International Journal of Cardiology Cardiovascular Risk and Prevention 10 (2021) 200105

Contents lists available at ScienceDirect

International Journal of Cardiology Cardiovascular Risk and Prevention

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-cardiovascular-risk-and-prevention

Association of second trimester uterine artery Doppler parameters with maternal hypertension 2–7 years after delivery

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ARTICLE INFO

Keywords:
Pregnancy
Preeclampsia
Hypertension
Vascular ultrasound
Doppler
Biomarkers

ABSTRACT

Background: Reduced uterine artery compliance is associated with adverse pregnancy outcomes (APOs) and may indicate underlying maternal cardiovascular pathology. We investigated associations between second trimester uterine artery Doppler (UAD) parameters and incident maternal hypertension 2–7 years after delivery.

Methods: A cohort of 10,038 nulliparous US participants was recruited early in pregnancy. A subgroup of 3739, without baseline hypertension and with complete follow-up visits 2–7 years after delivery, were included in this analysis. We investigated UAD indicators of compliance including: 1) early diastolic notch; 2) resistance index (RI); and 3) pulsatility index (PI). We defined hypertension as systolic blood pressure ≥130 mmHg, diastolic ≥80 mmHg, or antihypertensive medication use. We calculated odds ratios (OR) and 95 % confidence intervals (95% CI) for associations between UAD parameters and hypertension, adjusting for age, obesity, race/ethnicity, insurance, smoking, and APOs.

Results: A total of 187 (5 %) participants developed hypertension after the index pregnancy. Presence of early diastolic notch on UAD was not associated with incident hypertension. Increased RI and PI correlated with higher odds of hypertension (RI: adjusted OR 1.15 [95 % CI 1.03–1.30]; PI: adjusted OR 1.03 [95%CI 1.01–1.05] for each 0.1 unit increase). Maximum RI above 0.84 or maximum PI above 2.3 more than doubled the odds of incident hypertension (RI: adjusted OR 2.49, 95%CI 1.45–4.26; PI: adjusted OR 2.36, 95%CI 1.45–3.86).

Conclusion: Higher resistance and pulsatility indices measured on second trimester UAD were associated with increased odds of incident hypertension 2–7 years later, and may be biomarkers of higher maternal cardiovascular risk.

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https://doi.org/10.1016/j.ijcrp.2021.200105
Received 23 April 2021; Received in revised form 12 July 2021; Accepted 14 July 2021
Available online 12 August 2021

Abbreviations

APO = adverse pregnancy outcome
UAD = uterine artery Doppler
OR = odds ratio
95%CI = 95 % confidence interval
RI = resistance index
PI = pulsatility index
BMI = body mass index
SBP = systolic blood pressure
DBP = diastolic blood pressure

1. Introduction

Adverse pregnancy outcomes (APOs), including preeclampsia, preterm delivery, and fetal growth restriction, are associated with future maternal cardiovascular disease [1–3], but the mechanisms underlying these associations are not well characterized. APOs share multiple risk factors with cardiovascular disease, such as obesity, older age, social determinants of health, and chronic inflammation [4,5]. Thus, APOs may unmask an underlying maternal phenotype with higher risk of cardiovascular disease [6]. Alternatively, these disorders, particularly preeclampsia, may cause endothelial dysfunction with vascular effects that persist long after the pregnancy [4,7,8], resulting in earlier development of chronic hypertension and other vascular risk factors. Onset of hypertension earlier in life is associated with higher risk of heart failure, stroke, and cognitive decline [9–15]. Consequently, development of hypertension subsequent to pregnancy may play an important role on the pathway linking APOs to increased risk of future cardiovascular and cerebrovascular disease.

