Long-Term Mortality After Preeclampsia

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Background: Many believe that preeclampsia is not associated with future morbidity or mortality. We sought to investigate the long-term risk of mortality in women with preeclampsia, focusing on those known to be subsequently normotensive.

Study Design: We ascertained deaths during 24–36 years' follow-up in a cohort of 37,061 women who delivered in Jerusalem in 1964–1976, including 1,070 women with preeclampsia. We used Cox proportional hazard models to estimate the risk of mortality associated with preeclampsia while controlling for the woman's age and education, history of diabetes, heart disease and low birth weight birth, the husband's social class, and the calendar year at the start of follow-up.

Results: Compared with women who were not diagnosed with preeclampsia, the relative risk of death after preeclampsia was 2.1 (95% confidence interval = 1.8–2.5). Deaths from cardiovascular disease contributed most strongly to this increase. Among women with preeclampsia who had subsequent births without preeclampsia, the excess risk of mortality became manifest only after 20 years.

Conclusions: These findings, together with other recent cohort studies, define preeclampsia as a risk marker for mortality from cardiovascular disease. They suggest that the observation of a normal blood pressure after preeclampsia should not discourage the search for other cardiovascular risk factors or abrogate the need for other preventive measures.

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Preeclampsia, manifested by new-onset hypertension and proteinuria during pregnancy, is estimated to complicate 3–5% of all deliveries.[1] The etiology of preeclampsia is unclear. Associated abnormalities may include poor trophoblast invasion,[2] oxidative stress,[3] endothelial cell dysfunction,[4] and immunologic disturbances.[5] Risk factors for preeclampsia include nulliparity,[1] increasing age of the woman[1] and her husband,[6] diabetes,[7] chronic hypertension,[8] obesity,[9] and family history of the condition,[10] whereas smoking has a negative association.[11]

Whether preeclampsia has long-term sequelae is controversial because it is difficult to separate preeclampsia from contributing conditions. A working group in the United States has concluded that increased future health risks are heralded by recurrent hypertension in pregnancy, preeclampsia in a multipara, or early-onset disease in any pregnancy.[12] Some investigators have ascribed preeclampsia in these clinical situations to unrecognized hypertension or other cardiovascular disease, and suggested that the diagnosis of preeclampsia would often be erroneous;[13] similarly, long-term sequelae would be attributable to the (as-yet) unrecognized underlying disease, rather than to preeclampsia per se. A recent report[14] from Norway has suggested that nulliparous patients with preeclampsia would suffer no long-term threat to survival provided that the pregnancy went to term, implying that mild preeclampsia would pose no threat to survival. The median follow-up in the Norwegian study was only 13 years, however; neither that study, nor any other, could assess mortality beyond 25 years, and none has taken into account potential confounding factors and associated conditions, such as diabetes. The present study addresses these issues.

METHODS

The Jerusalem Perinatal Study is a population-based research cohort derived from births in 1964–1976. The design and methods have been described previously;[15] briefly, the study recorded all births to Israeli residents of urban Jerusalem and its rural county and undertook active surveillance of infant mortality and birth defects reported from multiple sources. The study targeted residents of a geographic area, regardless of ethnicity or religion. Active surveillance of pregnancy complications and obstetric conditions was carried

out weekly, by abstracting data from the labor ward logbooks. This was done in the 3 largest obstetric units, covering 90% of all births.

Ascertainment and Definition of Preeclampsia

The original purpose of the Jerusalem Perinatal Study was to investigate hypertensive diseases of pregnancy. At the time the study was conducted, a diagnosis of preeclampsia (then called toxemia) required a systolic blood pressure ≥140 mmHg or a diastolic pressure ≥90 mmHg, or both, together with 1+ or more proteinuria and edema. For the duration of the study period, ascertainment was based on a precoded rubric, which was checked by the fieldworkers (all nurses) whenever preeclampsia (or eclampsia) was mentioned in labor ward logs. Pre-existing hypertension and other rare diagnoses (such as renal or autoimmune disease) were coded into a rubric for "other maternal conditions" and are not studied in this report.

