Cerebrovascular function in women with a history of hypertensive complications of pregnancy

by

Sarah Ann Fenn

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Britton C. Scheuermann, PhD

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Abstract

Background and Objective: Cerebrovascular function is fundamental to maintaining global brain health, supporting processes including cognition, emotion, memory, attention, and perception. Tight regulation of cerebral blood flow (CBF) is achieved through several intrinsic mechanisms, among which arterial carbon dioxide ($PaCO_2$) is the most potent modulator, particularly at the level of the cerebral microvasculature. Cerebrovascular reactivity (CVR) to CO_2 is widely used to assess vascular function; however, its characterization in certain high-risk populations remains limited. Preeclampsia (PE), a hypertensive disorder of pregnancy marked by systemic endothelial and microvascular dysfunction, is associated with increased long-term risk of cerebrovascular disease and cognitive decline. While impairments in cerebral macrovascular function have been reported in women with a history of PE, microvascular CVR remains incompletely understood in this population. Therefore, we aimed to determine whether women with a history of preeclampsia exhibit impaired cerebral microvascular reactivity compared to women with a history of uncomplicated pregnancy.

Methods: Women with a history of PE (n = 9) and normotensive pregnancy history controls (CON; n = 11), an average of 8 (range 2–24) years postpartum, were studied. Cerebral microvascular hemodynamics were assessed using near-infrared spectroscopy (NIRS) during repeated 30-second breath-hold maneuvers to induce hypercapnia. CVR was quantified as the change in total hemoglobin (THb) relative to changes in end-tidal CO_2 ($EtCO_2$, %). Cerebrovascular conductance index (CVCi) was calculated to account for changes in mean arterial pressure (MAP). As part of an exploratory analysis, a subset of participants performed a Valsalva Maneuver with measurement of middle cerebral artery velocity using transcranial

doppler ultrasound to assess cerebral autoregulation (CAi_{I-II}; CAi_{III-IV}) and indices of autonomic function.

Results: Baseline characteristics, including MAP, $EtCO_2$, and THb, were not different between groups ($p > 0.05$). Microvascular CVR did not differ between PE and CON ($p = 0.389$), and no group differences were observed in CVCi ($p = 0.724$). Exploratory analyses revealed no differences in cerebral autoregulatory indices or autonomic function ($p > 0.05$); however, cardiometabolic health - reflected by BMI and CVD risk factor burden - was significantly associated with CVR (BMI $p = 0.046$; CVD risk factor burden $p = 0.007$).

Conclusions: Contrary to our hypothesis, CVR to CO_2 is unaltered compared to controls in women several years following preeclamptic pregnancy. These findings suggest that PE alone may not result in persistent cerebrovascular dysfunction. This highlights the potential importance of cardiometabolic health and lifestyle factors compounded with aging and pregnancy history in shaping long-term cerebrovascular risk. Longitudinal studies are warranted to further define the trajectory of cerebrovascular function following PE and further elucidate the impact of postpartum cardiometabolic and lifestyle influences.

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Chapter 1 - Review of the Literature

Cerebrovascular Function: A Main Driver of Brain Health

The brain forms the basis of our perceptions, personhood, actions, motivations, and experiences that shape our life. It is approximately 2% of adult body weight, but commands 15% of cardiac output and 20% of resting total body oxygen consumption.[1] It is dependent on uninterrupted blood flow, as the brain lacks its own fuel supply and has constant high energy demands.[2] Drastic perturbations in blood flow cause irreversible neuronal damage; therefore, the brain has innate mechanisms to ensure maintenance of cerebral blood flow (CBF). The brain's vasculature plays a vital role in governing brain health, as the neuronal component of the brain commands the vasculature to maintain oxygen and substrate delivery, remove metabolic waste products, preserve acid-base balance, and buffer transmission of pressure to the delicate microvasculature.[3,4] There are five key mechanisms that regulate CBF; metabolic (in response to nerve cell activity), cerebral autoregulation (changes in vessel diameter in response to perturbations in arterial blood pressure), neurogenic control (cerebral sympathetic nerve activity), chemical perturbations (pressure of arterial carbon dioxide), and systemic changes (cardiac output). While all stimuli play important roles in regulating CBF, this review will focus on the chemical and autoregulatory components of CBF maintenance.

Cerebral Autoregulation

Briefly, cerebral autoregulation is the brain blood vessel's ability to regulate perfusion in the face of physiologic changes to arterial blood pressure.[5] This innate mechanism regulates CBF

during both steady state fluctuations in pressure - static cerebral autoregulation - and during transition phases that produce drastic swings in blood pressure -dynamic cerebral autoregulation.[6] Pressures outside the autoregulatory capacity, classically defined as ~60-160 mmHg, mean that cerebral perfusion becomes directly dependent on the driving force of mean arterial pressure (MAP), and render the brain at risk for hypo or hyperperfusion.[7] The governing equation, Q = MAP/R, depicts how cerebral autoregulation regulates brain blood flow (Q) to physiologic changes in perfusion pressure (MAP) by controlling cerebrovascular resistance (R) through vasodilation or constriction upon mechanical transmission of the pressure wave.[8] Cerebral autoregulation is highly dependent on autonomic neuroregulation; as the cerebral vessels are richly innervated by sympathetic and parasympathetic neurons[9], therefore autonomic function plays an innate role in maintaining CBF.[10]

Chemical Changes

The main focus of this review pertains to chemical control of CBF. Alteration in arterial PCO_2 is the most potent regulator of cerebrovascular tone, responsible for tightly regulating CBF.[11] The ability of the cerebrovascular bed to dilate or constrict and modulate CBF in response to changes in $PaCO_2$ (mm Hg) is termed cerebrovascular reactivity (CVR). Elevations in $PaCO_2$ cause the cerebral vessels to vasodilate, leading to increases in CBF, while the opposite – to a lesser degree – is true for reduction in $PaCO_2$.[11] To better understand this relationship, it is necessary to examine how changes in arterial carbon dioxide ($PaCO_2$) influence vascular reactivity, as cerebral vessels do not possess dedicated CO_2 receptors.

Increases in $PaCO_2$ elicit movement of CO_2 across the blood brain barrier (BBB). Once in the perivascular space – consisting of cerebrospinal fluid and neuronal cells – carbonic

anhydrase (H_2CO_3) catalyzes the breakdown of CO_2 and water to bicarbonate ($HCO3^-$) and hydrogen ions (H^+). This relationship between $PaCO_2$ and HCO_3- (equation 1) dictate the pH of the perivascular space, described by the Henderson Hasselback equation (equation 2).[12] Acidosis causes vasodilation of the vascular smooth muscle cells (VSMC) in the arterial wall, opening the potassium (K^+) channels (e.g., K_{ATP} and BK_{Ca} channels) causing an efflux of K^+. This hyperpolarizes the VSMC, actively inhibiting voltage gated calcium channels, decreasing intracellular calcium (Ca^+), leading to smooth muscle relaxation and ultimately, vasodilation.[13] This vasodilation leads to increased CBF.

