

History of Preeclampsia in Patients Undergoing a Kidney Biopsy: A Biphasic, Multiple-Hit Pathogenic Hypothesis



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Introduction: It is not fully elucidated whether preeclampsia (PE) is a marker or a cause of chronic kidney disease (CKD). To test the hypothesis of a biphasic relationship between PE and CKD, we assessed PE prevalence in women who underwent a kidney biopsy.

Methods: This retrospective, observational study recruited patients who underwent a kidney biopsy after delivery in 2014 to 2019 in 3 Italian Centers (Cagliari, Bari, Messina); low-risk pregnancies observed in Cagliari served as controls. A history of PE was assessed on the clinical charts and by phone interview.

Results: In the biopsy cohort (379 pregnancies, 205 patients; 38 PE in 32 patients), kidney biopsy shows clustering in the first 5 years after PE (11 of 32). Pre-existing CKD was detected in 8 of 11 of these cases. Focal-segmental glomerulosclerosis (FSGS) and complex lesions were found in 12 of 32 biopsies. The odds ratio (OR) of having had a PE episode, compared with 561 low-risk pregnancies, was 10.071 (95% CI: 4.859–20.875; $P < 0.001$); multiparity maintained a protective effect (OR: 0.208). The delivery-to-biopsy time was significantly shorter in women with PE, both considering the first or the last PE versus the first or last delivery in patients with or without PE episodes. The characteristics of PE did not differ as compared with low-risk controls.

Conclusion: Within the limitation of the retrospective design, our study, quantifying the association between needing a kidney biopsy and history of PE, suggests a biphasic pattern, with a peak in the first 5 years after delivery (probably due to pre-existing diseases) and a later increase, suggesting that PE may have later played as one hit in a multiple-hit pathogenesis.

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KEYWORDS: chronic kidney disease; hypertensive disorders of pregnancy; preeclampsia; risk factors

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PE is a potentially severe syndrome characterized by kidney involvement in pregnancy, manifesting with hypertension, proteinuria, kidney function impairment, or fetal growth restriction.^{1–4} Its prevalence has been variously estimated: the range most frequently reported is 3% to 5%, decreasing to 1% to 2% in low-risk

pregnancies; overall, 10% to 15% of pregnancies are affected by the hypertensive disorders of pregnancy.^{5–8}

PE is no longer considered to be a transitory kidney disease that is cured when the baby is delivered; its importance as a marker of future health is now acknowledged. The link with kidney diseases is close and PE may be a herald, a cause, or a consequence of a kidney disease.^{9–14}

Conversely, patients with CKD have an increased risk of developing proteinuria and hypertension in pregnancy or an increased level of proteinuria and worse control of hypertension, if these are already present (superimposed PE).^{15–18} This risk, calculated

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differently according to the criteria chosen, ranges from the same as in the overall population (3%–5%) to over 50%; risk is modulated by CKD stage, increasing in the advanced stages.^{19,20}

Although the lifetime risk of developing end-stage kidney disease is significantly increased after ≥ 1 episodes of PE, the natural history of kidney diseases following PE is not fully known.^{9,21} A few studies suggest that a kidney disease is already present in 15% to 20% of patients developing PE.^{22,23} The study of glomerular diseases, although not explaining the overall increase in end-stage kidney disease after PE, offers interesting insights into the natural history of the evolution of PE-CKD, as the kidney biopsy makes it possible to obtain a more precise definition of the associated disease/s.

A pivotal study done by Norway's Medical Birth Registry and its Kidney Biopsy Registry suggested that women with PE have a higher probability of undergoing kidney biopsy later in life.²⁴ Likewise, a high prevalence of glomerular diseases in patients with PE was recently reported in Denmark.²⁵

On these bases, we developed the hypothesis that the association between kidney diseases and PE could be biphasic. PE may reveal an already existing kidney disease, and in this case, the clinical expression is expected to occur soon after the episode. In addition, PE may be the first of a multiple-hit pathogenesis, and in this case, an increase in all types of CKD would be expected to develop over time. Kidney diseases diagnosed through a kidney biopsy are particularly suitable for testing this hypothesis, as glomerular diseases are usually less elusive than interstitial or vascular ones, and a biopsy performed in the context of an acute kidney disease may allow appreciating also pre-existing chronic lesions, allowing us to better understand the patterns observed.

This hypothesis was tested in a multicentre Italian cohort gathering 3 large referral centers (Cagliari, Bari, and Messina), also in comparison with a cohort of low-risk pregnancies observed in Cagliari in a similar period.