Long-Term Follow-Up

We undertook follow-up studies of the women (and offspring) using personal identification numbers to link the subjects to national registries. Although the Jerusalem Perinatal study had recorded the women's identifications, the 7-digit numbers used in 1964–1976 contained no check digit and could not be distinguished from the passport numbers of foreign visitors. Therefore, we first verified the validity of these numbers, using the Population Registry of Israel, and checked demographic details such as country of birth and year of birth, while simultaneously, ascertaining the vital status of each woman. The work was undertaken after approval of the Institutional Review Boards in New York and Jerusalem and by authorities at Israel's Ministry of Health and Ministry of the Interior. This report is based on vital status of women whose identifications were validated before August 2000; follow-up is complete through 30 June 2000, at which time we had successfully traced 92% of women.

A priori, we focused on the subgroup of women whose preeclamptic pregnancy was followed by at least one subsequent birth without this condition, ie, women known to have been normotensive after preeclampsia. Because we have no knowledge of health surveillance between pregnancies and because pre-existing hypertension in any pregnancy was noted under a separate rubric, we used a subsequent normotensive pregnancy as a surrogate for the absence of chronic hypertension. The other group of patients either had no subsequent births in the study period, or had recurrent preeclampsia. Since we could not ascertain any further normotensive pregnancies in these circumstances, we analyzed these 2 groups together (and they are referred to as "Unknown whether normotensive after preeclampsia").

Data Analysis

We have no information on the occurrence of preeclampsia in births before 1964 or after 1976. We therefore compared women who had preeclampsia at any delivery in 1964–1976 with women who never had preeclampsia during that period. We also did other analyses to investigate effects of preeclampsia only at first deliveries and to run the models only from the date of delivery of a preeclamptic pregnancy. Because results of these additional analyses were similar, we are presenting only the first type of analysis.

We began by comparing Kaplan–Meier survival curves using log rank statistics, calculated within 5-year age strata; survivors were censored on June 30, 2000. We then analyzed survival with Cox proportional hazards models, computing the relative risk (RR) of death and the associated 95% confidence interval (CI). Efron's method was used to handle ties.[16] To ensure that the assumptions for proportional hazards were met, we assessed Schoenfeld residuals.[16] To determine whether the effect of preeclampsia on mortality was time-dependent, we tested it as a continuously varying function and as a dichotomy to 20 years and after, as suggested by the survival plot.

Maternal age at the baseline delivery was modeled first in 5-year groups, but we then found that fit was better (comparing the overall Wald-type χ^2) with age as a continuous variable, after setting unknowns (n = 50) to the mean (26.2) and expressing age in deviations from the mean. Age was therefore modeled as a continuous variable, as was year of the first delivery. Variables related to both preeclampsia and mortality were included in the models as confounders, after first testing them as potential effect-modifiers. Confounders modeled as dichotomies were insulin-dependent diabetes mellitus, gestational diabetes, and maternal heart disease (each diagnosed before a birth), and women with one or more offspring weighing <2500 g. Also included were sets of variables for maternal education (unknown, 0–4 years, 5–8 years vs. more) and social class (based on rank of husband's occupation; 6 [lowest], 5 and 4 vs. the 3 highest categories). Variables for which adjustment did not affect mortality were parity at baseline, religion (Muslims versus Jews), ethnic groups (continent of birth of the woman's father), immigrants versus Israel-born, major infant malformations, multiple births and rhesus negative.

Causes of Death

Causes of death, coded according to International Classification of Diseases-9, were available in the Population Registry for deaths occurring in 1979–1997. Classification of causes of the 245 deaths that occurred before 1978 was considered to be unreliable. After 1998, the authorities interpreted Israeli law in a way that denied us access to information on causes of death on individuals. Therefore, to analyze causes of death we used the subset of women who survived

beyond 1978 and censored the remaining survivors on 1 January 1998.

Numbers and Exclusions

There were 91,252 deliveries (92,408 offspring) in the Jerusalem Perinatal Study in 1964–1976. After excluding 1503 (1.6%) deliveries without women's identification numbers (mainly foreign visitors) there were 44,067 women's identification or passport numbers. We verified 40,455 (91.8%) of the numbers by the closing date for this report (January 2001). These included 39,802 whose vital status and current address in Israel was known, and 653 (1.6%) known to be unavailable for follow-up due to emigration or having been assigned new identities (eg, after domestic violence). The 8.2% who remained untraced included a higher proportion of wives of exchange students or of rabbis and students in Talmudic academies, compared with those traced; a major proportion of these are assumed to be foreign nationals. In this untraced group were 121 (2.8%) women who were diagnosed with preeclampsia compared with 1080 (2.7%) in those traced and available. We excluded 2741 traced women (6.9%), including 10 known to have had preeclampsia, who had not delivered in the 3 largest hospitals in which we surveyed other obstetric information, so that the cohort available for this study was 37,061 women.

