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Pre-eclampsia and risk of subsequent hypertension: In an American Indian population

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Introduction:

Pre-eclampsia (PE) and the more severe “eclampsia” together affect approximately 2–8% of pregnancies; and result in more than 50,000 maternal deaths globally.(1) The incidence of hypertensive disorders of pregnancy in the U.S. appears to have increased 25% in the last two decades,(2) and is a leading contributor to maternal and infant morbidity and mortality.(3) Diagnostic criteria have recently been revised to de-emphasize the previously required documentation of proteinuria; and to allow greater emphasis on clinical findings.(4) None the less, PE has been classically based on the new onset of hypertension and proteinuria after 20 weeks of gestation.(5) With severe PE, multiple organ systems can be affected, potentially resulting in complications such as renal failure, stroke, congestive heart failure, disseminated intravascular coagulopathy, and liver failure. Obstetric risk factors for development of PE have previously been identified, such as primiparity, multifetal pregnancy, and prior pregnancy with PE. In addition, traditional cardiovascular disease risk factors, such as increased age, obesity, altered glucose metabolism and pre-existing hypertension also play a role.(4) Specific details of the underlying etiology of PE are unknown; but the condition seems to develop initially from reduced placental perfusion, which leads to systemic inflammatory, metabolic, and thrombotic changes that impair maternal vascular function and lead to multi-organ damage.(6)

Although the blood pressure and albuminuria of patients with PE typically return to normal values within months of delivery, evidence is accumulating that acute episodes of PE are linked to future cardiovascular disease. From a few reports beginning in 1976,(7) to increasingly strong analyses in the past two decades evidence is showing that women who experience PE have an increased risk of hypertension and other cardiovascular conditions in later life.(8–10) In addition to a four-fold increased risk of hypertension,(5) PE is also associated with increased risk of other serious morbidity, including myocardial infarction,(11) renal disease,(12) diabetes(13) and stroke.(14) There also appears to be a “dose effect”(15–16) with those experiencing more severe, or earlier manifestations of PE being at increased risk of adverse outcomes, compared with those having had less severe PE.

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One interpretation of these findings is PE and cardiovascular disease (CVD) share risk factors that may be subtle or currently unrecognized in young, pregnant women; and that the additional physiologic stress of pregnancy unmasks this predisposition years ahead of its eventual manifestation. Thus PE is viewed as a positive “stress test”, predictive of future CVD.(17)

Regardless of whether PE is an independent factor in the causal chain of future CVD, or simply shares other primary risk factors with CVD, pre-eclampsia was identified by the American Heart Association and the American College of Cardiology as a useful, clinical risk factor for heart disease and stroke. Indeed, the additional risk of future CVD attributed to a history of PE is comparable to that of smoking.(9)

The purpose of this study was to determine if there is an association between a history pre-eclampsia and future development of hypertension in an American Indian population.

Methods:

This investigation utilized data of American Indian women from a previously described case-control study of genetic influences on risk of PE.(18) Case status is equivalent to exposure status in this analysis. A retrospective review of medical records was conducted of women with and without PE that gave birth from January 1, 1995 to December 31, 2012. Institutional Review Board (IRB) permission for this study was obtained from the Indian Health Service facility in the northern plains, the American Indian community and the University of North Dakota. Cases comprised women with PE (N=130), of which 96 met criteria as severe PE as defined by the American College of Obstetrics and Gynecology.(19) Controls are women (N=288) women that did not meet criteria for PE.

Hospital diagnostic codes were searched from 1995 forward to ascertain potential cases. Criteria for the case and control definitions of PE in this study are fully described in previous publications.(18) In brief, cases were defined as those meeting criteria for PE if at least 2 of the following were identified:

1. At least two BP values above either 140 mmHg systolic or 90 mmHg diastolic on separate occasions at least 4 hours apart; and absence of a diagnosis of, or treatment for hypertension (during the year prior to conception and the first 20 weeks of gestation).
2. Proteinuria as indicated by a 24-hour excretion of >300 mg, or at least two +1 dipstick measurements in the absence of prior proteinuria.
3. A diagnosis of PE, eclampsia, or the hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome by an attending physician after 20 weeks of gestation.