Equation 1

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

Equation 2

$$pH = 6.1 + \log [HCO_3^-] * (0.03 \cdot PCO_2)$$

Measuring CVR provides insight on the function of the cerebral blood vessels that, as described previously, play an essential role in determining global brain health. Historically, CVR has been measured through various techniques, including magnetic resonance imaging (MRI)[14] or transcranial doppler (TCD).[15] Germaine to this review, TCD uses an ultrasound probe placed on the temporal window; a thin area of the skull that allows penetration of the ultrasound waves for visualization of the vasculature within the cranium.[16] TCD measures the velocity of blood flow through branches of the circle of Willis - the anterior, middle, and posterior cerebral arteries - whose branches perfuse a majority of the neuronal brain.[16-18] TCD-measured middle cerebral artery velocity (MCAv) has been used to quantify CVR in health, acute and chronic disease, aging, and exercise[15,19-22] and is an extensively used measure across diverse populations and

conditions. This makes TCD-measured MCAv a common, reliable, and reproducible measure of CVR.[23]

Until recently, there have been gaps in investigating non-traditional, female specific conditions that may impair cerebrovascular function through decreases in CVR. However, in 2018, Barnes and colleagues demonstrated that 35 years after pregnancy, women with a history of preeclampsia (PE) exhibit lower MCAv and impaired CVR in response to stepwise increases in $PaCO_2$, particularly in relation to changes in MAP - an index referred to as cerebrovascular conductance (CVC).[24] It is important to note, however, that the majority of cerebrovascular CO_2 reactivity occurs within the brain's microvasculature – the small arterioles and capillaries.[25] While Barnes' group demonstrated compromises in the MCA (a larger cerebral vessel) in women with a history of PE, measurement of the microvasculature has yet to be more fully elucidated. In this context, TCD has been used extensively to measure CVR. However, using near infrared spectroscopy (NIRS) to measure microvascular CVR is less common, but has been demonstrated to correlate with TCD measured CVR.[26] Our lab, as well as others, has utilized NIRS to measure CVR in health, disease, aging, and exercise[26-30] making this a suitable choice for investigating microvascular CVR in women with a history of PE.

In light of the importance of cerebrovascular function in maintaining brain health, the following section evaluates evidence indicating potential impairment in women who have experienced preeclampsia during pregnancy.

Pathophysiology of Preeclampsia: an Acute Insult that Leads to Chronic Morbidity

During Pregnancy

Pregnancy is a 9-month stress test as the women's body must adapt to support the growth and development of the fetus.[31,32] Upon conception, the bundle of cells called the trophoblast implants into the myometrial layer of the uterus; this signals the beginning of remodeling of the maternal vasculature. Narrow, tightly coiled spiral arteries in the uterus remodel to large "conduit" arteries that facilitate increases in blood flow to this new organ; the placenta. Peripheral vascular resistance drops and cardiac output increases to accommodate the increased need for blood flow and nutrients to the fetus and placenta.[33] In healthy pregnancy, systolic, diastolic, and mean arterial pressure decrease.[33]

Conversely, inadequate spiral artery remodeling increases uteroplacental vascular resistance and results in placental ischemia, a process described as small vessel dysfunction at the level of the uterus, termed maternal vascular malperfusion.[34] Reduced placental perfusion triggers a systemic pro-inflammatory cascade.[35] In response to hypoxia, the placenta generates reactive oxygen species, releases antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFLT-1) and soluble endoglin (sEng), and sheds damage-associated microvesicles into the maternal circulation. This leads to widespread endothelial injury and scavenging of vascular endothelial growth factor (VEGF).[36] This inhibits angiogenesis and capillary proliferation necessary for adequate perfusion and subsequently reduces systemic vascular resistance (SVR), which is primarily controlled by the small resistance vessels.[37]

Endothelial dysfunction promotes upregulation of potent vasoconstrictors, including endothelin-1 (ET-1) and angiotensin II (Ang II), further increasing SVR and blood pressure.[35]

Enhanced sensitivity to Ang II also promotes renal sodium and water retention, increasing fluid volume (stroke volume) and cardiac output.[31,35] Together, the conceptual equation for MAP ($MAP = Q \times SVR$) guides us in how these mechanisms elevate mean arterial pressure through concurrent increases in both cardiac output and vascular resistance. In summary, antiangiogenic signaling and oxidative stress reduce endothelial nitric oxide bioavailability, disrupt endothelial-dependent vasodilation, and promote microvascular rarefaction, further exacerbating maternal vascular resistance and end-organ damage.[38,39] This highlights that microvascular/endothelial dysfunction is at the center of the pathophysiology of preeclampsia, which disproportionately affects vulnerable microvascular beds - of utmost importance, the cerebral microvasculature.[40]

During preeclampsia, the inflammatory sequela of placental-derived oxidative stress, systemic inflammation, endothelial dysfunction, and severe hypertension promote breakdown of the delicate blood–brain barrier (BBB) by disrupting tight junctions within the cerebral endothelium.[41] Cerebrovascular endothelial injury impairs smooth muscle regulation, increases vascular resistance, and exposes the brain to elevated perfusion pressures that can damage microvessels, disrupting the key regulators of CBF - including autoregulation, CO_2 reactivity, and neurovascular coupling.[42,43] This microvascular dysfunction and increased BBB permeability allows fluid and circulating molecules to enter the cerebral interstitial and perivascular spaces, leading to vasogenic edema and elevated intracranial pressure.[44]

In preeclampsia, this cerebral edema compresses the brain within the rigid cranial skull and manifests as neurological symptoms such as headache, nausea, vomiting, cortical blindness, and seizures.[45] At this stage, preeclampsia poses a critical threat to the mother and fetus, as the risk of cerebrovascular complications—including stroke—is dangerously elevated in the peripartum period, particularly in the case of severe preeclampsia.[42,46]

Postpartum

While delivery presents its own physiological challenges beyond the scope of this review, it remains the only cure for the acute hypertensive, multi-organ crisis of preeclampsia. Historically, pregnancy and delivery have been viewed as the endpoint of maternal cardiovascular and cerebrovascular risk; however, growing evidence indicates that pregnancy represents only the beginning of a long-term trajectory of cardiometabolic and cerebrovascular risk, with physiological alterations persisting for years after delivery in women with a history of preeclampsia.[31,47-54] Despite this, postpartum care is often deprioritized, in part due to the demands of new motherhood and societal expectations for rapid recovery.[55] This "finish line" mentality may contribute to missed opportunities for early intervention and long-term risk reduction in this high-risk population.[32,56] In order to properly monitor and treat long term complications in women with a history of preeclampsia, we must first understand the persisting physiologic changes, especially to the brain.