METHODS

Settings of Study

The study cohorts were recruited in the Brotzu Hospital in Cagliari, Sardinia, and in the university hospitals in Bari and Messina, Italy. All are referral centers for a large area and are the main referral hospitals for kidney biopsies. Since 1989, the nephrology unit in Cagliari has developed an outpatient facility for the follow-up of pregnant women with CKD, thus allowing also for the availability of a control cohort, as described in the next section.

Selection of the Patients and Extraction of Data

All women who underwent a native kidney biopsy between January 1, 2014 and June 30, 2019 were contacted. Kidney transplant biopsies were excluded. The data at the time the kidney biopsy was performed were extracted from the patient's clinical charts and the laboratory database. Information about previous PE, usually only in part available from clinical charts, was gathered by phone interview with the patients when they were called to be informed about the study and ask for their consent for the anonymous management of their data. Recall data were matched with data on the clinical charts whenever available and the latter ones were retained in case of discrepancy.

The clinical charts were evaluated by a nephrologist in training, supervised by a senior nephrologist (in Cagliari, AL supervised by GC; in Bari-Messina, by EL and EC supervised by DS in Messina and by LG in Bari).

The following data were gathered for patients and controls: age, ethnicity, parity, multiple pregnancy, date of kidney biopsy, diagnosis, details of the biopsy, serum creatinine, proteinuria, hypertension, and body mass index (BMI) at the kidney biopsy.

Data regarding pregnancies included, whenever available: BMI before pregnancy, weight gain, gestational diabetes, gestational week of delivery, type of delivery, and weight at birth. For PE pregnancies: gestational week of diagnosis of PE, presence of hemolysis, elevated liver enzymes, low platelet count syndrome, need for maternal or neonatal intensive care unit, and perinatal death. Whenever available, the database also included previous miscarriages, any other maternal disease; assisted fertilization, family history of CKD, cardiovascular disorders, and PE.

Control Low-Risk Population

The low-risk controls were selected in the maternity unit of the Brotzu Hospital in Cagliari. The women chosen had had spontaneous singleton pregnancies occurring in the absence of baseline hypertension, diabetes, CKD, cardiovascular diseases, or any other severe disease or condition potentially affecting pregnancy. Although BMI was not considered *per se* a risk factor, the control group consisted of 561 singleton pregnancies, as elsewhere described in greater detail (TOCOS cohort [Torino Cagliari Observational Study]).²⁶ The flow charts of cases and controls are reported in Figures 1a and b. Although BMI was not considered *a priori* a risk factor, women with high BMI were less likely to be followed-up in outpatient units dedicated to low-risk pregnancies.

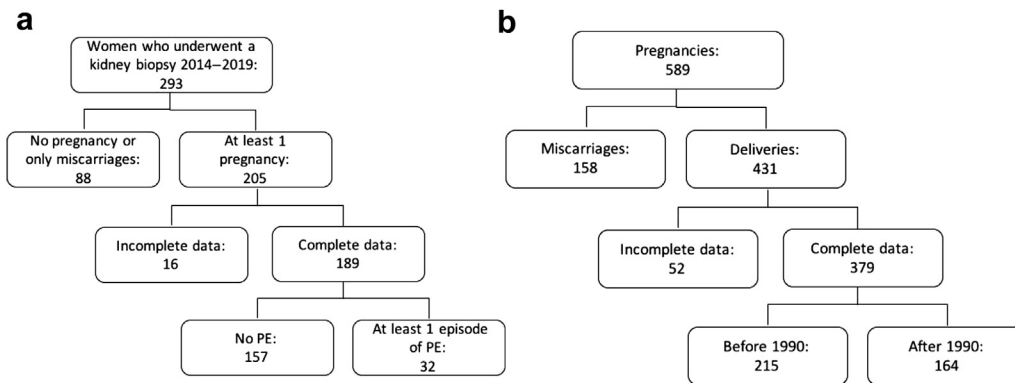


Figure 1. Flowchart of (a) patient selection and (b) deliveries. PE, preeclampsia.