Potential controls were chosen by contacting the two women delivering just prior and after the case; and repeating the process until two control women consented to participate. Both cases and controls were excluded if they had a clinical diagnosis of hypertension prior to the identified pregnancy. The two highest blood pressure readings recorded within the period

from 1 year prior to the pregnancy up to 20 weeks of gestation were collected. When available, the mean of both the systolic and diastolic pressures were calculated and used as covariates to adjust models.

The electronic medical records were searched for the four most recent blood pressure (BP) readings that were measured on separate office visits during the 2 years prior to follow-up; and if a hypertensive medication were prescribed in the past two years. Anti-hypertensive medications included: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and/or thiazide diuretics. The mean systolic and diastolic blood pressures were calculated from at least 2 of the 4 possible measurements. Defining criteria for "subsequent" hypertension of both cases and controls were a mean systolic BP ≥@140…AND a mean diastolic ≥90 …OR a prescription for anti-hypertensive medication (AHM). The most recent body mass index (BMI) during the prior 3 years was also recorded. The BMI calculated at the time of pregnancy used the recorded weight and height at the first prenatal visit.

The statistical software, SPSS 13.0.1 for Windows, was used to analyze demographic and clinical characteristics of patients. Frequencies and relative percentages were computed for each categorical variable. Chi-square tests and Fisher's exact tests were performed to determine which categories were significantly different from one another, and Student's t-test was used to compare continuous variables. Cytel Studio software, version 11.0.0 was used to calculate logistic regression results. All p-values were two-sided, and p-value < 0.05 was considered significant. Missing data was excluded from analysis.

Results:

The relevant baseline characteristics of the cases and controls are shown in Table 1. Women with a history of PE were more likely to be primiparous, have a higher BMI, have higher recorded blood pressures prior to 20 weeks of gestation and have exhibited gestational diabetes during their pregnancy. The mean gestational age at the time of first prenatal visit (when BMI was calculated) was 13.02 and only 4.7% of cases and controls attended their first prenatal visit at 30 weeks of gestation or later. Smoking prevalence was similar between cases and controls.

Characteristics of women at follow-up are found in Table 2. Follow-up occurred at a mean (standard deviation, minimum, maximum) of 13.5 years (7.1, 3.6, 36.7) for cases and 12.9 years (6.7, 3.6, 36.6) for controls. There was no significant difference in length of follow-up between cases and controls (p=0.421). At follow-up cases had higher mean BMI, systolic and diastolic BP, prevalence of anti-hypertensive medication and study-defined hypertension;but otherwise were of similar age.)

The results of linear regression models are shown in Table 3. This analysis shows increased subsequent systolic blood pressure of approximately 3mm of mercury among those with a history of prior PE, even when simultaneously adjusted for age, BMI and average systolic pressure prior to 20 weeks of gestation. . The association is also seen when the analysis is limited to those participants in the lowest quartile of follow-up time (between 3.59 and 7.19

years) as detailed in Table 3, along with summary results from the remaining quartiles. If baseline (rather than current) measures of age, and BMI were used as adjusting covariates in these linear models, the covariate association with follow-up blood pressures lost independent significance. Models including gestational diabetes failed to show significant, independent association in either the linear or logistic regression analyses. Analysis of controls only indicates significant and independent association between blood pressures prior to 20 weeks of gestation, age and BMI.

Table 4 indicates the results of multivariate logistic regression analysis with subsequent, study-defined hypertension as the outcome and adjusting covariates as noted for the linear analyses. This also showsassociation between prior PE and future hypertension (OR 3.43, 95% CI 1.83 – 6.43, p=0.001), even when limited to those within the lowest quartile of follow-up. When the analysis is limited to the controls and those with severe PE (mild cases omitted), the point estimate of the odds ratio is greater (OR 4.18, 95% CI 2.19 – 8.00, p=0.001). If the history of PE is entered as an ordinal variable, with control status, mild PE and severe PE entered as 0, 1 and 2 respectively, the odds ratio is 2.19 (95% CI 1.54 – 3.10, p=0.001) for each increasing step of severity. In logistic analyses, substituting baseline age or BMI for current measures did not materially affect the association with PE; but did result in a loss of independent association for age at delivery.

