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Original Article
Epidemiology

Maternal risk of hypertension 7–15 years after pregnancy: clues from the placenta

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Objective To assess whether pre-eclampsia (PE)-related placental/extraplacental membrane findings are linked to moderately elevated blood pressure (BP) in pregnancy and later-life hypertension.

Design Prospective cohort.

Setting 52 prenatal clinics, 5 Michigan communities.

Sample The POUCH Study recruited women at 16–27 weeks' gestation (1998–2004) and studied a sub-cohort in depth. This sample (n = 490) includes sub-cohort women with detailed placental assessments and cardiovascular health evaluations 7–15 years later in the POUCHmoms follow-up study.

Methods PE-related placental/extraplacental membrane findings (i.e. mural hyperplasia, unaltered/abnormal vessels or atherosis in decidua; infarcts) were evaluated in relation to pregnancy BP and odds of Stage 2 hypertension at follow up using weighted polytomous regression. Follow-up hypertension odds also were compared in three pregnancy BP groups: normotensives (referent) and moderately elevated BP with or without PE-related placental/extraplacental membrane findings.

Main outcome measures Stage 2 hypertension (SBP ≥140 mmHg and/or DBP ≥90 mmHg, or using antihypertensive medications) at follow up.

Results After excluding women with pregnancy hypertension (i.e. chronic, PE, gestational), mural hyperplasia and unaltered/abnormal decidual vessels were each associated with Stage 2 hypertension at follow up: adjusted odds ratio (aOR) = 2.7, 95% CI 1.1–6.6, and aOR = 1.7 (95% CI 0.8–3.4), respectively. Women with moderately elevated BP in pregnancy and evidence of mural hyperplasia or unaltered/abnormal decidual vessels had greater odds of Stage 2 hypertension at follow up: aOR = 4.5 (95% CI 1.6–12.5 and aOR = 2.6, 95% CI 1.1–5.9, respectively.

Conclusions PE-related placental/extraplacental membrane findings help risk-stratify women with moderately elevated BP in pregnancy for later development of hypertension.

Keywords Epidemiology: general obstetrics, maternal physiology, medical disorders in pregnancy, placental pathology, risk management, translational research.

Tweetable Abstract Placental findings associated with mother's risk of later-life hypertension.

Linked article This article is commented on by SC Lean, p. 837 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16579.

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Introduction

A larger percentage of cardiovascular disease (CVD) is attributable to hypertension among women than among men,[1] and women experience blood pressure (BP) increases at a younger age.[2] Early identification of women at increased risk of hypertension, close monitoring and timely interventions could mitigate diseases such as CVD and chronic kidney disease. Studies consistently observe a positive link between pre-eclampsia (PE) in pregnancy and a woman's risk of later-life hypertension and CVD.[3-6] Investigators hypothesise that PE and later-life hypertension share underlying risk factors that pre-date pregnancy,[7] and the physiological experience of PE might contribute to later

hypertension and CVD.[8] Currently, the American Heart Association and the American College of Obstetricians and Gynecologists recommend using history of PE for CVD risk stratification and targeted medical care management.[9]

Recently we reported on blood pressure among women in the Pregnancy Outcomes and Community Health (POUCH) Study who were re-evaluated in the POUCHmoms Study 7–15 years later. Those with even moderately elevated BP during the POUCH Study pregnancy (defined by 2015 criteria for 'pre-hypertension' in non-pregnant populations) were more likely to have hypertension at follow up, with an odds ratio of 2.6 compared with normotensive in pregnancy.[10] A considerable proportion of POUCH Study women (64%) met the criteria for moderately elevated BP in pregnancy. We hypothesised that within this large group, a subset carried the greatest risk for later-life hypertension, potentially with underlying pathology similar to that of women with hypertensive disorders of pregnancy.