Definitions and Indications for a Kidney Biopsy

CKD was classified according to Kidney Disease Outcomes Quality Initiative guidelines by means of the CKD-Epidemiology Collaboration formula at the time of kidney biopsy.^{27,28}

PE was defined either as hypertension accompanied by proteinuria ≥ 300 mg/24 hours after 20 weeks of gestational age in a previously normotensive, non-proteinuric woman in the absence of signs of CKD, or according to the onset of thrombocytopenia and increase in liver enzymes of AKI.^{29,30} In the patient interview, the questions related to PE included diagnosis of PE or eclampsia, the history of proteinuria and/or hypertension, or other clinical problems in

pregnancy. Patients were also asked the week of delivery and their baby's birth weight, pieces of information that are usually correctly remembered.^{31–33}

A newborn was defined small-for-gestational age when birth weight was below the 5th or the 10th percentile according to Italian birth weight references (IneS charts).³⁴

Preterm delivery was defined as before 37 completed gestational weeks; early-preterm as before 32 or 34 gestational weeks, according to the different indications available in the literature; and extremely preterm delivery as before 28 completed gestational weeks.^{35,36}

The indications for a kidney biopsy follow current clinical practice, without setting limits on age and severity of kidney disease, but balancing the cost-benefit ratio on a case-by-case basis.^{37,38}

Statistical Evaluation

Statistical analysis was performed with JASP v0.14.1 (University of Amsterdam, Amsterdam, The Netherlands). Continuous series were tested for normality using the Shapiro-Wilke test and Levene's test was used to assess homoscedasticity. Data were displayed as appropriate (median and range for nonnormal data, mean and SD for normally-distributed data), and compared by means of an unpaired *t* test or Wilcoxon rank sum test according to standard indications for continuous variables. Risks, rates and proportions were compared using the chi-square test or Fisher exact test.

To reduce the heterogeneity linked to the differences in maternal care that have occurred over time, we limited the comparison between the pregnancy group and the low-risk population to women who had delivered after 1990.

To, at least partially, account for the confounding effect of obesity and the effect of multiple pregnancies on the risk for PE, we also compared the incidence of PE in nonobese women (deliveries after 1990 in the biopsy cohort versus low-risk controls) with available

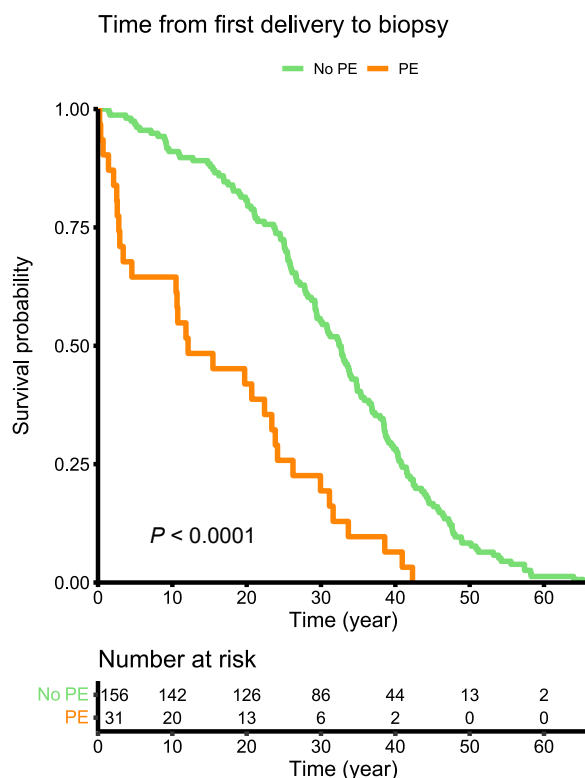


Figure 2. Interval between first delivery or first PE episode and kidney biopsy. PE, preeclampsia.

Table 1. Characteristics of deliveries in patients who underwent a renal biopsy in the period 2014 to 2019 and had at least 1 delivery and complete delivery data

	Overall	No PE	PE	P-value
n (%)	379	341	38 ^a	
Age at delivery (yr), mean ± SD	27.5 ± 5.4	27.3 ± 5.3	29.6 ± 5.7	0.019
Interval between pregnancy and biopsy (yr), mean ± SD	29.3 ± 13.6	30.6 ± 13.0	17.1 ± 13.2	<0.001
sCr at biopsy (mg/dl), mean ± SD	1.65 ± 1.50	1.67 ± 1.55	1.55 ± 1.04	0.644
Proteinuria at biopsy (g/24 h), mean ± SD	3.90 ± 4.07	3.89 ± 3.99	4.00 ± 4.85	0.040
Parity (first baby), n (%)	197 (52.0)	184 (54.0)	13 (34.2)	0.026
Birthweight centile, mean ± SD	56 ± 31	57 ± 30	48 ± 33	0.131
Birthweight centile <10, n (%)	31 (8.5)	26 (7.8)	5 (15.2)	0.220
Birthweight centile <5, n (%)	15 (4.1)	11 (3.3)	4 (12.1)	0.052
Term (wk), mean ± SD	38.6 ± 2.8	39 ± 2	36 ± 5	<0.001
Term <37 wk, n (%)	37 (9.8)	21 (6.2)	16 (42.1)	<0.001
Term <34 wk, n (%)	23 (6.1)	15 (4.4)	8 (21.1)	<0.001
Term <32 wk, n (%)	14 (3.7)	6 (1.8)	8 (21.1)	<0.001
Baby's weight (g), mean ± SD	3306 ± 578	3358 ± 521	2802 ± 821	<0.001