The inclusion of pre-natal tobacco use showed only marginally significant association with systolic blood pressure (p=0.055) and no association in other fully adjusted linear or logistic models for diastolic pressure and subsequent hypertension respectively. Results of logistic regression analysis of the controls alone indicated significant, independent association with prior systolic blood pressure and age; but not BMI.

A number of analyses were conducted in an attempt to separate the effects of PE per se from the effects of increasing obesity during the follow-up period, As seen in Table 2, the prevalence of hypertension among cases was nominally lower (17/65=26.2%) among those with the greatest increase in BMI, compared with (22/60=36.7%) among those with the least; but this was not statistically significant (p=0.463). The participants were stratified into those with a change in BMI below or above the median increase of 3.7 BMI units; and these results are presented in Table 5. Among those with the lesser change (mean and median change of −0.53, and +0.37 BMI units respectively) both the linear and logistic regression relationship to history of PE remained significant and strong. Among those with the greater change in BMI (mean and median change of +8.08, and +7.08 units respectively), the linear models now showed no association with systolic or diastolic pressure, whereas the logistic models continued to show statistically significant association with future hypertension as defined (OR 2.67, 95% CI 1.06 – 6.70, p=0.036). Lastly, an additive model, attempting to scale the effects of PE and increasing BMI over time showed a strong relationship to subsequent hypertension, as seen in Table 5.

Women with a history of PE were also more likely to be prescribed antihypertensive medication (OR 3.07, 95% CI 1.60 – 5.91, p=0.001) compared to women experiencing normal pregnancies.

Discussion:

Our findings clearly demonstrate that this cohort of American Indian women with a history of pre-eclampsia (PE) have an increased risk of future hypertension both over relatively short or longer periods of follow-up. This is in agreement with several investigations, primarily conducted among European populations.(8,13,20,21) Bellamy et al.(15) conducted a meta-analysis of 13 studies with a mean follow-up of 14.1 years, finding a composite relative risk (RR 3.70, 95% CI 2.70 – 5.05) for subsequent hypertension, albeit with significant heterogeneity between studies (smaller studies showing increased RR). This result is nearly identical to our present study. Of note, case-control studies were excluded in this meta-analysis of cohorts, of which all but three (8,14,22) evaluated fewer cases and controls than the present study. Only one of the larger cohorts (14) adjusted for BMI and obtained an odds ratio of 3.98 for a physician's diagnosis of hypertension.

Although not our primary objective and well established in the literature,(23) we provide additional evidence of the association between obesity and hypertension; both as an independent factor in the relationship between PE and subsequent hypertension and among those with previously normal pregnancies. The lack of a difference in hypertension prevalence between those with greater or lesser increases in BMI supports the independent influence of PE on the risk of subsequent hypertension.The stratified analysis showing a strong association with PE and subsequent hypertension among those with less than the median increase in BMI during follow-up, gives further weight to the hypothesis that risk of future hypertension is not due merely to a tendency of those with PE toward obesity. Interestingly, those with the greatest increase in BMI continued to show a relationship between hypertension and PE in logistic analysis, but not in linear analysis of blood pressure. This may be due to the increased effect of obesity overwhelming the influence of prior PE. There are relatively few studies of PE associated with an outcome of hypertension that are adjusted for BMI, but one moderate sized investigation[14] found an odds ratio of 2.62 (95% CI 1.77 – 3.86, p=0.001).

We have been able to identify only three reports relating PE to hypertension among non-European populations. These include studies among Samoan,(24) Jordanian,(25) and primarily African American.(22) There is no prior information available regarding subsequent hypertension among American Indian women.