To examine this hypothesis we used placental/extraplacental membrane pathology data and pregnancy BP data from the original POUCH Study in combination with BP data from the POUCHmoms follow up. We focused on placental/extraplacental membrane maternal vessel findings frequently associated with PE, i.e. unusually thick maternal vessel walls (mural hyperplasia), decreased remodelling of maternal vessels, placental disc infarcts and decidual blood vessel 'atherosis'. We also considered placental evidence of chorioamnionitis, a pathology not typically linked to PE, to make sure our findings were specific to PE-related placental pathology. Our main goals were to answer the following questions:

- Is PE-associated placental/extraplacental membrane pathology related to an increased risk of moderately elevated BP in pregnancy?
- After excluding women with hypertensive disorders of pregnancy, is PE-associated placental/extraplacental membrane pathology linked to an increased risk of later-life hypertension?
- Does the presence/absence of PE-associated placental/extraplacental membrane modify the relation between moderately elevated BP in pregnancy and risk of later-life hypertension?

Materials and methods

Study design

This prospective cohort includes a pregnancy study, the POUCH Study, and a maternal follow-up component, the POUCHmoms Study.[11] The POUCH Study enrolled 3019 pregnant women at 16–27 weeks' gestation (1998–2004) from 52 clinics in five Michigan communities[12] with the aim of studying biological and social factors affecting adverse pregnancy outcomes. Inclusion criteria were singleton pregnancy with no known congenital anomaly, maternal age ≥15 years, maternal serum alpha-fetoprotein (MSAFP) screening, no pre-pregnancy diabetes mellitus, and English speaking. Approval for this study was obtained from institutional review boards at MSU, Michigan Department of Community Health, and nine community hospitals. This study did not include core outcome sets and participants were not directly involved in shaping the research.

To conserve resources, a sub-cohort of 1371 POUCH Study participants was studied in greater depth (e.g. medical records abstracted, biological samples analysed, placental pathology). The sub-cohort was constructed by oversampling women with preterm delivery (PTD) and women with a higher risk of pregnancy complications (i.e. African-Americans, women with high MSAFP). To account for the cohort and sub-cohort sampling strategy, inverse-probability sampling weights are used in all POUCH and POUCHmoms Study analyses. For example, African-American women, women with high MSAFP and women with PTD who were oversampled into the sub-cohort are assigned a 'smaller weight' so that they represent their proportion in the eligible population agreeing to participate in the original POUCH Study.

Of the 1371 sub-cohort women, 1280 accepted future study participation and were presumed alive at the initiation of the POUCHmoms Study (Figure S1), which was designed primarily to assess risk factors for early evidence of CVD at 7–15 years post-POUCH Study pregnancy. Between 2011 and 2014, 678 POUCHmoms Study participants completed interviews and CVD-related assessments, i.e. BP, carotid ultrasounds, anthropometrics, heart rate variability and blood biomarkers. Women's age at follow up ranged from 25 to 58 years. For the current analyses, we excluded women if they lacked complete placenta information, i.e. placentas not saved at delivery or insufficient decidual tissue for assessment (n = 160), had chronic hypertension before/during the POUCH Study pregnancy (n = 22) or were missing prenatal records (n = 6), leading to a final sample of 490 women.

Measures

Blood pressure in pregnancy

Eight pregnancy BP measures were abstracted from the medical records, i.e. the two highest systolic blood pressures (SBP) and diastolic blood pressures (DBP) recorded *before* 20 weeks' gestation, and the two highest SBP and DBP recorded *at or after* 20 weeks' gestation. Women were categorised into four groups: (1) normal BP, i.e. SBP <120 mmHg and DBP <80 mmHg or can exceed this only one time; (2) moderately elevated BP, i.e. at least two

SBP ≥120 mmHg or at least two DBP ≥80 mmHg but no hypertensive disorder of pregnancy; (3) gestational hypertension (GH), i.e. explicit diagnosis of GH in medical records and/SBP ≥140 mmHg or DBP ≥90 mmHg on two occasions after 20 weeks' gestation without proteinuria; and (4) PE, i.e. the criteria of group 3 plus proteinuria. The Group 3 and 4 criteria were standard at the time of the POUCH Study[13] and details of the data/process used for group assignment appear in a previous POUCH Study publication.[14]

Placental pathology findings

The POUCH Study developed a detailed protocol for placental evaluation.[12] Briefly, formalin-fixed placentas were examined grossly and nine tissue samples were embedded in paraffin blocks for microscopic assessment: two extra-placental membrane (membrane roll) samples; two umbilical cord samples (one proximal and one distal to disc insertion); and five full-thickness disc samples, one at the cord insertion, one in central tissue that appeared normal on gross exam, two from central tissue and one at the margin (these latter three were representative of grossly visible abnormalities if present). The study pathologist (PKS) was blinded to all clinical data and to gross examination findings when performing microscopic examinations.