RESULTS

Characteristics of the Cohort

The median age (years) at the baseline birth was 25 (range, 12–54) for the whole cohort and 23 (range, 12–45) for the women having their first birth. The median length of follow-up was 30 years (range, 24.5–36.5) with 1900 deaths observed; the median age at death was 53 years (range 19–80). There were 1070 women (2.9%) with preeclampsia. For 479 of these, we observed one or more subsequent births without preeclampsia; we classified these women as normotensive after preeclampsia. The remaining 591 women are classified as unknown with regard to subsequent normotensive status; this group is composed of women for whom we observed no further births in 1964–1976 (n = 538) and women whose subsequent pregnancies were also complicated by preeclampsia (n = 53).

Table 1 shows the distribution of demographic and health characteristics by preeclampsia category and, among these with preeclampsia, by subsequent preeclampsia. Compared with women who did not have preeclampsia, those diagnosed with preeclampsia in 1964–1976 were likely to have a history of diabetes, heart disease, multiple deliveries, or infants weighing less than 2500 g.

Risk Factors for Mortality

Table 2 shows the relation of selected characteristics to subsequent death. Apart from age, the strongest relative risks of death were found for preexisting insulin-dependent diabetes mellitus and heart disease. The woman's education and the husband's social class rank were both strong predictors of future mortality, with lowest relative risks seen in the better educated women and those with more affluent husbands. The upper part of Table 2 shows the variables that we chose to include in the set of covariates in the subsequent analyses relating to preeclampsia; these variables were independent predictors of both mortality and preeclampsia. The lower part of the table shows effects of other variables that we tested either because we had previously found them to be risk factors for preeclampsia (parity, multiple births, birth defects, religion of mother) or because of intrinsic interest (ethnic origin and immigration). Table 2 shows that none of these were independent risk factors of mortality.

Relation of Preeclampsia to Subsequent Mortality

Table 3 presents the relation of preeclampsia to mortality, composing the estimates of relative risk adjusted for age and additionally adjusted for other covariates. Preeclampsia was associated with more than doubled risk of deaths during the 24–36 years of follow-up. The relative risk increased steadily with the number of episodes of preeclampsia that we recorded in 1964–1976. Mortality was similarly elevated in the 2 subgroups of preeclampsia—those known to have been subsequently normotensive, and those whose subsequent status was unknown.

Table 4 compares women known, or not known, to be normotensive after preeclampsia according to baseline birth order and age and according to the 3 main risk factors for preeclampsia: insulin-dependent diabetes, gestational diabetes, and low birth weight.

Because a history of low birth weight has been shown to modify the risk of mortality associated with preeclampsia,[16] we reanalyzed our data restricted to women followed from their first delivery, comparing women with and without preeclampsia in that pregnancy (data not shown). After preeclampsia and low birth weight in a first delivery, the relative risk (RR) of death was 2.68 (95% CI = 1.80–4.01; based on 27 deaths). After preeclampsia and normal birth weight at the first delivery RR = 2.47 (1.98–3.10; based on 34 deaths).

Although the association between preeclampsia and death was somewhat stronger in women who were older or multiparous at baseline, the confidence limits for each of these groups overlap, and any differences in relative risk are likely to be due to chance.

Causes of Death

Within 60 days of delivery there were 3 maternal deaths among women who had preeclampsia in 1964–1976, for an estimated maternal death rate of 112/100,000 deliveries, compared with 18 (23/100,000) among women never diagnosed with preeclampsia.