An interesting question is whether the pathophysiologic changes of PE alter the cardiovascular system of women in a lasting way that increases the risk of future hypertension and CVD events, or whether the stress of pregnancy merely unmasks underlying pathophysiology that is common to both PE and CVD. This debate is well described in a review by Garovic et al;(26) but remains unresolved. The current study offers additional support for PE as an independent, intrinsic risk factor, in that those with a lesser increase in BMI during follow-up continued to show a strong association with PE, discounting the theory that obesity is perhaps one of multiple primary risk factors for future hypertension. While the addition of blood pressure prior to pregnancy and up to 20 weeks of gestation attenuates the association of PE with subsequent blood pressures in both linear and logistic analyses, a couple of caveats need to be considered. First, the blood pressure at

follow-up will be lessened in those under treatment for hypertension, thus decreasing the power of these linear analyses. The logistic models take into account hypertensive treatment; and thus capture this potential effect of PE exposure. Secondly, a large portion of the “prior” blood pressure measures were obtained during the first 20 weeks of gestation; and could well have captured mild elevations from PE that preceded the formal definition of PE (ie “after 20 weeks of gestation”). Thus the use of these prior blood pressures as a covariate may result in “over adjustment”. The results of logistic models showing subsequent hypertension significantly and independently associated with a history of PE, even among those with the shortest follow-up, is especially impressive in the light of these caveats.

Other studies provide clear evidence of persisting abnormalities in cardiovascular function (27) and even anatomy (28) post PE; but no comparable measures from these women prior to pregnancy. To know whether PE, directly affects these changes, detailed longitudinal studies of a cohort of women from pre-pregnancy to a couple years post pregnancy would be ideal; but would be difficult due to the large population needed, continuing difficulty discriminating between possibly distinct forms of PE (eg early vs late pregnancy, young vs older women) and the need to control or adjust for pre-existing risk factors. This question is not without practical implications. If PE is the cause of a persistent increase in CVD risk, then management of women with PE may require more aggressive interventions to prevent adverse outcomes.(26)

Strengths of this study include PE as a well-defined exposure, confirmed by clinical measures and a conservative definition; and similarly reliable clinical measures of outcome (blood pressure and prescribed medications). Important covariates were also well documented, in some cases both during pregnancy and at the end of follow-up; and there was adequate power to analyze both long and short term outcome. These results from a non-European population support the view that there is a generalizable physiology underlying this association.

Limitations to this investigation include the possibility that some BMI’s from the time of pregnancy were obtained during a late prenatal visit, and thus biased upward, although the proportion of women over 30 weeks gestation at first prenatal was less than 5%. It is possible that some women were seen and actively treated for hypertension at a facility other than the Indian Health Service in this community. If there was a systematic bias in loss to follow-up, this could have affected the results. Reassuringly, although abstraction was limited to about 200 per abstractor due to time constraints, of the 418 abstracted (out of a potential 542), all but one had at least three blood pressures measured within the prior 3 years (resulting in a minimum follow-up of 77%). Loss to follow-up did occur due to death for 2 control women from the original study; and the cause is unknown. We also caution that these findings from a single community may not generalize to other American Indian populations; and further studies in other areas would be useful.

Cardiovascular disease is the leading cause of death for women ≥ 65 years of age in the United States,(29) and the American Heart Association has recognized the importance of PE as a CVD risk factor,(30) which is comparable to the effects of smoking.(9) These insights

and the development of clinical recommendations for the prevention and treatment of PE have made vital contributions to women's health.(31)

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Table 1:

Characteristics of cases and controls at the time of pregnancy.

Characteristic	Cases 31.1%(n=130)	Controls 68.9%(n=288)	p value
Age, mean years (SD)	26.5 (35.7)	23.9 (7.3)	0.411
Parity (% primiparous)	88/130 (67.7%)	123/286 (43.0%)	0.001
Mean systolic BP < 20wk gestation (SD)	133.2 (20.3)	122.3 (17.7)	0.001
Mean diastolic BP < 20wk gestation (SD)	79.2 (12.7)	71.7 (11.6)	0.001
Body-Mass index (SD) at first prenatal visit	30.5 (7.09)	28.0 (7.08)	0.001
Gestational diabetes (% yes)	17/129 (13.2%)	12/220 (5.5%)	0.007
Maternal smoking (% yes)	34/87 (39.1%)	85/173 (49.1%)	0.125

Table 2:

Characteristics of cases and controls at follow-up.