Of particular interest for these analyses, the pathologist recorded two groups of placental/extra-placental membrane findings often linked to PE. The first group, known as 'maternal vascular-developmental', included mural hyperplasia and unaltered/abnormal decidual (meaning inadequately remodelled or otherwise abnormal) vessels (Figure S2a–d).[15] Mural hyperplasia, defined as an increased thickening of the decidual vessel wall with three or more visible muscle cell layers and decreased luminal diameter, was not common in POUCH Study placentas. Only 15% of placentas showed evidence of mural hyperplasia in one or more of the seven decidual samples examined per placenta. Therefore, one positive decidual sample was the cut-point for a positive placenta. By contrast, unaltered/abnormal decidual vessels often appeared in a single decidual sample but less often were observed in two or more decidual samples (about 38% of placentas), therefore the latter was used as the cut-point for positive. Previous POUCH Study results showed these placental findings, using the aforementioned cut-points, were associated with an increased risk of both medically indicated and spontaneous PTD at <35 weeks' gestation.[15]

A second group of PE-related placental findings, 'maternal vascular obstructive', included infarcts and decidual blood vessel 'atherosis'[15] (Figure S2e). Some pathologists consider placenta margin infarcts less important/informative than central disc infarcts,[16,17] motivating us to evaluate the two locations separately. We categorised 'atherosis', margin infarcts and central disc infarcts as present if observed in any one placental/extra-placental membrane sample. In our previous work, 'atherosis' and infarcts were associated with increased risk of medically indicated PTD.[15]

As a test of specificity, we also considered histological chorioamnionitis (HCA), which typically is not associated with PE. HCA, defined as an advanced maternal inflammatory response or fetal inflammatory response in the chorion/amnion, was linked to increased risk of spontaneous PTD at <35 weeks' gestation in the POUCH Study.[12]

Blood pressure at follow up

Blood pressure measures in the POUCHmoms Study were obtained by study nurses or ultrasonographers who followed the Joint National Committee (JNC) guidelines.[18] Women sat with the arm extended level to the heart and three consecutive BPs were recorded 1 minute apart using either a Panasonic EW3109W (Panasonic Corp., Newark, NJ, USA) or an Omron Hem-907 (Omron Healthcare, Inc., Lake Forest, IL, USA) with a small, medium or large cuff as indicated by arm size. Digital monitors were compared with manual readings to ensure accuracy. The second and third BP measures were averaged to create a final SBP and DBP. According to JNC-8 Guidelines, women were categorised as either normotensive/slightly elevated BP (SBP <130 mmHg and DBP <80 mmHg), Stage I hypertension (SBP 130–139 mmHg and/or DBP 80–89 mmHg) or Stage 2 hypertension (SBP ≥140 mmHg and/or DBP ≥90 mmHg or using antihypertensive medications). The normal BP and the slightly elevated BP were combined due to the small number of the latter.

Covariates

Women's age (continuous) and body mass index (BMI, continuous) at enrolment in the POUCH Study, number of years to the follow-up visit (continuous 7–15 years), race/ethnicity (binary: white/other and African-American) and smoking status during pregnancy (yes, no) were each evaluated as potential confounding variables in our analyses. Pregnancy BMI was highly correlated with BMI at follow up; we chose to use the former given that follow-up BMI can't directly influence previous placental findings (and therefore is not a direct confounder).