TABLE 1. Percent Distribution of Characteristics of Women With and Without Preeclampsia in 1964–1976 (%)

Characteristics	Preeclampsia in 1964–1976			
	Yes			
	Known to Be Normotensive Later (n = 479)	Unknown Whether Normotensive Later (n = 591)	Total (n = 1070)	No (n = 35,991)
Woman's age at baseline birth (years)				
<20	8	3	5	7
20–24	41	32	36	40
25–29	28	20	24	28
30–34	17	19	18	15
35–39	4	16	11	8
40+	2	10	7	3
Unknown	0	0	0	0
History of insulin-dependent diabetes mellitus				
Yes	3	3	3	0
No	97	97	97	100
History of gestational diabetes				
Yes	5	6	5	1
No	95	94	95	99
History of heart disease				
Yes	1	1	1	1
No	99	99	99	99
1+infant weighed <2500 g (low-birth weight)				
Yes	27	25	26	11
No	73	75	74	89
Woman's education (years)				
Unknown	3	5	4	4
0–4	10	13	12	8
5–8	25	20	22	22
9+	63	61	62	66
Social class (occupation of husband)				
6 (lowest)	15	20	18	14
5	16	11	13	12
4	18	17	18	20
1–3 (higher)	33	34	33	36
Birth order (parity) of baseline birth				
1	67	50	58	61
2+	33	50	42	39
1+ offspring with major birth defect(s)				
Yes	14	8	11	8
No	86	92	90	93
1+ multiple deliveries				
Yes	7	5	6	3
No	93	95	94	97
Religion of woman				
Moslem	2	2	2	1
Jewish or other	98	98	98	99
Birthplace of woman's father				
Israel	13	15	14	15
Other West Asia	32	31	31	29
North Africa	22	20	21	22
Europe or elsewhere	33	34	34	35
Woman born abroad				
Yes	60	57	58	54
No	41	43	42	46

TABLE 2. Association of Selected Characteristics With Death During 24–36 Years of Follow-Up

Variable	Survival Status		Age-adjusted*		Additionally Adjusted for Other Covariates†	
	Died (n = 1,900)	Survived (n = 35,161)	RR	(95% CI)	RR	(95% CI)
Variables included in multivariate analysis						
Woman's age (year)						
<20	61	2,511	1.00	(0.76–1.32)	0.92	(0.70–1.21)
20–24‡	339	14,410	1.00	—	1.00	—
25–29	452	9,885	1.75	(1.52–2.02)	1.69	(1.47–1.95)
30–34	473	2,522	3.15	(2.74–3.62)	2.77	(2.40–3.21)
35–39	390	689	5.10	(4.40–5.90)	4.35	(3.74–5.07)
40+	185	770	7.60	(6.35–9.09)	6.12	(5.07–7.40)
Insulin-dependent diabetes mellitus						
Yes	38	108	3.63	(2.63–2.90)	3.49	(2.53–4.83)
No‡	1,862	35,053	1.00		1.00	
Gestational diabetes						
Yes	36	370	1.54	(1.11–2.14)	1.42	(1.02–1.98)
No‡	1,864	34,791	1.00		1.00	
Heart disease						
Yes	41	229	2.74	(2.57–2.93)	2.88	(2.11–3.93)
No	1,859	34,932	1.00		1.00	
1+ low-birth weight infant <2500 g						
Yes	255	3,836	1.33	(1.17–1.52)	1.28	(1.12–1.47)
No‡	1,645	31,325	1.00		1.00	
Women's education (years)						
Unknown	162	1,450	1.58	(1.31–1.91)	1.31	(1.07–1.61)
0–4	388	2,647	1.64	(1.41–1.90)	1.27	(1.06–1.52)
5–8	515	7,551	1.38	(1.21–1.58)	1.16	(1.00–1.35)
9–12	466	12,907	1.08	(0.95–1.240)	1.00	(0.87–1.15)
13+‡	369	10,606	1.00	—	1.00	—
Social class						
6 (low)	438	4,648	1.64	(1.40–1.92)	1.37	(1.15–1.63)
5	303	4,065	1.51	(1.28–1.79)	1.29	(1.08–1.55)
4	357	7,018	1.34	(1.14–1.57)	1.19	(1.00–1.40)
3	303	6,684	1.04	(0.88–1.23)	0.98	(0.83–1.16)
2	245	5,786	1.23	(1.03–1.47)	1.16	(0.97–1.39)
1 (high)‡	254	6,960	1.00	—	1.00	—
Year of baseline birth						
1964–1966	1,054	11,120	1.29	(1.12–1.49)	1.10	(0.95–1.28)
1967–1971	550	11,326	1.07	(0.93–1.24)	0.99	(0.86–1.15)
1972–1976‡	296	12,715	1.00	—	1.00	—
per 5 years (continuous)	—	—	0.84	(0.79–0.81)	0.92	(0.85–0.99)
Other variables						
Birth order						
1‡	662	22,068	1.00	—	1.00	—
2–3	459	7,565	0.99	(0.86–1.12)	0.91	(0.80–1.04)
4–6	401	3,772	1.20	(1.03–1.39)	0.98	(0.84–1.15)
7+	373	1,702	1.53	(1.29–1.82)	1.12	(0.92–1.37)

