

## ORIGINAL ARTICLE

# Preeclampsia and the Risk of End-Stage Renal Disease

Bjørn Egil Vikse, M.D., Ph.D., Lorentz M. Irgens, M.D., Ph.D.,  
Torbjørn Leivestad, M.D., Ph.D., Rolv Skjærven, Ph.D.,  
and Bjarne M. Iversen, M.D., Ph.D.

## ABSTRACT

**BACKGROUND**

It is unknown whether preeclampsia is a risk marker for subsequent end-stage renal disease (ESRD).

**METHODS**

We linked data from the Medical Birth Registry of Norway, which contains data on all births in Norway since 1967, with data from the Norwegian Renal Registry, which contains data on all patients receiving a diagnosis of end-stage renal disease (ESRD) since 1980, to assess the association between preeclampsia in one or more pregnancies and the subsequent development of ESRD. The study population consisted of women who had had a first singleton birth between 1967 and 1991; we included data from up to three pregnancies.

**RESULTS**

ESRD developed in 477 of 570,433 women a mean ( $\pm$ SD) of  $17\pm 9$  years after the first pregnancy (overall rate, 3.7 per 100,000 women per year). Among women who had been pregnant one or more times, preeclampsia during the first pregnancy was associated with a relative risk of ESRD of 4.7 (95% confidence interval [CI], 3.6 to 6.1). Among women who had been pregnant two or more times, preeclampsia during the first pregnancy was associated with a relative risk of ESRD of 3.2 (95% CI, 2.2 to 4.9), preeclampsia during the second pregnancy with a relative risk of 6.7 (95% CI, 4.3 to 10.6), and preeclampsia during both pregnancies with a relative risk of 6.4 (95% CI, 3.0 to 13.5). Among women who had been pregnant three or more times, preeclampsia during one pregnancy was associated with a relative risk of ESRD of 6.3 (95% CI, 4.1 to 9.9), and preeclampsia during two or three pregnancies was associated with a relative risk of 15.5 (95% CI, 7.8 to 30.8). Having a low-birth-weight or preterm infant increased the relative risk of ESRD. The results were similar after adjustment for possible confounders and after exclusion of women who had kidney disease, rheumatic disease, essential hypertension, or diabetes mellitus before pregnancy.

**CONCLUSIONS**

Although the absolute risk of ESRD in women who have had preeclampsia is low, preeclampsia is a marker for an increased risk of subsequent ESRD.

From the Renal Research Group, Institute of Medicine (B.E.V., B.M.I.), the Section for Epidemiology and Medical Statistics (L.M.I., R.S.), and the Locus for Registry-Based Epidemiology (B.E.V., L.M.I., R.S., B.M.I.), University of Bergen; the Department of Medicine, Haukeland University Hospital (B.E.V., B.M.I.); and the Medical Birth Registry of Norway, Norwegian Institute of Public Health (L.M.I., R.S.) — all in Bergen, Norway; and the Norwegian Renal Registry, Institute of Immunology, Rikshospitalet, Oslo (T.L.). Address reprint requests to Dr. Vikse at the Renal Research Group, Institute of Medicine, Haukeland University Hospital, Bergen 5021, Norway, or at [bjorn.vikse@med.uib.no](mailto:bjorn.vikse@med.uib.no).

N Engl J Med 2008;359:800-9.  
Copyright © 2008 Massachusetts Medical Society.

SEVERAL INVESTIGATIONS HAVE SUGGESTED that preeclampsia may be associated with the development of cardiovascular disease,<sup>1-4</sup> renal disease,<sup>5</sup> and cardiovascular risk factors<sup>6-11</sup> for several years after pregnancy. Other studies have shown increased rates of microalbuminuria up to 5 years after pregnancy in women with previous preeclampsia,<sup>12,13</sup> a finding that is compatible with the presence of underlying unrecognized renal disease or a damaging effect of preeclampsia on the kidney. It is uncertain whether these associations are explained by adverse effects of preeclampsia itself or by underlying risk factors that predispose women to both preeclampsia and later cardiovascular and renal disease.

We previously reported that preeclampsia in a woman's first pregnancy is a risk marker for undergoing a kidney biopsy later in life.<sup>5</sup> However, it is not known whether preeclampsia is associated with end-stage renal disease (ESRD) and, if so, whether a history of preeclampsia in more than one pregnancy increases this risk.

We linked data from two large registries, the Medical Birth Registry of Norway and the Norwegian Renal Registry, to assess the association between preeclampsia in one or more pregnancies and the subsequent risk of ESRD. We also assessed the relationships between having a low-birth-weight infant or a preterm birth and the risk of later ESRD.

## METHODS

### STUDY SUBJECTS

Since 1967, medical data on all births in Norway (total population, 4.5 million) with a gestational age of at least 16 weeks have been forwarded to the Medical Birth Registry of Norway.<sup>14</sup> Notification is compulsory and is carried out with the use of a form that is completed by the attending midwife or doctor. The form includes extensive data on maternal disease and conditions of the newborn, which are coded at the registry according to the definitions in the *International Classification of Diseases* (the 8th revision was used from 1967 to 1998 and the 10th revision from 1999 to the present). Since 1980, data from all patients in Norway who have end-stage renal disease (which is defined as the need for long-term dialysis treatment or renal transplantation), including the date of onset and the cause of the disease, have been entered in the Norwegian Renal Registry; these data are avail-

able through December 2005. The national Cause of Death Registry contains data on all deaths; these data are available through December 2004.