Analytic strategy

Analyses were performed with survey procedures in SAS v9.3 (SAS Institute Inc., Cary, NC, USA) to account for the original POUCH Study sampling design and weighting. Maternal characteristics were compared between the POUCHmoms Study follow-up sample with our inclusion criteria (n = 490) and the remaining sub-cohort POUCH Study mothers (Chi-square test). We first evaluated placental findings (positive and negative cut-points described

Table 1. Characteristics of study sample during the POUCH Study and 7–15 years later at follow-up POUCHmoms Study

	POUCH Study			At POUCHmoms Follow up 7–15 years later		
	n	%	Weighted %*	*n*	%	Weighted %*
Maternal age (years)						
<0	355	72	72	38	8	8
30–39	134	27	28	277	56	54
≥40	1	0.2	0.04	175	36	38
Maternal education (years)						
<12	92	19	18	32	7	6
=12	124	25	24	66	13	12
>12	274	56	58	392	80	82
Maternal race/ethnicity						
White/other	318	65	75			
African-American	172	35	25			
Medicaid insurance						
No	251	51	56	317	65	69
Yes	239	49	44	173	35	31
Pre-pregnancy BMI						
Underweight	26	5	4			
Normal	222	45	47			
Overweight	102	21	22			
Obese	140	29	27			
Parity						
0	215	44	44	0	0	0
1	31	6	4	44	9	8
≥2	244	50	52	446	91	92
Smoking during pregnancy						
Yes	137	28	28			
No	353	72	72			
Preterm						
Yes	118	24	11			
No	372	76	89			
Blood pressure during pregnancy						
Normal blood pressure	152	31	28			
Moderately elevated blood pressure	298	61	65			
Gestational hypertension	25	5	4			
PE	15	3	3			
Blood pressure at follow up						
Normal blood pressure				287	58	59
Elevated blood pressure				21	4	5
Stage I hypertension				96	20	20
Stage II hypertension				86	18	16

*Weighted for POUCH Study sampling protocol of cohort and sub-cohort; these percentages approximate prevalences in eligible population agreeing to participate in the POUCH Study.

above) as 'exposure variables' with a four-level 'outcome variable' of maternal BP in pregnancy, i.e. normal BP, moderately elevated BP, GH, PE (Chi-square test). Next, we used weighted polytomous regression models, unadjusted and adjusted with all the previously described covariates, to assess associations between the 'exposure variable, 'placental findings' and our three-level 'outcome variable' of BP at follow up after excluding women with GH and PE.

In a final set of analyses, we considered whether placental findings could help identify which women with moderately elevated BP in pregnancy were at greatest risk of hypertension at follow up. We created a three-group 'exposure' variable for BP in pregnancy and each placental

finding, i.e. group 1 normal BP (ref), group 2 moderately elevated BP and (−) placental finding, and group 3 moderately elevated BP and (+) placental finding. We used this as exposure variable and in relation to the 'outcome variable', BP at follow up, in the polytomous regression models.

Results

Maternal characteristics at the time of enrolment in the original POUCH Study and at the follow up POUCHmoms Study are described in Table 1 for our analytic sample; we provide absolute percentages and percentages weighted for the POUCH Study sampling scheme. We compared these characteristics among three groups (data not shown); (1) women in the current analyses (n = 490); (2) women in the POUCHmoms follow-up study who were removed from these analyses because of incomplete placenta assessments, chronic hypertension or incomplete pregnancy BP data (188); and (3) women eligible for the POUCHmoms Study but not followed up (n = 693). Groups 1 and 2 are similar on all variables listed in Table 1. Group 3, those not followed, had lower levels of education and were more likely to be insured by Medicaid at entry to the POUCH Study. In addition, African-American women were less likely to be in the follow-up study (unweighted 35% of the current study, 47% of those not followed). The variables pre-pregnancy BMI, hypertension disorders of pregnancy and PTD were comparable across all three groups.

First, we examined placental pathology and BP in pregnancy. The prevalence of PE appeared higher in women with PE-associated placental pathology findings, i.e. mural hyperplasia, unaltered/abnormal decidual vessels, infarcts and decidual blood vessel atherosis, as compared with women without these placental findings. However, the small numbers of women with PE made estimates and comparisons imprecise (Table 2). Two of the PE-associated placental findings – mural hyperplasia and unaltered/abnormal decidual vessels – also were linked to a higher prevalence of moderately elevated BP in pregnancy. Placental infarcts were positively associated with GH. By contrast, histological chorioamnionitis did not raise the risk of elevated BP in pregnancy.