Uterine artery Doppler (UAD) has been investigated as a screening test to identify patients at risk of placentally-mediated complications such as fetal growth restriction, spontaneous preterm delivery, and preeclampsia [16]. Uterine artery compliance increases during pregnancy, with resultant predictable changes in Doppler profiles. UAD parameters indicating decreased uterine artery compliance, such as persistence of a diastolic notch, higher resistance index (RI), and higher pulsatility index (PI), have been associated with APOs [17]. UAD parameters may also be biomarkers of maternal vascular dysfunction during pregnancy; recent work demonstrated that the uterine artery PI was negatively correlated with maternal cardiac output, and positively correlated with maternal peripheral vascular resistance [18]. Whether UAD parameters are associated with a higher maternal vascular risk profile following pregnancy is not known. Many patients with UAD abnormalities do not go on to develop APOs [17]. However, UAD abnormalities sometimes reflect incomplete uterine artery remodeling during pregnancy, which could be an early biomarker of maternal vasculopathy and endothelial dysfunction. Thus, these indicators might help identify pregnant patients at heightened risk of developing hypertension after pregnancy, regardless of pregnancy outcome.

We hypothesized that markers of poor uterine artery compliance observed with second trimester UAD in nulliparous, normotensive participants would be associated with higher odds of developing incident hypertension within 2–7 years following delivery. We further hypothesized that APOs would modify this effect.

2. Methods

2.1. Study design

From 2010 to 2013, the National Institutes of Health-funded Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) enrolled 10,038 nulliparous US participants with singleton gestation in early pregnancy and followed them through delivery [19]. The study performed detailed pregnancy phenotyping, including a planned UAD analysis at the second study visit between 16 weeks and 22 weeks' gestation. Doppler studies were performed by certified sonographers via the transabdominal approach, with transvaginal approach used if transabdominal views were inadequate. Among these participants, 4508 were assessed 2–7 years (mean 3.2 years) after their initial delivery as part of the nuMoM2b Heart Health Study (nuMoM2b-HHS), an ongoing prospective study [20].

2.2. Study population

Detailed study protocols for the nuMoM2b study and follow up nuMoM2b-HHS have been previously published [19,21]. For this analysis, we included all nuMoM2b participants who had nuMoM2b protocol-related UAD studies performed at the second study visit between 16 weeks 0 days and 22 weeks 6 days, and had complete follow up nuMoM2b-HHS in-person blood pressure measurements at 2–7 years after delivery. Participants with a diagnosis of chronic hypertension at time of enrollment in the initial nuMoM2b study, those with incident gestational and sustained post-partum hypertension, and those who were missing information for a hypertension diagnosis at follow up, were excluded from this analysis. We also excluded participants whose second-trimester ultrasound showed maternal bradycardia (<40 bpm) or tachycardia (>130 bpm) which could affect UAD parameters; participants with a non-viable pregnancy (N = 19); participants with incomplete UAD measurements (N = 588); and participants whose nuMoM2b visit 2 was delayed by > 1 week outside of the visit window (N = 15), consistent with prior analyses [17]. Thus, of 4508 participants who were evaluated 2–7 years after delivery, 3739 were included in the analysis (Fig. 1).

2.3. Exposures of interest

In accordance with accepted obstetric definitions, resistance index (RI) was defined as (maximum - minimum flow velocity)/maximum velocity, and pulsatility index (PI) was defined as (maximum - minimum flow velocity)/mean velocity [16]. A minimum of 3 waves were included in the calculation of the RI and PI for each participant [19]. The higher of the two values of RI and PI (right or left) was selected to produce values of maximum RI and PI for each participant. We investigated the following exposures of interest, all of which reflect poor uterine artery compliance [16]: 1) presence of an early diastolic notch in both UAD profiles; 2) maximum RI as a continuous variable; and 3) maximum PI as a continuous variable.

