Nephrol Dial Transplant (2022) 37: 1488–1498
doi: 10.1093/ndt/gfab225
Advance Access publication 2 August 2021

ORIGINAL ARTICLE

Pre-eclampsia is a valuable opportunity to diagnose chronic kidney disease: a multicentre study

Gianfranca Cabiddu[1], Claudia Mannucci[2,3], Antioco Fois[2], Stefania Maxia[1], Antoine Chatrenet[2], Sarah Osadolor[2,4], Emily Kimani[2,4], Massimo Torreggiani [2], Rossella Attini[5], Bianca Masturzo[5], Marie Thérèse Cheve[6] and Giorgina Barbara Piccoli[2,7]

[1]Department of Nephrology, Brotzu Hospital, University of Cagliari, Cagliari, Italy, [2]Department of Nephrology, Centre Hospitalier, Le Mans, France, [3]Department of Nephrology, University of Pisa, Pisa, Italy, [4]Medical School of Alberta, Alberta, Canada, [5]Department of Obstetrics, University of Turin, Turin, Italy, [6]Department of Obstetrics, Centre Hospitalier Le Mans, Le Mans, France and [7]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

Correspondence to: Giorgina Barbara Piccoli; E-mail: gbpiccoli@yahoo.it

ABSTRACT

Background. Pre-eclampsia (PE) and chronic kidney disease (CKD) are known to be associated. Our objective was to assess the prevalence of CKD in a large multicentre cohort of women without acknowledged CKD who experienced a PE episode.

Methods. The setting for the study was France (Le Mans, Central France) and Italy (Cagliari, Sardinia). The study participants were patients who experienced PE in 2018–19, identified from the obstetric charts. Patients with known–acknowledged CKD were excluded. Only singletons were considered. Persistent (micro)albuminuria was defined as present and confirmed at least 3 months after delivery. CKD was defined according to the Kidney Disease Outcomes Quality Initiative guidelines; urinary alterations or low eGFR confirmed at a distance of at least 3 months, or morphologic changes. Patients were divided into four groups: evidence of CKD; no evidence of CKD; unclear diagnosis-ongoing work-up; or persistent microalbuminuria. The outcome 'diagnosis of CKD' was analysed by simple and multiple logistic regressions. Temporal series (week of delivery) were analysed with Kaplan–Meier curves and Cox analysis.

Results. Two hundred and eighty-two PE pregnancies were analysed (Le Mans: 162; Cagliari: 120). The incidence of CKD diagnosis was identical (Le Mans: 19.1%; Cagliari: 19.2%); no significant difference was found in unclear-ongoing diagnosis (6.2%; 5.8%) and microalbuminuria (10.5%; 5.8%). Glomerulonephritis and diabetic nephropathy were more frequent in Cagliari (higher age and diabetes prevalence), and interstitial diseases in Le Mans. In the multivariate logistic regression, CKD diagnosis was associated with preterm delivery (adjusted $P = 0.035$). Gestation was 1 week shorter in patients diagnosed with CKD (Kaplan–Meier $P = 0.007$). In Cox analysis, CKD remained associated with shorter gestation after adjustment for age and parity.

Conclusions. The prevalence of newly diagnosed CKD is high after PE (19% versus expected 3% in women of childbearing age), supporting a systematic nephrology work-up after PE.

Keywords: chronic kidney disease, pre-eclampsia, pregnancy, preterm delivery, proteinuria

INTRODUCTION

The complex relationship between chronic kidney disease (CKD) and pre-eclampsia (PE) is still not fully clear and, although it is acknowledged that each disorder may predispose to the other, the lack of systematic assessment of women with a history of PE for detecting the presence of CKD is an important limit to our knowledge [1–9]. PE is recognized as a predictor of the future development of CKD, as well as a window on future cardiovascular health in the mother [3–8]. In the natural history of CKD after PE a role of pre-existing, yet undiagnosed, CKD has been suggested, but not quantified [3–6]. This is an important knowledge gap, and since early CKD is frequently asymptomatic, it is likely to go undetected unless a specific work-up is performed [9].

In spite of growing claims about the importance of follow-up after PE, few scientific societies recommend a nephrology evaluation after PE; such an evaluation should allow disclosure of the presence of a previously undetected CKD, and identification and correction, whenever possible, of risk factors, some of which are ultimately shared by CKD and PE [3, 6, 9].

In spite of over 2000 publications per year addressing different aspects of PE, only two small, single-centre studies have reported some data on the prevalence of CKD in patients who

KEY LEARNING POINTS

What is already known about this subject?

- pre-eclampsia (PE) and chronic kidney disease (CKD) are associated; and
- CKD is a risk factor for developing PE, but the prevalence of CKD among pre-eclamptic women is unknown.

What this study adds?

- the prevalence of CKD not previously known in patients experiencing an episode of PE is high, ∼20%; and
- this is the first large multicentre study on the prevalence of CKD in women with PE.

What impact this may have on practice or policy?

- A systematic nephrology work-up after PE allows early diagnosis and follow-up of CKD not previously known; and
- early CKD diagnosis may improve women's health.

experienced an episode of PE [3, 10]. The first study was aimed at quantifying common risk factors in end-stage kidney disease and PE, matching two cohorts of patients, one derived from the US Renal Data System, and one of the women who gave birth in Olmsted County, Minnesota. In a small cohort of 44 women that started renal replacement therapy on average 17 years after pregnancy, the incidence of previous PE was 18%; overall in 21% of the cases CKD was evident before the first pregnancy; no data were, however, available on pre-existing CKD and PE [3].

In a pilot study of our group, the records of 99 women who had experienced an episode of PE in our hospital in 2017 were examined; in this initial study, we did not exclude multiple pregnancies, and divided the evaluation into CKD versus no-CKD [10].

To overcome the limitations of a single-centre study, with small sample size, and to try to adjust for confounders, such as multiple pregnancies, we undertook the present multicentre study. We gathered data in the same period (2017–19) in two nephrology centres (Le Mans, France and Cagliari, Italy). The study's primary objective was to assess the prevalence and the characteristics of the newly diagnosed CKD in women who had experienced an episode of PE; furthermore, we tried to identify the characteristics, if any, of PE occurring in the context of CKD.

We named the study with the acronym PRE-Eclampsia Early CKD Diagnosis, to underline the possibility of profiting from the occurrence of PE to allow early CKD diagnosis.

MATERIALS AND METHODS

Settings of study

This study was undertaken in France (Le Mans, Sarthe district in Central France) and Italy (Cagliari, Sardinia Island). The Centre Hospitalier Le Mans (CHM), one of the largest non-university hospitals in France, has an obstetric service with ∼3500 deliveries per year; dedicated consultations for women experiencing an episode of PE have been available since 2017 [10]. The Obstetric Unit is the only tertiary care in the Sarthe (∼560 000 inhabitants). Patients with severe PE, haemolysis, elevated liver enzymes and low platelets (HELLP) or other relevant obstetric pathology are routinely referred to CHM. According to the hospital management system, in 2017–19, the estimated annual incidence of PE was 3–3.5%.

The Azienda Ospedaliera Brotzu, Cagliari, is the largest hospital in Sardinia, an Italian island with ∼1.6 million inhabitants. The obstetric ward follows 800–1000 deliveries per year, offering care for high-risk pregnancies (thalassaemia, diabetes, kidney and autoimmune diseases). Since 1995, a nephrology outpatient service is dedicated to kidney diseases in pregnancy. According to the hospital data, the annual incidence of PE was ∼5% in 2017–19.

