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PREECLAMPSIA AND CARDIOVASCULAR DISEASE DEATH: PROSPECTIVE EVIDENCE FROM THE CHILD HEATLH AND DEVELOPMENT STUDIES COHORT

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Abstract

This study prospectively investigates the contribution of pregnancy complications and other reproductive age risk factors on the risk of subsequent cardiovascular disease death. Participants were 14,403 women in the Child Health and Development Studies pregnancy cohort drawn from the Kaiser Permanente Health Plan in California. Only women with non-missing parity and no previously diagnosed heart conditions were included. 481 had observed preeclampsia and 266 died from cardiovascular disease. The median age at enrollment was 26 years and the median follow-up time was 37 years. Cardiovascular disease death was determined by linkage with the California Department of Vital Statistics.

Observed preeclampsia was independently associated with cardiovascular disease death (Mutually adjusted Hazard Ratio = 2.14 (1.29 to 3.57)). The risk of subsequent cardiovascular disease death was notably higher among women with onset of preeclampsia before 34 weeks of gestation (Hazard Ratio = 9.54 (4.50, 20.26)). At 30 years of follow-up and a median age of 56 the cumulative cardiovascular disease death survival for women with early preeclampsia was 85.9% compared to 98.3% for women with late preeclampsia and 99.3% for women without preeclampsia. Women with preeclampsia had an increased risk of cardiovascular disease death later in life, independent of other measured risk factors. These findings reinforce previously reported recommendations that a history of preeclampsia should be used to target women at risk for cardiovascular disease. Additionally, women with preeclampsia earlier in pregnancy may be particularly at risk for cardiovascular disease death and could be targeted for early and intensive screening and intervention.

Keywords

Cardiovascular disease; Preeclampsia; Gestational timing; Prospective; Cohort

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INTRODUCTION

A growing body of literature indicates that preeclampsia (PE) in pregnancy may indicate increased risk for cardiovascular disease (CVD) later in life.[1, 2] It has been suggested that pregnancy forms an early stress test for pre-clinical later life risk factors[3, 4] and that preeclampsia is one indicator of this health burden.[5] Following from the idea of pregnancy as a stress test, there is continuing debate around whether preeclampsia is only an indication of preexisting risk factors or is itself an independent factor on the causal pathway to cardiovascular disease.[4-7]

Complicating this debate, preeclampsia is a complex syndrome that has yet to be homogeneously diagnosed or defined.[8] Many researchers consider early or severe preeclampsia to be a different diagnosis than late preeclampsia that occurs near or at delivery and is usually milder.[9-12] This is borne out by observations that early preeclampsia is linked with decreased gestational age and birth weight as well as intrauterine growth restriction (IUGR) more generally, while late preeclampsia is characterized by a disproportionate number of high birth weight babies.[13, 14]

The problem of overlapping risk factors (exemplified by the strong association between PE and IUGR) is ubiquitous in investigations of the association between PE and CVD. Traditional risk factors for cardiovascular disease such as increased body mass index (BMI) and preexisting hypertension are also known to be associated with increased risk of preeclampsia. Such overlapping risk factors continue to provoke a multitude of questions about independence and confounding.

This study investigates the predictors of preeclampsia to establish the sequence of maternal markers. Then the separate and combined effects of preeclampsia and other cardiovascular disease risk factors are examined in an attempt to unravel their relationship with the causes of cardiovascular disease death. This study further investigates the varying effects of preeclampsia on cardiovascular disease death by gestational timing to clarify the spectrum of preeclampsia and its impact on subsequent cardiovascular disease.