Next, we assessed placental pathology and BP at follow up after excluding women with PE and GH. The odds of Stage 2 hypertension 7–15 years after the POUCH Study pregnancy were elevated among women with placental evidence of mural hyperplasia during the POUCH Study: adjusted odds ratio (aOR) = 2.7, 95% CI 1.1–6.6 (Table 3). In an unadjusted model, a twofold increased odds of Stage 2 hypertension at follow up were observed among women with unaltered/abnormal decidual vessels, though in the adjusted model the confidence interval included one:

Table 2. Placental/extraplacental membrane findings and maternal blood pressure in the POUCH Study pregnancy (n = 490)

Placental/extraplacental membrane findings	*n* (%*)	Normal blood pressure (*n* = 152)	Moderately elevated blood pressure (*n* = 298)	Gestational hypertension (*n* = 25)	Pre-eclampsia (*n* = 15)
		n (%*)	*n* (%*)	*n* (%*)	*N* (%*)
Mural hyperplasia					
No (0/7)**	413 (84%)	139 (34%)	237 (57%)	25 (6%)	12 (3%)
Yes (≥1/7)**	77 (16%)	13 (17%)	61 (79%) P = 0.05***	0	3 (4%) P = 0.36***
Unaltered/abnormal decidual vessels					
None or one (0/7 or 1/7)**	261 (53%)	91 (35%)	145 (56%)	19 (7%)	6 (2%)
Two or more (≥2/7)**	229 (47%)	61 (27%)	153 (67%) P = 0.08***	6 (2%) P = 0.15***	9 (4%) P = 0.32***
Atherosis					
No	464 (95%)	145 (31%)	282 (61%)	25 (5%)	12 (3%)
Yes	26 (5%)	7 (27%)	16 (61%) P = 0.79***	0	3 (12%) P = 0.66***
Infarct					
None	324 (66%)	108 (33%)	200 (62%) P = 0.32***	11 (3%) P <0.05***	5 (2%) P <0.05***
Disc margin only	108 (22%)	27 (25%)	64 (59%)	9 (9%)	8 (7%)
central disc	58 (12%)	17 (29%)	34 (59%)	5 (9%)	2 (3%)
Histological chorioamnionitis					
No	437 (89%)	126 (29%)	272 (62%)	25 (100%)	14 (88%)
Yes	53 (11%)	26 (49%)	26 (44%) P <0.05***	0	1 (2%) P = 0.92***

*Weighted for the sub-cohort sampling scheme.
**Number of positive samples among the seven decidual samples examined per placenta.
***Chi-square comparison with no placental abnormality and normal blood pressure as referents.

Table 3. Associations between placental/extraplacental membrane findings and maternal blood pressure at follow up (7–15 years after POUCH Study pregnancy) among women with no hypertensive disorders during the POUCH Study pregnancy (n = 450)

	Blood pressure at follow up						
	Normal/slightly elevated (ref) <130 systolic BP and <80 diastolic BP	Stage 1 hypertension 130–139 systolic BP and/or 80–89 diastolic BP			Stage 2 hypertension ≥140 systolic BP and/or ≥90 diastolic BP or currently taking medications		
	n (ref)	*n*	OR*	aOR***	*n*	OR*	aOR***
Placental/extraplacental membrane findings							
Mural hyperplasia							
No (0/7)**	253	71	1.0	1.0	52	1.0	1.0
Yes (≥1/7)**	42	12	0.8 (0.4–1.8)	0.8 (0.3–2.0)	20	**2.9 (1.4–5.8)**	**2.7 (1.1, 6.6)**
Unaltered/abnormal decidual vessels							
None or one (0–1/7)**	167	42	1.0	1.0	27	1.0	1.0
Two or more (≥2/7)**	128	41	1.1 (0.6–1.9)	0.9 (0.5–1.8)	45	**2.1 (1.1–3.9)**	1.7 (0.8, 3.4)
Atherosis							
No	284	78	1.0	1.0	65	1.0	1.0
Yes	11	5	1.0 (0.3–3.3)	0.8 (0.2–3.1)	7	1.9 (0.7–5.6)	1.3 (0.4, 4.7)
Infarct							
None	200	55	1.0	1.0	53	1.0	1.0
Disc margin only	60	21	1.2 (0.6–2.5)	1.4 (0.7–2.8)	10	0.8 (0.3–1.8)	0.9 (0.4, 2.4)
Central disc	35	7	0.8 (0.3–2.1)	0.8 (0.3–2.0)	9	1.0 (0.4–2.4)	0.8 (0.3, 2.1)
Histological chorioamnionitis							
No	264	72	1.0	1.0	62	1.0	1.0
Yes	31	11	0.9 (0.4–2.2)	0.9 (0.3–2.3)	10	1.3 (0.5–3.2)	1.1 (0.5–2.5)

