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Original Article

ORIGINAL ARTICLE

Recurrence of preeclampsia is common, even during rigorously controlled multidisciplinary follow-up: a pilot experience

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ABSTRACT

Background. The risk of kidney failure increases after preeclampsia (PE), further increasing after two or more episodes. Recurrence is variably estimated. The aim of this study was to assess the recurrence rate and its predictors in the setting of obstetric–nephrology follow-up of pregnancies after PE.

Methods. In a prospective study (2018–24), from 108 pregnancies with prior hypertensive disorders of pregnancy we selected 77 singleton deliveries after excluding twins, miscarriages, terminations, ongoing pregnancies, and drop-outs. PE recurrence and potential associated factors were tested in univariable and multivariable logistic regression models. Gestational age at time of delivery was analyzed using Kaplan–Meier curves and Cox regression. The diagnostic potential of angiogenic placental biomarkers (soluble FMS-like tyrosine kinase-1 and placental growth factor) was likewise tested.

Results. In the context of a high prevalence of previous preterm delivery (53.6%), PE recurrence was 42.9%. Furthermore, 19.5% of the women experienced other complications and only 37.7% had an uneventful pregnancy; 60.6% of recurrences occurred after the 37th gestational week (GW), making later delivery possible (median: 38 GW in the index pregnancy versus 35 GW in the previous pregnancy). The covariates associated with PE recurrence were chronic hypertension (OR 7.662, 95% CI 2.122–33.379) and having had a baby with a centile <10th (OR 7.049, 95% CI 1.56–41.027), while those associated with time to delivery were hypertension and maternal age. Being diagnosed with chronic kidney disease after a previous PE episode was not associated with a significantly increased risk of recurrent PE.

Conclusions. Risk of PE recurrence was high but delayed in this cohort on multidisciplinary follow-up. The question of whether a proactive approach to delivery can help to preserve long-term maternal kidney health is open.

Keywords: chronic kidney disease, CKD, hypertensive disorders of pregnancy, pregnancy, women's health

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KEY LEARNING POINTS

What was known:

- Preeclampsia (PE) and hypertensive disorders of pregnancy (HDP) complicate respectively 2% and >10% of all pregnancies and represent a risk factor for the occurrence of kidney failure, cardiovascular disease, and early-onset hypertension.
- The incidence of recurrent PE is high, but estimates vary (from ~15% to >70%).
- An underlying kidney disease is found in up to 20% of women who undergo a diagnostic follow-up after PE.

This study adds:

- Despite strict controls, the use of acetylsalicylic acid, correction of vitamin D deficits, and intensive hypertension monitoring, the recurrence rate of PE was high (43%). Most of the recurrences occurred after the 37th gestational week and were delayed compared with the previous PE episode, in keeping with the current literature.
- This is the first study performed in the setting of conjoint nephrology–obstetrics follow-up after a PE episode, quantifying the recurrence risk also in patients with initial chronic kidney disease.
- A longitudinal assessment of the placental biomarkers soluble FMS-like tyrosine kinase-1 and placental growth factor can help to timely identify pregnancies at higher risk of PE recurrence.

Potential impact:

- Strict multidisciplinary obstetrics–nephrology follow-up of pregnant women with a medical history of PE can help to delay recurrences.
- Further studies should be designed to assess whether a proactive approach to delivery after 37 gestational weeks can reduce the long-term risk of kidney disease.
- The finding of a high risk of recurrences, even with 'optimized' follow-up, with expected consequences on the kidney health, underlines the importance of the involvement of nephrologists in the care plans.

INTRODUCTION

Preeclampsia (PE) and hypertensive disorders of pregnancy (HDP), which include PE, gestational hypertension, hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome), and, according to most authors, intrauterine growth restriction (IUGR), occur frequently. The fact that their incidence varies worldwide is due to a number of factors: genetic and epigenetic (women born small or preterm have a higher risk of PE-HDP), demographic (teen or older-age pregnancies are at higher risk), social (poverty and social deprivation are associated with a higher incidence of PE-HDP), and clinical [chronic kidney disease (CKD), immunologic diseases, diabetes, obesity, and anorexia increase the risk of PE-HDP]; the risk is also higher in women undergoing assisted fertilization treatment [1–3]. A general estimate of PE incidence is 2%–3% per pregnancy, corresponding to a 5%–7% risk for multiparous women during their lifetime. HDP are more common; definitions vary, but they are estimated to be present in ~10% of pregnancies and 15%–20% of multiparous women during their lifetime [4].

PE and HDP are syndromes and not single diseases, and their pathogeneses are multifactorial [2–6]. While clinical remission of hypertension, proteinuria, or other signs of organ damage is common after delivery, the long-term health of women who experience one or more PE episodes is lower than that of parous women with non-complicated pregnancies, and the main health problems are cardiovascular and metabolic diseases, CKD, and kidney failure [7–9].