PE, preeclampsia; sCr, serum creatinine.

Bold value indicates significant differences.

^aOne patient had incomplete delivery data thus it was not taken into account for this analysis.

data on BMI, limiting the analysis to the first delivery (Fisher exact test).

If the patient experienced >1 episode of PE, the interval between PE and kidney biopsy was calculated either between the first PE episode and the first pregnancy for patients who did not experience PE and from the last delivery or last PE episode which was, in all cases with multiple PE episodes, the last pregnancy.

The interval between first or last delivery/PE and kidney biopsy, was visually represented by means of Kaplan–Meier curves, and differences between cohorts were analyzed by the log-rank test.

The multivariable logistic analysis considered the following outcomes: PE, preterm delivery (<37 gestational weeks), and small-for-gestational age baby (<10th centile); the analysis considered as explicatory variables: age (dichotomized at the median); parity

(subsequent pregnancies versus first pregnancy), and group (patients with a kidney biopsy versus low-risk controls).

A 2-sided alpha risk was set at 5%.

Ethical Issues

All patients had given informed consent for anonymous treatment of their data at the time of their kidney biopsy and gave their consent again for using their data in this study. Only 1 patient (Cagliari Unit) refused to participate and was therefore excluded. As the study is a retrospective one that deals with clinical history and does not entail any therapeutic modifications, it did not need formal approval by an ethics committee. The ethics committee at the Brotzu Hospital that was leading the multicenter study was notified on July 1, 2019 that the study would be carried out.

Table 2. Characteristics of women who underwent a renal biopsy in the period 2014 to 2019 at the first delivery or at the first PE

	Overall	No PE	First PE	p-value
n (%)	189	157	32 ^a	
Age at delivery (years), mean ± SD	25.9 ± 5.5	25.2 ± 5.0	29.7 ± 6.0	<0.000
Interval pregnancy and biopsy (yr), mean ± SD	29.0 ± 14.7	31.5 ± 13.6	16.2 ± 13.4	<0.000
sCr at biopsy (mg/dl), mean ± SD	1.74 ± 1.63	1.79 ± 1.72	1.48 ± 1.01	0.352
Proteinuria at biopsy (g/24 h), mean ± SD	3.91 ± 4.04	3.98 ± 3.98	3.50 ± 4.13	0.552
Birthweight centile, mean ± SD	54 ± 32	55 ± 31	49 ± 35	0.351
Birthweight centile <10, n (%)	20 (10.6)	15 (9.6)	5 (15.6)	0.343
Birthweight centile <5, n (%)	10 (5.3)	6 (3.8)	4 (12.5)	0.0678
Term (wk), mean ± SD	38.2 ± 3.1	38.8 ± 2.4	35.5 ± 4.6	<0.000
Term <37 wk, n (%)	26 (13.8)	12 (7.6)	14 (43.8)	<0.000
Term <34 wk, n (%)	16 (8.5)	9 (5.7)	7 (21.9)	0.008
Term <32 wk, n (%)	11 (5.8)	4 (2.6)	7 (21.9)	<0.000
Baby's weight (g), mean ± SD	3207 ± 640	3300 ± 545	2726 ± 850	<0.000

PE, preeclampsia; sCr, serum creatinine

Bold value indicates significant differences.

^aOne women with incomplete data at delivery.

A total of 6 women with 2 episodes of PE and 1 woman with a twin pregnancy.