Bold indicates to highlight the results that have a confidence interval that does not include 1.0 (there by statistically signifcant).
*Weighted for the POUCH Study sub-cohort sampling scheme.
**Number of positive samples among the seven decidual samples examined per placenta.
***Adjusted for maternal race, maternal age at enrolment, interval of follow up, smoking before pregnancy and pre-pregnancy BMI at POUCH Study.

aOR = 1.7, 95% CI 0.8–3.4. Placental infarcts, 'atherosis' and HCA were not associated with blood pressure at follow up; however, the number of women with decidual blood vessel 'atherosis' was too small to adequately assess their risk.

A final set of analyses used findings in POUCH Study placentas to stratify women with moderately elevated BP during the POUCH Study pregnancy. The focus was on two placental findings associated with follow-up hypertension in the previous analyses, i.e. mural hyperplasia or unaltered/abnormal decidual vessels. The odds of Stage 2 hypertension in the placenta pathology-stratified, moderately elevated BP groups were compared with that of women with normal BP in pregnancy. Approximately one-third of women with both moderately elevated BP in pregnancy and placental mural hyperplasia went on to have Stage 2 hypertension at follow up; aOR = 4.5 (95% CI 1.6, 12.5) (Table 4). A similar pattern was observed for women with both moderately elevated BP in pregnancy and unaltered/abnormal decidual vessels: aOR = 2.6, 95% CI 1.1–5.9. Women with moderately elevated BP in pregnancy but no mural hyperplasia or unaltered/abnormal decidual vessels were not at increased risk of Stage 2 hypertension at follow up.

Discussion

Main findings

We assessed BP and placental/extraplacental membrane findings among pregnant women who later were evaluated (7–15 years after the pregnancy) for CVD risk factors including hypertension. We observed that women who did not meet the definition of hypertensive disorders of pregnancy but whose placentas showed evidence of decidual vessel mural hyperplasia and/or unaltered/abnormal vessels were at increased risk of Stage 2 hypertension at follow up. In addition, these same decidual vessel findings helped risk-stratify women with moderately elevated BP in

Table 4. Associations between moderately elevated blood pressure during pregnancy, stratified by placental/placental membrane findings, and maternal blood pressure at follow up (7–15 years after POUCH Study pregnancy) among women with no hypertensive disorders during the POUCH Study pregnancy (n = 450)

	Blood pressure (BP) at follow up (n = 450)						
	Normal/slightly elevated BP (ref) <130 systolic BP and <80 diastolic BP	Stage 1 hypertension			Stage 2 hypertension		
		130–139 systolic BP and/or 80–89 diastolic BP			≥140 systolic BP and/or ≥90 diastolic BP or currently taking medications		
	n (ref)	*n*	OR*	aOR**	*n*	OR*	aOR**
Blood pressure in pregnancy and placental/extraplacental membrane findings							
Normal BP (ref)	106	30	1.0	1.0	16	1.0	1.0
Moderately elevated BP/− Mural hyperplasia (0/7)	155	46	1.1 (0.6–2.0)	1.0 (0.5–2.1)	36	1.5 (0.7–3.2)	1.6 (0.7–3.6)
Moderately elevated BP/+ Mural hyperplasia (≥1/7)	34	7	0.6 (0.2–1.9)	0.6 (0.2–2.0)	**20**	**5.1 (2.1–12.4)**	**4.5 (1.6–12.5)**
Normal BP (ref)	106	30	1.0	1.0	16	1.0	1.0
Moderately elevated BP/None or one (0–1/7) unaltered/abnormal decidual vessels	99	27	1.0 (0.5–2.0)	1.0 (0.4–2.2)	19	1.3 (0.6–3.1)	1.6 (0.6–4.1)
Moderately elevated BP/Two or more (≥2/7) unaltered/abnormal decidual vessels	90	26	1.0 (0.5–2.1)	0.9 (0.4–2.0)	37	**2.9 (1.3–6.2)**	**2.6 (1.1–5.9)**