(*Continued*)

TABLE 2. (*Continued*)

Variable	Survival Status		Age-adjusted*		Additionally Adjusted for Other Covariates†	
	Died (n = 1,900)	Survived (n = 35,161)	RR	(95% CI)	RR	(95% CI)
1+ offspring with major birth defect(s)						
Yes	142	2,651	1.05	(0.88–1.24)	0.95	(0.80–1.12)
No‡	1,758	32,510	1.00		1.00	
1+ multiple deliveries						
Yes	65	929	1.27	(0.99–1.63)	1.10	(0.85–1.41)
No‡	1,835	34,232	1.00		1.00	
Religion of woman						
Moslem	27	355	1.44	(0.95–2.90)	1.06	(0.70–1.62)
Jewish or other‡	1,873	34,806	1.00	—	1.00	—
Birthplace of woman's father						
Israel‡	256	5,218	1.0	—	1.0	—
Other West Asia	616	10,031	1.03	(0.87–1.23)	0.90	(0.75–1.07)
North Africa	484	7,591	1.17	(0.97–1.42)	1.02	(0.84–1.25)
Europe, etc.	544	12,321	0.94	(0.80–1.17)	1.08	(0.91–1.28)
Woman born abroad						
Yes	1,228	18,717	1.06	(0.94–1.19)	0.98	(0.86–1.10)
No‡	672	16,444	1.00		1.00	

*Except for age of woman at baseline birth for which unadjusted results are presented.
†Adjusted, where appropriate, for age (continuous), insulin-dependent diabetes, gestational diabetes, birth of infant(s) weighing <2500 g, education (unknown, 0–4, 5–8 vs. 9+), social class (6, 5, 4 vs. 1–3), and year of baseline birth (continuous).
‡Reference group

TABLE 3. Association of Preeclampsia (1964–1976) With Death Over 24–36 Yr of Follow-Up

Preeclampsia variable	Survival Status		Age-adjusted		Additionally Adjusted for Other Covariates*	
	Died (n = 1,900)	Survived (n = 35,161)	RR	(95% CI)	RR	(95% CI)
Total preeclampsia						
None†	1,752	34,239	1.00		1.00	
Any	148	922	2.37	(2.00–2.80)	2.13	(1.79–2.53)
Number of deliveries with preeclampsia in 1964–1976						
0†			1.00		1.00	
1	122	843	2.18	(1.81–2.62)	2.01	(1.67–2.43)
2	19	65	3.49	(2.22–5.49)	2.68	(1.69–4.25)
3+	7	14	6.18	(2.95–13.0)	4.40	(2.07–9.35)
Normotensive after preeclampsia						
Never had preeclampsia†			1.00		1.00	
Yes	52	427	2.20	(1.67–2.90)	1.95	(1.47–2.57)
Unknown	96	495	2.47	(2.01–3.04)	2.24	(1.81–2.77)

*Adjusted for some variables as noted in Table 2.
†Reference groups.

TABLE 4. Association* of Preeclampsia With Death, by Preeclampsia Subgroup, and Risk Factors for Preeclampsia Preeclampsia in 1964–1976