Covariates of interest: Covariates included factors at the first pregnancy known to be associated with hypertension, including age, body mass index (BMI) in early pregnancy, self-identified race/ethnicity, smoking in the 3 months prior to pregnancy, health insurance status (as an indicator of socioeconomic status), and any APO [20]. We defined APO as one or more of the following conditions, all of which were defined rigorously according to standardized definitions and adjudicated by maternal-fetal medicine specialists: gestational hypertension diagnosed antenatally, preeclampsia, eclampsia, preterm delivery (medically indicated or spontaneous live birth at < 37 weeks gestational age), small for gestational age (<5th percentile by Alexander nomogram), or stillbirth [19,20].

2.4. Primary outcome

The primary outcome of interest was incident hypertension that developed subsequent to the index pregnancy, defined as systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥80 mm Hg, based on 2017 guidelines [22], or self-reported use of an antihypertensive medication at the nuMoM2b-HHS study visit. Blood pressure measures were obtained following a standard protocol, as follows:

trained research personnel recorded 3 standardized blood pressure measurements using calibrated automated oscillometric devices (OMRON HEM-907XL, Omron Healthcare Incorporated, Lake Forest, Illinois). Blood pressure measurements were recorded following 5 min of seated rest and the average of the last 2 systolic and diastolic pressures were used for analyses.

2.5. Statistical analysis

Baseline characteristics of the study population at the time of the index pregnancy were compared using t-tests for continuous variables, and Chi-square tests for categorical variables. Logistic regression models were used to estimate unadjusted and adjusted odds ratios (OR) and 95 % confidence intervals (95 % CI) for the association of each UAD parameter with development of hypertension 2–7 years after delivery. Adjusted models included adjustments for maternal age, early pregnancy BMI, self-identified race/ethnicity, smoking status prior to pregnancy, health insurance, and presence of APO in the index pregnancy. We tested for interactions on both the additive and multiplicative scale between UAD parameters and presence of any APO, for the outcome of incident hypertension [23]. In secondary analyses, we investigated maximum RI and maximum PI to identify potential cut-points for predicting future hypertension, using an optimization algorithm based on chi-square tests and simultaneously scoring of the odds ratio and the p-value [24]. In a pre-specified sensitivity analysis, we restricted the sample to participants who did not have a reported pregnancy between the end of the index pregnancy and the follow-up at 2–7 years after the index pregnancy. All statistical analyses are considered exploratory and are not adjusted for multiple comparisons. All statistical analyses were performed using SAS (v9.4, Cary, NC, USA).

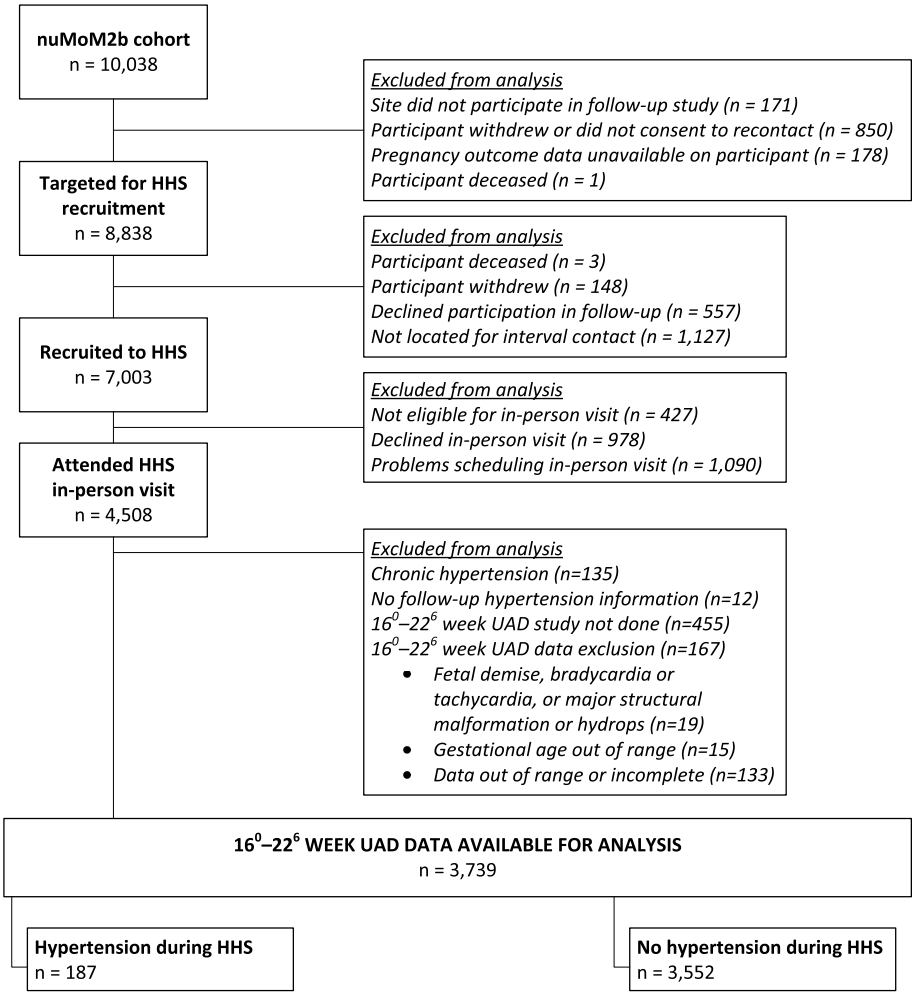
2.6. Ethical considerations and data sharing