Furthermore, a vicious circle links kidney impairment with placental damage [10]. Women with CKD have a higher incidence of PE-HDP, and those who experience PE-HDP have an increased risk of being diagnosed with CKD [7, 9–15]. Whether and to what extent this risk is due to pre-existing CKD, and is revealed by pregnancy, or PE-HDP are instead causation factors for CKD is still a matter of discussion. Our knowledge is limited; early CKD often goes undetected unless searched for (the few studies available on this issue find evidence of CKD after PE in ~20% of cases), and long-term follow-up after PE-HDP is rarely available [14, 16, 17]. Whatever the pathogenesis and the 'relative weight' of CKD, the risk of recurrence of PE and HDP is higher in subsequent pregnancies. Estimates vary from 15% to 80%, 20.7% in one of the largest meta-analyses, but studies are heterogeneous in terms of populations and definition of recurrences (PE only or all HDP); moreover, the severity of the previous episode of PE-HDP varies significantly [18, 19]. As a general rule, recurrences are more frequent after severe and/or early PE. Obstetric policies play a significant role in this heterogeneity: earlier delivery can theoretically prevent late PE, but increases the number of cesarean sections.

Some experts hold that PE-HDP are valuable opportunities to improve long-term health, through early diagnosis of CKD and of its risk factors, and see a nephrology assessment after delivery as a goal to be met; however, the long-term advantages are still to be proven, and long-term follow-up programs are needed to explore this issue [20, 21]. Preventing or at least attenuating recurrences in future pregnancies is expected not only to protect maternal health but also to break the transgenerational vicious circle of 'small babies' that will deliver small babies who will have a higher incidence of CKD, cardiovascular and metabolic disorders, and complicated pregnancies [10, 11, 22].

In the context of a follow-up program, established for women who have experienced an episode of preeclampsia, which includes searching for risk factors (including hypertension, CKD, other systemic diseases), optimization of care (for example of hypertension or diabetes), and nutritional status (with a dedicated program for obese women), particular attention was paid to optimizing the clinical conditions, and whenever possible reducing the risk factors before and offering a strict follow-up during a subsequent pregnancy [23].

The aim of this study was to assess the recurrence rate and duration of pregnancy and identify the main factors associated with recurrences and duration of pregnancy in women followed up after a PE episode, in the context of a pilot experience of joint nephrology and obstetric management Hence, the present study

offers some insights into the results of pilot multidisciplinary obstetric–nephrology management, characterized by a longitudinal follow-up in nephrology of women who experienced an episode of PE, who were followed up whenever possible since the start of pregnancy with the same protocols that are used in CKD G1 [20].

MATERIALS AND METHODS

Setting of care

This study was conducted at the Centre Hospitalier Le Mans (CHM), one of the largest non-university hospitals in France. The CHM has an obstetric service with ∼3500 deliveries per year [24]. Dedicated nephology consultations for women who have experienced an episode of PE have been available since 2017, and nephrology follow-up of subsequent pregnancies has also been available since then, integrating standard obstetric care with nephrology consultations (blood pressure control, specific follow-up of CKD cases, and dietary management) [23].

The work-up after PE includes a search for an underlying kidney disease (kidney ultrasounds, blood and urine tests, according to patient's initial data and medical history) and other risk factors (obesity, hypertension, immunological or other maternal diseases). Patients are offered a specific consultation (whenever wished with the partner) before planning a subsequent pregnancy, to discuss risks and questions, and plan follow-up, that is started early in subsequent pregnancies [14].

The Obstetric Unit is the only tertiary care center in the Sarthe Department (∼560 000 inhabitants) [25]. Patients throughout the department with severe PE, HELLP, or other relevant obstetric pathologies are routinely referred to the CHM. The hospital discharge codes indicate that the annual incidence of PE in the time period 2017–2023 was 2%–3%.

Definitions

HPDs were defined in keeping with the American College of Obstetricians and Gynecologists (ACOG) guidelines: PE as hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg), associated with proteinuria (24-h excretion ≥300 mg), diagnosed after 20 weeks of uneventful gestation and continuing up to 2 weeks post partum [1]. In the absence of proteinuria, one of the following had to be present: new-onset hypertension with new onset of platelet count <100 000/μL, serum creatinine >1.1 mg/dL, or doubling of concentration in the absence of other renal diseases, transaminitis to twice the normal concentration of liver enzymes, pulmonary edema, and cerebral/visual symptoms [1]. Intrauterine growth restriction was included in end-organ damage.

HELLP syndrome was defined in keeping with the above guidelines (alanine or aspartate transaminase levels ≥2 times the upper limit of normal); hemolysis (lactate dehydrogenase >600 U/L; peripheral blood smears with evidence of damaged erythrocytes; serum bilirubin ≥1.2 mg/dL; platelet count <100 000/μL) [1].