Definitions employed

CKD was defined according to the 2002 Kidney Disease Outcomes Quality Initiative classification and stratification: kidney damage for $\geq$3 months as defined by structural or functional anomalies of the kidney, with or without decreased glomerular filtration rate (GFR), manifest by either pathological abnormalities or markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests; or GFR $<$60 mL/min/1.73 m^2 for $\geq$3 months with or without kidney damage [11].

In the cases that attended one or more consultations in nephrology, CKD staging was confirmed at least once, at a distance of at least 3 months, after the initial evaluation.

Otherwise, cases waiting for confirmation of CKD, or with unclear data, were classified as unclear diagnosis-ongoing work-up.

eGFR at diagnosis was not considered, due to its variable behaviour in PE, and only data available for at least 3 months after delivery were considered for definition of persistent microalbuminuria or reduced eGFR. Furthermore, while severe PE may reduce the eGFR, hyperfiltration is common in pregnancy and data recorded shortly after delivery may still reflect this physiological adaptation. In this context, to avoid overestimation of the prevalence of CKD, we chose to risk the bias of underestimation, considering as without CKD the women who

displayed normal eGFR, no proteinuria and who were normotensive at hospital discharge. In other terms, cases with normalization of the kidney function, hypertension and proteinuria at hospital discharge, and not evaluated in nephrology were considered as without CKD, even in the absence of demonstration of normal kidney morphology.

PE and HELLP syndrome were defined according to the American College of Obstetricians and Gynecologists guidelines: PE: hypertension (systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg known to predate conception or detected before 20 weeks of gestation, with no underlying cause), associated with proteinuria (24-h excretion $\geq$300 mg), diagnosed after 20 weeks of uneventful gestation up to 2 weeks post-partum. In the absence of proteinuria, new-onset hypertension with new onset of any of the following: platelet count $<$100 000/μL, serum creatinine $>$1.1 mg/dL, or doubling of concentration in absence of other renal diseases, transaminitis to twice normal concentration of liver enzymes, pulmonary oedema and cerebral/visual symptoms.

HELLP syndrome was defined as per the above guidelines (alanine or aspartate transaminase levels $\geq$2 times upper limit of normal); haemolysis (lactate dehydrogenase $>$600 U/L; peripheral blood smears with evidence of damaged erythrocytes; serum bilirubin $\geq$1.2 mg/dL; platelet count $<$100 000/μL) [12].

Superimposed PE was defined as PE on already known, pregestational hypertension, treated or not, or on already known CKD [13].

Patients with known CKD who had been referred to the obstetric ward by a nephrologist were excluded from this analysis. Cases in which a kidney disease was known but had been overlooked as a risk factor in pregnancy were retained, since we considered that, in the absence of specific follow-up, the natural history of PE was not influenced by prenatal care. There were eight cases, four in Cagliari (one patient with single kidney due to nephrectomy for carcinoma; one with nephrectomy for malformation; two cases of diabetic nephropathy, with proteinuria before pregnancy) four in Le Mans (two patients with kidney graft; one case with vesicoureteral reflux with surgery in infancy; one case with relapsing pyelonephritis).

Small for gestational age babies were defined according to the two most commonly used cut-points: below the 5th and 10th centiles, following INTERGROWTH standards [14].

Preterm delivery was defined as delivery before 37 completed gestational weeks; early preterm delivery as before 34 and very-early preterm delivery as delivery before 28 completed gestational weeks.

Obesity was defined by a pre-gestational body mass index (BMI) $\geq$30 kg/m^2; overweight as BMI between 25 and 30 kg/m^2, and underweight as BMI $<$20 kg/m^2.

Age was considered as a risk factor when $\geq$40 years and $\leq$20 years at delivery. The following clinical data were likewise considered as potential risk factors for the development of PE: previous hypertension, diabetes, collagen disease, assisted fertilization, multiple pregnancies, personal or family history of PE, BMI $\geq$30 and BMI $<$20 kg/m^2.

Selection of the patients

The diagnoses of PE and HELLP syndrome were retrieved from the diagnostic hospital discharge codes (Figure 1). All clinical charts (electronic in Le Mans and paper-based in Cagliari) were examined by a nephrology fellow (in Le Mans) or a junior nephrologist (in Cagliari) and reviewed by the senior physicians (respectively, G.B.P. in Le Mans and G.C. in Cagliari), to confirm the diagnosis of PE and assess the risk factors, as well as the diagnosis of CKD.

In each setting, the nephrology seniors and the nephrology fellows were unaware of the results found in the other setting. The databases were merged, and a final coherence control was performed by a senior nephrology fellow (C.M.) and a trained statistician (A.C.).

As previously mentioned, the cases referred to obstetricians by nephrologists (known and acknowledged CKD) were excluded; the cases in which CKD was known, but was not considered as being a risk factor for pregnancy-related outcomes, were retained. Data about multiple pregnancies were gathered, but were not considered in the statistical analysis.

All patients evaluated in the nephrology outpatient units were seen by senior nephrologists (G.B.P. and G.C.). None of the patients included in this study had been included in the previous analysis performed by our group in Le Mans [10].

The full list of gathered data is available as Supplementary data.

Patients were divided into two groups: those evaluated solely on the basis of their clinical charts and those evaluated in nephrology.

In the case of evaluation on the basis of the clinical charts, the diagnosis of CKD was retained when it was available in the obstetrics clinical charts, or in other documents available in the informatics system of the hospital, including further blood or urinary tests (performed, e.g. in diabetology). In the absence of evidence of CKD, patients not further seen, were classified as without evidence of CKD. Exceptions were cases for which we found only one test showing either proteinuria or low eGFR at least 3 months after pregnancy; they were classified as 'uncertain'; all these patients were repeatedly invited to perform a nephrology consultation, free of charge (three cases in Le Mans, five in Cagliari).

The usual work-up for patients seen in nephrology encompasses a first nephrology consultation, usually 1–3 months after delivery, followed by a day-hospital assessment (kidney ultrasounds, renal clearances, proteinuria and urinary electrolytes on 24-h urine collection, coagulation, antinuclear and anti-DNA antibody tests, nutritional evaluation) at least 3 months after delivery. Further tests were prescribed on a case-by-case basis. In case of normal ultrasounds and laboratory data, and in the absence of a clinical history of kidney disease, the patients were considered as without evidence of CKD. For the sake of CKD diagnosis, the presence of proteinuria, albuminuria or microalbuminuria, in a test performed at least 3 months after delivery, was confirmed at least once, after at least 3 months. The same criterion was applied to reduced eGFR. Patients with persistent isolated microalbuminuria (likewise confirmed) were analysed