All study participants provided written informed consent at the time of enrollment in the study, approved by each site's institutional review board. Data from the nuMoM2b study are publicly available through the National Institutes of Health Data and Specimen Hub (DASH; https://dash.nichd.nih.gov/). nuMoM2b-HHS data collection is ongoing.

3. Results

3.1. Baseline characteristics

Baseline characteristics of the study sample are summarized in Table 1. The median time between the end of the index pregnancy and the nuMoM2b-HHS single in-person study visit was 3.1 years (interquartile range, 2.5–3.7 years). At the time of the follow up study visit, 187 of the 3739 participants (5 %) in this analysis were determined to have incident hypertension. Participants who had hypertension at the time of the follow-up study visit were on average older at the time of their first pregnancy, had a lower proportion of commercial insurance, and had higher proportions of self-identified Black race, obesity, and



Abbreviations: UAD=Uterine Artery Doppler.

Fig. 1. Flow diagram of study enrollment.
Legend: This analysis included all nuMoM2b participants who had UAD studies performed at the second study visit between 16 weeks 0 days and 22 weeks 6 days, and had follow up in-person blood pressure measurements at 2–7 years after delivery. Participants were excluded if they had a diagnosis of chronic hypertension at time of enrollment in the initial nuMoM2b study; were missing information for hypertension diagnosis at follow up; had nuMoM2b study visit ultrasound showed severe maternal tachycardia or bradycardia interfering with UAD measurement; had non-viable pregnancy; or if their UAD measurements were not available or incomplete.

Table 1
Demographic and Index Pregnancy Characteristics of nuMoM2b-HHS Participants.