	Known to Be Normotensive Later (n = 479)		Unknown Whether Normotensive Later (n = 591)		Total Preeclampsia (n = 1070)		No Preeclampsia† (n = 35,991)	
	No. Died; No. Survived	RR (95% CI)	No. Died; No. Survived	RR (95% CI)	No. Died; No. Survived	RR (95% CI)	No. Died; No. Survived	RR (95% CI)
Mother's age								
<30	24; 343	1.68 (1.11–2.53)	21; 301	2.16 (1.40–3.34)	45; 644	1.88 (1.38–2.54)	807; 26,162	1.00
+30	28; 84	2.23 (1.52–3.26)	75; 192	2.32 (1.82–2.95)	103; 276	2.29 (1.86–2.83)	945; 8,029	1.00
Birth Order								
1	22; 301	1.73 (1.12–2.66)	17; 277	1.76 (1.08–2.86)	39; 598	1.74 (1.25–2.42)	623; 21,490	1.00
2	30; 126	2.08 (1.44–3.00)	79; 218	2.39 (1.89–3.03)	109; 344	2.30 (1.87–2.82)	1,129; 12,749	1.00
Insulin-dependent diabetes mellitus	5; 9	2.14 (0.77–5.96)	9; 8	2.91 (1.28–6.66)	14; 17	2.58 (1.29–5.16)	29; 100	1.00
Gestational diabetes	2; 21	1.16 (0.27–4.99)	10; 23	2.89 (1.20–6.92)	12; 44	2.18 (1.00–4.71)	24; 326	1.00
Low birth weight	10; 120	1.11 (0.58–2.10)	25; 122	1.95 (1.27–2.96)	35; 242	1.60 (1.11–2.30)	220; 3,594	1.00
Total	52; 437	1.95 (1.47–2.57)	96; 495	2.24 (1.81–2.77)	148; 942	2.13 (1.79–2.53)	1,752; 34,239	1.00

*Adjusted for some variables as noted in Table 2.
†Reference groups.

Information on causes of death was available for the 1384 deaths unrelated to preeclampsia that occurred in 1979–1997; of these, nearly half were attributed to neoplastic diseases (n = 658) and 22% were from cardiovascular causes (n = 310), including cerebrovascular disease (n = 64) or sudden death (n = 9). The remaining 416 were from external causes (n = 84), diabetes (n = 44), miscellaneous (n = 280) and no cause recorded in the Population Registry (n = 92). We estimated the relation of preeclampsia to mortality in 1979–1997 among women who survived beyond 1978 (Table 5), finding the strongest relationship with deaths due to cardiovascular diseases. Overall, the pattern of risk factors in this restricted data set was almost identical to the pattern seen in Table 2, although the contribution of each risk factor differed according to cause of death (data not shown). Table 5 shows that for preeclampsia, the strongest relationship was with deaths attributable to cardiovascular diseases. There were no obvious differences between women known to have been normotensive after a preeclamptic pregnancy, and those whom subsequent status was not known.

Timing of Deaths

Because preliminary analyses, using life-table plots, had suggested differences among the study groups, we also

TABLE 5. Association* of Preeclampsia With Risk of Death (1978–1997), by Cause of Death

Cause of Death	Known to Be Normotensive Later (n = 476)	Unknown Whether Normotensive Later (n = 579)	Total Preeclampsia (n = 1,055)	No Preeclampsia (n = 36,858)
Neoplastic diseases				
Deaths	12	15	27	631
RR (95% CI)	1.37 (0.77–2.43)	1.19 (0.71–1.99)	1.26 (0.85–1.86)	1.00
Cardiovascular diseases				
Deaths	14	27	41	269
RR (95% CI)	3.08 (1.78–5.31)	3.07 (2.03–4.65)	3.07 (2.18–4.34)	1.00
Other causes				
Deaths	13	22	35	381
RR (95% CI)	2.10 (1.20–3.68)	2.16 (1.39–3.36)	2.14 (1.49–3.06)	1.00
Total				
Deaths	39	64	103	1281
RR (95% CI)	1.98 (1.44–2.73)	2.02 (1.56–2.61)	2.00 (1.63–2.46)	1.00

*Adjusted for some variables (where appropriate) as noted in Table 2.

compared them using various time-dependent approaches. Figure 1 shows the survival curves. There is a clear difference between the women with no preeclampsia and the group with preeclampsia and subsequent status unknown. For the latter group, there was a reduced survival discernible within 2 years of follow-up, and by 30 years the estimated cumulative death rate was 9.5% compared with 3.6% in those who never had preeclampsia. On the other hand, the women we knew to have been normotensive after preeclampsia differed from both of the other groups; their survival curve changed suddenly after 2 decades of follow-up. In the first 2 decades, they survived as well as women who never had preeclampsia. In the third and fourth decades, however, their survival curve paralleled that of the other women with preeclampsia, and diverged sharply from the women who never had preeclampsia.