Table 3. Diagnosis and follow-up in patients who underwent a kidney biopsy after ≥ 1 episodes of PE

Cagliari cohort								
Pt	Age at delivery (yr) ^a	Age at biopsy (yr) ^a	Interval delivery-biopsy (yr) ^a	Diagnosis	sCr at biopsy (mg/dl)	PtU at biopsy (g/24 h)	HTA at biopsy	Comorbidity-information on kidney diseases
1	22	22	2.5 months	Membranous nephropathy	0.45	13.0	No	No data available before pregnancy
2	32	32	8 months	Complex lesions, FSGS	0.65	1.7	No	History of TTP treated by steroids and plasma exchange in childhood; proteinuria 100 mg/dl 3 years before pregnancy.
3	42	43	1.4	FSGS with interstitial chronic lesions	0.80	3.2	Yes	Obesity, albuminuria detectable at least 3 years before pregnancy.
4	31	33	2.1	FSGS	1.70	1.6	No	Proteinuria at dipstick present 1 year before pregnancy
5	31	34	2.5	Chronic interstitial nephropathy	0.58	4.2	No	Sjogren syndrome, diagnosed after delivery but signs present before pregnancy
6	35	38	2.6	Acute interstitial nephritis	3.5	1.5	Yes	AKI, probably drug induced.
7	33	36	3.4	IgA nephropathy	0.7	0.8	Yes	Basedow's disease, Mild proteinuria 3 years before pregnancy.
8	33	48	15	Minimal change disease	1.4	6.8	Yes	Complete remission 2 years after biopsy
9 ^b	26 first 32 second	49	23 first 16.5 second	FSGS	1.2	8.6	No	Comorbidity, developed after pregnancy: Hashimoto thyroiditis, rheumatoid arthritis, obesity
10	28	52	24	FSGS	1.89	8.0	Yes	Obesity, hypertension, developed after pregnancy
11 ^b	28 first 30 second	59	32 first 29 second	RPGN	2.7	1.2	Yes	Autoimmune hypothyroidism, dyslipidaemia, hypertension developed after pregnancy
12 ^b	27 first 30 second	60	34 first 30 second	Chronic interstitial nephritis	2.8	0.3	Yes	Rheumatoid arthritis developed after pregnancy
13 ^b	25 first 27 second	64	38 first 37 second	Mesangial-proliferative GN	1.4	3.0	Yes	Hypertension developed after pregnancy
Bari-Messina cohort								
Pt	Age at delivery (yr) ^a	Age at biopsy (yr) ^a	Interval delivery-biopsy (yr) ^a	Diagnosis	sCr at biopsy (mg/dl)	PtU at biopsy (g/24 h)	HTA at biopsy	Comorbidity-information on kidney diseases
1	33	34	5 months	FSGS	4.6	1.6	Yes	Kidney function impairment and hypertension present before pregnancy.
2 ^b	21 first 23 second	23	3 first 0.92 second	FSGS	0.8	8.5	Yes	No data available before pregnancy
3	35	38	3	Lupus GN (class 3c)	0.6	0.6	Yes	Pre-existing SLE; proteinuria and hypertension in early pregnancy
4	29	34	5	Lupus GN, interstitial fibrosis (25%)	0.7	0.9	No	Pre-existing SLE; proteinuria since early pregnancy
5 ^c	34	45	10.5	FSGS	1.1	1.39	No	None reported
6	43	54	11	IgA nephropathy	2	1.53	No	None reported
7	38	49	11	Complex lesions	1.66	3.22	Yes	Hypertension developed after pregnancy
8	34	46	12	FSGS with vascular involvement	0.8	0.4	Yes	Comorbidity : obesity, lost to follow-up
9	28	40	12	Lupus GN	1.3	2.2	Yes	Hypertension developed after pregnancy
10	29	49	20	Diabetic nephropathy	0.8	1.1	Yes	Hypertension developed after pregnancy
11 ^b	22 first 27 second	48	26 first 21second	Minimal change nephropathy	3.5	17.95	Yes	Obesity.
12	32	53	21	FSGS with vascular involvement	2.4	3.2	Yes	Previous thrombotic microangiopathy.
13	37	59	22	IgA nephropathy	1.5	2.3	Yes	Hypertension developed after pregnancy
14	25	48	23	Complex lesions with vascular involvement	0.8	2.4	Yes	Hypertension developed after pregnancy
15	23	53	30	IgA nephropathy	1.8	0.4	Yes	Subsequent progression to ESKD
16	19	50	31	Lupus GN; interstitial fibrosis (30%)	1.2	1.2	No	None reported
17	23	63	40.8	Light chain deposition disease	2.2	0.2	No	None reported
18	24	66	42	Membranous nephropathy	0.5	4.7	Yes	Hypertension developed after pregnancy
19	30	85	55	Membranous nephropathy	0.4	5.3	No	None reported

AKI, acute kidney injury; ESKD, end-stage stage kidney disease; FSGS, focal-segmental segmental glomerulosclerosis; GN, glomerulonephritis; HTA, arterial hypertension; PE, pre-eclampsia; Pt, patient; PtU, proteinuria; sCr, serum creatinine; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

Bold indicates biopsies performed in the first 5 years after pregnancy.