We included data on the first three pregnancies that resulted in a live birth or a stillbirth after at least 16 weeks of gestation for all women for whom a first delivery was recorded between 1967 and 1991. Data on second and third pregnancies were available through 2004. Data from women with multiple deliveries were excluded. We used national identification numbers to link data from the included women with the Norwegian Renal Registry and the national Cause of Death Registry. The study was approved by the Regional Committee for Medical Research Ethics in Western Norway.

### EXPLANATORY VARIABLES

The criteria for preeclampsia that are used by the reporting midwives and obstetricians are in accordance with the 1972 recommendations of the American College of Obstetricians and Gynecologists.<sup>15</sup> These criteria include increased blood pressure after 20 weeks of gestation ( $\geq 140/90$  mm Hg or an increase in systolic pressure of  $\geq 30$  mm Hg or in diastolic pressure of  $\geq 15$  mm Hg from measurements made before 20 weeks of gestation) and proteinuria ( $\geq 0.3$  g of protein in a 24-hour urine specimen or a urine dipstick result of  $\geq 1+$ ). The diagnoses of preeclampsia in the Medical Birth Registry have not been directly validated, but consistency of reported rates has been demonstrated among counties and over time.<sup>16-18</sup> Birth weight was measured shortly after birth; a weight below 2.5 kg was categorized as low birth weight. From 1967 through 1998, the estimated gestational age was based on the last menstrual period, and from 1999 onward, it was based on routine ultrasonographic examination between gestational weeks 17 and 20. Birth at a gestational age of less than 37 weeks was defined as preterm. Infants whose birth weight for gestational age was below the 10th percentile (on the basis of sex-specific reference values reported previously<sup>19</sup>) were considered small for gestational age.

The registration of diabetes mellitus, kidney disease (including kidney or urinary tract disease), rheumatic disease (autoimmune connective-tissue disease or inflammatory arthritides), and essential hypertension before pregnancy relies on the ascertainment of these conditions by the woman's general practitioner or obstetrician. Validation

studies have shown that 97% of patients with a previous diagnosis of diabetes mellitus and 88% of those with a previous diagnosis of rheumatic disease are registered with these conditions in the Medical Birth Registry.<sup>20,21</sup> A birth was recorded as a stillbirth if the infant died before or during labor. Marital status was dichotomized as either single (divorced or not living with a partner) or not single (married or living with a partner). Congenital malformation of the infant was recorded as present if any congenital malformation was reported shortly after birth. The year of delivery and maternal age at delivery were included in the analyses as continuous variables.

#### OUTCOME VARIABLES

The outcome of the study was ESRD. The date of onset of ESRD was defined as the date of initiation of dialysis treatment or the date of renal transplantation. The causes of ESRD were categorized as glomerulonephritis, interstitial nephritis, congenital disease, diabetic nephropathy, and other causes. Women in whom ESRD did not develop were followed until December 31, 2005, or death.

#### STATISTICAL ANALYSIS

Data were analyzed in a cohort design, with preeclampsia, birth weight, and gestational age at birth as explanatory variables and ESRD as the outcome variable. We performed separate analyses of data from women with one or more, two or more, and three or more pregnancies. Explanatory variables that were related to one, two, or three pregnancies were included in the respective analyses, and baselines were set at the dates of the first, second, or third births. Pregnancies occurring after the development of ESRD were excluded. Absolute risk estimates were calculated as rates per 100,000 person-years of observation. Estimates of the relative risk of ESRD according to selected risk factors were obtained by Cox regression analyses. Analyses were adjusted by including the described variables as covariates in the Cox models. Using Cox regression models, we tested for effects of interactions between preeclampsia and low birth weight or preterm birth in each of the analyses. Data from women who died without having ESRD were censored at the time of death. Because cases of ESRD were not registered between 1967 and 1979, data from mothers who gave birth during this period were left truncated in the survival analyses before January 1980. Consequently, the count-

ing-process formulation of proportional hazards (Cox regression) was applied.<sup>22</sup> According to this method, mothers were not included in the analysis until the occurrence of ESRD could be registered, beginning in 1980; for example, a mother with her last delivery in 1973 would be included in the analyses 7 years after the delivery, and her data would be censored 32 years after the delivery if she did not have ESRD or if she died. The analyses were performed with the use of the statistical software packages SPSS, version 15, and S-Plus, version 7.0.

## RESULTS

#### STUDY POPULATION

The study population consisted of 570,433 women who had given birth to at least one child with a gestational age of 16 weeks or more; 480,006 of these women gave birth to a second child and 210,660 to a third child. The mean ( $\pm$ SD) durations of follow-up after the first, second, and third pregnancy were 26.5 $\pm$ 7.5, 22.8 $\pm$ 8.0, and 18.7 $\pm$ 8.2 years, respectively. The mean ages of the mother at the first, second, and third delivery were 23.5 $\pm$ 4.3, 26.9 $\pm$ 4.3, and 30.2 $\pm$ 4.3 years, respectively. As compared with women with only one pregnancy, women with two or more pregnancies were younger, less likely to be single, and less likely to have had preeclampsia in their first pregnancy (Table 1). As compared with women who did not have stillbirth, a history of stillbirth in the first pregnancy was associated with a greater likelihood of having a second pregnancy (87% vs. 84%) and a third pregnancy (67% vs. 37%). As compared with women who did not have preeclampsia, women who had preeclampsia in a first pregnancy resulting in a live birth were less likely to have a second pregnancy (81% vs. 84%) or a third pregnancy (34% vs. 37%). As compared with women who had no preeclamptic pregnancies, women who had preeclampsia in a second pregnancy were less likely to have a third pregnancy (35% vs. 44%). Among women who had preeclampsia during pregnancy, those who had a low-birth-weight infant were less likely to have a subsequent pregnancy than those who had an infant of normal weight.