Within the 1070 women who had preeclampsia, we compared the 2 groups using proportional hazards models, adjusted for age and social class. We first estimated the relative risk of death in the group whose subsequent status was unknown, relative to the women known to have been normotensive after preeclampsia, by modeling this dichotomy over the whole period of follow-up (RR = 1.2; 95% CI = 0.84–1.73). Then we tested the difference between the 2 preeclampsia groups as a time-dependent variable constructed from the product of the dichotomy with month of follow-up (RR = 0.998; 95% CI = 0.994–1.001). We also modeled this comparison as time-dependent dichotomies for the first 20 years (RR = 2.28; 95% CI = 1.04–5.10) and the subsequent time period (RR = 1.00; 95% CI = 0.67–1.49). Further adjustment for diabetes, heart disease, low birth weight, and maternal education did not materially alter these estimates. These findings are similar to the patterns seen in the survival plots (Fig. 1) where the 2 groups with preeclampsia differed during the first 20 years of follow-up, but did not differ during years 21–36.

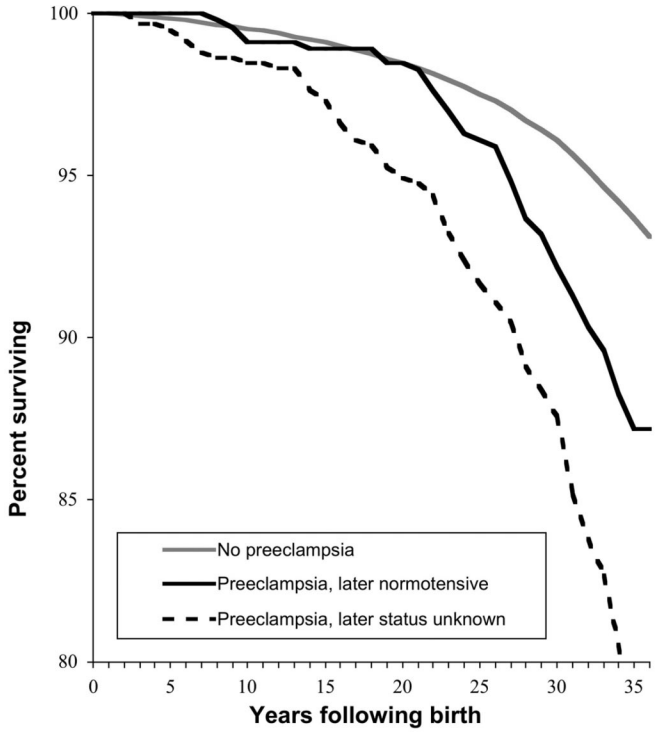

FIGURE 1. Life table cumulative estimates of maternal survival after preeclampsia. "Preeclampsia, subsequently, normotensive" refers to women with preeclampsia who had at least one subsequent normotensive birth. "Preeclampsia, subsequent status unknown" refers to all other women with preeclampsia.

Table 6 applies similar analyses to the whole cohort, comparing the 2 preeclampsia groups with the reference group of women who never had preeclampsia. Model 1 assumes no time-dependent effects of preeclampsia. Model 2 tests whether the effects of preeclampsia changed progressively over time (RR = 1.003; 95% CI = 1.000–1.006), which does not substantially improve the goodness-of-fit compared with the previous model. Model 3 confirms the impression seen in Figure 1 that the increased risk of death in the group of women known to have been normotensive following preeclampsia was restricted to the third and fourth decades of follow-up (RR = 1.94; 95% CI = 1.35–2.78). For the group whose subsequent status was unknown, on the other hand, there was essentially no difference in risk during the first 20 years (2.50; 1.84–3.38) or the later years (2.42; 1.87–3.12).

Findings were not materially altered by restricting the definition of preeclampsia to cases occurring in first births. Similarly, the conclusions were unchanged by further controlling for parity, ethnic groups or any of the other variables shown in Table 2.

DISCUSSION

Our results support some existing views about long-term sequelae of preeclampsia, but challenge the belief that women who have preeclampsia only in their first birth have no excess risk of death. Overall, our study confirms the excess risk of mortality after preeclampsia that has been demonstrated recently by studies in Scotland[17] and Norway.[14] Our results point to a substantial risk of death in women who had preeclampsia and yet, by virtue of being subsequently normotensive, may be assumed unlikely to have underlying hypertension. This group, mostly nulliparous, has been thought to be without excess risk of future sequelae, let alone death.[12] No previous study has followed such women into the third and fourth decades after preeclampsia. The association is strong and time-dependent, starting after 20 years and continuing during the next decade and a half. The specificity for cardiovascular disease accords with the results from the Norwegian study.[14]