METHODS

Study Population

The subjects in this study were women enrolled in the original Child Health and Development Studies (CHDS) cohort.[15] They were members of the Kaiser Permanente Health Plan in the East Bay Area of California who became pregnant between 1959 and 1967. The CHDS cohort is socio-economically broadly based with access to health care and representation from multiple race/ethnicity groups. A total of 20,530 pregnancies were observed in the CHDS. Women in the study received regular prenatal workups including blood pressure and albumin readings during each trimester. Blood pressures were taken by the nurses, using a standard protocol, at the regular prenatal clinic visits.[16] Information was collected on all pregnancies in the CHDS cohort including: 1) from interview at baseline: socio-economic, demographic, behavioral variables, and pregnancy history and pregnancy-related variables; and 2) from medical records abstraction: prenatal measures (blood pressures and proteinuria), mother's medical conditions 6 months before and during pregnancy, and labor and delivery data. The Institutional Review Board of the Public Health Institute approved the protocols for this study and all human subjects gave full consent before the use of their information.

Cohort Surveillance

After active surveillance of the cohort ended in 1972, CHDS families were regularly matched to the California Department of Motor Vehicles (DMV) files and the California Vital Status records. The regular DMV matching provides a history of location and timing of residence, which allows identification of the population at risk for cardiovascular disease death. All members of CHDS families are regularly matched to the California Department of Motor Vehicles files on full name and birth date. For each match, all of the names that an individual has ever registered with the DMV, current and past, are used to determine a match. The DMV provides both residence and date at last active contact so it is possible to establish if and when a subject is residing in a given area. Next, the complete CHDS cohort is matched to the California Vital Status records. A comparison of address history for all members of a family is made to verify that a match is accurate. Using all names that a subject has registered with the DMV to find matches within the California Vital Status records substantially reduces the likelihood that deaths are missed as a result of incomplete identifier information. The CHDS uses a rigorous protocol of both exact and probabilistic matching followed by manual review to determine acceptable matches. Death certificates are requested to further validate questionable matches. If an individual does not match to either the Motor Vehicles or Vital Status files then the subject is considered lost to follow-up.

Study Sample

Initially, the analysis file was constructed at the pregnancy level in order to determine the comparability of risk in a primiparous sample versus a multiparous sample. For this comparison, we created one observation for each singleton pregnancy and then separate datasets for the primiparous and multiparous pregnancies. This resulted in 5,749 primiparous pregnancies of which 228 had observed preeclampsia and 57 had cardiovascular disease death. Among the 10,253 multiparous pregnancies 265 had observed preeclampsia and 223 had cardiovascular disease death.

All associations were examined separately for primiparas and mulitparas (Supplemental Table 1 please see http://hyper.ahajournals.org). Among primiparous pregnancies 228 of 5,749 women (4.0%) experienced preeclampsia while only 265 of 10,253 (2.6%) multiparous pregnancies had an observed preeclampsia. This approximate doubling of the incidence of preeclampsia in primiparous pregnancies is common in the literature.[17] Since risks were comparable by parity for all factors examined, the groups were combined to allow sufficient power to examine the contribution of gestational timing of preeclampsia. Once it was determined that primiparous and multiparous pregnancies could be combined, the analysis file was constructed to have one observation for each woman to examine the outcome of cardiovascular disease death. Parity was examined as a confounder of the other associations. We excluded multiple birth pregnancies and pregnancies missing on parity. We also excluded all pregnancies that ended in abortion or fetal death prior to 20 weeks gestation and women with pre-existing heart conditions diagnosed before enrollment. This resulted in an analysis sample of 14,403 women of whom 481 had observed preeclampsia (3.3%) and 266 died from cardiovascular disease (64.99 per 100,000). The median follow-up time was 37 years and median age at death from CVD was 65 years. The sample includes all race/ethnic groups: African American (23%), Asian (4%), Hispanic/Latino (3%), Caucasian (68%), and Other (2%). Women in the study sample had a mean age at first observed CHDS pregnancy of 26 years and 69% were multiparous.