Between 1980 and 2005, ESRD developed in 477 women at a mean age of 41 $\pm$ 10 years (range, 19 to 77) and at a mean of 17 $\pm$ 9 years after the first pregnancy. ESRD developed in 0.007%, 0.015%, 0.051%, 0.10%, and 0.18% of the women within 5, 10, 20, 30, and 38 years after the

**Table 1. Characteristics of First and Second Pregnancies in Relation to the Subsequent Development of End-Stage Renal Disease (ESRD) and the Lifetime Number of Pregnancies.\***

Variable	All Women	Women with ESRD	Lifetime No. of Pregnancies		
			1	2	≥3
<b>First pregnancy</b>					
No. of women	570,433	477	90,427	269,346	210,660
Maternal age at delivery — yr	23.5±4.3	24.0±5.1	25.8±5.7	23.7±4.0	22.4±3.5
Single marital status — no. (%)	114,217 (20.0)	108 (22.6)	26,867 (29.7)	43,664 (16.2)	43,686 (20.7)
Preeclampsia — no. (%)	20,918 (3.7)	67 (14.0)	3,919 (4.3)	9,678 (3.6)	7,321 (3.5)
Low-birth-weight infant — no. (%)	27,764 (4.9)	92 (19.3)	5,898 (6.5)	11,092 (4.1)	10,776 (5.1)
Preterm birth — no. (%)	31,957 (5.6)	94 (19.7)	6,425 (7.1)	13,313 (4.9)	12,219 (5.8)
Congenital malformation — no. (%)	17,343 (3.0)	21 (4.4)	3,034 (3.4)	7,813 (2.9)	6,496 (3.1)
Stillbirth — no. (%)	4,923 (0.9)	25 (5.2)	638 (0.7)	987 (0.4)	3,298 (1.6)
Maternal diabetes mellitus — no. (%)	1,271 (0.2)	49 (10.3)	423 (0.5)	582 (0.2)	266 (0.1)
Maternal kidney or urinary tract disease — no. (%)	12,872 (2.3)	80 (16.8)	2,347 (2.6)	5,894 (2.2)	4,631 (2.2)
Maternal essential hypertension — no. (%)	909 (0.2)	10 (2.1)	259 (0.3)	427 (0.2)	223 (0.1)
Maternal rheumatic disease — no. (%)	1,389 (0.2)	12 (2.5)	375 (0.4)	654 (0.2)	360 (0.2)
<b>Second pregnancy</b>					
No. of women	480,006	318		269,346	210,660
Maternal age at delivery — yr	26.9±4.3	26.8±4.7		28.0±4.4	25.6±3.8
Single marital status — no. (%)	26,076 (5.4)	23 (7.2)		13,085 (4.9)	12,991 (6.2)
Preeclampsia — no. (%)	8,531 (1.8)	27 (8.5)		5,448 (2.0)	3,083 (1.5)
Low-birth-weight infant — no. (%)	14,612 (3.0)	31 (9.7)		7,723 (2.9)	6,889 (3.3)
Preterm birth — no. (%)	20,029 (4.2)	33 (10.4)		10,841 (4.0)	9,188 (4.4)
Congenital malformation — no. (%)	12,684 (2.6)	16 (5.0)		7,083 (2.6)	5,601 (2.7)
Stillbirth — no. (%)	2,977 (0.6)	10 (3.1)		662 (0.2)	2,315 (1.1)

\* Plus-minus values are means ±SD. The number of pregnancies recorded between 1967 and 2004 is given. Maternal diabetes mellitus, kidney or urinary tract disease, essential hypertension, and rheumatic disease are recorded if they were present before pregnancy. Data on pregnancies between 1967 and 2004 were available from the Medical Birth Registry of Norway; data on ESRD between 1980 and 2005 were available from the Norwegian Renal Registry.

first birth, respectively. The overall rate of ESRD after the first birth was 3.7 per 100,000 women per year.

#### PREECLAMPSIA AS A RISK MARKER

Among women who had been pregnant one or more times, preeclampsia during the first pregnancy was associated with a relative risk of ESRD of 4.7 (95% confidence interval [CI], 3.6 to 6.1) (Table 2). Among women who had been pregnant two or more times, preeclampsia during the first pregnancy was associated with a relative risk of ESRD of 3.2 (95% CI, 2.2 to 4.9), preeclampsia during the second pregnancy with a relative risk of 6.7 (95% CI, 4.3 to 10.6), and preeclampsia during both

pregnancies with a relative risk of 6.4 (95% CI, 3.0 to 13.5). Among women who had been pregnant three or more times, preeclampsia during one pregnancy was associated with a relative risk of ESRD of 6.3 (95% CI, 4.1 to 9.9), and preeclampsia during two or three pregnancies was associated with a relative risk of 15.5 (95% CI, 7.8 to 30.8).

