expected outcomes will include; chronic endothelial dysfunction, maladaptive cardiac remodelling and hemodynamic parameter changes that likely explain the increased lifetime risk of cardiovascular disease in women who have had prior pregnancy complications. These findings will also inform future monitoring and treatment strategies for women with an increased risk of cardiovascular disease following pregnancy.

IMPLICATIONS

This research has the potential to greatly impact maternal health and cardiovascular medicine. Identification of chronic postpartum cardiovascular dysfunction may enable the formation of screening programs to identify high-risk women prior to the development of clinical cardiovascular disease. Identification of endothelial dysfunction, arterial stiffness, or cardiac remodeling may provide healthcare providers with the ability to implement prevention strategies at a time when the progression of disease may still be alterable.

A better understanding of the biological mechanisms linking pregnancy complications with future cardiovascular disease will help to improve risk stratification, and facilitate the development of targeted therapeutic approaches. The eventual integration of cardiovascular monitoring into routine postpartum care may ultimately result in a decrease in long-term cardiovascular morbidity and an increase in the quality of maternal health for those who suffer adverse pregnancy outcomes.

This research will also add to a growing body of evidence that pregnancy serves as a natural stress test for the cardiovascular system. Pregnancy complications such as preeclampsia, gestational hypertension, and gestational diabetes may help to uncover pre-existing susceptibility to cardiovascular disease, which otherwise might remain undetected until later in life. If habitual endothelial dysfunction and maladaptive cardiac remodelling can be detected shortly after the time of delivery, healthcare providers may be able to start treatment for years prior to the onset of clinically evident cardiovascular disease. Recognizing reliable indicators to identify longer-term effects of pregnancy on health, such as impaired postpartum recovery, can improve the quality of clinical decision-making. Then, providing healthcare professionals with biometrics related to inflammation, oxidative stress, and vascular injury can begin to be included in assessments and predictive tools of women's cardiovascular complications, allowing them to individually monitor their patients and better allocate preventive health resources.

In addition to their direct clinical use, these findings may provide future research support for investigations into sex-differentiated cardiovascular disease mechanisms. In the past, cardiovascular studies have centered on standard risk factors, so pregnancy-related variables have been significantly underserved. An improved comprehension of postpartum cardiovascular recovery could work to close this gap in knowledge and move towards creating a guide that includes women's reproductive history as a factor in assessing cardiovascular risk. In the end, these findings could promote a holistic strategy for improving women's cardiovascular health and wellbeing throughout the course of their lives.

CONCLUSION

A significant amount of cardiovascular changes occur in women over the course of their pregnancies. Most women return to pre-pregnancy states quickly after delivery. However, there is considerable evidence that some women have cardiovascular issues that persist into their postpartum period. The manuscript provides evidence that incomplete regression of cardiovascular system remodelling (rearrangement) due to pregnancy, along with ongoing issues with endothelial dysfunction (inside the blood vessel), inflammation, and oxidative stress (too many free radicals), contribute to the increased risk of developing disease in the long term.

The proposed hypothesis provides an avenue for exploring the biology behind the increased prevalence of hypertension, coronary artery disease, heart failure, and other cardiovascular related disorders in women who have experienced pregnancy complications later on in their lives. The persistent vascular dysfunction, abnormal cardiac structure, and abnormal hemodynamic (blood pressure) regulation associated with cardiovascular disease may be the beginning stages of the disease that begin during pregnancy or shortly afterwards, but are asymptomatic until much later in life. Through these studies done on humans and animals longitudinally, this research aims to identify the early indicators of maladaptive cardiovascular

recovery and define the biological pathways involved. This study will combine three different areas of interest: cardiovascular imaging, vascular function assessments, and biomarker analyses, and provide a comprehensive assessment of the cardiovascular health of postpartum women and the differences between normal recovery and persistent dysfunction.

Supporting the proposed hypothesis could create new possibilities for early screening, risk stratification, and preventative measures for postpartum women. Identifying individuals who have an increased risk of cardiovascular disease earlier can allow for the timely start of lifestyle modifications, medication, and long-term clinical monitoring. These interventions have the ability to reduce the morbidity associated with cardiovascular disease and improve the health outcomes of all women over their lifetimes. Through this research, I hope to help clarify how pregnancy affects cardiovascular disease in women. The identification of mechanisms that connect complications of pregnancy with future cardiovascular disease will enable the identification of more effective strategies for protecting the cardiovascular health of mothers and reducing the overall burden of cardiovascular disease in women.