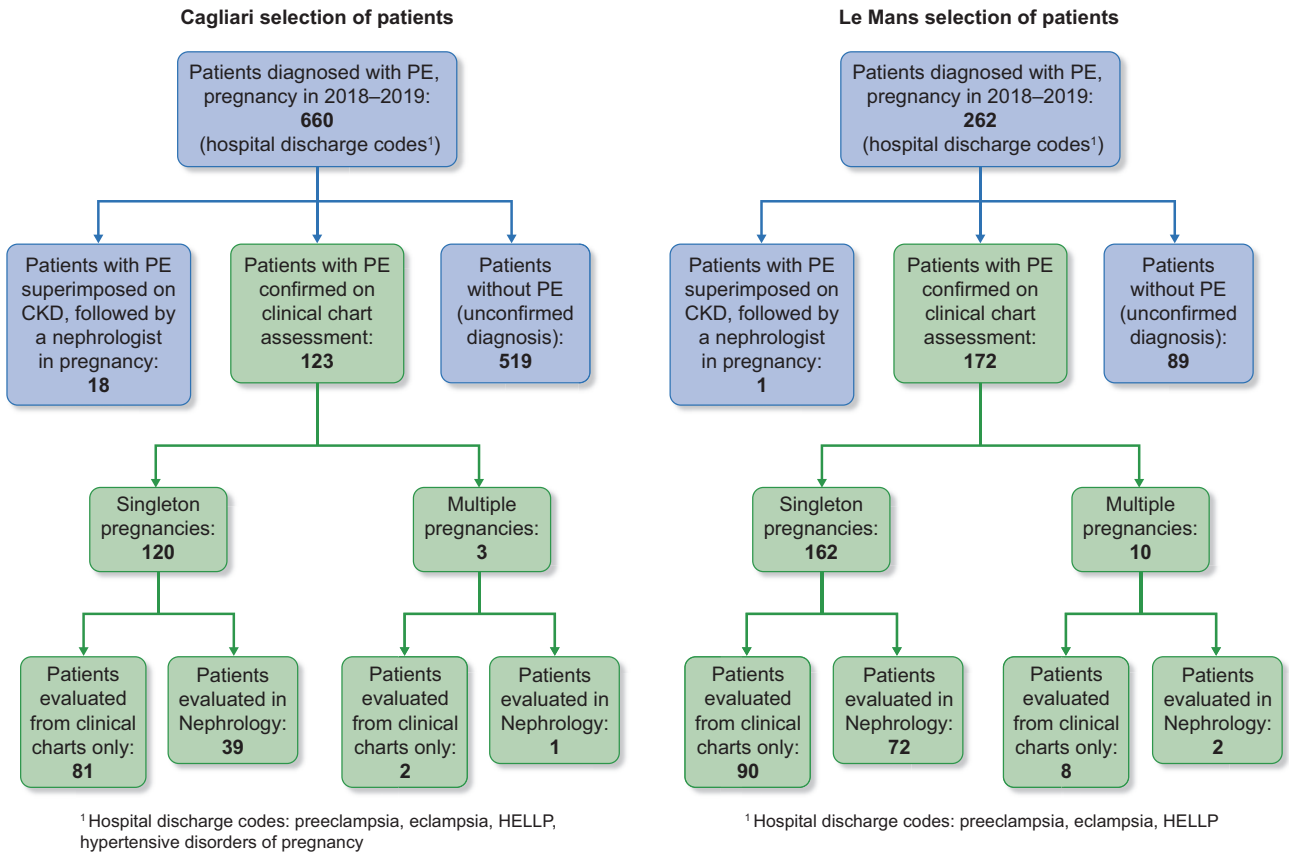

FIGURE 1: Study flowchart. In Le Mans, the codes relative to PE, eclampsia and HELLP were analysed (262 codes, 89 miscoded—hypertensive disorders of pregnancy without proteinuria or other markers of PE; one patient followed-up conjointly with the nephrologist), since a previous study showed misclassification of PE as hypertensive disorders of pregnancy in <5% of the cases [10], while the code PE was commonly chosen in the case of other hypertensive disorders of pregnancy. In Cagliari, all the codes of hypertensive disorders of pregnancy were assessed, since at a preliminary random sampling of the data, both coding errors were found to be present.

separately, since microalbuminuria may be a consequence of PE and a marker of the increased risk of CKD after PE.

Statistical evaluation

The statistical analysis was performed with SPSS version 14 (IBM Corp., Armonk, NY, USA).

Results were displayed with the median and the interquartile range (IQR).

With respect to the diagnosis of CKD, patients were divided into four groups: evidence of CKD diagnosis; no evidence of CKD diagnosis; unclear CKD diagnosis (e.g. intermittent proteinuria; possible kidney scars, waiting for imaging confirmation; unexplained early-onset hypertension and family history of CKD); isolated microalbuminuria following the PE episode.

The continuous series were tested for normality using the Shapiro–Wilk test, and homoscedasticity with Leven's test. According to the conditions of application, for comparing two groups (e.g. seen in nephrology versus not seen in nephrology), the independent Student's *t*-test and Wilcoxon rank-sum test were used. To compare three or more groups, one-way analysis of variance and Kruskal–Wallis test were used.

The comparison of proportions was made with the chi-squared or the Fisher's exact test according to the subsampling size involved.

The outcome 'no evidence of CKD' was tested against 'evidence of kidney involvement or possible kidney involvement' (including in this definition the three categories of: CKD; ongoing diagnostic work-up and microalbuminuria) by means of multiple logistic regression, after testing for collinearity. The choice of the covariates to include in the multivariate model was based on either the statistical significance at the univariate analysis, or the well-acknowledged clinical relevance (for instance, age and week of delivery).

In the regression model, we tested the relationship with age (dichotomized at the median, i.e. 34 years), week of delivery (dichotomized at 37 weeks), BMI before pregnancy (dichotomized at 25 kg/m^2), small for gestational age (<10th centile) and primiparity. The model employed a backward deletion method and standardized residuals were verified.

Temporal series (e.g. weeks of delivery) were visually analysed with the inversed Kaplan–Meier curves and the differences were tested through the log-rank test. Cox regression analysis was performed through a backward deletion method to

assess the effect on week of delivery of the presence of kidney involvement, and baseline age, BMI and parity (analysed as dichotomous data). Also in this case, the choice of the covariates to include was based upon either the statistical significance at the univariate analysis, or the well-acknowledged clinical relevance (for instance, age or BMI).

Alpha error was fixed at 5%.

Ethical issues

All patients received written information about the retrospective study. Patients who were seen in the nephrology settings gave written consent for the anonymous treatment of their data for research purposes. Patients whose data were retrieved from the clinical charts received a written communication by mail (last available address). All patients seen in the nephrology settings agreed to participate; no patient contacted by mail or phone asked to be withdrawn from the study.

In accordance with the rules in force in each setting, the study was approved by the hospital's ethics committee in Le Mans (session of 14 June 2018, updated 15 July 2020) and notification was given to the hospital's ethics committee in Cagliari.

RESULTS

Baseline data

Table 1 reports the baseline data retrieved in the study's two settings. Overall, 282 singleton pregnancies complicated by a PE episode were analysed (162 in Le Mans and 120 in Cagliari). The most remarkable differences regard age, which is 6 years higher in Cagliari, and the prevalence of diabetes, roughly double in Cagliari. The prevalence of risk factors for PE was cumulatively >70% (Supplementary data, Table S1); previous PE was found to be a potential contributory factor in ∼20% of cases. In Le Mans, 44.4% of the patients were seen at least once by a nephrologist, versus 32.5% in Cagliari. Patients seen in nephrology were older than those not seen in nephrology in Le Mans, and had a higher prevalence of hypertension in Cagliari.