Measures

Results from the California Vital Status matches to CHDS files through year 2004 were used to append underlying cause and year of death. Since follow-up of the cohort spanned over

40 years, codes for the underlying cause of death from several ICD revisions were used to define cardiovascular disease death, including: 420.1 for ICD-7; 410 and 412 for ICD-8; 410, 411, 414 and 429 for ICD-9,and I21-I25 for ICD-10.

The primary analysis variables were preeclampsia, preexisting hypertension, preexisting diabetes, gestational hypertension, and having a baby with intrauterine growth restriction. These variables were coded as ever versus never for each CHDS subject. In this way, each woman has one observation with each of the above variables was coded as either: 0 = no occurrence or 1 = one or more occurrences while under CHDS observation.

Proteinuria is defined as a reading of 1 (0.5% or 300 mg/24 hours) or above on a urine dipstick. Blood pressure is measured as systolic over diastolic pressure in mm Hg. Preeclampsia is defined as either of the following occurring after 20 weeks of gestation[18, 19]:

- Two or more blood pressure readings greater than 140/90 mmHG and proteinuria

-Two or more systolic readings greater than 140 mmHG or two or more diastolic readings of greater than 90 mmHG and proteinuria.

Preexisting hypertension was defined as at least one blood pressure reading of 140/90 mmHG or greater before 20 weeks of pregnancy or doctor diagnosed hypertension from the medical record. Gestational hypertension was defined as at least one blood pressure reading of 140/90 mmHG or greater that developed after the 20th week of pregnancy and not accompanied by proteinuria. Intrauterine growth restriction was defined as below the 10th percentile of z-scores in birth weight by sex and gestational age for the CHDS distribution. Preexisting diabetes was defined as doctor diagnosed diabetes before the current pregnancy. Early onset preeclampsia was defined as onset of preeclampsia before 34 weeks of gestation. There were 22 subjects with an observed recurrence of preeclampsia between 1959 and 1967. Of these 17 had onset only after 34 weeks gestation and 5 had at least one pregnancy with onset of preeclampsia by 34 weeks. These were not considered for separate examination due to small numbers nor was self-reported pre-study recurrence since they could not be clinically defined.

Statistical Methods

Unadjusted cardiovascular disease death rates were calculated per 100,000 person-years bracketed by 95% Confidence Limits. Hazard ratios were calculated using Cox proportional hazards models. The full model was constructed using all variables of interest that were either independently significant and/or confounders to the 10% level after mutual adjustment. Residence history and vital status were used to calculate the person-years of cardiovascular disease death and to construct a censoring variable for the Cox proportional hazards models. Kaplan-Meier curves were constructed to further differentiate the effects of gestational timing of preeclampsia on cardiovascular disease survival. All analysis was conducted using SAS 9.1.

RESULTS

Table 1 shows that the unadjusted cardiovascular disease death rates in the CHDS were higher for established cardiovascular disease risk groups and other factors measured during pregnancy. Table 2 presents results for univariate and multivariate Cox models estimating risk of CVD death for the same exposures. Results from univariate models are very similar to those observed for data-based rates described above. These results do not change when the models are analyzed in a restricted dataset (N=9,491) with only non-missing data for all variables of interest (Data not shown). The multivariate model demonstrates the effects of

mutual adjustment for exposures. The increased risk of CVD death with preeclampsia remains even after adjusting for other known risk factors, including preexisting hypertension and delivering an IUGR infant. Maternal completion of high school and maternal occupational level, but not annual family income, remained significantly associated after mutual adjustment in the full model (Data not shown), but the addition of the socioeconomic variables available (family income, maternal education, and maternal employment category) did not explain the other associations in the model. Similarly, parity of the observed pregnancy did not alter or account for the other associations (data not shown). Table 3 shows that the strongest associations between preeclampsia and CVD death are observed for preeclamptic onset before 34 weeks of gestation. This association is not explained by adjusting for age at enrollment (data not shown). Figure 1 depicts the Kaplan-Meier curves for the same groups.