REFERENCE

1. Afrose, D., Chen, H., Ranashinghe, A. et al. The diagnostic potential of oxidative stress biomarkers for preeclampsia: systematic review and meta-analysis. Biol Sex Differ 13, 26 (2022). https://doi.org/10.1186/s13293-022-00436-0.
2. Guerby P, Tasta O, Swiader A, Pont F, Bujold E, Parant O, Vayssiere C, Salvayre R, Negre-Salvayre A. Role of oxidative stress in the dysfunction of the placental endothelial nitric oxide synthase in preeclampsia. Redox Biol. 2021 Apr;40:101861. doi: 10.1016/j.redox.2021.101861. Epub 2021 Jan 19. PMID: 33548859; PMCID: PMC7873691.
3. Khan SS, Yee LM. Assessment for Long-Term Cardiovascular Disease Risk in Pregnancy. JAMA Cardiol. 2026;11(4):317–319. doi:10.1001/jamacardio.2025.5602.
4. Kim SY, Ryu HM, Yang JH, Kim MY, Ahn HK, Lim HJ, Shin JS, Woo HJ, Park SY, Kim YM, Kim JW, Cho EH. Maternal serum levels of VCAM-1, ICAM-1 and E-selectin in preeclampsia. J Korean Med Sci. 2004 Oct;19(5):688-92. doi: 10.3346/jkms.2004.19.5.688. PMID: 15483345; PMCID: PMC2816332.
5. Lazdam M, Davis EF, Lewandowski AJ, Worton SA, Kenworthy Y, Kelly B, Leeson P. Prevention of vascular dysfunction after preeclampsia: a potential long-term outcome measure and an emerging goal for treatment. J Pregnancy. 2012;2012:704146. doi: 10.1155/2012/704146. Epub 2011 Dec 8. PMID: 22175025; PMCID: PMC3235810.
6. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. Hypertension. 2011

Oct;58(4):709-15. doi: 10.1161/HYPERTENSIONAHA.111.176537. Epub 2011 Aug 15. PMID: 21844489.

7. Minhas AS, Ying W, Ogunwole SM, Miller M, Zakaria S, Vaught AJ, Hays AG, Creanga AA, Cedars A, Michos ED, Blumenthal RS, Sharma G. The Association of Adverse Pregnancy Outcomes and Cardiovascular Disease: Current Knowledge and Future Directions. Curr Treat Options Cardiovasc Med. 2020 Dec;22(12):61. doi: 10.1007/s11936-020-00862-6. Epub 2020 Oct 31. PMID: 35296064; PMCID: PMC8923621.
8. de Oliveira LG, Karumanchi A, Sass N. Pré-eclâmpsia: estresse oxidativo, inflamação e disfunção endotelial [Preeclampsia: oxidative stress, inflammation and endothelial dysfunction]. Rev Bras Ginecol Obstet. 2010 Dec;32(12):609-16. Portuguese. doi: 10.1590/s0100-72032010001200008. PMID: 21484030.
9. Petrozella L, Mahendroo M, Timmons B, Roberts S, McIntire D, Alexander JM. Endothelial microparticles and the antiangiogenic state in preeclampsia and the postpartum period. Am J Obstet Gynecol. 2012 Aug;207(2):140.e20-6. doi: 10.1016/j.ajog.2012.06.011. Epub 2012 Jun 11. PMID: 22840727; PMCID: PMC3432453.
10. Sánchez-Aranguren LC, Prada CE, Riaño-Medina CE, Lopez M. Endothelial dysfunction and preeclampsia: role of oxidative stress. Front Physiol. 2014 Oct 10;5:372. doi: 10.3389/fphys.2014.00372. PMID: 25346691; PMCID: PMC4193194.
11. Tyldum EV, Backe B, Støylen A, Slørdahl SA. Maternal left ventricular and endothelial functions in preeclampsia. Acta Obstet Gynecol Scand. 2012 May;91(5):566-73. doi: 10.1111/j.1600-0412.2011.01282.x. PMID: 21943052.