Clinical characteristics of PE

The pattern of PE was significantly different in Le Mans and Cagliari (Table 1). Gestation was ∼1 week longer in Cagliari, while proteinuria was higher in Le Mans. Proteinuria at delivery was <0.3 g/day only in two cases (PE diagnosed upon other criteria). Caesarean section was more often employed in Cagliari, while, despite the fact that babies born in Cagliari were in a higher centile, they were more often hospitalized in the intensive care unit. Supplementary data, Figure S1 reports the delivery curves in both settings.

In both settings, the patients who underwent a nephrology evaluation had a significantly lower gestational week, and, as a consequence, smaller babies and higher proteinuria, suggesting that patients with severe PE are more often referred to a nephrologist, and/or are more motivated to go to the recommended consultation.

Prevalence of CKD, of microalbuminuria and of unclear cases

The prevalence of newly diagnosed CKD was almost identical in the two settings: 19.1% in Le Mans and 19.2% in Cagliari (Table 2). Likewise, the prevalence of unclear cases, still under evaluation (6.2 and 5.8%) and the prevalence of isolated microalbuminuria after delivery (10.5 and 5.8%) were not significantly different. As expected, both by non-random selection and by in-depth evaluation, CKDs were most often diagnosed in patients seen in nephrology; however, in 15/54 cases a diagnosis of CKD was retrospectively evident in the clinical chart.

In spite of a similar prevalence of CKD, the diseases found were different. A glomerulonephritis or a diabetic nephropathy was diagnosed in 9/23 cases in Cagliari, while in Le Mans 17/31 cases displayed urologic malformation, or pyelonephritis scars (Supplementary data, Table S1). The role of imaging, biochemical data and clinical history in diagnosis is reported in Supplementary data, Table S1. Of note, imaging was crucial to the diagnosis of CKD in 32/54 cases. Pregnancy was the occasion for diagnosing polycystic kidney disease in three cases. Of note, in two patients the presence of a kidney graft was not considered an indication for specific stricter obstetric follow-up. Overall, most cases were in CKD Stage 1 (64.8%); however, 5/54 (9.3%) were classified as CKD Stage 3, and one patient was in CKD Stage 4 after delivery, while 13/54 were in Stage 2 (24.1%).

Characteristics of PE occurring in patients with CKD

Patients diagnosed with CKD were significantly older compared with patients without evidence of CKD, and also compared with cases with an unclear diagnosis and those with isolated microalbuminuria (Table 3). Probably as a reflection of age, the prevalence of primiparity was lower in patients with evidence of CKD while hypertension was significantly associated with a diagnosis of CKD (Table 3).

As for the outcomes, no specific factors stand out as clearly identifying patients who received a diagnosis of CKD after PE (Table 4).

This was found either analysing patients according to CKD diagnostic category or stratifying patients according to outcomes (term of delivery, centiles and peak of proteinuria) (Table 4). The only exceptions were a higher prevalence of microalbuminuria in patients with babies with lower birth centile, possibly as a reflection of the severity of PE and a lower peak proteinuria in patients without evidence of CKD (Table 4).

Patients with a later diagnosis of CKD have a lower chance of delivery at term, compared with those with no evidence of CKD, and gestation is 1 week shorter (37 versus 38 weeks). These differences are statistically significant in the Kaplan–Maier analysis ($P = 0.007$; Figure 2).

Conversely, no difference was found in the prevalence of small for gestational age babies, weight gain or Caesarean section. The patterns are confirmed when analysis is limited to the cases seen in nephrology (Supplementary data, Table S2). In the context of a high prevalence of risk factors other than CKD,

Table 1. Baseline and delivery data for the study population, according to type of evaluation and study setting

	All cases	Le Mans all cases	Le Mans Evaluation in nephrology	Evaluation on clinical charts	P-value (evaluation)	Cagliari all cases	Cagliari Evaluation in nephrology	Evaluation on clinical charts	P-value (Evaluation)	P-value (Le Mans—Cagliari)
N	282	162	72	90		120	39	81		
Baseline data and risk factors										
Age, median (IQR), years	33 (9)	30 (8)	31 (11)	29 (7)	0.097	36 (6)	36 (7)	36 (6)	0.747	**<0.001**
Age ≥40 years, *n* (%)	43 (15.2)	15 (9.3)	11 (15.3)	4 (4.4)	**0.018**	28 (23.3)	9 (23.1)	19 (23.5)	0.963	**0.001**
Parity (first), *n* (%)	145 (51.6)	81 (50.3)	36 (50.0)	45 (50.6)	0.943	64 (53.3)	18 (46.2)	46 (56.8)	0.274	0.616
Known HTA, *n* (%)	52 (18.4)	29 (17.9)	12 (16.7)	17 (18.9)	0.714	23 (19.2)	13 (33.3)	10 (12.3)	**0.006**	0.786
Known diabetes, *n* (%)	13 (4.6)	2 (1.2)	1 (1.4)	1 (1.1)	0.999	11 (9.2)	5 (12.8)	6 (7.4)	0.336	**0.002**
History of PE, *n* (%)	52 (18.4)	26 (16.0)	14 (19.4)	12 (13.3)	0.292	26 (21.7)	11 (28.2)	15 (18.5)	0.228	0.344
At least one risk factor, *n* (%)	188 (66.7)	102 (63.0)	49 (68.1)	53 (58.9)	0.230	86 (71.7)	35 (89.7)	51 (63.0)	**0.002**	**0.001**
BMI, median (IQR), kg/m^2	26.0 (10.0)	28.0 (10.0)	28.0 (11.2)	28.0 (9.0)	0.847	25.0 (10.0)	25.0 (15.0)	24.0 (7.0)	0.422	0.053
BMI ≥30 kg/m^2, *n* (%)	85 (30.1)	52 (32.1)	26 (36.1)	26 (28.9)	0.138	33 (27.5)	15 (38.5)	18 (22.2)	0.085	0.521
Weight gain, median (IQR), kg	10.0 (7.0)	10.0 (8.0)	11.0 (5.3)	9.0 (11.0)	0.384	10.0 (7.0)	10.0 (7.0)	10.0 (7.0)	0.576	0.284
Maternal and foetal data at delivery										
Week of delivery, median (IQR)	37 (4)	37 (6)	36 (7)	37 (5)	**0.009**	37 (3)	37 (3)	38 (3)	0.068	**0.030**
Week of delivery <28, *n* (%)	• 12 (4.3) • 40	10 (6.2)	8 (11.3)	2 (2.2)	0.187	2 (1.7)	1 (2.6)	1 (1.2)	0.546	0.062
Week of delivery ≥28 to <34, *n* (%)	• (14.2) • 59	32 (19.9)	19 (26.8)	13 (14.4)	0.052	8 (6.7)	2 (5.1)	6 (7.4)	0.999	**0.002**
Week of delivery ≥34 to <37, *n* (%)	(21.0)	31 (19.3)	12 (16.9)	19 (21.1)	0.501	28 (23.3)	12 (30.8)	16 (19.8)	0.181	0.406
Week of delivery ≥37, *n* (%)	170 (60.5)	88 (54.7)	32 (45.1)	56 (62.2)	**0.030**	82 (68.3)	24 (61.5)	58 (71.6)	0.267	**0.020**
Proteinuria, median (IQR), g/24 h	0.90 (2.67)	1.70 (3.61)	2.75 (4.36)	1.30 (2.57)	**0.037**	0.41 (0.79)	0.60 (1.47)	0.34 (0.75)	**0.003**	**<0.001**
Caesarian, *n* (%)	203 (72.0)	105 (64.8)	48 (66.7)	57 (63.3)	0.106	98 (81.7)	33 (84.6)	65 (80.2)	0.562	**0.005**
HELLP, *n* (%)	40 (14.2)	26 (16.0)	14 (19.4)	12 (13.3)	0.149	14 (11.7)	8 (20.5)	6 (7.4)	**0.036**	0.263
ICU maternal, *n* (%)	14 (5.0)	12 (7.4)	5 (6.9)	7 (7.8)	0.726	2 (1.7)	1 (2.6)	1 (1.2)	0.546	**0.001**
Offspring data										
Weight (g), median (IQR)	2670 (1125)	2378 (1232)	2127 (1490)	2553 (940)	**0.010**	2915 (681)	2950 (810)	2900 (660)	0.931	**<0.001**
Weight <2500 g, *n* (%)	115 (40.8)	85 (52.5)	44 (61.1)	41 (45.6)	**0.027**	30 (25.0%)	10 (25.6)	20 (24.7)	0.910	**<0.001**
Weight <1500 g, *n* (%)	13 (13.5)	30 (18.5)	22 (30.6)	8 (8.9)	**<0.001**	8 (6.7%)	1 (2.6)	7 (8.6)	0.272	**0.007**
Centiles, median (IQR)	20 (53)	10 (40)	9 (25)	14 (47)	0.261	32 (50)	31 (56)	32 (46)	0.181	**<0.001**
Centiles <10, *n* (%)	99 (35.1)	77 (47.5)	38 (52.8)	39 (43.3)	0.313	22 (18.3)	5 (12.8)	17 (21.0)	0.279	**<0.001**
Centiles <5, *n* (%)	67 (23.8)	55 (34.0)	22 (30.6)	28 (31.1)	0.476	12 (10.0)	1 (2.6)	11 (13.6)	0.101	**<0.001**
NICU, *n* (%)	80 (28.5)	37 (22.8)	21 (29.2)	16 (17.8)	0.151	43 (35.8)	14 (35.9)	29 (35.8)	0.992	**0.023**
NICU, median (IQR), days	8.5 (15)	7 (29)	31 (35)	5.5 (4)	0.180	9 (11)	12 (10)	8 (11)	0.320	0.607