In the years following pregnancy, women with a history of preeclampsia exhibit an increased risk of long-term systemic vascular, and endothelial dysfunction[52,57-60], observed from months to years postpartum. Compounding with vascular abnormalities, women with prior preeclampsia face a substantially elevated risk of chronic cardiometabolic disease, facing a fourfold higher risk of chronic hypertension and heart failure and a threefold increased risk of type 2 diabetes mellitus.[61-64]

This systemic vascular dysfunction extends to the cerebrovascular system, while adverse cardiometabolic health further heightens risk for cerebrovascular decline. Women with a history of preeclampsia demonstrate smaller brain volumes and a greater prevalence of white matter lesions—hallmarks of cerebral small vessel disease—as well as increased risk of ischemic and

hemorrhagic stroke, and vascular dementia.[43,65] In addition, cerebrovascular reactivity at the level of the MCA has been shown to decline in postmenopausal women with prior preeclampsia[24], and recent evidence indicates that blood–brain barrier leakage may persist years after the affected pregnancy.[66]

Although structural brain changes and large-vessel cerebrovascular dysfunction have been documented in women with a history of preeclampsia[24,67,68], direct assessment of microvascular CVR in this population remains a critically underexplored area.

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Chapter 2 - Cerebrovascular Regulation in Women with a History of Preeclampsia

Abstract

Background and Objectives: Preeclampsia (PE) is a hypertensive disorder of pregnancy associated with increased long-term cerebrovascular dysfunction, including stroke and cognitive decline. While prior studies demonstrate impairments in cerebral macrovascular function in women with a history of PE, cerebral microvascular reactivity, particularly CO_2-mediated vasodilation, has not been directly assessed in this population. Given the critical role of the cerebral microcirculation in regulating cerebral blood flow and maintaining brain health, we aimed to determine whether women with a history of PE exhibit impaired cerebral microvascular reactivity compared to women with uncomplicated pregnancy histories.

Methods: Women with a history of preeclampsia (PE; n=9) and women with a history of uncomplicated pregnancy (CON; n=11) were recruited from the Manhattan, Kansas area. Testing included resting measurements of cerebral microvascular hemodynamics using near-infrared spectroscopy (NIRS), with total hemoglobin (THb) as the primary measure. Participants then completed repeated 30-second breath-hold maneuvers to induce a hypercapnic stimulus while THb, mean arterial pressure (MAP), and percent end-tidal CO_2 ($EtCO_2$, %) were continuously recorded. Cerebrovascular reactivity (CVR) was calculated as the change in THb from baseline to end breath-hold relative to the change in $EtCO_2$. MAP was used to calculate indices of cerebrovascular conductance (CVCi). A subset of participants performed a Valsalva Maneuver

with continuous recording of middle cerebral artery velocity with transcranial doppler ultrasound to assess cerebral autoregulation and indices of autonomic function.

Results: Twenty women were included in the analysis (PE: n=9; CON: n=11). Participant characteristics and baseline measures, including MAP, $EtCO_2$, and THb, did not differ between groups ($p>0.05$). Contrary to our hypothesis, there were no significant differences in CVR between PE and CON ($p=0.389$), nor in CVCi ($p=0.724$) at the level of the microvasculature. Sensitivity analyses accounting for changes in blood gas stimuli yielded consistent findings ($p=0.299$). In the subset analysis, cerebral autoregulatory indices ($CAi_{I–II}$, $CAi_{III–IV}$) and Valsalva ratio were not different between groups ($p>0.05$). A significant association was observed between $CAi_{I–II}$ and CVCi ($R^2=0.50$, $p=0.027$), suggesting a relationship between pressure-flow regulation and microvascular conductance.

Conclusions: Women with a history of preeclampsia demonstrate preserved cerebral microvascular reactivity to CO_2 an average of 8 years postpartum. These findings suggest that incident PE alone may not result in persistent cerebral microvascular dysfunction in the years following pregnancy. Instead, long-term cerebrovascular risk in this population may reflect the combined influence of aging, cardiometabolic health, and lifestyle factors, underscoring the importance of continued monitoring and risk factor management across the lifespan.

Introduction

Preeclampsia affects 3-8% of women globally[1], is responsible for >70,000 deaths annually[2], and paves the way for chronic maternal morbidity.[3] While preeclampsia (PE) is a pregnancy-specific disorder characterized by *de novo* hypertension and proteinuria after 20 weeks gestation[4], ischemic insult to the placenta induces maternal multiorgan dysfunction that persists beyond the delivery of the fetus.[5] This poses especially debilitating consequences for the maternal brain, in fact, the American Heart Association/American Stroke Association recognizes preeclampsia as a sex-specific risk factor for future stroke.[6]

While the pathophysiology of PE has yet to be fully elucidated, inadequate remodeling of the spiral arteries increases uteroplacental vascular resistance and results in inadequate perfusion to the placenta.[7] The ischemic placenta releases antiangiogenic factors and proinflammatory molecules that activate the maternal endothelium.[8] At the level of the brain, this endothelial damage impairs cerebral autoregulation - a key mechanism for controlling cerebral perfusion to physiologic changes in arterial blood pressure - and increases permeability of the blood brain barrier (BBB).[9-11] This isolated insult to the brain's delicate vasculature is sufficient to cause chronic dysfunction, as women with a history of preeclampsia have evidence of white matter hyperintensities (a marker of cerebral small vessel disease[12]), global BBB leakage[13], and impaired cerebral blood flow regulation[14] up to 35 years past delivery compared to women who had uncomplicated pregnancies.

Prior work demonstrates impaired macrovascular function at the level of the middle cerebral artery and global cerebral vascular dysfunction in women with a history of preeclampsia.[14-18] Cerebral microvascular function is critical for neurocognitive processes including working memory, attention, and information processing[19], as well as for reducing the

risk of cerebrovascular diseases such as stroke, vascular dementia, and cerebral small vessel disease.[20-22] However, cerebral microvascular function - specifically CO_2-induced dilation of cerebral arterioles - has not yet been quantified in this population. Given the governing role of arterial $PaCO_2$ on cerebral blood flow control[23], and the function of the cerebral microvasculature in matching cerebral blood flow to neuronal metabolic need and maintaining cerebral pH, alterations in this system may underlie early neurocognitive decline and elevated cerebrovascular risk in otherwise young, healthy women. We therefore hypothesized that women with a history of preeclampsia will exhibit impaired cerebral microvascular reactivity compared with women with an uncomplicated pregnancy history.