DISCUSSION

This paper offers the unique contribution of following cardiovascular disease risk factors from their association with preeclampsia (Supplemental table 2 please see http://hyper.ahajournals.org) through to their relationship with cardiovascular disease death in a prospective cohort. Many of the traditional cardiovascular disease risk factors have been suggested as underlying factors for both diseases.[20-22] However, since the higher risk of CVD death for women with preeclampsia is independent of body mass index, gestational hypertension, preexisting hypertension, preexisting diabetes, and having an IUGR child, it appears that preeclampsia may indicate more than simply a combination of other risk factors. While there may be an underlying factor (such as immune function, oxidative stress, and vascular factors) that explains the association between PE and CVD death, none has yet to be solidly identified.

One of the major weaknesses of this study is the inability to accurately assess preeclampsia and other events that occurred before or after the CHDS active study period. While some misclassification of preeclampsia may have occurred, it would have led to an underestimation of the exposure and therefore biased the study towards null results. The strong positive association observed for preeclampsia and CVD death suggests that underestimation is low. Likewise, due to the small number of observed recurrent preeclamptic pregnancies, it was not feasible to investigate the association between preeclampsia recurrence and CVD. Another major weakness of this study is the inability to adjust for serum cholesterol level as a known predictor of cardiovascular disease.23 While preeclampsia has long been strongly associated with hypertension, it has also been shown to be connected to dyslipidemia.24 While it is rather unlikely that preeclampsia would be a strong or complete mediator of any cholesterol effects on CVD during the reproductive years, this study cannot investigate such a relationship. A weakness shared with other articles on this topic is the reliance on baseline behavior data as proxy for ongoing risk exposure.[1, 2] This is most problematic with the potential for change over time, as subjects age, in smoking status, body mass index, indications of hypertension, and other known contributors to cardiovascular disease. Despite many of the competing risk factors for cardiovascular disease beginning by reproductive age, it is reasonable to assume that the increased risk of CVD death from these factors may be underestimated in studies that use baseline values, particularly for those factors known to be strongly linked to aging. Regardless, these findings remain relevant to prevention as they provide a much earlier target for intervention before other risk factors become clinically apparent. Finally, this study (even with 14,403 women) lacks the power to fully investigate the connections between all the risk factors. In particular, the relationship between preeclamptic subgroups and traditional CVD risk factors cannot be elaborated due to the loss of power from stratification of relatively small groups.

In contrast, a major strength is that this study used detailed clinical records concurrent with pregnancy and prior to age of cardiovascular disease risk to provide diagnostic criteria for defining preeclampsia, pre-existing hypertension, and gestational hypertension. Additionally, the CHDS cohort provides more than 40 years of follow-up starting from early in a woman's pregnancy (before pregnancy complications like preeclampsia are diagnosed) and includes the ultimate outcome of cardiovascular disease death. It is a major strength that this study investigates cardiovascular disease mortality, a well-defined endpoint, instead of the disease's intermediary markers. Compared to the previous longitudinal studies of this topic, all but one of which are retrospective cohort studies[1], this study allows for the investigation of preeclampsia as a mediator of major known CVD risk factors (with the exception of cholesterol) that temporally preceded the preeclamptic events as well as robust assessment of confounding. Moreover, while Hannaford et al. provided the first evidence from a prospective cohort study, this is the first prospective cohort study on the topic that uses standardized definitions of preeclampsia and CVD. 25 The long follow-up period allows observation through the age of peak risk for cardiovascular disease and past what may be a latency between the initiation of endothelial dysfunction marked by preeclampsia and the emergence of cardiovascular disease.26 The exceptionally long follow-up period of this study additionally allows the findings of the previous literature, especially that of Irgens et al. to be further generalized to women over the age of menopause.27, 28 Prospective data collection in a study population with access to health care reduces the chance that associations are the result of recall or detection bias.