n, cohort size; HTA, arterial hypertension; ICU, intensive care unit; NICU, neonatal intensive care unit. In bold: statistically significant differences.

Table 2. Prevalence of chronic kidney disease in the study population, according to type of evaluation and study setting

	All cases	Le Mans all cases	Le Mans Evaluation in nephrology	Evaluation on clinical charts	P-value (evaluation)	Cagliari all cases	Cagliari Evaluation in nephrology	Evaluation on clinical charts	P-value (evaluation)	P-value (Le Mans—Cagliari)
n	282	162	72	90		120	39	81		
Evidence of CKD, *n* (%)	54 (19.1)	31 (19.1)	21 (29.2)	10 (11.1)	**0.004**	23 (19.2)	18 (46.2)	5 (6.2)	**<0.001**	0.995
No evidence of CKD, *n* (%)	187 (66.3)	104 (64.2)	29 (40.3)	75 (83.3)	**<0.001**	83 (69.2)	12 (30.8)	71 (87.7)	**<0.001**	0.383
Unclear, work-up ongoing, *n* (%)	17 (6.0)	10 (6.2)	7 (9.3)	3 (3.3)	0.093	7 (5.8)	2 (5.1)	5 (6.2)	0.819	0.906
Microalbuminuria after pregnancy, *n* (%)	24 (8.5)	17 (10.5)	15 (20.8)	2 (2.2)	**0.001**	7 (5.8)	7 (17.9)	0	*<0.001*	0.166

Italic P-values in the case of one cell equal 0. In bold: statistically significant differences.

their presence was not associated with a specific pattern of PE (Supplementary data, Table S3).

Multiple regression analysis and Cox analysis

In the multiple regression analysis, the outcome 'any kind of kidney involvement' (including CKD diagnosis, microalbuminuria and ongoing work-up) was confirmed as significantly associated with preterm delivery (adjusted odds ratio: 1.761; P = 0.035, unadjusted odds ratio: 1.797; P = 0.027), whereas age, centile <10, BMI and parity were not (Table 5).

In Cox analysis, timing of delivery was significantly associated with CKD (higher probability of earlier delivery in the presence of signs of kidney involvement), after adjustment for age, BMI and parity (Table 6). No difference was found after adjustment for centre.

DISCUSSION

This is the first study aimed at detecting the presence of CKD not previously diagnosed in a large multicentre cohort of patients who experienced an episode of PE. The main result is an astonishingly similar prevalence of CKD (19.1 and 19.2%) found after a PE episode in patients in the two study settings, in spite of differences in the population, type of care and genetic background (Tables 1 and 2). Of note, the definitions were determined by two senior nephrologists, unaware of the other's data. The prevalence of 'unclear cases', i.e. cases in which there were isolated clues suggesting a kidney disease, but evaluation was still ongoing, and of isolated microalbuminuria, that could represent the effect of PE, were likewise strikingly similar (Table 2).

This finding is remarkably higher than the expected prevalence of CKD in women of childbearing age [15–18]. In fact, the global prevalence of CKD worldwide considering all the five stages and all ages, has been estimated at 13.4% [17] or, more recently, 9.1% [19]. CKD prevalence increases with age [15, 17]. According to the National Health and Nutrition Examination Survey data, the global prevalence of CKD Stages 1–4 in the USA, in the period 1999–2004, was 13.07%. In the same sample, in the age group 20–39 years, the prevalence of CKD Stages 1 and 2 was 3% and the prevalence of CKD Stages 3 or 4 was <1% [15]. In Australia, the prevalence of CKD Stages 1–5 in the age group 25–44 years has been estimated around 5% in the period 2011–12 [20].

Data on the prevalence of CKD Stages 1 and 2 in the overall population in France are lacking. In Italy, a study recently published in Sardinia, the region of one of the participating centres, found the prevalence of CKD Stages 1–5 at 15.1% [21]. In another study performed in central Italy, the prevalence of CKD Stages 3–5 among subjects aged 18–44 years was 0.6% in men and 1.3% in women [22].

Interestingly, while the overall prevalence is similar, kidney diseases are different: Sardinia has a well-known high incidence of diabetes and immunologic diseases, and those were found in about one-third of CKD diagnoses, while in Central France, interstitial nephropathies, kidney malformations and pyelonephritis scars were more common, possibly in line with a higher prevalence of obesity (Supplementary data, Table S1) [23, 24].