Methods

All procedures in this study were conducted in accordance with the Declaration of Helsinki and received institutional ethical approval from Kansas State University (IRB #13423). The authors declare that all supporting data are available upon reasonable request to the corresponding author.

Women with a history of at least one pregnancy complicated by preeclampsia (PE) or women with a history of uncomplicated pregnancy (CON) were recruited for the present study. Participants were recruited from January 2026 through April 2026 from the Manhattan, Kansas area and surrounding regions through word of mouth, campus media announcements, and social media campaigns. Eligibility criteria for PE were women who: 1) have had at least one previous pregnancy 2) have self-reported development of preeclampsia in at least one pregnancy, and 3) are at least one year postpartum. For CON, criteria were women who: 1) have had at least one previous pregnancy, and 2) have no self-reported pregnancy complications. Exclusion criteria for

both groups were women: 1) currently pregnant, 2) without a history of at least 1 pregnancy, 3) currently taking antioxidant supplements and were unwilling or unable to withhold supplementation for the duration of the study, 4) who have metabolic or inflammatory chronic disease (e.g., diabetes mellitus, rheumatoid arthritis, etc.), 5) who were unable to speak or write in English, 6) unable to provide written and verbal informed consent.

Experimental Design

Experiments were performed in Manhattan, Kansas (altitude of 327 meters above sea level) in a controlled laboratory setting (Lafene Health Center, Kansas State University). Temperature, humidity, and ambient pressure were kept within a set range (20.8 °C ± 0.4; 32.6% ± 9.5; 763.94 mmHg ± 9.4) on all testing days. Visits lasted 60-90 minutes in total, and started between 7:00am and 6:00pm with no difference in morning or afternoon visit allocation between PE and CON groups. Participants were instructed to refrain from caffeine, alcohol, and strenuous exercise for at least 12 hours prior to the experimental visit, but to maintain any daily medication and supplement use according to their normal schedule.

At the beginning of each visit, informed consent, health history information, and record of habitual physical activity (I-PAQ[24]), sleep health (Pittsburgh Sleep Health Questionnaire[25]), and diet quality (Mini-Eat Questionnaire[26]) were completed. Following surveys, resting brachial blood pressure (OMRON Intellisense Pro; OMRON Healthcare, Inc., IL, USA) was assessed as the average of two measurements performed after a period of quiet rest in a seated position. Anthropometric measures, including height and weight, were determined using a standard scale and stadiometer. Body mass index (BMI) was calculated as kg/m^2. Body composition was

assessed with dual x-ray absorptiometry (Prodigy DXA System, General Electric Healthcare Technologies, Inc., Chicago, IL, USA).

Near-infrared Spectroscopy

Non-invasive measurements of cerebrovascular hemodynamics were performed serially by cerebral near-infrared spectroscopy (NIRS) using a commercially available frequency-domain system (OxiplexTS, ISS Inc., Champaign, IL, USA). In brief, NIRS devices emit near-infrared light into biological tissue which is absorbed primarily by heme; in cerebral tissue, heme is primarily found circulating as hemoglobin in red blood cells.[27] The optical properties of hemoglobin vary if oxygen is bound to hemoglobin, allowing NIRS to differentiate between oxygenated and deoxygenated hemoglobin (HbO_2 and HHb, respectively).[28] The absolute concentrations of these species, along with their sum (THb) and the oxygen-saturation percent, provide non-invasive indices of cerebral microvascular hemodynamics.[29,30] For the present work, we used THb as our primary measurement in line with previous literature.[29-31]

Transcranial Doppler

In a subset of participants, transcranial Doppler (TCD) ultrasonography was used to assess cerebral macrovascular hemodynamics in line with published recommendations.[32] Participants were seated in an upright position while the TCD operator (B.S., S.F.) positioned a convex probe within a secure headframe. The system was connected to a monitor display (Spencer Technologies, ST3 Digital Transcranial Doppler, Redmond, WA, USA). Recordings were obtained using a 2-MHz transducer with power M-mode Doppler to identify the middle cerebral artery (MCA) at a depth of 40–65 mm through the temporal window. Pulse-wave

doppler scans assessed minimum, maximum, and mean MCA velocities at an insonation angle maintained at less than 15 degrees.[32]

Assessment of Cerebrovascular Reactivity

To assess cerebral microcirculation and MCA responsiveness to changes in blood gases (e.g., $PaCO_2$), a repeated breath hold maneuver was utilized.[33] To begin, participants breathed normally at a self-selected ventilatory frequency for a 2-minute baseline period. Then, subjects were instructed to inhale slightly deeper than a normal tidal breath before beginning the 30 second breath hold. At the end of the breath hold, participants were instructed to slowly exhale for ~5 seconds to ensure adequate and consistent end-tidal measures. Two minutes of rest followed, and a total of three breath holds were performed per subject. 30 seconds was chosen as this time period has been shown previously to achieve a hypercapnic stimulus.[34] Participants were fitted with a mouthpiece and nose clip to measure inspired and expired gases, with end-tidal oxygen (EtO_2) and carbon dioxide ($EtCO_2$) percentages collected breath-by-breath using a cardiorespiratory monitor (CardioCap 5, General Electric HealthCare, IL, USA). The final 30 seconds of baseline and the last 3 seconds of breath-hold data were used for analyses. To describe the arterial PCO_2 stimulus for cerebrovascular responses at the microvascular level, cerebrovascular reactivity (CVR) was quantified in the microcirculation as the NIRS-derived change in THb over the change in E_tCO_2 (%) from baseline to end-breath hold. To account for changes in blood pressure and their contribution to measured changes in cerebral blood flow, cerebrovascular conductance indices (CVCi) were calculated as THb divided by MAP.[35] Additionally, a sensitivity analysis was performed to account for changes in E_tO_2 during the

breath hold. This was done by using a stimulus index where the change in the E_tCO_2/E_tO_2 ratio was substituted for the change in E_tCO_2, as previously described.[36]

Exploratory Assessment of Cerebral Autoregulation and Autonomic Function

Cerebral autoregulation (CA) is a mechanism by which the cerebral vasculature regulates CBF in response to changes in MAP – both rapid and prolonged – to maintain cerebral perfusion.[37] Additionally, the vasculature that responds to these pressure changes are richly innervated by neuronal extensions from the sympathetic and parasympathetic nervous system.[38] Therefore, in a subset of subjects, an exploratory analysis was conducted to examine CA and cerebral autonomic function between PE and CON.