Characteristic	Cases 31.1%(n=130)	Controls 68.9%(n=288)	p value
Current age, mean (SD)	36.1 (9.6)	35.9 (9.0)	0.832
Current body-mass index (SD)	34.3 (7.24)	31.6 (7.53)	0.001
Mean systolic BP	127.2 (13.2)	121.3 (12.1)	0.001
Mean diastolic BP	76.2 (9.0)	72.6 (8.6)	0.001
Hypertensive medication use (% yes)	35/130 (26.9%)	25/288 (8.7%)	0.001
Study-defined, subsequent hypertension, any BMI increase	41/130 (31.5%)	29/288 (10.1%)	0.001
Subsequent hypertension among those with less than median BMI increase	22/60 (36.7%)	14/140 (10.0%)	0.001
Subsequent hypertension among those with more than median BMI increase	17/65 (26.2%)	15/135 (11.1%)	0.012
Follow-up time from pregnancy to current analysis (years)	13.5 (7.1)	12.9 (6.7)	0.421

Table 3.

Multivariate linear regression model analyses.

Linear Regression Model, Systolic Blood Pressure, N=337*				
	B**	S.E.	β***	P value
Previous pre-eclampsia	2.75	1.33	0.109	0.040
Mean prior systolic BP****	0.14	0.03	0.220	0.001
Current age	0.19	0.07	0.138	0.007
Current BMI	0.28	0.09	0.170	0.002
Linear Regression Model, Diastolic Blood Pressure, N=337				
Previous pre-eclampsia	1.74	0.96	0.182	0.070
Mean prior systolic BP	0.08	0.03	0.179	0.001
Current age	0.12	0.05	0.129	0.013
Current BMI	0.20	0.06	0.170	0.002
Participants in first quartile with shortest follow-up				
Linear Regression Model, Systolic Blood Pressure, N=69				
Previous pre-eclampsia	4.26	2.68	0.188	0.116
Mean prior systolic BP	0.20	0.09	0.273	0.038
Current age	0.233	0.21	1.093	0.278
Current BMI	0.16	0.17	0.115	0.362
Remaining quartiles, same model, results given for previous pre-eclampsia only				
Second quartile of follow-up, N=89	2.45	2.52	0.106	0.335
Third quartile, N=91	4.22	2.77	0.154	0.131
Fourth quartile, N=89	−1.81	2.83	−0.070	0.523
Linear Regression Model, Diastolic Blood Pressure, N=69				
Previous pre-eclampsia	3.35	1.67	0.217	0.049
Mean prior diastolic BP***	0.26	0.09	0.319	0.007
Current age	0.35	0.13	0.271	0.012
Current BMI	0.09	0.10	0.102	0.360
Remaining quartiles, same model, results given for previous pre-eclampsia only				
Second quartile of follow-up, N=89	1.83	1.97	0.102	0.356
Third quartile, N=91	0.31	1.92	0.017	0.872
Fourth quartile, N=89	−1.02	1.95	−0.058	0.601
Cases excluded, Controls only				
Linear Regression Model, Systolic Blood Pressure, N=211				
Mean prior systolic BP	0.13	0.04	0.20	0.003
Current age	0.25	0.09	0.19	0.003
Current BMI	0.43	0.11	0.27	0.001
Linear Regression Model, Diastolic Blood Pressure, N=211				
Mean prior diastolic BP	0.15	0.05	0.21	0.001

Current age	0.18	0.06	0.19	0.004
Current BMI	0.30	0.07	0.26	0.001

*N= the number of participants with available covariates for a particular analysis

**Unstandardized regression coefficient

***Standardized regression coefficient

****Mean systolic or diastolic blood pressure, one year pre-pregnancy through 20 weeks gestation

Table 4.

Multivariate logistic regression model analyses.