Figure 1 shows the association between preeclampsia and ESRD during the follow-up period. Separate analyses setting the baseline at 10 years after the pregnancy of interest confirmed a significant association between preeclampsia and ESRD. These analyses showed that after one pregnancy, the relative risk of ESRD that was associated with preeclampsia was 4.1 (95% CI, 3.1 to

**Table 2. Preeclampsia and the Risk of End-Stage Renal Disease (ESRD) after a First, Second, or Third Pregnancy.\***

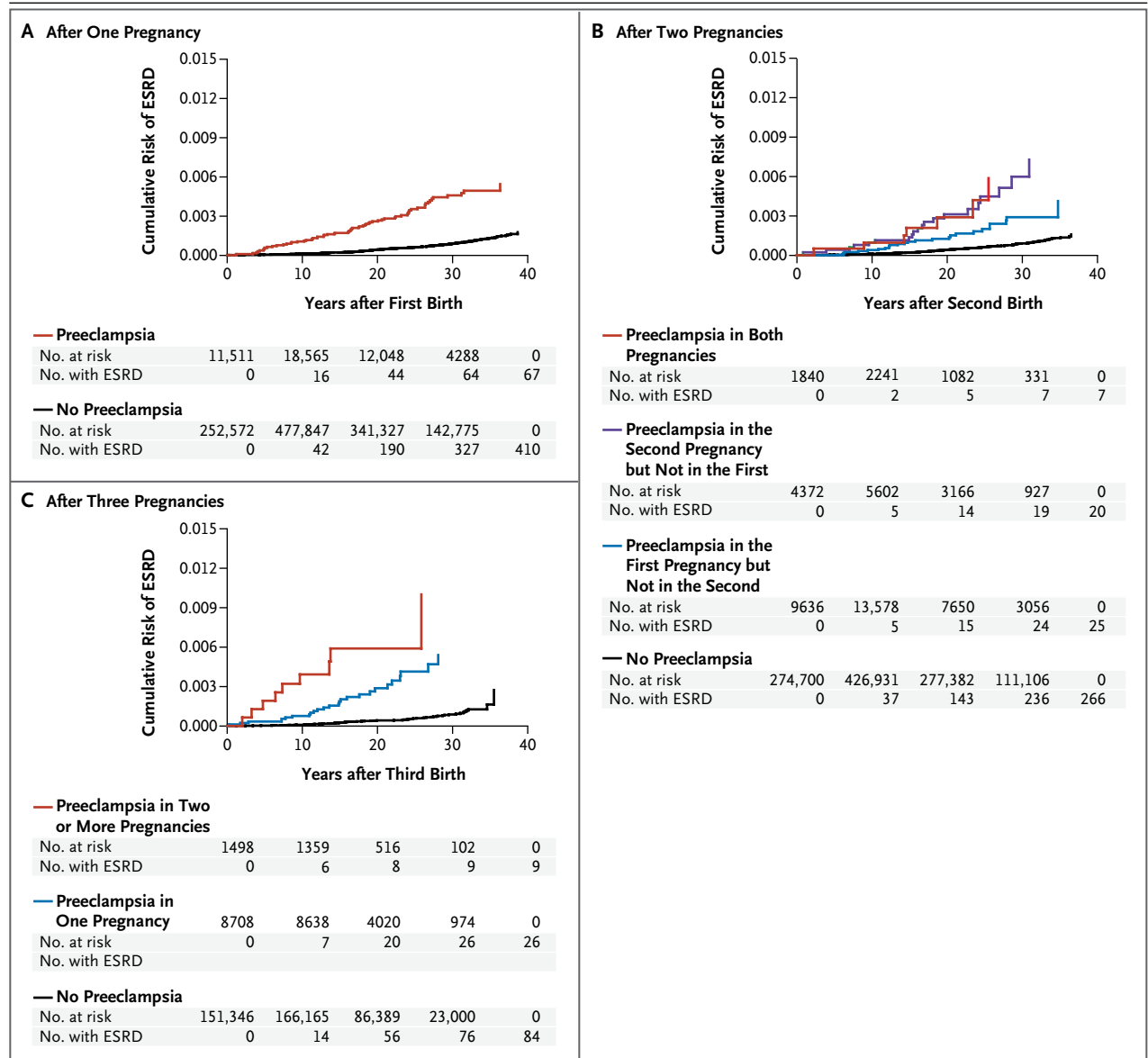
Variable	Total No. of Women	No. with ESRD	No. with Data Censored at Time of Death	No./100,000 Person-Yr (95% CI)†	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI) Model 1‡	Adjusted Relative Risk (95% CI) Model 2§
After 1 pregnancy (all women)							
No preeclampsia	549,515	410	12,848	3.3 (2.9–3.6)	1.0	1.0	1.0
Preeclampsia	20,918	67	495	14.5 (11.2–18.1)	4.7 (3.6–6.1)	4.3 (3.3–5.6)	3.2 (2.2–4.5)
After 2 pregnancies (women with ≥2 pregnancies)							
No preeclampsia	456,884	266	9,033	2.8 (2.5–3.1)	1.0	1.0	1.0
Preeclampsia in first pregnancy only	14,588	25	255	8.6 (5.6–12.3)	3.2 (2.2–4.9)	3.1 (2.0–4.7)	2.3 (1.3–4.1)
Preeclampsia in second pregnancy only	6,120	20	124	16.8 (10.3–25.0)	6.7 (4.3–10.6)	5.3 (3.3–8.5)	4.7 (2.5–9.0)
Preeclampsia in both pregnancies	2,411	7	39	15.4 (6.1–29.0)	6.4 (3.0–13.5)	4.7 (2.1–10.7)	2.6 (0.6–10.6)
After 3 pregnancies (women with ≥3 pregnancies)							
No preeclampsia	198,192	84	3,315	2.4 (1.9–2.9)	1.0	1.0	1.0
Preeclampsia in 1 pregnancy only	10,727	26	159	14.4 (9.4–20.5)	6.3 (4.1–9.9)	5.8 (3.7–9.1)	5.3 (3.0–9.6)
Preeclampsia in first pregnancy only	5,930	6	80	6.0 (2.1–11.7)	2.6 (1.1–5.9)		
Preeclampsia in second pregnancy only	1,875	5	28	16.2 (5.1–33.4)	7.3 (3.0–18.1)		
Preeclampsia in third pregnancy only	2,922	15	51	30.6 (17.1–48.1)	14.3 (8.2–24.7)		
Preeclampsia in ≥2 pregnancies	1,741	9	27	32.9 (14.9–57.9)	15.5 (7.8–30.8)	10.9 (5.0–23.8)	3.0 (0.4–21.9)