Similar to others[39,40], we elected to use the Valsalva Maneuver (VM) to test autoregulatory and sympathetic adrenergic functions using the blood pressure and heart rate responses, as this test elicits predictable and repeatable changes to MAP.[41] Subjects were instrumented with TCD to measure MCAv and had MAP continuously monitored with Finapres. Subjects were instructed to perform the VM for 15 seconds by forcefully expiring against a closed valve connected to pressure gauge and maintain a pressure of 40 mmHg.[42] The VM is further divided into five stages; phase I, early phase II, late phase II, phase III and phase IV.[43,44] Autoregulatory function was defined using two different metrics described previously.[42] Cerebral autoregulatory index from phases I-II of the VM (CAi_{I-II}) assesses the contribution from MAP to changes in MCAv at the onset of the maneuver. During phase I, initiation of the strain causes mechanical compression of the aorta, resulting in a transient increase in MAP that is passively transmitted to the peripheral circulation. This is followed by phase II, during which reduced venous return leads to a decrease in stroke volume and a compensatory increase in sympathetic

activity. The cerebral autoregulatory index from phases III-IV of the VM (CAi_{III-IV}) examines the change in pressure and flow from the nadir in MAP at the end of the maneuver (phase III) to the subsequent MAP overshoot (phase IV) following release of the strain. The initial drop in MAP during phase III reflects the release of expiratory pressure and expansion of intrathoracic blood vessels, whereas the phase IV overshoot is attributed to persistent vasoconstriction initiated during phase II. The short duration of the VM performed did not lead to a clearly defined phase IIb response in all subjects. Therefore, phase II was represented as the average of all variables following the peak of the phase I response until the release of the VM, as done previously.[42] Lower values in CAi_{I-II} and CAi_{III-IV} metrics suggest impairments in cerebral autoregulation. Quantifications of these metrics are presented visually in Figure 1.

Additionally, the Gosling pulsatility index for MCAv was calculated as ($MCAv_{systolic} - MCAv_{diastolic}$)/$MCAv_{mean}$.[45] Autonomic function was also quantified using the Valsalva Ratio (VR); the R-R interval nadir during phase III over the maximal R-R interval during 30 seconds of recovery from the nadir during the VM.[39,46]

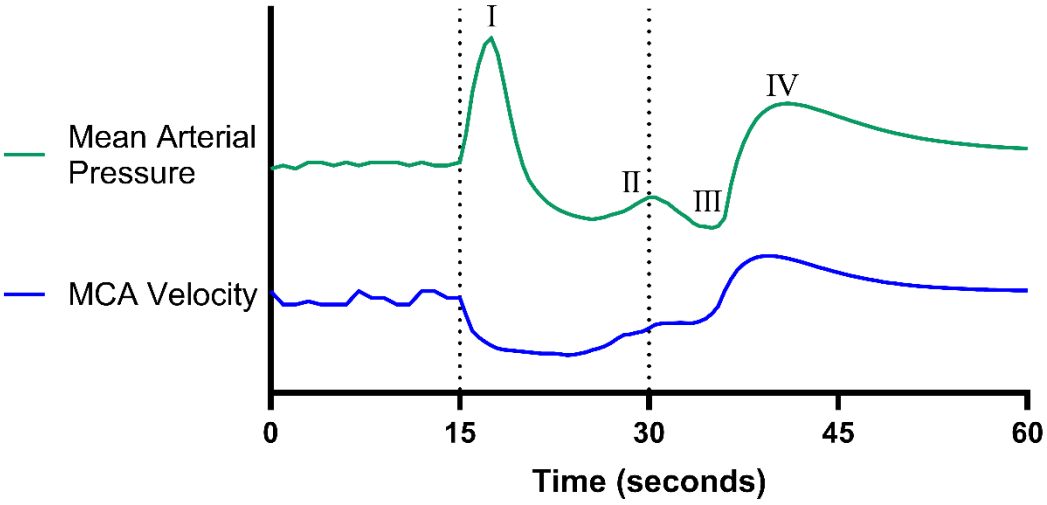
Statistical Analyses

Statistical analyses were performed in SigmaPlot 13.0 (Systat Software Inc., Chicago, IL, USA) and GraphPad Prism 10.3.0 (Dotmatics, Boston, MA, USA). Normality of data was assessed with Shapiro-Wilks tests. Outliers were determined with the ROUT method set at a standard threshold (Q=1%). Comparisons between groups were assessed as independent t-tests, Mann-Whitney tests if the normality assumption was violated, or t-test with Welch's correction if variances were unequal. Associations between cerebral autoregulatory and autonomic metrics

Figure 2.1. Visual representation of mean arterial pressure (MAP) and middle cerebral artery velocity (MCAv) during the Valsalva Maneuver and calculation of cerebral autoregulatory indices (CAi_{I-II} and CAi_{III-IV}).

$$CAi_{I-II} = [(MCAv_{II} - MCAv_{I})/(MCAv_{I})] / [(MAP_{II} - MAP_{I})/(MAP_{I})]$$

$$CAi_{III-IV} = [(MCAv_{IV} - MCAv_{III})/(MCAv_{III})] / [(MAP_{IV} - MAP_{III})/(MAP_{III})]$$



derived from the VM and NIRS-derived microcirculatory measures were assessed using the Spearman correlations. Statistical significance was set a priori at $p< 0.05$. Data in results are presented as means ± standard deviations unless otherwise noted.

Results

Participant characteristics and baseline metrics did not differ between women with a history of PE and CON (Table 2.1). Additionally, no differences between groups were present for baseline MAP or E_tCO_2 during normal tidal breaths ($p>0.05$). Baseline THb was not different between groups ($p>0.05$).

Cerebrovascular Reactivity and Conductance

Shown in Figure 2.1, microvascular CVR, expressed as the change in THb over the change in E_tCO_2, was not significantly different in women with a history of PE compared to CON ($p=0.389$). CVCi, which accounts for changes in MAP, was not significantly different between groups ($p=0.724$). Results are presented visually in Figure 2.2 and numerically in Table 2.2. The sensitivity analysis conducted with the blood gas stimulus index was consistent with main findings; there was no difference ($p=0.299$) between CON (0.67 ± 0.54 μM/%) and PE (0.36 ± 0.18 μM/%).