Baseline characteristics at time of index pregnancy	All participants (N = 3739)
Maternal age, years, mean (SD)	26.9 (5.5)
Category (years): n (%)	
13-21	757 (20.2)
22-35	2744 (73.4)
> 35	238 (6.4)
Maternal race/ethnicity: n (%)	
Non-Hispanic White	2380 (63.7)
Non-Hispanic Black	477 (12.8)
Hispanic	599 (16.0)
Asian	110 (2.9)
Other	173 (4.6)
Insurance status[1/]: n (%)	
Government/military insurance	1028 (27.6)
Commercial health insurance	2612 (70.3)
Personal household income/other	608 (16.4)
BMI, kg/m^2, mean (SD)	26.4 (6.2)
Category: n (%)	
< 25	1919 (52.3)
25 to < 30	912 (24.8)
≥ 30	841 (22.9)
Systolic Blood Pressure at Visit 1, mmHg	
Mean (standard deviation)	109.1 (10.7)
Median (interquartile range)	110.0 (100.0, 118.0)
Diastolic Blood Pressure at Visit 1, mmHg	
Mean (standard deviation)	67.2 (8.4)
Median (interquartile range)	68.0 (60.0, 72.0)
Pre-gestational diabetes: n (%)	35 (0.9)
Smoked during 3 months prior to pregnancy: n (%)	579 (15.5)
Consumed alcohol during 3 months prior to pregnancy: n (%)	2304 (74.4)
Adverse pregnancy outcome (APO): n (%)	
No APO	2901 (77.8 %)
Any APO	829 (22.2 %)
Gestational hypertension	499 (13.3 %)
Preeclampsia or eclampsia	228 (6.1 %)
Spontaneous preterm birth	185 (5.0 %)
Iatrogenic preterm birth	112 (3.0 %)
Small for gestational age (Alexander)	146 (3.9 %)
Stillbirth	12 (0.3 %)

Abbreviations: N = sample size; SD = standard deviation; n = number in category; BMI = body mass index; APO = adverse pregnancy outcome; UAD = uterine artery Doppler.
[1/]Percentages do not add up to 100 % because participants were allowed to select multiple methods.

pre-gestational diabetes.

3.2. Primary and secondary analysis results

Results of the primary analysis are presented in Table 2. There was no significant association between presence of bilateral diastolic notch and development of future hypertension. Each 0.1-unit increase in maximum RI and PI was associated with higher odds of incident hypertension (RI, adjusted OR 1.15, 95%CI 1.03–1.3; PI, adjusted OR 1.03, 95%CI 1.005–1.05) (Table 2). There were no significant interactions between UAD indices and presence of APOs, either on the additive or multiplicative scale. Secondary analysis showed that a maximum RI value above a cut-point of 0.84 was associated with higher odds of incident hypertension (adjusted OR 2.49, 95%CI 1.45–4.26). A maximum PI value above a cut-point of 2.3 was also associated with higher odds of incident hypertension (adjusted OR 2.36, 95%CI 1.45–3.86) (Table 3).

3.3. Sensitivity analysis

Our pre-planned sensitivity analysis restricted the sample to participants without pregnancies after the nuMoM2b index pregnancy (n = 1263). Compared with participants who had a subsequent pregnancy, participants who did not have an intervening pregnancy had a higher proportion of self-identified White race and commercial insurance, and lower proportion of obesity. In this subgroup, each 0.1-unit increase in maximum PI was associated with a 4 % increased odds of incident hypertension (adjusted OR 1.04, 95%CI 1.00–1.07). There were no other significant associations between UAD parameters and future hypertension in this subgroup.

Table 2
Association of Uterine Artery Doppler Parameters with Incident Hypertension 2–7 Years Later Among nuMoM2b-HHS Participants.

	Hypertension	No hypertension	Unadjusted OR (95 % CI)[2/]	Adjusted OR (95 % CI)[1/2/]
	n/N (%)	*n/N (%)*		
Bilateral diastolic notch	37/706 (5.2 %)	669/3033 (4.9 %)	1.06 (0.73, 1.53)	1.05 (0.70, 1.55)
	Mean (SD)	*Mean (SD)*		
RI_{max}[3/]	0.65 (0.14)	0.63 (0.12)	1.17 (1.05, 1.31)*	1.15 (1.03, 1.30)*
PI_{max}[4/]	1.37 (0.65)	1.24 (0.57)	1.03 (1.01, 1.05)*	1.03 (1.00, 1.05)*