Bold indicates to highlight the results that have a confidence interval that does not include 1.0 (there by statistically signifcant).
*Weighted for the POUCH Study sub-cohort sampling scheme.**Adjusted for maternal race, maternal age at enrolment, interval of follow up, smoking before pregnancy and pre-pregnancy BMI at POUCH Study.

pregnancy, i.e. those with mural hyperplasia and/or unaltered/abnormal vessels had a two- to five-fold increased odds of Stage 2 hypertension at follow up, whereas those without these vessel findings showed no significant elevated risk.

Strengths and limitations

There are several major strengths of this study. Participants were diverse in socio-economic indicators and were sampled from multiple prenatal clinics situated within multiple communities, thereby enhancing the generalisability of our findings. We looked at the prevalence of 'normal BP' in pregnancy, hypertensive disorders (PE, GH) and an understudied group – women with moderately elevated BP in pregnancy – in relation to placental pathology findings. The placental findings were identified through a rigorous, unbiased protocol (pathologist blinded to pregnancy outcome, clinical complications and gross placental examination data) applied equally to placentas from routine and complicated pregnancies. Many studies rely on placentas selected for examination at inner city teaching hospitals and rarely are placentas analysed without knowledge of clinical information. We showed specificity of the positive association between decidual vessel findings and later risk of hypertension by demonstrating no link with the placental complication HCA. Trained study professionals obtained BP measures at follow up using a standard protocol. Often, women's health from pregnancy to later life is studied with extant data and there is considerable variability in measures of BP documented later in life.

Limitations of our study include small sample sizes for some placental findings, e.g. 'atherosis'. The study sample was not entirely comparable to the original POUCH Study sub-cohort, e.g. the latter had a larger proportion of African-American women. Race/ethnicity was a POUCH Study sampling stratum, therefore sampling weights used in our analytic models provide some adjustment for this discrepancy. Still, we recognise that within a sampling stratum those followed up may not be completely representative. It seems unlikely, however, that follow up would be biased according to placental findings, and the proportions of women with PTD or hypertensive disorders of pregnancy in our study sample (weighted 11 and 7%, respectively) and in the remaining sub-cohort women (weighted 11 and 7%, respectively) were the same. Women in the follow-up POUCHmoms Study were 25–58 years of age with a modest prevalence of hypertension consistent with this age range; our results may be most applicable to women who become hypertensive at these earlier ages. Although the placentas/extraplacental membranes offered compelling

information on women's future health, it may be challenging clinically to identify these decidual vessel findings in large groups of deliveries, e.g. all women with moderately elevated BP in pregnancy. Thus, our results also motivate future research to identify biomarkers that correlate with placental vessel findings and, along with other co-factors, can be used to predict later-life hypertension.

Interpretation

For decades, studies repeatedly demonstrated that women with PE are more likely to develop CVD[4,19] including hypertension[20] later in life. More recent reports extended this increased risk to include women with GH.[21,22] As a result, clinicians are encouraged to query woman about their history of hypertensive disorders of pregnancy and manage these patients accordingly. Thus, pregnancy is unique in offering a window into future CVD risk before overt, persistent clinical signs begin.