It has been suggested that a history of preeclampsia might be used to target women at greater risk for cardiovascular disease death for early intervention,[1, 2, 4, 29, 30] and that these women may be more receptive to behavioral change.[31] This study supports the idea that there may be a benefit to early cardiovascular disease screening for preeclamptic women even in the absence of other risk factors.

It is also of interest that gestational hypertension alone does not convey a higher risk of CVD death. As suggested by Bellamy et al., the literature may be hindered by some level of misclassification between gestational hypertension and preeclampsia.[1] For this reason the separation of these two categories by strict clinical criteria, in this study, may provide an indication that de novo blood pressure elevation in pregnancy absent proteinuria may not be associated with CVD death.

PERSPECTIVES

This paper allows further stratification of preeclamptic subgroups in an attempt to refine the level of potential risk by timing of onset during pregnancy. The findings are not surprising in light of the wealth of evidence that onset of preeclampsia earlier in gestation may have different causes and outcomes than preeclampsia developing later. These differences occur in markers of angiogenesis,[32-35]dyslipidemia,[24] insulin resistance,[36, 37] and hemodynamics[38]- both before preeclamptic onset and postpartum.[39] Moreover, this study provides reinforcement to the currently sparse evidence that the differences in timing of preeclamptic onset play a role in long term risk for cardiovascular disease.[1, 27] Perhaps a more specific classification of preeclampsia by gestational onset can be used to further target women at highest risk for cardiovascular disease for intensive screening and early intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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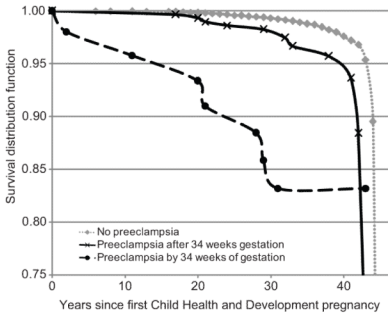

Figure 1.

Cardiovascular disease death Kaplan-Meier survival according to gestational timing of preeclampsia

* Survival analysis is based on 14,403 women and 266 events of cardiovascular disease death.

† All groups are statistically significantly different.

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Table 1

Unadjusted Rates of Cardiovascular Disease Death by Baseline Characteristics and Reproductive Factors

Study Variable	Mean (SD)	Cases	Person-years	Incidence Rate per 100,000	95% Confidence Interval
Maternal Race *					
Caucasian	-	146	266,796	54.72	46.21, 64.35
African American	-	96	98,001	98.00	79.35, 119.61
Latino/Hispanic	-	5	11,515	43.42	14.10, 101.30
Asian	-	5	15,862	31.52	10.24, 73.54
Other	-	10	10,751	93.01	44.61, 170.99
Maternal Smoking *					
Never	-	91	163,315	55.72	44.87, 68.41
Previous	-	21	58,666	35.80	22.16, 54.71
Current	-	117	121,481	96.31	79.66, 115.42
Parity (previous pregnancies) *					
No prior pregnancy	-	56	157,822	35.48	26.80, 46.08
One prior pregnancy	-	41	96,398	42.53	30.52, 57.70
Two or more prior pregnancies	-	169	153,906	109.81	93.88, 127.66
Maternal Education *					
Did not complete high school	-	162	291,506	55.57	47.35, 64.82
Completed high school	-	72	60,167	119.67	93.64, 150.68
Annual Family Income *					
< $5,000	-	29	52,251	55.50	37.17, 79.70
$5,000 to $8,999	-	122	154,285	79.07	65.67, 94.41
> $9,000	-	44	82,714	53.20	38.65, 71.41
Maternal Age (years) *					
First Quartile (<20)	19.88 (1.79)	34	110,623	30.74	21.29, 42.95
Second Quartile (20-26)	24.47 (1.13)	40	100,296	39.88	28.49, 54.30
Third Quartile (26-31)	28.78 (1.40)	53	95,865	55.29	41.42, 72.31