Abbreviations: RI = resistance index [(maximum - minimum velocity)/maximum flow velocity]; PI = pulsatility index [(maximum - minimum velocity)/mean flow velocity]; SD = standard deviation; OR = odds ratio; CI = confidence interval; APO = adverse pregnancy outcome.
[1/]Adjusted for maternal age, BMI, race/ethnicity, smoking, health insurance, and any APO.
[2/]ORs are calculated for a 0.1 unit increase. * indicates OR CI excludes 1.
[3/]RI_{max} = higher of the two RI values (right or left uterine artery). Reference range of RI_{max} from entire nuMoM2b cohort (N = 8024) at this time point: median 0.57 (IQR 0.49–0.66).[17].
[4/]PI_{max} = higher of the two PI values (right or left uterine artery). Reference range of PI_{max} from entire nuMoM2b cohort (N = 8024) at this time point: median 0.95 (IQR 0.75–1.26).[17].

Table 3
Unadjusted and Adjusted Association of Dichotomized Maximum RI and PI with Incident Hypertension 2–7 Years Later Among nuMoM2b-HHS Participants.

	Hypertension	No hypertension	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)[1/]
	n/N (%)	n/N (%)		
Maximum RI > 0.84	19/164 (11.6 %)	168/3575 (4.7 %)	2.66 (1.61, 4.39)*	2.49 (1.45, 4.26)*
Maximum PI > 2.30	23/207 (11.1 %)	164/3532 (4.6 %)	2.57 (1.62, 4.07)*	2.36 (1.45, 3.86)*

Abbreviations: RI = resistance index; PI = pulsatility index; N = sample size; n = number in category; OR = odds ratio; CI = confidence interval. * indicates OR CI excludes 1.
[1/]Adjusted for maternal age, BMI, race/ethnicity, smoking, health insurance, and any APO.

4. Discussion

4.1. Summary of results

In this analysis of a prospective cohort of nulliparous people without baseline hypertension, we investigated whether second trimester UAD parameters indicative of reduced uterine compliance were associated with the development of maternal hypertension 2–7 years after the index pregnancy. We found that high thresholds of resistance and pulsatility indices were associated with a two-fold higher odds of developing hypertension, an association which persisted after multivariable adjustment.

4.2. Interpretation of results

The hypothesis that UAD parameters might reflect maternal cardiovascular risk is biologically plausible. The "Great Obstetrical Syndromes" including preeclampsia and other hypertensive disorders of pregnancy, preterm delivery, fetal growth restriction, placental abruption and stillbirth, are classically described as disorders of placental insufficiency [25]. Early in pregnancy, fetal trophoblast cells migrate along maternal spiral arteries in the endometrium and induce vascular remodeling, resulting in a low-resistance, high-flow state which promotes delivery of oxygen and nutrients from the maternal circulation to the placenta [25,26]. This increased compliance is reflected in uterine Doppler indices such as the RI and PI: on average, by 18 weeks of healthy gestation, the RI decreases from 0.8 to 0.63 and the PI from 2.0 to 1.3 [27]. Failure of remodeling results in maternal spiral arteries remaining in a high-resistance state [26]. This increased resistance of the uteroplacental system is reflected by increases in the RI and PI, and is thought to indicate placental insufficiency [28,29]. However, recent work showed that higher uterine artery PI also correlated with abnormalities in maternal cardiovascular function during pregnancy, such as decreased cardiac output and increased peripheral vascular resistance [18]. Our results suggest that some UAD parameters, specifically the RI and PI, might be physiological biomarkers revealing underlying maternal vascular pathology in addition to placental pathology, offering insight into potential mechanisms to explain the well-described link between abnormal uteroplacental function and future maternal cardiovascular risk. Spiral artery remodeling in pregnancy is a complex process, occurring in coordinated stages involving vascular endothelial cells, vascular smooth muscle cells and surrounding extracellular matrix proteins, and maternal immune cells, particularly cytokine-producing decidual natural killer cells [30] and regulatory T cells [31]. We hypothesize that failure of spiral artery remodeling and subsequent poor uterine artery compliance reflects underlying maternal vascular dysfunction and immune dysregulation, factors which are also associated with future maternal cardiovascular risk. Failure of spiral artery remodeling and consequent changes in uteroplacental flow dynamics (i.e. increased pulsatility and resistance) have also been shown to result in the release of placental inflammatory factors leading to acute placental atherosis [31] and a systemic maternal inflammatory response [32], which may have lasting effects on maternal cardiovascular risk [33]. It is possible that failure of spiral artery remodeling may itself contribute to chronic inflammation, accelerated atherosclerosis and the pathogenesis of maternal cardiovascular disease.