^aThe interval is calculated between delivery of the PE pregnancy and the biopsy; in case of two episodes, the two intervals are reported.

^bPatients who experienced 2 episodes of preeclampsia.

^cTwin birth.

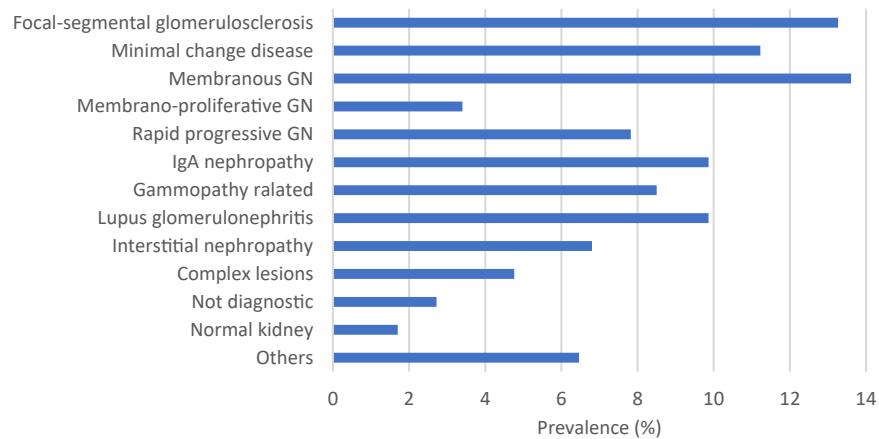


Figure 3. Histologic diagnoses of kidney diseases. GN, glomerulonephritis.

RESULTS

Baseline Data

In the biopsy cohort, 86 of 294 patients had no pregnancy or only ≥ 1 miscarriage; 208 patients had ≥ 1 pregnancies; 32 had ≥ 1 episodes of PE for a total of 38 episodes. The prevalence of women who experienced at least 1 episode of PE was 15.4% and was identical in the settings of study. The prevalence of PE was 10.3%, considering all pregnancies (Figure 1). The details of the 2 groups of women in the study centers are available in Supplementary Table S1.

Pregnancy Outcomes

Table 1 reports the main characteristics of deliveries, in biopsy cohort stratified on the basis of PE status. Table 2 reports the same data at the first delivery or at the first PE episode. The interval between delivery and kidney biopsy was shorter in women who had experienced an episode of PE, both considering the first episode of PE versus the first delivery, and the last episode of PE versus the last delivery respectively in women who experienced at least 1 episode of PE versus those who did not. The differences are highly significant in both cases (Kaplan–Meier curves, Figure 2 and Supplementary Figure S1).

Diagnoses at the Kidney Biopsy

Table 3 reports the main diagnoses and the indications for performing a kidney biopsy in the patients who experienced ≥ 1 episodes of PE, ordered according to the intervals between the last episode of PE and the kidney biopsy. It should be noted that the diagnoses differ from those performed in women without history of PE for a higher percentage of FSGS and complex lesions found in 12 of 32 biopsies (37.5%) in women who had experienced at least 1 episode of PE (Table 3 and Figure 3).

The intervals between delivery and kidney biopsy show a clustering in the first 5 years (Figure 4). A clinical history highly suggestive of pre-existing kidney disease was found in 8 of 11 cases who underwent a kidney biopsy in the first period (Table 3).

Comparison Between Low-Risk Pregnancies and Characteristics of PE

Table 4 reports on the comparison between the pregnancies in the biopsy cohort that occurred since 1990 with 561 low-risk pregnancies. Despite a significantly higher prevalence of PE (16.1% vs. 2.5% $P < 0.001$), no consistent difference in centiles or week of birth was observed in the biopsy cohort versus low-risk cases.

The lower prevalence of obesity in the low-risk cohort was probably due to a selection bias (even if obesity is not formally considered as a risk factor for PE, obese patients are less commonly referred to outpatient units dedicated to physiological pregnancies). Of note, no significant difference in BMI was found in patients with or without a history of PE in the biopsy cohort ($P = 0.614$).