Study Variable	Mean (SD)	Cases	Person-years	Incidence Rate per 100,000	Incidence 95% Confidence Interval
Fourth Quartile (≥31)	35.95 (3.18)	138	99,732	138.37	116.26, 163.46
Body Mass Index (kg/m^2) *					
First Quartile (<19.81)	18.66 (0.93)	29	77,788	37.28	24.97, 53.54
Second Quartile (19.82-21.29)	20.58 (0.41)	29	79,054	36.68	24.57, 52.68
Third Quartile (21.30-23.16)	22.11 (0.52)	35	74,153	47.20	32.88, 65.64
Fourth Quartile (≥23.16)	26.39 (3.41)	112	78,756	142.21	117.11, 171.09
Preexisting Hypertension †					
Absent	-	228	397,924	57.30	50.10, 65.24
Present	-	38	10,202	372.48	263.72, 510.90
Gestational hypertension †					
Absent	-	222	345,281	64.30	56.12, 73.30
Present	-	44	62,845	70.01	50.88, 93.98
Intrauterine Growth Restricted Infant †					
Absent	-	227	362,525	62.62	54.74, 71.31
Present	-	39	45,601	85.52	60.82, 116.90
Preexisting Diabetes †					
Absent	-	260	404,777	64.23	56.66, 72.53
Present	-	6	3,280	182.93	67.16, 397.72
Preeclamptic Pregnancy †					
Absent	-	242	394,596	61.33	53.85, 69.56
Present	-	24	13,530	177.38	113.69, 263.82
Gestational Timing of Preeclampsia †					
No Preeclampsia	-	242	394,596	61.33	53.85, 69.56
Preeclampsia After 34 weeks	-	17	11,999	141.68	82.55, 226.74
Preeclampsia Before 34 weeks	-	7	1,531	457.22	184.02, 939.76

*Variables represent subject characteristics recorded at study enrollment and do not reflect changes over the follow-up period.

†Variables were recorded as ever occurring in a CHDS observed pregnancy or never occurring in a CHDS observed pregnancy.

Table 2

Associations of Pregnancy Conditions with Cardiovascular Disease Death

Model Number	Variable*	Hazard Ratio	95% Confidence Interval
Univariate †			
1	Ever had a Preeclamptic Pregnancy	2.73	1.78, 4.18
2	Ever had an IUGR Child	1.44	1.03, 2.03
3	Ever had Preexisting Hypertension	6.17	4.34, 8.77
4	Age at Enrollment (years)	1.11	1.09, 1.13
5	BMI at Enrollment (kg/m^2)	1.16	1.13, 1.19
6	Current Smoking at Enrollment	1.31	1.14, 1.51
Multivariate			
7‡	Ever had a Preeclamptic Pregnancy	2.14	1.29, 3.57
	Ever had an IUGR Child	1.68	1.12, 2.52
	Ever had Preexisting Hypertension	2.20	1.36, 3.57
	Age at Enrollment (years)	1.10	1.07, 1.12
	BMI at Enrollment (kg/m^2)	1.14	1.11, 1.17
	Current Smoking at Enrollment	1.55	1.31, 1.82

*Variables beginning “Ever had” were recorded as ever occurring in a CHDS observed pregnancy or never occurring in a CHDS observed pregnancy.

†Univariate models are unadjusted and may be based on different sample sizes due to missing values (Age n=14,170, BMI n=10,828, Current Smoking n=11,697, All others n=14,320).

‡Full model contains variables that were either independently significant and/or confounders to the 10% level after mutual adjustment. The full model includes n=9,491 women.

Table 3

Cardiovascular disease death hazard ratios by gestational timing

Model	Risk Group	Hazard Ratio	Confidence Interval	Deaths	Person Years
	Preeclampsia ≤ 34 weeks gestation	9.54	4.50, 20.26	7	1,531
	Preeclampsia > 34 weeks gestation	2.08	1.26, 3.44	17	11,999
	No preeclampsia	1.0	-	242	394,596