4.3. Study strengths

Strengths of our study include its prospective nature, the diversity of the cohort, and the collection of detailed physiological parameters during the index pregnancy and at the follow up HHS visit. UADs were performed according to a rigorous and standardized protocol. All index pregnancy outcomes were defined according to standardized protocols and adjudicated by study investigators, making it unlikely that APOs were misclassified.

4.4. Study limitations

Our study has limitations. Subsequent pregnancies have not undergone similar deep phenotyping to date, and thus we were unable to evaluate whether Doppler findings in subsequent pregnancies showed similar associations. The relatively low incidence of hypertension of 5 % limited our power to detect some associations and interactions. In addition, the 588 participants who were excluded due to incomplete UAD measurements may have had characteristics, such as obesity, that would both increase the chance for incomplete UAD measurements and increase the risk for hypertension in the future. As participants in this important cohort continue to age and return for subsequent study visits, we intend to evaluate the impact of additional pregnancy APOs to modify the association between Doppler indices and future hypertension. In addition, not all participants in the nuMoM2b cohort who underwent UAD returned for the nuMoM2b-HHS study visit. However, a prior analysis showed that people in the original nuMoM2b cohort who did not participate in the nuMoM2b-HHS study visit did not differ significantly in demographic characteristics, pregnancy outcomes or comorbidities from people who did participate [20].

5. Conclusion

In a prospective cohort of 3739 participants followed from early in their first pregnancies through several years after delivery, higher RI and PI detected via second-trimester uterine artery Doppler were independently associated with increased odds of incident hypertension after the index pregnancy, regardless of pregnancy outcome. Future research should investigate RI and PI as candidate biomarkers of maternal vascular risk.

Credit author statement

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Disclosures

Dr. Miller received personal compensation from Finch McCranie, LLP and Argionis & Associates, LLC for expert testimony regarding maternal stroke, and personal compensation from Elsevier, Inc for editorial work on Handbook of Clinical Neurology, Vols 171 and 172 (Neurology of Pregnancy). Dr. Miller has no relationships with industry. No other authors have disclosures or relationships with industry.

Funding

Dr. Miller is supported by the National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (Bethesda, MD) (K23NS107645, 3K23NS107645-02S1), NIH National Institute on Aging (R21AG069111) and the Louis V. Gerstner, Jr. Foundation (Gerstner Scholars Program). This study is supported by cooperative agreement funding from the NIH National Heart, Lung, and Blood Institute (Bethesda, MD) and the NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (Bethesda, MD): U10-HL119991; U10-HL119989; U10-HL120034; U10-HL119990; U10-HL120006; U10-HL119992; U10-HL120019; U10-HL119993; U10-HL120018, and U01-HL145358. Support was also provided by the National Center for Advancing Translational Sciences (Bethesda, MD) through UL-1-TR000124, UL-1-TR000153, UL-1-TR000439, and UL-1-TR001108; and the Barbra Streisand Women's Cardiovascular Research and Education Program (Los Angeles, CA); and the Erika J. Glazer Women's Heart Research Initiative, Cedars-Sinai Medical Center (Los Angeles, CA). Dr. Bello is supported by the NIH/NHLBI (K23HL136853, R01HL153382).

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and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the U. S. Department of Health and Human Services.

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