\* Data on pregnancies between 1967 and 2004 were available from the Medical Birth Registry of Norway; data on ESRD between 1980 and 2005 were available from the Norwegian Renal Registry. CI denotes confidence interval.

† The number of cases of ESRD per 100,000 person-years of observation after the last included pregnancy is given.

‡ The relative risks are adjusted for year of delivery, maternal age at delivery, maternal marital status, stillbirth, and congenital malformation of the infant in all included pregnancies.

§ Women with a diagnosis of essential hypertension, kidney disease, rheumatic disease, or diabetes mellitus before the first, second, or third pregnancy were excluded; relative risks are adjusted for year of delivery, maternal age at delivery, maternal marital status, stillbirth, and congenital malformation of the infant in all included pregnancies. After the first pregnancy, 16,268 women with 139 end points were excluded; after the second pregnancy, 21,164 women with 94 end points were excluded; after the third pregnancy, 12,142 women with 45 end points were excluded.



**Figure 1. Cumulative Risk of End-Stage Renal Disease (ESRD) after a First, Second, or Third Pregnancy, According to the Number of Preeclamptic Pregnancies.**

Data on pregnancies between 1967 and 2004 were available from the Medical Birth Registry of Norway; data on ESRD between 1980 and 2005 were available from the Norwegian Renal Registry.

5.5); after two pregnancies, the relative risk of ESRD was 3.1 (95% CI, 2.0 to 4.9) for preeclampsia in the first pregnancy, 6.1 (95% CI, 3.6 to 10.3) for preeclampsia in the second pregnancy, and 5.7 (95% CI, 2.3 to 13.7) for preeclampsia in both pregnancies; after three pregnancies, the relative risk was 5.8 (95% CI, 3.5 to 9.6) for preeclampsia in one pregnancy and 6.7 (95% CI, 2.1 to 21.3) for preeclampsia in two or more pregnancies. Further

analyses showed that among women with three pregnancies, one of which was complicated by preeclampsia, the relative risk of ESRD varied, depending on whether preeclampsia occurred during the first pregnancy (relative risk, 2.6; 95% CI, 1.1 to 5.9), the second pregnancy (relative risk, 7.3; 95% CI, 3.0 to 18.1), or the third pregnancy (relative risk, 14.3; 95% CI, 8.2 to 24.7). The associations between preeclampsia and ESRD remained

significant after adjustment for potential confounders and after the exclusion of women who had received a diagnosis of diabetes mellitus, kidney disease, essential hypertension, or rheumatic disease before the included pregnancies.

#### **BIRTH WEIGHT AND PRETERM BIRTH AS RISK MARKERS**

Further analyses showed that having a low-birth-weight infant and preeclampsia were additive risk markers for ESRD (Table 3). Because of the small number of subjects in individual categories, it was not possible to stratify analyses of women with more than one pregnancy according to the particular pregnancy or pregnancies complicated by preeclampsia and by having a low-birth-weight infant. When these analyses were repeated for preterm birth, the results were similar to those for having a low-birth-weight infant (see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). There were no significant interactions between the effects of preeclampsia and having a low-birth-weight infant on the risk of ESRD. We also looked at the effect of having a small-for-gestational-age infant on the risk of ESRD and found that the association was weaker than that with having a low-birth-weight or preterm infant (i.e., the association was significant only after one pregnancy; data not shown).

#### **RISK FACTORS FOR SPECIFIC CAUSES OF RENAL FAILURE**

Of the 477 cases of ESRD among the women, 168 were due to glomerulonephritis, 59 to interstitial nephritis, 100 to hereditary or congenital causes (84 of these patients had autosomal dominant polycystic kidney disease), 68 to diabetic nephropathy, and 82 to other causes. Preeclampsia was associated with similar relative risks for the development of ESRD due to a specific cause and for the development of ESRD in general. The interpretation of this analysis, however, is limited by the small numbers of women in each category of ESRD.