The clinical convention of BP cutoffs to define hypertensive disorders of pregnancy is guided by risks to mother and fetus during pregnancy and not by mother's future risk of hypertension. We have been interested in moderately elevated BP in pregnancy because in non-pregnant populations, future risk of CVD increases across the BP spectrum[23] and cut-offs for intervention have been shifting downward.[24] Many factors influence BP during pregnancy, but our previous report of increased risk for later-life hypertension among women with moderately elevated BP in pregnancy[10] motivated further consideration of this group. Here we showed that the addition of placental/extraplacental membrane findings associated with PE can help further risk-stratify women with moderately elevated BP in pregnancy.

Among the few reports of placental findings and later maternal health, most include women with clinical complications such as PE[25] or preterm birth[25,26] as added risk factors. One Swedish study reported a positive association between history of placental abruption and higher maternal BP at age 40.[27] Another study observed a link between delivery of an small-for-gestational-age (SGA) infant (a possible proxy for placental vascular pathology) and maternal endothelial dysfunction 6 months after delivery, even in the absence of PE.[28] Among women in our study with moderately elevated BP in pregnancy and evidence of placental vascular pathology (mural hyperplasia and/or unaltered/abnormal vessels in the decidua) who went on to have hypertension at follow up, most (two-thirds) had neither a preterm birth nor an SGA infant during the POUCH Study pregnancy.

In POUCH Study placentas, mural hyperplasia in decidual vessels occurred less frequently than unaltered/abnormal vessels did, and these two findings were strongly correlated, i.e. 94% of placentas with mural hyperplasia in decidual vessels showed evidence of unaltered/abnormal vessels, whereas 31% of women with at least two of seven decidual samples showing unaltered/abnormal vessels had evidence of mural hyperplasia. Mural hyperplasia may represent an extreme of unaltered/abnormal vessels, with inability of the trophoblasts to remodel vessel walls and atypical vessel response to pregnancy. Of note, about 18% of POUCH Study women with PE in our initial analysis showed evidence of mural hyperplasia in decidual vessels and 52% showed unaltered/abnormal vessels in two more decidual vessel samples. Although we excluded 22 POUCH Study sub-cohort women with chronic hypertension (CH) from this analysis, a look back at their placental findings indicate that their prevalence of mural hyperplasia in decidual vessels (8%) was similar to that of women with normal BP in pregnancy. Their prevalence of unaltered/abnormal vessels was high (54%) and similar to that of women with PE, but the small number of women with CH and placental data precludes any strong inferences. Interestingly, whereas placental infarcts were more common in women with GH and PE, they were not associated with hypertension 7–15 years post-delivery.

Conclusion

Our findings suggest the 'window of pregnancy' contains clues beyond the obvious complications of PE, GH, PTD or SGA, to mothers' future vascular health. Maternal vessel placental/extraplacental membrane findings typically associated with PE help risk-stratify women with moderately elevated BP in pregnancy who are at greater risk of later-life hypertension.

Disclosure of interests

None declared. Completed disclosure of interests forms are available to view online as Supporting Information.

Contribution to authorship

CBH, PS, GLD, KLS, JMC originated the idea for this specific project. CBH, PS, GLD, KLS, JMC designed this project. CBH, PS, BLB and JMC contributed to the design of the POUCH and POUCHmoms Studies and the acquisition of the data. CBH, PS, GLD, KLS, YT, JX, ME, JMC contributed to the development of the analytical plan and interpretation of results. JX and YT analysed the data. CBH, PS, ME drafted the article. All authors reviewed and revised the drafts and approved the final version of the manuscript.

Details of ethics approval

The POUCH Study has received continuous approval by the institutional review boards at Michigan State University (IRB# 95–590) since January 1996, and at the Michigan

Department of Health and Human Services (IRB# 44-LHAS) since February 1998. The POUCHmoms Study has also received continuous approval by the institutional review boards at Michigan State University (IRB# 10–161) since January 2011, and at the University of Pittsburgh (IRB# REN15070264) since December 2011.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Current study sample: from the POUCH Study (parent cohort) and maternal follow up 7-15 years later in the POUCHmoms Study.

Figure S2. Representative placental/extra-placental membrane findings from POUCH Study participants. (A) Unaltered maternal decidual vessel. (B) Abnormal maternal decidual vessel. (C) Mural hyperplasia. (D) Mural hyperplasia. (E) Fibrinoid necrosis/atherosis. ■

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