Cerebral Autoregulation and Gosling's Pulsatility

As shown in Table 2.2, autoregulatory indices (CAi_{I-II} and CAi_{III-IV}) and Gosling's pulsatility index were assessed in 10 women (PE = 3, CON =7). CAi_{I-II} and CAi_{III-IV} were not significantly different in women with a history of PE compared to CON (CAi_{I-II}; $p= 0.301$, CAi_{III-}

Table 2.1. Comparison of demographic characteristics between women without a history of preeclampsia (CON) versus those with a history of preeclampsia (PE).

	CON (N = 11)	**PE (N = 9)**	**P-value**
Age, years	40.7 ± 6.2	39.6 ± 5.5	0.658
Time since index pregnancy, years	6.5 ± 6.1	10.3 ± 5.7	0.194
BMI, kg/m^2	26.6 ± 6.8	27.8 ± 7.9	0.722
Body fat composition, % [a]	38.4 ± 11.4	41.7 ± 9.0	0.532
SBP, mmHg [a]	114.0 ± 10.0	115.4 ± 6.5	0.721
DBP, mmHg [a]	72.8 ± 7.8	79.6 ± 9.0	0.109
Hypertension	1 (9.1)	2 (22.2)	0.413
Dyslipidemia	0 (0)	1 (11.1)	0.257
Self-reported lifestyle behaviors			
Exercise, MET-min/week	1017.0 ± 852.2	1107.0 ± 841.7	0.818
Diet Quality, Mini-Eat Score [a]	18.3 ± 6.0	15.2 ± 5.8	0.277
Sleep Quality, PSQI Score	5.5 ± 4.2	6.9 ± 2.7	0.365

BMI, body mass index; CON, control/uncomplicated pregnancy history; DBP, diastolic blood pressure; MET, metabolic equivalents; PSQI, Pittsburgh Sleep Quality index; SBP, systolic blood pressure.
Continuous variables are given as mean ± standard deviation; categorical variables as n (%). P-values were determined using unpaired t-tests (or Mann-Whitney comparisons where appropriate) or χ^2 tests.
[a] Data missing due to technical difficulties during collection (missing n = 1 except for body fat %, missing n = 4).

Table 2.2. Baseline and regulatory metrics for cerebrovascular and cardiovascular responses to the breath-hold assessments.

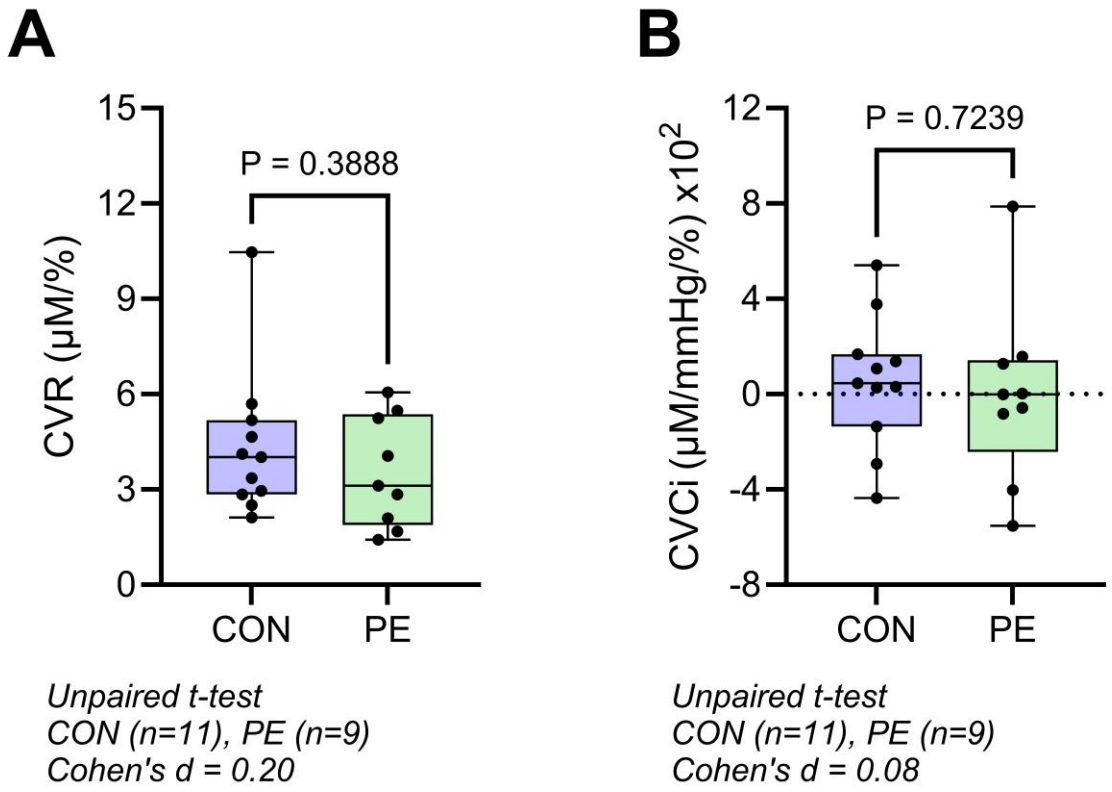
	CON (N = 11)	**PE (N = 9)**	**P-value**
Baseline Metrics			
HR, bpm	87.6 ± 12.1	88.4 ± 8.2	0.870
MAP, mmHg	107.5 ± 15.8	112.2 ± 7.0	0.129
E_tCO_2, %	4.6 ± 0.5	4.6 ± 0.7	0.942
E_tO_2, %	19.0 ± 0.92	19.4 ± 0.8	0.316
Total-Hb, μM	36.9 ± 6.2	37.1 ± 6.6	0.932
MCA velocity, cm/s [a]	83.8 ± 12.4	86.0 ± 13.2	0.821
Gosling's Pulsatility Index, a.u. [a]	0.86 ± 0.10	0.78 ± 0.05	0.157
Reactivity Indices			
CVR, μM/%	4.4 ± 2.3	3.6 ± 1.7	0.389
CVCi, μM/mmHg/% x10^2	0.52 ± 2.8	-0.02 ± 3.8	0.724
CAi_{I-II}, a.u. [a]	0.80 ± 0.10	0.83 ± 0.09	0.607
CAi_{III-IV}, a.u. [a]	0.92 ± 0.33	1.06 ± 0.38	0.618
VR, a.u. [a]	1.8 ± 0.5	2.1 ± 0.2	0.245

CAi, cerebral autoregulation index; CVCi, cerebrovascular conductance index; CON, control participant; CVR, cerebrovascular reactivity; E_tO_2, end-tidal oxygen percent; E_tCO_2, end-tidal carbon dioxide percent; HR, heart rate; MAP, mean arterial pressure; MCA, middle cerebral artery; PE, preeclampsia; Total-Hb, total hemoglobin; VR, Valsalva ratio.