Table 3. Maternal and delivery characteristics at delivery according to the diagnosis of CKD after a PE episode

	Overall				P-value	
	No evidence of CKD	Evidence of CKD	Unclear	Micro albuminuria	Overall	Evidence versus no evidence of CKD
N	187	54	17	24		
Anthropometric and clinical information						
Age, median (IQR), years	31 (9)	37 (9)	31 (7)	32 (11)	**0.002**	**<0.001**
Age <20 years, *n* (%)	3 (1.6)	2 (3.7)	0	0	*0.588*	0.312
Age ≥40 years, *n* (%)	23 (12.3)	15 (27.8)	1 (5.9)	4 (16.7)	**0.029**	**0.006**
Parity (first), *n* (%)	104 (55.9)	22 (40.7)	8 (47.1)	11 (45.8)	0.222	**0.003**
Known HTA, *n* (%)	27 (14.4)	18 (23.3)	4 (23.5)	3 (12.5)	**0.013**	**0.002**
Known diabetes, *n* (%)	5 (2.7)	6 (11.1)	2 (11.8)	0	*0.019*	**0.009**
History of PE, *n* (%)	35 (18.7)	8 (14.8)	2 (11.8)	7 (29.2)	0.765	0.688
At least one risk factor, *n* (%)	116 (62.0)	45 (83.3)	10 (58.8)	17 (70.8)	**0.027**	**0.003**
BMI (kg/m^2), median (IQR)	27.0 (10.0)	25.0 (12.0)	28.0 (10.0)	27.5 (13.0)	*0.884*	0.700
BMI ≥30 kg/m^2, *n* (%)	54 (28.9)	18 (33.3)	5 (49.4)	8 (33.3)	0.111	0.274
Maternal and pregnancy information						
Weight gain, median (IQR), kg	11.0 (8.0)	9.5 (7.0)	10.5 (7.3)	10.5 (8.8)	0.354	0.073
Week of delivery, median (IQR)	38 (4)	37 (4)	36 (3)	37 (6)	0.062	**0.014**
Week of delivery <28, *n* (%)	6 (3.2)	3 (5.6)	1 (5.9)	2 (8.3)	0.617	0.423
Week of delivery ≥28 to <34, *n* (%)	24 (12.9)	10 (18.5)	2 (11.8)	4 (16.7)	0.733	0.298
Week of delivery ≥34 to <37, *n* (%)	35 (18.8)	12 (22.2)	7 (41.2)	5 (20.8)	0.191	0.579
Week of delivery ≥37, *n* (%)	121 (65.1)	29 (53.7)	7 (41.2)	13 (54.2)	0.126	0.129
Proteinuria at delivery median (IQR), g/24 h	0.70 (2.00)	1.10 (3.64)	1.85 (4.03)	1.20 (3.72)	**0.030**	**0.022**
Caesarian, *n* (%)	132 (70.6)	41 (75.9)	12 (70.6)	18 (75.0)	0.952	0.621
HELLP, *n* (%)	26 (13.9)	5 (9.3)	3 (17.6)	6 (25.0)	0.567	0.442
ICU maternal, *n* (%)	7 (3.7)	2 (3.7)	2 (11.8)	3 (12.5)	0.422	0.999
Offspring information						
Weight (g), median (IQR)	2750 (1080)	2560 (1360)	2530 (1010)	2380 (935)	0.250	0.331
Weight <2500 g, *n* (%)	70 (37.4)	24 (44.4)	8 (47.1)	13 (54.2)	0.591	0.389
Weight <1500 g, *n* (%)	22 (11.8)	8 (14.8)	3 (17.6)	5 (20.8)	0.722	0.527
Centiles, median (IQR)	23 (52)	19 (64)	23 (22)	8 (21)	0.274	0.805
Centiles <10, *n* (%)	61 (32.6)	17 (31.5)	6 (35.3)	15 (62.5)	0.159	0.894
Centiles <5, *n* (%)	41 (21.9)	13 (24.1)	5 (29.4)	8 (33.3)	0.864	0.844
NICU, *n* (%)	51 (27.3)	17 (31.5)	4 (23.5)	8 (33.3)	0.949	0.735
NICU, median (IQR), days	8 (11)	9 (13)	24 (13)	7 (26)	0.609	0.626

n, cohort size; HTA, arterial hypertension; ICU, intensive care unit; NICU, neonatal intensive care unit. Italic P-values in the case of one cell equal 0. In bold: statistically significant differences.

Of note, only about two-thirds of patients diagnosed with CKD were in Stage 1, while 13/54 were in Stage 2 (24.1%) and 6/54 (11.1%) in Stage 3 (Supplementary data, Table S1).

While in most of the cases the diagnostic clues were based on imaging and/or clinical history (imaging data were fundamental for diagnosis in 32/54 cases), we cannot exclude that in some cases diagnosed upon persistence of proteinuria or reduction of the kidney function this might be the result of the PE episode in itself; only eight cases were diagnosed solely upon biochemical data. Of note, one patient was later diagnosed with membranous nephropathy and two had persistent haematuria and proteinuria, while CKD was in Stage 3 in two further cases (Supplementary data, Table S1). To try to limit the bias of considering as CKD those cases whose renal derangements result from PE, patients with persistent microalbuminuria were considered as a separate category.

The second main result is that, when PE is associated with a previously undiagnosed CKD, it is characterized by a gestation time ∼1 week shorter. The duration of pregnancy is the only difference in the features of PE in patients with or without signs of CKD found in our study, while the risk of having a child small for gestational age was not different. The difference in the duration of pregnancy is significant in the univariate and multivariate logistic regressions, results also from the analysis of the delivery curve (Kaplan–Maier) and is confirmed in the Cox analysis, after adjustment for age, BMI and parity (Tables 5 and 6; Figure 2). No centre effect was likewise detected.

The differences in timing of delivery are not fully explained by the presence of other clinical features of PE: patients with and without CKD have similar BMI, and weight gain, while patients with diagnosis of CKD are significantly older and with higher prevalence of previous hypertension than patients without sign of CKD. The differences are, however, of limited value for allowing a clear clinical discrimination (hypertension: 23.3% versus 14.4%; age 37 versus 31 years; Table 3). This lack of highly specific features supports a policy of nephrology evaluation for all patients having experienced a PE episode.

The reasons why a pregnancy in which PE is superimposed on CKD should be shorter than a pregnancy not in the context of CKD are not clear. While in many of the cases the diagnostic hints suggest that CKD was already present [small kidneys, kidney scars and autosomal dominant polycystic kidney disease

Table 4. Prevalence of CKD in the study population according to week of delivery, newborn centile and proteinuria

	All cases			
	Week of delivery			
	<34	34–37	≥37	P-value
N	52	59	170	
Evidence of CKD, *n* (%)	13 (25.0)	12 (20.3)	29 (17.1)	0.432
No evidence of CKD, *n* (%)	30 (57.7)	35 (59.3)	121 (71.2)	0.090
Unclear, work-up ongoing, *n* (%)	3 (5.8)	7 (11.9)	7 (4.1)	0.117
Microalbuminuria after pregnancy, *n* (%)	6 (11.5)	5 (8.5)	13 (7.6)	0.680
	Centile			
	<10	≥10		P-value
n	99	180		
Evidence of CKD, *n* (%)	17 (17.2)	36 (20.0)		0.564
No evidence of CKD, *n* (%)	61 (61.6)	124 (68.9)		0.219
Unclear, work-up ongoing, *n* (%)	6 (6.1)	11 (6.1)		0.987
Microalbuminuria after pregnancy, *n* (%)	15 (15.2)	9 (5.0)		**0.004**
	Proteinuria			
	<3	≥3		P-value
n	198	73		
Evidence of CKD, *n* (%)	37 (18.7)	17 (23.3)		0.400
No evidence of CKD, *n* (%)	138 (69.7)	40 (54.8)		**0.022**
Unclear, work-up ongoing, *n* (%)	9 (4.5)	7 (9.6)		0.118
Microalbuminuria after pregnancy, *n* (%)	14 (7.1)	9 (12.3)		0.168

Data about delivery week were not available for one patient; data about centile was not available for three patients; data about proteinuria were not available for 11 patients. In bold: statistically significant differences.