---

### DISCUSSION

---

Large cohort studies have shown that preeclampsia in a first pregnancy predicts an increased risk of subsequent ischemic heart disease, hypertension, stroke, and death from cardiovascular causes.<sup>1-4,23</sup> Our previous study showed that preeclampsia is a risk marker for a later kidney biopsy.<sup>5</sup>

In our current study, we found a strong association between preeclampsia and subsequent ESRD. The association was stronger if the preeclamptic pregnancy resulted in a low-birth-weight or preterm infant. These results were independent of potential birth-related confounders, including maternal age at delivery, year of delivery, maternal marital status, congenital malformation of the infant, and stillbirth, and were apparent more than 10 years after the end of the pregnancy.

We found that having a low-birth-weight or preterm infant was a risk marker for ESRD, even among women who did not have preeclampsia. This finding was also shown in our previous study,<sup>5</sup> and similar observations have been made for death from cardiovascular causes<sup>4</sup>; these results suggest that placental dysfunction, even in the absence of preeclampsia, might be a marker of future disease risks. Our finding that the risk of ESRD was higher among women with a history of preeclampsia that resulted in a preterm delivery or a low-birth-weight infant suggests that the severity of the preeclampsia may also be a marker of later risk, although we do not have data available on the timing of the onset of preeclampsia or other information on severity to further assess this question.

Among women who had preeclampsia in only one of their three pregnancies, the risk of ESRD was higher if preeclampsia occurred in the third pregnancy than if it occurred in the first pregnancy. The same trend was seen for women with two pregnancies: the risk was higher if preeclampsia occurred in the second pregnancy. Women with severe preeclampsia in a first pregnancy are less likely to become pregnant again than are women with no preeclampsia; this finding may reflect that preeclampsia was likely to have been mild in a first pregnancy in women who went on to have subsequent pregnancies. The risk of ESRD also was greater in women with more than one preeclamptic pregnancy than in those with only one such pregnancy.

Several mechanisms might explain the observed association between preeclampsia and subsequent renal disease. One possibility is that kidney disease and preeclampsia are caused by the same factors. Obesity, hypertension, insulin resistance, and endothelial dysfunction, for example, have been linked to both disorders.<sup>24-27</sup> Antiangiogenic factors have been suggested to have an important role in the pathogenesis of preeclampsia<sup>28</sup>

**Table 3. Preeclampsia, Birth Weight of Infant, and the Risk of End-Stage Renal Disease (ESRD) after a First, Second, or Third Pregnancy.\***

Variable	Total No. of Women	No. with ESRD	No./100,000 Person-Yr (95% CI)†	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI) Model 1‡	Adjusted Relative Risk (95% CI) Model 2§
After 1 pregnancy (all women)						
No preeclampsia						
No low-birth-weight infant	524,489	344	2.9 (2.6–3.2)	1.0	1.0	1.0
Low-birth-weight infant	23,831	64	11.7 (9.0–14.8)	4.0 (3.0–5.2)	3.4 (2.5–4.5)	2.7 (1.8–3.8)
Preeclampsia						
No low-birth-weight infant	16,952	39	10.3 (7.4–13.8)	3.8 (2.8–5.3)	3.8 (2.7–5.2)	2.7 (1.8–4.3)
Low-birth-weight infant	3,933	28	32.6 (21.7–45.8)	12.0 (8.2–17.6)	9.9 (6.6–14.8)	6.8 (3.9–12.0)
After 2 pregnancies (women with ≥2 pregnancies)						
No preeclampsia						
No low-birth-weight infant	426,964	220	2.5 (2.2–2.8)	1.0	1.0	1.0
≥1 Low-birth-weight infants	28,316	45	7.6 (5.5–10.0)	2.9 (2.1–4.0)	2.5 (1.8–3.5)	2.1 (1.4–3.3)
1 Pregnancy with preeclampsia						
No low-birth-weight infant	16,699	31	9.4 (6.4–13.0)	4.0 (2.8–5.9)	3.8 (2.6–5.5)	2.8 (1.7–4.6)
≥1 Low-birth-weight infants	3,951	13	17.0 (9.0–27.5)	7.1 (4.1–12.5)	5.6 (3.1–10.1)	4.4 (1.9–10.0)
2 Pregnancies with preeclampsia						
No low-birth-weight infant	2,411	7	15.4 (6.1–29.0)	7.2 (3.4–15.2)	5.5 (2.4–12.5)	2.9 (0.7–11.5)
After 3 pregnancies (women with ≥3 pregnancies)						
No preeclampsia						
No low-birth-weight infant	178,595	66	2.1 (1.6–2.6)	1.0	1.0	1.0
1 Low-birth-weight infant	15,845	12	4.1 (2.1–6.7)	1.8 (1.0–3.4)	1.6 (0.8–3.0)	1.3 (0.6–3.2)
≥2 Low-birth-weight infants	2,521	6	12.5 (4.5–24.6)	5.1 (2.2–12.0)	4.2 (1.7–10.4)	2.8 (0.7–11.7)
1 Pregnancy with preeclampsia						
No low-birth-weight infant	8,337	17	12.2 (7.1–18.7)	6.2 (3.6–10.5)	6.0 (3.5–10.3)	5.5 (2.9–10.7)
≥1 Low-birth-weight infants	2,329	9	22.6 (10.2–39.8)	10.8 (5.4–21.6)	8.3 (3.9–17.9)	5.7 (1.8–18.7)
≥2 Pregnancies with preeclampsia	1,733	9	33.1 (15.0–58.2)	17.5 (8.7–35.1)	12.7 (5.7–27.8)	3.2 (0.4–23.1)

\* Data on pregnancies between 1967 and 2004 were available from the Medical Birth Registry of Norway; data on end-stage renal disease between 1980 and 2005 were available from the Norwegian Renal Registry. Women for whom information on their infant's birth weight was missing were excluded from these analyses. CI denotes confidence interval.