To account for the potential selection bias, we also assessed the prevalence of PE in pregnancies occurring after 1990, considering only primiparous pregnancies and BMIs $< 30 \text{ kg/m}^2$. Of 270 pregnancies with complete data, we observed 15 PE in 64 women in the biopsy cohort (23.4%) versus 7 PE in 206 low-risk pregnancies (3.4%) ($P < 0.0001$).

Notably, the characteristics of the PE episode show no significant difference for any of the items studied, in the low-risk population, and in the study cohorts (Table 4).

Multivariable Analysis

Table 5 reports the OR of having had a PE episode for women who had at least 1 delivery and underwent a kidney biopsy at any time after delivery, compared with

Table 5. Regression analysis for risk of PE: biopsy cohorts (singleton deliveries after 1990) and low-risk pregnancy

	95% CI				95% CI			
	Unadjusted OR	Lower	Higher	P-values	Adjusted OR	Lower	Higher	P-values
Age (≥ 33)	0.840	0.443	1.594	0.594	1.907	0.919	3.961	0.083
Parity (not primiparous)	0.305	0.143	0.651	0.002	0.208	0.092	0.472	<0.001
Biopsy cohort	7.470	3.798	14.690	<0.001	10.071	4.859	20.875	<0.001

OR, odds ratio; PE, preeclampsia.
Bold value indicates significant differences.

adjusted OR of 2.111 (95% CI 1.224–3.640) (Supplementary Tables S2 and S3).

DISCUSSION

The complex relationship between PE and CKD is only partially understood. In this context, we designed this multicentre study to try to add some further insight into the definition of the natural history of CKD after PE. Because an increased risk of needing a kidney biopsy after PE had been described in a few studies, we expected a high prevalence of PE in a cohort of patients who later underwent a kidney biopsy.^{21,22,31} This turned out to be also true in our cohort; about 15% of the women who delivered at least 1 child and had had a biopsy reported on at least 1 previous PE episode. Overall, a PE episode was recorded in over 10% of deliveries. This figure is remarkably higher compared with the low-risk controls gathered in the same setting (2.5% of the cases). The difference holds true even considering the first pregnancy in nonobese patients: 23.4% in cases versus 3.4% in controls.

This background allowed us to explore more in detail the hypothesis of a biphasic relationship between PE and CKD, with a first short-term phase in which PE mainly represents a manifestation of an underlying kidney disease and a second one in which PE represents one of multiple hits, leading to overt CKD. In line with this hypothesis, we expected that the kidney biopsy would diagnose different kidney diseases in the first phase with a late increase in complex and nonspecific lesions, corroborating a multiple-hit pathogenesis. Following this hypothesis, we did not expect to identify specific aspects of PE in women undergoing a kidney biopsy many years after delivery. We considered that PE could have been modulated by type of underlying kidney diseases in the cases in which a kidney biopsy was needed shortly after delivery. However, due to the rarity of these cases, we considered this would be a hint for future research.

The distribution of the interval between deliveries complicated by PE and kidney biopsy reached a peak in the first 5 years, followed by a gap between 5 and 10 years, and then by an overall stabilization (Table 3 and Figure 4). This distribution was confirmed even after

considering the first or the last delivery or episode of PE (Table 3 and Figure 4).

Furthermore, to confirm the importance of previous unacknowledged CKD in the first 5 years after the PE episode, a clinical history highly suggestive of pre-existing kidney disease was retrospectively found in 8 of 11 cases (Table 3).

The interval between delivery and the kidney biopsy was shorter in patients who experienced PE compared with the patients who did not (Figure 2). This holds true considering the first PE episode versus the first pregnancy or the last PE episode versus the last pregnancy in the cohorts with and without PE (Supplementary Figure S1).

In terms of intervals between delivery and the kidney biopsy, our data are in line with the registry study from Denmark, not limited to patients who later received a kidney biopsy, which found a strong association between PE and glomerular and proteinuric diseases within 5 years of the latest pregnancy; however, no attempt to classify the diagnoses was possible.²⁵ The data are also partially in keeping with the study by Oliverio *et al.*,³¹ who found a shorter interval between delivery and biopsy in women who had a history of PE with a similar recruitment policy (analysis of adverse pregnancy related outcomes in a cohort of women who underwent a kidney biopsy).

Although the number of cases is still too small to allow stratification, it is nonetheless worth noting that FSGS and complex lesions encompassing vascular, interstitial, and glomerular damage of difficult definition, were found in 12 of 32 biopsies in women who had experienced at least 1 episode of PE; 9 of 21 (42.9%) in biopsies performed after at least 10 years from the PE episode (Table 3).