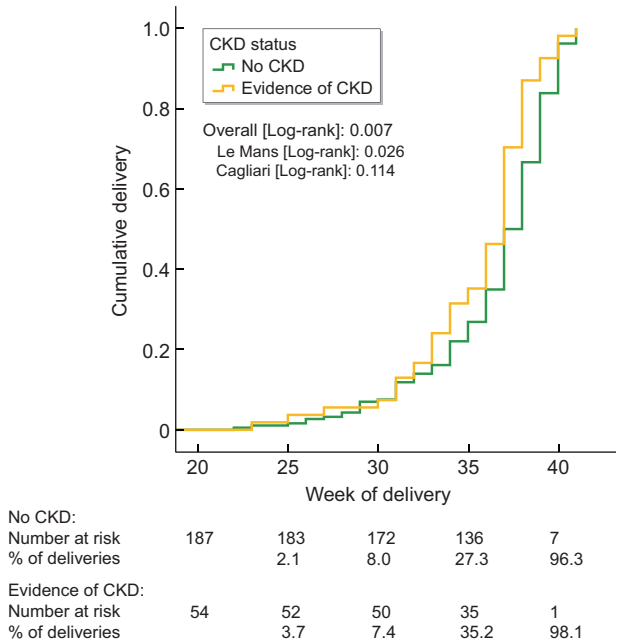

FIGURE 2: Timing of delivery in CKD and non-CK pre-eclamptic patients (P = 0.007).

(ADPKD)], we cannot exclude that PE has played a sole or additive role in cases with residual proteinuria or mild reduction of kidney function. Notwithstanding this limitation, this finding is here reported for the first time in the context of PE associated with not previously known or acknowledged CKD, and is in line with the unexplained higher incidence of pre-term delivery in patients with known CKD, previously described, even in Stage 1 patients. Likewise, data are in keeping with some suggestions of a higher incidence of 'late maternal' PE in CKD patients [25–27]. A different signature of placental biomarkers has been described in known CKD, PE without known CKD and superimposed PE on CKD [28–30]. Prospective studies should be addressed at combining these suggestions, by proposing a diagnostic work-up for diagnosing CKD in cohorts of PE patients, systematically studied with placental biomarkers. The observation that CKD was unacknowledged in eight cases, including nephrectomy, other surgical interventions or kidney transplantation, and that a family history of ADPKD does not lead to further investigation underlines the need for higher awareness of the link between CKD and PE.

Collaterally, our study also found that, in addition to CKD, other risk factors for PE were present in the majority of cases (Tables 1 and 3; Supplementary data, Table S3) [31, 32]. Of note, previous PE was recorded in ∼20% of our cases, and its prevalence rose to >35% when only multiparous women were considered (Table 1). Overweight and obesity, risk factors shared by CKD and PE, were extremely frequent, as the median preconception BMI in our population was 26 kg/m^2 (Table 1) [3, 33]. In keeping with previous studies, proteinuria levels during pregnancy were not associated with an increased prevalence of CKD, although patients with no evidence of CKD displayed lower peak proteinuria (Table 4) [34].

Our study, which has the advantage of being the first multicentre one aimed at assessing the prevalence of CKD in a large cohort of patients with a history of PE, is not devoid of limitations. It is retrospective, and not all the patients were evaluated in nephrology. The prevalence of attendance to the post-partum obstetric visits is reported as between 50% and 80% [35, 36]. The attendance to a nephrology visit, the importance of which is less immediately evident, is expected

to be lower, as was observed in our study (39.4%); this drawback indicates the importance of strengthening the cooperation between obstetrics and nephrology to improve adherence to the post-partum work-up.

This bias does not reduce, and may on the contrary enhance the weight of the key message, i.e. the high prevalence of CKD in PE, since CKD prevalence may be underestimated in our study, considering that several kidney diseases are only detectable using imaging techniques, performed only for the cases evaluated in nephrology (Supplementary data, Table S1).

The two study populations are heterogeneous; the baseline differences regard age, and prevalence of diabetes and are reflected by the different kidney diseases detected in the two settings, possibly linked with different genetic backgrounds. Differences are probably also related to clinical approaches (higher rate of Caesarean section in Cagliari, with a greater degree of expectant management) (Table 1; Supplementary data, Figure S1). However, this heterogeneity may give value to the finding of an identical prevalence in the two settings (Table 2).

Several questions remain unanswered: the role of kidney function reduction before pregnancy, the specific role of PE in the functional impairment or in persistent proteinuria and the type of kidney disease that cannot be analysed in this cohort. It would be interesting to understand if there is a loss of chance if the diagnosis of CKD is unknown until pregnancy; due to the high heterogeneity of CKD, we think that an answer will be found by following up these patients in subsequent pregnancies, to evaluate if there are differences between pregnancies followed up in nephrology or not. Moreover, we found no differences in newborns' centiles or birth weight between mothers with or without evidence of CKD, but subtle differences could have been missed due to the fact that we were not able to assess all patients in the nephrology setting, or to evaluate them at PE onset. These are goals for a future prospective, multicentre study.

In conclusion, the prevalence of unknown, or unacknowledged CKD is high in patients who experienced one episode of PE, and was found to be around 19% in a large multicentre cohort. This finding supports the need for including a nephrology work-up for all patients who have experienced an episode of PE.

Table 5. Backward logistical regression analysis: no evidence of CKD versus any sign of present or possible kidney involvement (evidence of CKD, ongoing follow-up and microalbuminuria)

	Odds ratio	95% CI	P-value
Step 1			
Age ≥34 years	1.483	0.860–2.556	0.156
Week of delivery <37	1.761	1.039–2.983	**0.035**
BMI >25 kg/m^2	0.905	0.535–1.533	0.712
Primiparity	0.664	0.390–1.131	0.132
Centile <10	1.415	0.810–2.471	0.222
Step 2			
Age ≥34 years	1.499	0.872–2.577	0.143
Week of delivery <37	1.769	1.045–2.995	**0.034**
Primiparity	0.673	0.397–1.141	0.141
Centile <10	1.414	0.810–2.469	0.223
Step 3			
Age ≥34 years	1.397	0.825–2.364	0.213
Week of delivery <37	1.834	1.087–3.092	**0.023**
Primiparity	0.680	0.402–1.150	0.150
Step 4			
Week of delivery <37	1.797	1.069–3.022	**0.027**
Primiparity	0.640	0.382–1.072	0.090

CI, confidence interval.
In bold: statistically significant differences.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

ACKNOWLEDGEMENTS

Thanks to Susan Finnel for her careful language editing.

FUNDING

No fund was received for this study; the CHM supports editing and publishing expenses.