Continuous variables are given as mean ± standard deviation. P-values were determined using unpaired t-tests (or Mann-Whitney comparisons where appropriate).

[a] Exploratory analyses were conducted in a subset of participants (CON: n = 7, PE: n = 3).

Figure 2.2. Cerebrovascular reactivity (CVR) and Cerebrovascular Conductance (CVCi) during a 30-second breath-hold. Data are mean ± SD. Women with a history of preeclampsia (PE) are shown in green, women with normotensive pregnancy history (CON) are shown in blue.



IV; p= 0.618). Similarly, Gosling's pulsatility index was not significantly different between groups (p=0.157).

Exploration of Cardiometabolic Contributions

In exploratory analyses, linear regression was used to examine the relationships between indices of cardiometabolic health and cerebrovascular regulation. Notably, as shown in Figure 2.3, there was a significant inverse relationship between body mass index and CVR (p=0.046). To further investigate this, a cardiometabolic risk factor burden score was determined by summing risk factors within each participant – namely, menopause, poor diet, sedentary lifestyle, hypertension, dyslipidemia, poor sleep, and obesity. Scores from questionnaires were cutoff using tertiles. When split by high risk factor burden (> 2 risk factors) versus low burden, the group of participants with high risk factor burden had a significantly lower CVR (p=0.007; Figure 2.4).

Discussion

We hypothesized that women with a history of preeclampsia would exhibit impaired cerebral microvascular reactivity compared to women with an uncomplicated pregnancy history. Contrary to this hypothesis, our findings demonstrate that women who were on average 8 (range 2-24) years postpartum exhibit preserved microvascular CVR. To our knowledge, this study is the first to directly assess cerebral microvascular reactivity in previously pre-eclamptic women using NIRS. This measurement is physiologically relevant because the cerebral resistance vasculature accounts for the majority of CO_2-mediated cerebrovascular reactivity[23] and changes in arterial PCO_2 represent one of the most potent regulators of cerebrovascular tone[47], which

Figure 2.3. A linear regression plot depicting the relationship between body mass index and cerebrovascular reactivity (CVR).

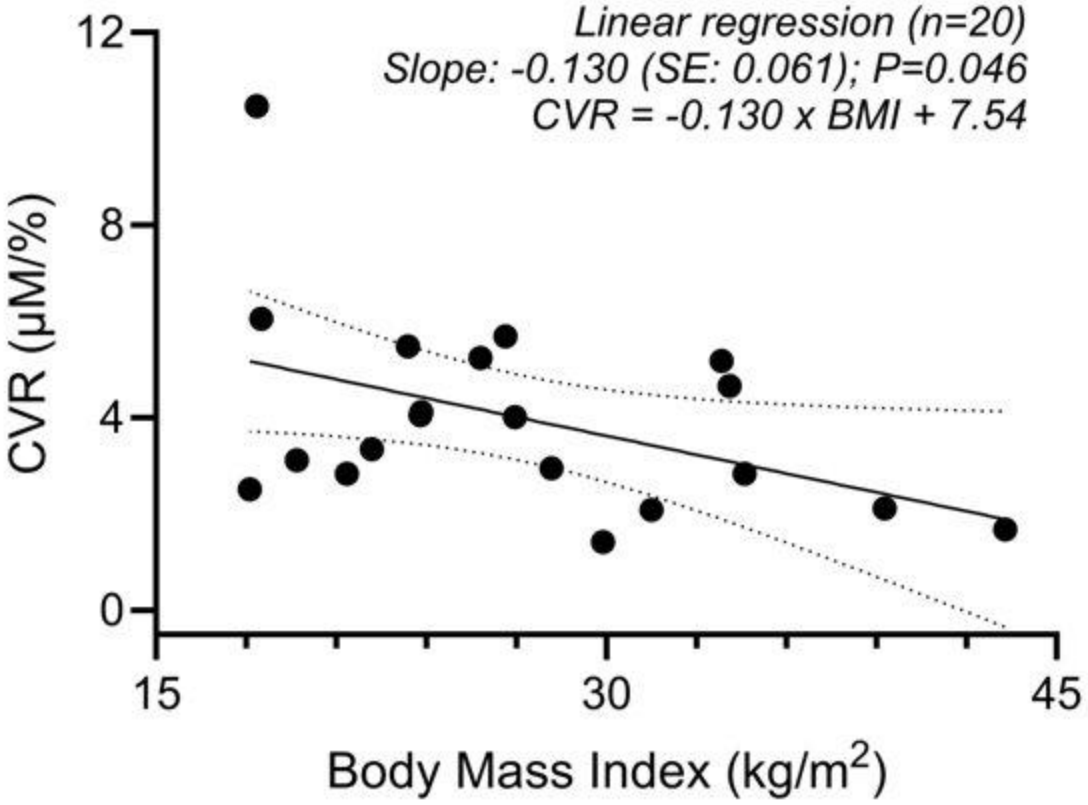
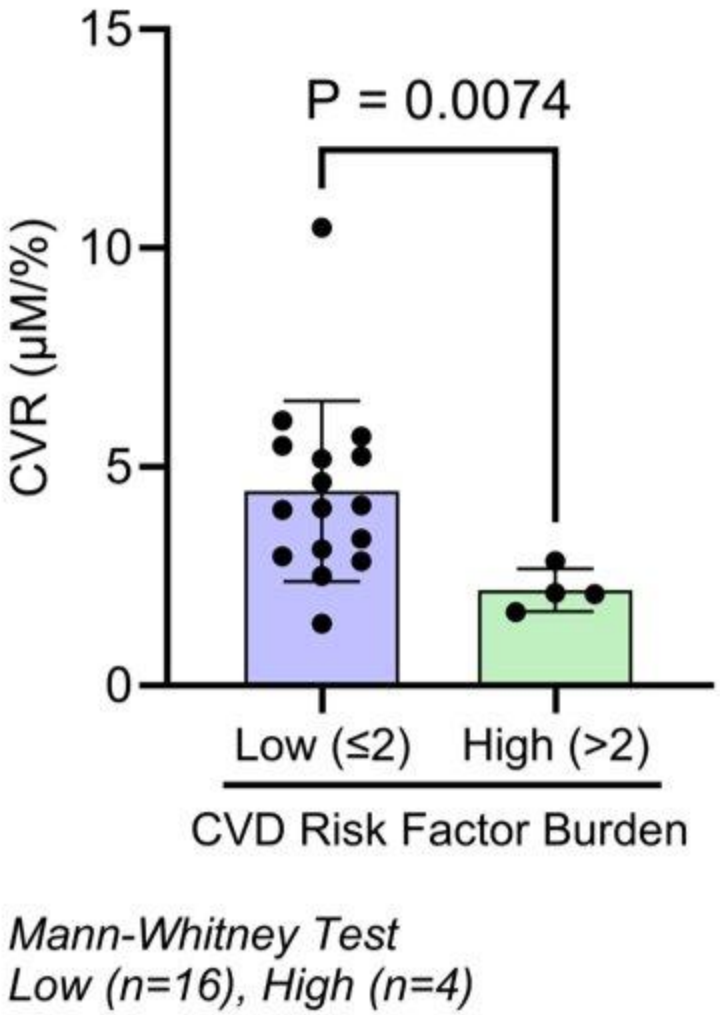