Within the limits of a small series, it is worth noting that 5 of 6 patients who experienced 2 episodes of PE underwent a kidney biopsy in this second period, an observation that could further support the multiple-hit pathogenesis hypothesis of CKD in these cases.

Retrospective studies like ours only make it possible to define and test hypotheses; however, these findings are in keeping with reports by Garovic *et al.*³⁹ on podocyte shedding in PE because podocyte loss is a well-acknowledged basis for subsequent development

of FSGS.^{39–41} Conversely, the study by Oliverio *et al.*³¹ did not find a higher frequency of FSGS or of complex lesions; the different study design (all pregnancy related adverse outcomes instead of PE only) may, however, have added to the heterogeneity. Furthermore, the authors did not stratify for time between delivery and kidney biopsy.³²

In the context of a very strong association between needing a kidney biopsy and a previous history of PE, as measured by an OR of about 10 and adjusted for age and parity (Table 5), our data supports certain practical considerations.

Different from other reports, the 2 main elements characterizing PE, week of delivery, and fetal growth are not significantly different in PE recorded in the patients who later underwent a kidney biopsy and in low-risk individuals (Table 4).^{25,42}

Even if the small number of cases did not allow us to detect minor differences, the lack of specificities identifying PE associated with the later need for a kidney biopsy suggests that postpartum evaluation should not be limited to women with severe PE. Indeed, recent data from a Franco-Italian study found a very high prevalence of CKD (19%) in women who experienced an episode of PE and suggested that a nephrology work-up should be performed after all PE episodes. This observation is also in keeping with data from the Mayo Clinic which reported a 20% prevalence of CKD in women with a history of PE.^{22,43} The importance for correctly identifying CKD in this context may be even higher in low-income countries, where pregnancy is often the first occasion to undergo a medical evaluation.^{44,45} Definition of follow-up might be guided by the consideration that the first time peak in between the last pregnancy and the kidney biopsy lasts about 5 years. Although attention should not be limited to glomerular diseases, increased knowledge on this subset of cases will also help us understand the development of CKD.

Our study has several limitations. Involving 293 kidney biopsies and reporting on 379 pregnancies, the study allowed us to analyze only 38 PE episodes in 32 women. These numbers did not permit us to make detailed stratifications, and it is possible that they failed to take the complete picture into account. Risk estimates have wide intervals of confidence due to the limited number of cases. The small number of cases and, in particular, the small number of patients experiencing >1 PE impaired the use of more sophisticated analyses that take into account the conditional probability to develop PE in a pregnancy following a PE episode for instance. Furthermore, the control group was followed-up during 1 pregnancy only, and the history of previous PE was not taken into account.

These limitations may guide further studies and lead to a more precise definition of low-risk cohorts.

Another point is that the analysis relied mainly on patients' recall of their week of delivery and baby's birth weight. Although, according to some recent studies, this information is usually accurately remembered up to 30 years after delivery, we cannot be sure that what we were told by participants was entirely correct.^{32–34}

Our study has the novelty of employing a well-phenotyped low-risk cohort, thus improving the characterization of PE episodes and defining the strength of the association compared with the overall population. Prospectively, the hypothesis proposed in this study could be tested in larger series by a detailed search for chronic or old lesions in the kidney biopsy, trying to discriminate between new and pre-existing damage in the first period postpregnancy and to get better insights into the natural history of kidney lesions attributable to PE in all cases.

In the context of a close association between having undergone a kidney biopsy and having a history of PE, the absence of specific features characterizing PE episodes associated with needing a kidney biopsy may support the claim that all PE episodes deserve a nephrology work-up after pregnancy.^{22,43} The clustering of biopsies in the first 5 years after delivery may further suggest that attention to glomerular diseases should be the greatest in this period. If confirmed, the multiple-hit hypothesis proposed in this study may underline the importance of searching for and, wherever possible, correcting other potential noxae (e.g., obesity, hypertension, and nephrotoxic drugs) as a way to limit the renal risks associated with PE.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#).

Figure S1. Interval between last delivery or last PE episode and kidney biopsy.

Table S1. Characteristics of deliveries in patients who underwent a renal biopsy in the period 2014–2019 and had at least one delivery.

Table S2. Regression analysis for the biopsy cohort (singleton deliveries after 1990): outcome: pre-term delivery.

Table S3. Regression analysis for the biopsy cohort (singleton deliveries after 1990): outcome: small-for-gestational age baby.

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