TABLE 6. Time-Dependent Association* of Preeclampsia With Risk of Death by Preeclampsia Subgroup and Method of Estimating the Effects

	Known to Be Normotensive Later (n = 476) No. Deaths	Unknown Whether Normotensive Later (n = 579) RR (95% CI)	Model χ^2	*df*
Model 1: No change over time				
Preeclampsia				
Deaths	52	96		
RR	1.95	2.24	1227	14
95% CI	(1.47–2.57)	(1.81–2.77)		
Model 2: Continuous change over time				
Preeclampsia				
Deaths	52	96		
RR	0.81	1.77	1234	16
95% CI	(0.32–2.03)	(1.00–3.10)		
Preeclampsia × month of survival				
RR	1.003	1.000		
95% CI	(1.000–1.006)	(0.999–1.003)		
Model 3: Dichotomous change over time				
Preeclampsia × month of survival				
Months 0–240				
Deaths	8	31		
RR	0.88	1.94		
95% CI	(0.44–1.72)	(1.35–2.78)		
Months 241+			1240	16
Deaths	44	65		
RR	2.50	2.42		
95% CI	(1.84–3.38)	(1.87–3.12)		
Model 0: Without considering preeclampsia			1122	12

*Adjusted for some variables as noted in Table 2.

We also confirm that, in the short term, women who are found to be normotensive in another pregnancy after preeclampsia are at no greater risk of death than the general population. This view was put forward Chesley[15] and has been taken up by others[14] in the United States, albeit cautiously. Chesley's finding led to speculation that multiparous women with preeclampsia would be more likely to have had the diagnosis confounded by underlying chronic hypertension; this underlying disease, but not the preeclampsia, was thought to be the cause of any subsequent morbidity and mortality.[12] However, we show that women with preeclampsia who have subsequently normotensive pregnancies have an excess risk of death in the third and fourth decades of follow up.

What might explain a latent period of 20 years? We speculate that the first steps in endothelial damage, as a precursor of atherosclerosis, might occur at the time of the preeclamptic pregnancy. There is evidence for endothelial cell dysfunction in preeclampsia[1] and oxidative stress may contribute to this dysfunction.[18,19] This endothelial damage, coupled with lipid changes described in preeclampsia,[20] might be the first lesions precipitating atherosclerosis—changes that progress for 20 years or more before affecting mortality. In short, preeclampsia may either promote or hasten systemic vascular disease.

Although preeclampsia may trigger a cascade of events that result in early mortality, it is also possible that the converse might be true. Women at risk for cardiovascular disease might also be at risk for preeclampsia; this pregnancy complication would thus be a harbinger, a "risk marker," rather than a cause, of future morbidity and mortality.

Our study has the advantage of a prospective design, based on a cohort that is broadly representative of the total population, and follow-up is complete. Data were recorded at the time of birth and then could not be biased in respect of the

outcome. Similarly, the outcome was ascertained using population-based registries, and would have been unbiased with respect to the diagnosis of preeclampsia. Moreover, we could control for several variables known to influence mortality (ie, diabetes, pre-existing heart disease, low birthweight) in addition to several measures of socioeconomic status.

On the other hand, our study lacks information regarding common risk factors for cardiovascular disease such as smoking, lipid profile, diet and obesity. Furthermore, the Jerusalem Perinatal Study recorded only those births that occurred in 1964–1976; we have no knowledge of earlier or later births to the same women. Without a complete obstetric record, we cannot define which of the multiparous women at baseline might have previously had preeclampsia (typically in their first pregnancy) or which of those for whom we did not know the subsequent status might have gone on to be normotensive. It is also possible that a subject may have had preeclampsia in one birth, followed by a subsequent pregnancy in which chronic hypertension was diagnosed. This pregnancy would have been coded in a generic category for other maternal conditions and we would have no knowledge of these details. Nevertheless, such misclassification would have little impact on our estimates of relative risk, as preeclampsia was rare in this population. Our data might have underestimated the short-term risk of death in the group with unknown subsequent status, as this group may include women who were later normotensive.

Our results suggest that practitioners should not be reassured after preeclampsia, even if subsequent pregnancies are not complicated by this condition. Our findings provide evidence that preeclampsia is a risk marker for mortality from cardiovascular disease.

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