AUTHORS' CONTRIBUTIONS

Research idea and study design were done by G.B.P., R.A. and G.C.; data acquisition was carried out by C.M., A.F., S.M., S.O., E.K., R.A., B.M. and M.T.C.; data analysis/interpretation was performed by G.C., C.M., A.F., S.M., S.O., E.K., M.T., R.A., B.M., M.T.C. and G.B.P.; statistical analysiswas carried out by A.C.; drafting was done by G.B.P.; and the final version was produced by all authors. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Table 6. Cox regression analysis for timing of delivery

	Hazard ratio Univariate	95% CI	P-value	Hazard ratio Adjusted model dicotomized	95% CI	P-value
Age (≥33 years)	1.056	0.834–1.336	0.651	0.936	0.726–1.205	0.606
BMI (>25 kg/m^2)	0.835	0.656–1.064	0.146	0.814	0.636–1.041	0.100
Primiparity	1.075	0.947–1.220	0.264	0.794	0.616–1.024	0.076
CKD signs	1.375	1.071–1.764	**0.012**	1.426	1.099–1.850	**0.008**

CI: confidence interval ; CKD signs: sign of kidney involvement (evidence of CKD, ongoing follow-up and microalbuminuria). In bold: statistically significant differences.

CONFLICT OF INTEREST STATEMENT

No conflict of interest is reported by any of the authors. The results presented in this article have not been published previously in whole or part, except in abstract format.

DATA AVAILABILITY STATEMENT

Data presented in this study are available upon reasonable request to the corresponding author.

REFERENCES

1. Bartsch E, Medcalf KE, Park AL *et al.*; High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ* 2016; 353: i1753
2. Piccoli GB, Zakharova E, Attini R *et al.* Pregnancy in chronic kidney disease: need for higher awareness. A pragmatic review focused on what could be improved in the different CKD stages and phases. *J Clin Med* 2018; 7: 415
3. Kattah AG, Scantlebury DC, Agarwal S *et al.* Preeclampsia and ESRD: the role of shared risk factors. *Am J Kidney Dis* 2017; 69: 498–505
4. Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? *Ther Adv Cardiovasc Dis* 2008; 2: 249–259
5. McDonald SD, Han Z, Walsh MW *et al.* Kidney disease after preeclampsia: a systematic review and meta-analysis. *Am J Kidney Dis* 2010; 55: 1026–1039
6. Covella B, Vinturache AE, Cabiddu G *et al.* A systematic review and meta-analysis indicates long-term risk of chronic and end-stage kidney disease after preeclampsia. *Kidney Int* 2019; 96: 711–727
7. Vikse BE, Irgens LM, Bostad L *et al.* Adverse perinatal outcome and later kidney biopsy in the mother. *J Am Soc Nephrol* 2006; 17: 837–845
8. Oliverio AL, Zee J, Mariani LH *et al.* Renal complications in pregnancy preceding glomerulonephropathy diagnosis. *Kidney Int Rep* 2019; 4: 159–162
9. Piccoli GB, Cabiddu G, Castellino S *et al.*; Kidney and Pregnancy Study Group of Italian Society of Nephrology. A best practice position statement on the role of the nephrologist in the prevention and follow-up of pre-eclampsia: the Italian study group on kidney and pregnancy. *J Nephrol* 2017; 30: 307–317
10. Filali Khattabi Z, Biolcati M, Fois A *et al.* Chronic kidney disease in pre-eclamptic patients: not found unless searched for-is a nephrology evaluation useful after an episode of preeclampsia? *J Nephrol* 2019; 32: 977–987
11. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39: S1–S266
12. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. *Obstet Gynecol* 2020; 135: e237–e260
13. Phipps E, Prasanna D, Brima W *et al.* Preeclampsia: updates in pathogenesis, definitions, and guidelines. *Clin J Am Soc Nephrol* 2016; 11: 1102–1113
14. Stirnemann J, Villar J, Salomon LJ *et al.*; for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International estimated fetal weight standards of the INTERGROWTH-21(st) project. *Ultrasound Obstet Gynecol* 2017; 49: 478–486
15. Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007; 298: 2038–2047
16. Williams D, Davison J. Chronic kidney disease in pregnancy. *BMJ* 2008; 336: 211–215
17. Hill NR, Fatoba ST, Oke JL *et al.* Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One* 2016; 11: e0158765
18. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. *Nat Rev Nephrol* 2017; 13: 104–114
19. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020; 395: 709–733
20. Australian Institute of Health and Welfare. Chronic kidney disease prevalence among Australian adults over time. *Cardiovascular, Diabetes and Chronic Kidney Disease Series No. 6. Cat. no. CDK 6*. Canberra: AIHW, 2018. Available from: https://www.aihw.gov.au/getmedia/cbfc53e4-c6fc-4a8e-9a7f-e5dfa38ae10c/aihw-cdk-6.pdf.aspx?inline=true (15 March 2021, date last accessed)
21. Pani A, Bragg-Gresham J, Masala M *et al.* Prevalence of CKD and its relationship to eGFR-related genetic loci and clinical risk factors in the SardiNIA study cohort. *J Am Soc Nephrol* 2014; 25: 1533–1544
22. Cirillo M, Laurenzi M, Mancini M *et al.* Low glomerular filtration in the population: prevalence, associated disorders, and awareness. *Kidney Int* 2006; 70: 800–806
23. Songini M, Mannu C, Targhetta C *et al.* Type 1 diabetes in Sardinia: facts and hypotheses in the context of worldwide epidemiological data. *Acta Diabetol* 2017; 54: 9–17
24. Sardu C, Cocco E, Mereu A *et al.* Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. *PLoS One* 2012; 7: e32487
25. Piccoli GB, Cabiddu G, Attini R *et al.* Risk of adverse pregnancy outcomes in women with CKD. *J Am Soc Nephrol* 2015; 26: 2011–2022
26. Piccoli GB, Kooij IA, Attini R *et al.* A systematic review on materno-foetal outcomes in pregnant women with IgA nephropathy: a case of "late-maternal" preeclampsia? *J Clin Med* 2018; 7: 212
27. Attini R, Kooij I, Montersino B *et al.* Reflux nephropathy and the risk of preeclampsia and of other adverse pregnancy-related outcomes: a systematic review and meta-analysis of case series and reports in the new millennium. *J Nephrol* 2018; 31: 833–846
28. Rolfo A, Attini R, Nuzzo AM *et al.* Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers. *Kidney Int* 2013; 83: 177–181
29. Wiles K, Chappell LC, Lightstone L *et al.* Updates in diagnosis and management of preeclampsia in women with CKD. *Clin J Am Soc Nephrol* 2020; 15: 1371–1380
30. Wiles K, Bramham K, Seed PT *et al.* Diagnostic indicators of superimposed preeclampsia in women with CKD. *Kidney Int Rep* 2019; 4: 842–853
31. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005; 330: 565
32. Poon LC, Shennan A, Hyett JA *et al.* The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. *Int J Gynecol Obstet* 2019; 145: 1–33
33. Robillard PY, Dekker G, Scioscia M *et al.* Increased BMI has a linear association with late-onset preeclampsia: a population-based study. *PLoS One* 2019; 14: e0223888
34. Lampinen KH, Ronnback M, Groop PH *et al.* Renal and vascular function in women with previous preeclampsia: a comparison of low- and high-degree proteinuria. *Kidney Int* 2006; 70: 1818–1822
35. Rodin D, Silow-Carroll S, Cross-Barnet C *et al.* Strategies to promote postpartum visit attendance among medicaid participants. *J Womens Health (Larchmt)* 2019; 28: 1246–1253
36. Wilcox A, Levi EE, Garrett JM. Predictors of non-attendance to the postpartum follow-up visit. *Matern Child Health J* 2016; 20: 22–27

Received: 15.3.2021; Editorial decision: 5.7.2021