† The number of cases of ESRD per 100,000 person-years of observation after the last included pregnancy is given.

‡ The relative risks are adjusted for year of delivery, maternal age at delivery, maternal marital status, stillbirth, and congenital malformation of the infant in all included pregnancies.

§ Women with a diagnosis of essential hypertension, kidney disease, rheumatic disease, or diabetes mellitus before the first, second, or third pregnancy were excluded; relative risks are adjusted for year of delivery, maternal age at delivery, maternal marital status, stillbirth, and congenital malformation of the infant in all included pregnancies. After the first pregnancy, 16,239 women with 139 end points were excluded; after the second pregnancy, 21,087 women with 93 end points were excluded; after the third pregnancy, 12,057 women with 45 end points were excluded.

and in the progression of chronic renal disorders.<sup>29-31</sup> Alternatively, preeclampsia may exacerbate subclinical kidney disease that is present before pregnancy. This hypothesis is consistent with our previous finding that preeclampsia was associated with similar relative risks for receiving a diagnosis of a specific type of renal disease on renal biopsy and for undergoing a renal biopsy.<sup>5</sup> The hypothesis is also consistent with our present finding that preeclampsia is associated with similar relative risks for the development of ESRD due to a specific cause and for the development of ESRD in general. However, our results were not substantially changed after the exclusion of data from women who had kidney or urinary tract disease before pregnancy. A third possibility is that preeclampsia may cause later renal disease. The observation in other studies that 20 to 40% of women with preeclampsia have microalbuminuria 3 to 5 years after pregnancy, as compared with only 2% of women without preeclampsia,<sup>12,13</sup> may be interpreted as supporting a causal association. However, it is also possible that the women with preeclampsia and subsequent microalbuminuria had unrecognized renal disease before pregnancy.

The strengths of our study are that it includes a large national cohort of women, with complete registration of exposures and outcomes and with censoring of data from women who died, and that the primary outcome, ESRD, is well documented. A weakness is that the study included data on subjects from 1967 to 2004, but outcomes before 1980 were not registered; we addressed this limitation by using a statistical method that does not include women in the analyses until an outcome can be registered. On the assumption that the association between preeclampsia and ESRD did not change from 1967 to 1980, the statistical method is adequate.

Another limitation is the possibility of uncontrolled confounding. Previous validation studies

on diabetes mellitus and rheumatic disease have suggested that these diagnoses are well captured and are unlikely to be important confounders in our study.<sup>20,21</sup> Urinary dipstick and blood-pressure measurements are routinely performed at all pregnancy visits, and essential hypertension and kidney disease are recorded, although these reports have not been validated. We cannot rule out the possibility that mild kidney disease may have remained undetected or unreported during pregnancy in some women. Nevertheless, even if this were the case, preeclampsia would still be an important clinical marker for an increased risk of renal disease in these women.

We do not have data from these women on smoking or obesity, factors that have also been associated with both preeclampsia and chronic renal disease.<sup>32-34</sup> It is possible that a higher body weight among women with preeclampsia accounts in part for their observed increased risk of ESRD.<sup>32,34,35</sup> Since smoking is associated with a decreased risk of preeclampsia<sup>26</sup> but an increased risk of renal disease,<sup>33</sup> it would not explain the increased relative risks we observed.

In summary, our findings indicate that preeclampsia is a clinical marker for an increased risk of subsequent ESRD, although the absolute risk is low, even among women with this history. The risk is greater if a preeclamptic pregnancy results in the birth of a low-birth-weight or preterm infant or if preeclampsia occurs in more than one pregnancy. Future research is needed to better understand the mechanisms underlying the relationship between preeclampsia and subsequent ESRD and to guide the optimal clinical follow-up of women with this history.

Supported by grants from the Western Norway Regional Health Authority and the Strategic Research Program of Haukeland University Hospital.

No potential conflict of interest relevant to this article was reported.

We thank Stein Atle Lie for valuable statistical advice.

#### REFERENCES

- Smith GD, Whitley E, Gissler M, Hemminki E. Birth dimensions of offspring, premature birth, and the mortality of mothers. *Lancet* 2000;356:2066-7.
- Wilson BJ, Watson MS, Prescott GJ, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ* 2003;326:845.
- Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet* 2001;357:2002-6.
- Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ* 2001;323:1213-7.
- Vikse BE, Irgens LM, Bostad L, Iversen BM. Adverse perinatal outcome and later kidney biopsy in the mother. *J Am Soc Nephrol* 2006;17:837-45.
- Pouta A, Hartikainen AL, Sovio U, et al. Manifestations of metabolic syndrome after hypertensive pregnancy. *Hypertension* 2004;43:825-31.
- Agatista PK, Ness RB, Roberts JM, Costantino JP, Kuller LH, McLaughlin MK. Impairment of endothelial function in women with a history of preeclampsia: an indicator of cardiovascular risk. *Am J Physiol Heart Circ Physiol* 2004;286:H1389-H1393.