Figure 2.4. A comparison of cerebrovascular reactivity (CVR) in the overall cohort when stratified by risk factor burden – namely, the summed presence of menopause, hypertension, dyslipidemia, obesity, poor diet, poor sleep, and/or a sedentary lifestyle.



maintains CBF and preserves brain health. There are multiple possible explanations for why our findings may have been in contrast to our initial hypothesis.

First, while previous studies suggest that preeclampsia-associated vascular injury persists beyond delivery, much of the literature has examined only larger cerebral vessels.[14,48] The results from the present study help contextualize previous findings from Barnes and colleagues, which showed reduced CVR in the middle cerebral artery approximately 35 years after a preeclamptic pregnancy.[14] Not only did Barnes et al. measure a larger cerebral artery - which is known to have distinct, different functions from the microvasculature that our group measured[49-51] - but in Barnes' cohort, women with a history of preeclampsia also exhibited higher body mass index and a greater prevalence of hypertension, suggesting that cardiometabolic differences and menopausal status may have also contributed to the observed reductions in CVR. These differences complicate interpretation in translating macro to microvascular function and may confound the effects of aging and menopause with the long-term consequences of a preeclamptic pregnancy.

Second, epidemiologic evidence from large studies further suggests that age and cardiometabolic risk factors, including hypertension and obesity, may contribute more substantially to long-term cardiovascular and cerebrovascular risk in women with a history of preeclampsia than the index pregnancy itself.[52,53] For example, women with PE are more likely to develop hypertension.[54] Supporting this concept, longitudinal imaging studies indicate that women who effectively control blood pressure following a preeclamptic pregnancy maintain greater brain volume compared to those with poorly controlled blood pressure, suggesting that post-pregnancy cardiometabolic health may strongly influence long-term cerebrovascular outcomes.[55] This further contextualizes our present findings, as basic cardiometabolic

considerations, such as BMI and hypertension, were similar between groups. Lifestyle factors may also play an important protective role for CVR, as habitual physical activity and adherence to healthy dietary patterns have been associated with improved cerebrovascular health across the lifespan.[35,56,57] The average levels of physical activity in both groups of our cohort exceeded minimum ACSM physical activity guidelines.[58] In women with a history of PE, greater levels of light physical activity were associated with a lower arterial stiffness[59], which we and others have previously linked to CVR.[21,35,56] A more comprehensive investigation in the context of PE is warranted.

Third, while endothelial dysfunction is widely recognized as a central feature of preeclampsia and may persist after delivery, the trajectory and time course of recovery remain unclear. For example, Östlund et al. reported impaired endothelial function one year postpartum in women with prior preeclampsia compared with controls. However, when the same cohort was reassessed 11 years later, endothelial function had normalized in the preeclampsia group while remaining unchanged in controls.[60] These findings, along with the findings of others[61], suggest that vascular adaptations following preeclampsia may evolve, and recover, over time.

Taken together, the current literature suggests that although women with a history of preeclampsia face increased lifetime risk of cerebrovascular disease and cognitive decline[18,62-69], these outcomes may not be driven solely by the incident preeclamptic pregnancy. Rather, the interaction between postpartum cardiometabolic health, time since pregnancy, and disease severity appear to play a critical role in shaping long-term cerebrovascular risk. Consistent with this framework, our findings demonstrate preserved cerebral microvascular reactivity in women who are on average eight (range 2-24) years postpartum. Furthermore, pregnancy is increasingly recognized as a physiologic “stress test” that may unmask latent cardiovascular disease risk in

women.[70] Therefore, long-term cerebrovascular health in women likely reflects not only incidence of a hypertensive disorder of pregnancy, but the cumulative effects of pregnancy-related vascular stress, previous subclinical CVD risk factors, and subsequent adverse cardiometabolic profiles.

Study Considerations

There are a few limitations of this study should be acknowledged. First, we utilized NIRS to assess CVR, a methodology that has not been applied in this specific population. While NIRS-derived indices of CVR have been shown to correlate with those obtained via TCD - a more established and widely used technique - NIRS primarily reflects microvascular oxygenation changes and may not fully capture macrovascular cerebral blood flow dynamics.[71] As such, direct comparisons with studies using TCD should be made with caution.

Second, we did not assess circulating biomarkers of cardiometabolic health, including lipid profiles, fasting glucose, or inflammatory markers such as TNF-α and IL-6, nor did we evaluate anti-angiogenic factors relevant to a history of preeclampsia (e.g., sFlt-1). These factors are known to influence vascular and microvascular function and could provide important mechanistic insight into the observed lack of differences in CVR.[72]

Additionally, the relatively small sample size (n = 9-11 per group) precluded stratified analyses based on potential confounders such as habitual physical activity, dietary patterns, body mass index, and hypertension status. Therefore, any impacts these factors may have had on our outcomes remain speculative and warrant further investigation.

Finally, the cross-sectional design of this study limits the ability to infer causality or determine temporal relationships between a history of preeclampsia and alterations in

cerebrovascular function. Longitudinal studies incorporating multimodal cerebrovascular assessments and comprehensive cardiometabolic profiling are warranted to better elucidate underlying mechanisms and long-term clinical implications.

Conclusions

Our study found that microvascular CVR to CO_2 does not differ between women with a history of preeclampsia and those who were normotensive during pregnancy. These findings suggest that preeclampsia alone may not result in persistent cerebral microvascular dysfunction in the years following pregnancy. Future research is needed to better characterize the trajectory of cerebral microvascular function across the postpartum period, including the potential impacts of cardiometabolic and lifestyle factors.

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