Logistic Regression (Subsequent hypertension as the outcome), N=337 *			
	OR **	95% CI	P value
Previous pre-eclampsia	3.43	1.83 − 6.43	0.001
Mean prior systolic BP ***	1.02	1.00 − 1.04	0.032
Current age	1.08	1.04 − 1.11	0.001
Current BMI	1.01	0.97 − 1.06	0.505
Participants in quartile with shortest follow-up, N=69			
Logistic Regression (Subsequent hypertension as the outcome)			
	OR	95% CI	P value
Previous pre-eclampsia	11.31	1.15 − 111.2	0.038
Mean prior systolic BP	1.06	0.99 − 1.13	0.090
Current age	1.09	0.93 − 1.29	0.270
Current BMI	0.85	0.72 − 1.01	0.062
Remaining quartiles, same model, results given for previous pre-eclampsia only			
Second quartile of follow-up, N=89	3.52	0.69 − 18.1	0.132
Third quartile, N=91	3.65	1.05 − 12.7	0.042
Fourth quartile, N=89	2.20	0.80 − 6.08	0.128
Cases excluded, Controls only, N=211			
Logistic Regression (Subsequent hypertension as the outcome)			
	OR	95% CI	P value
Mean prior systolic BP	1.04	1.00 − 1.07	0.041
Current age	1.12	1.05 − 1.18	0.001
Current BMI	1.05	0.98 − 1.13	0.188

* N= the number of participants with available covariates for a particular analysis

** Odds Ratio

*** Mean systolic or diastolic blood pressure, one year pre-pregnancy through 20 weeks gestation

Table 5.

Analyses contrasting those above and those below the median change in BMI from pregnancy to follow-up.

Linear Regression Model, Systolic Blood Pressure				
Above median change in BMI, N=162 *				
	B **	S.E.	β ***	P value
Previous pre-eclampsia	−1.17	1.85	−0.05	0.529
Mean prior systolic BP ****	0.23	0.07	0.279	0.001
Current age	0.17	0.09	0.13	0.072
Current BMI	0.31	0.14	0.18	0.028
Below median change in BMI, N=167				
Previous pre-eclampsia	6.26	1.93	0.24	0.001
Mean prior systolic BP	0.13	0.05	0.21	0.008
Current age	0.26	0.11	0.18	0.016
Current BMI	0.12	0.14	0.07	0.393
Linear Regression Model, Diastolic Blood Pressure				
Above median change in BMI, N=162				
Previous pre-eclampsia	−0.62	1.43	−0.03	0.664
Mean prior diastolic BP	0.20	0.07	0.24	0.003
Current age	0.06	0.07	0.07	0.387
Current BMI	0.25	0.10	0.19	0.015
Below median change in BMI, N=167				
Previous pre-eclampsia	3.10	1.29	0.18	0.018
Mean prior diastolic BP	0.19	0.05	0.29	0.001
Current age	0.13	0.07	0.13	0.063
Current BMI	0.11	0.09	0.09	0.222
Logistic Regression Model (Subsequent hypertension as outcome)				
Above median change in BMI, N=162				
		OR	95% CI	
Previous pre-eclampsia		2.67	1.06 − 6.70	0.036
Mean prior systolic BP		1.04	1.01 − 1.07	0.041
Current age		1.07	1.02 − 1.13	0.006
Current BMI		0.99	0.92 − 1.07	0.800
Below median change in BMI, N=167				
Previous pre-eclampsia		4.22	1.76 − 10.1	0.001
Mean prior systolic BP		1.02	0.99 − 1.03	0.277
Current age		1.10	1.04 − 1.15	0.001
Current BMI		1.04	0.98 − 1.11	0.201
Logistic Regression Model (Subsequent hypertension as outcome)				
Additive model, N=329				

Additive risk score *****	1.55	1.16 − 2.06	0.003
Mean prior systolic BP	1.03	1.01 − 1.05	0.009
Current age	1.08	1.05 − 1.12	0.001
Current BMI	1.00	0.96 − 1.05	0.994

* N= the number of participants with available covariates for a particular analysis

** Unstandardized regression coefficient

*** Standardized regression coefficient

**** Mean systolic blood pressure, one year pre-pregnancy through 20 weeks gestation

***** 0=no PE, below median BMI increase (v BMI), 1=no PE, above median BMI increase (^BMI), 2= +PE, v BMI, 3= +PE, ^BMI