8. He S, Silveira A, Hamsten A, Blombäck M, Bremme K. Haemostatic, endothelial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. *Thromb Haemost* 1999;81:538-42.
9. Lawlor DA, Davey Smith G, Ebrahim S. Birth weight of offspring and insulin resistance in late adulthood: cross sectional survey. *BMJ* 2002;325:359.
10. Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. *JAMA* 2001;285:1607-12.
11. Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. *Hypertension* 2003;42:39-42.
12. Bar J, Kaplan B, Wittenberg C, et al. Microalbuminuria after pregnancy complicated by pre-eclampsia. *Nephrol Dial Transplant* 1999;14:1129-32.
13. Nisell H, Lintu H, Lunell NO, Möllerström G, Pettersson E. Blood pressure and renal function seven years after pregnancy complicated by hypertension. *Br J Obstet Gynaecol* 1995;102:876-81.
14. Irgens LM. The Medical Birth Registry of Norway: epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000;79:435-9.
15. National High Blood Pressure Education Program Working Group report on high blood pressure in pregnancy. *Am J Obstet Gynecol* 1990;163:1691-712.
16. Dahlström BL, Engh ME, Bukholm G, Oian P. Changes in the prevalence of preeclampsia in Akershus County and the rest of Norway during the past 35 years. *Acta Obstet Gynecol Scand* 2006;85:916-21.
17. Rasmussen S, Irgens LM. Pregnancy-induced hypertension in women who were born small. *Hypertension* 2007;49:806-12.
18. Skjærven R, Wilcox AJ, Lie RT. The interval between pregnancies and the risk of preeclampsia. *N Engl J Med* 2002;346:33-8.
19. Skjærven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand* 2000;79:440-9.
20. Skomsvoll J, Østensen M, Baste V, Irgens L. Validity of a rheumatic disease diagnosis in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand* 2002;81:831-4.
21. Stene LC, Eidem I, Vangen S, Joner G, Irgens LM, Moe N. The validity of the diabetes mellitus diagnosis in the Medical Birth Registry of Norway. *Norsk Epidemiol* 2007;17:165-74.
22. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat* 1982;10:1100-20.
23. Pell JP, Smith GC, Walsh D. Pregnancy complications and subsequent maternal cerebrovascular events: a retrospective cohort study of 119,668 births. *Am J Epidemiol* 2004;159:336-42.
24. Joffe GM, Esterlitz JR, Levine RJ, et al. The relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous women. *Am J Obstet Gynecol* 1998;179:1032-7.
25. Cotter AM, Molloy AM, Scott JM, Daly SF. Elevated plasma homocysteine in early pregnancy: a risk factor for the development of severe preeclampsia. *Am J Obstet Gynecol* 2001;185:781-5.
26. Sibai BM, Gordon T, Thom E, et al. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. *Am J Obstet Gynecol* 1995;172:642-8.
27. de Jong PE, Brenner BM. From secondary to primary prevention of progressive renal disease: the case for screening for albuminuria. *Kidney Int* 2004;66:2109-18.
28. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004;350:672-83.
29. Kang DH, Anderson S, Kim YG, et al. Impaired angiogenesis in the aging kidney: vascular endothelial growth factor and thrombospondin-1 in renal disease. *Am J Kidney Dis* 2001;37:601-11.
30. Choi YJ, Chakraborty S, Nguyen V, et al. Peritubular capillary loss is associated with chronic tubulointerstitial injury in human kidney: altered expression of vascular endothelial growth factor. *Hum Pathol* 2000;31:1491-7.
31. Kang DH, Hughes J, Mazzali M, Schreiner GF, Johnson RJ. Impaired angiogenesis in the remnant kidney model. II. Vascular endothelial growth factor administration reduces renal fibrosis and stabilizes renal function. *J Am Soc Nephrol* 2001;12:1448-57.
32. Hall JE, Kuo JJ, da Silva AA, de Paula RB, Liu J, Tallam L. Obesity-associated hypertension and kidney disease. *Curr Opin Nephrol Hypertens* 2003;12:195-200.
33. Orth SR. Smoking and the kidney. *J Am Soc Nephrol* 2002;13:1663-72.
34. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. *Ann Intern Med* 2006;144:21-8.
35. Sibai BM, Ewell M, Levine RJ, et al. Risk factors associated with preeclampsia in healthy nulliparous women. *Am J Obstet Gynecol* 1997;177:1003-10.

Copyright © 2008 Massachusetts Medical Society.

#### JOURNAL EDITORIAL FELLOW

The *Journal's* editorial office invites applications for a one-year research fellowship beginning in July 2009 from individuals at any stage of training. The editorial fellow will work on *Journal* projects and will participate in the day-to-day editorial activities of the *Journal* but is expected in addition to have his or her own independent projects. Please send curriculum vitae and research interests to the Editor-in-Chief, 10 Shattuck St., Boston, MA 02115 (fax, 617-739-9864), by September 30, 2008.