Small for gestational age babies were defined in line with the two most commonly used cut-points, below the 5th and 10th centiles, following INTERGROWTH standards [26, 27].

Preterm delivery was defined as delivery before 37 completed gestational weeks (starting from the first day of the last menses); early preterm delivery as before 34 gestational weeks (GW) and very early preterm delivery as delivery before 28 completed gestational weeks [28–30].

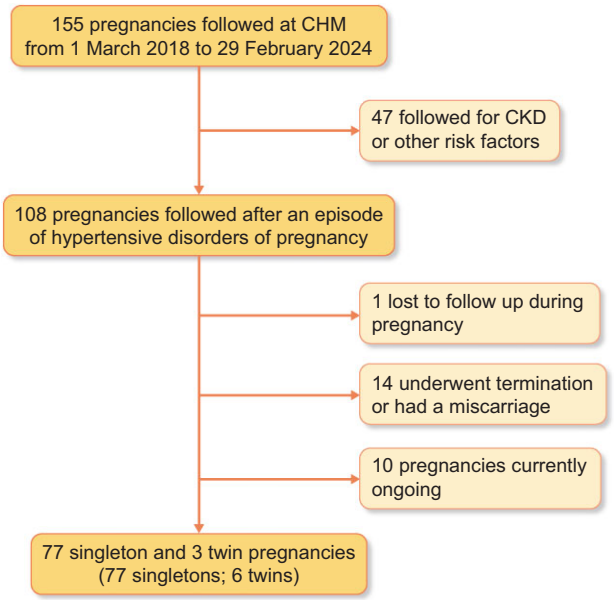

Figure 1: Study flow-chart. CHM, Centre Hospitalier Le Mans.

CKD was defined following the 2012 and 2024 Kidney Disease Improving Global Outcomes classification and stratification [31, 32]. Estimated GFR (eGFR) relied on the CKD-EPI equation, using preconception data [33].

Since patient selection was based upon the presence of a previous pregnancy complicated by PE or severe HDP, in our study we included only cases in which CKD had been diagnosed during the work-up after a previous pregnancy complicated by PE or related disorders. As a consequence, we excluded cases that were referred because of CKD, while in the study population we considered CKD as a covariate (as we did with chronic hypertension).

Obesity was defined by a pre-gestational body mass index (BMI) ≥30 kg/m^2; overweight as BMI between 25 and 30 kg/m^2, and underweight as BMI <20 kg/m^2 [34].

Clinical outcomes

The main outcomes were incidence of PE defined as above, and duration of pregnancy, considering only women who reached the viability term of 20 GW. Abortions and miscarriages (i.e. before 20 GW) were not included in the analysis (Fig. 1). Time to delivery was calculated as time from the last menses to delivery and expressed in GW.

A complicated pregnancy was defined as one with PE, HELLP or intrauterine death (if not ascribed to other cause, e.g. infectious ones).

Worsening of chronic hypertension, isolated hypertension, intrapartum hemorrhage, gestational diabetes mellitus, and isolated proteinuria were recorded as other complications.

Most of the patients were referred to the nephrologists by the hospital's obstetric department, by local midwives, or private obstetricians, for evaluation after a PE episode, intrauterine death, or HELLP syndrome (in which case they were already in follow-up in nephrology when the index pregnancy started), or during pregnancy, when there was a history of previous complications.

Multidisciplinary work-up

All women without contraindications who were referred before 14 GW were prescribed acetylsalicylate 75–150 mg per day, as agreed with the local obstetricians. Folic acid was prescribed before conception in planned pregnancies to prevent neural malformations. As part of their nephrology follow-up, all women underwent baseline evaluation of nutritional habits, seeking to ensure balanced nutrition (with a focus on energy, proteins, vitamins, and calcium), rich in fruit and vegetables and avoiding ultra-processed food [35]. Efforts were made to keep weight gain within the recommended limits [36].

Vitamins B12 and D and folic acid were dosed monthly and supplemented according to need; anemia and iron deficiency were corrected with oral or IV iron, as per current recommendations [37–39]; kidney function, albumin levels, and electrolytes were checked monthly and, if not determined before pregnancy, a basic immunologic work-up was performed. Likewise, kidney and urinary tract ultrasounds were prescribed, if one had not been performed in the previous year. Infection control followed local recommendations; anti-toxoplasma antibodies were checked monthly if negative at baseline, in keeping with the current French indications [40, 41]. Since >90% of our patients were toxoplasma-negative, we defined a monthly frequency of checkups, combining toxoplasma tests, tests requested by the obstetricians with kidney function and electrolyte assessment, measuring hemoglobin, iron stores, vitamin levels, further implemented according to clinical needs. Urinalysis and albuminuria to creatininuria ratio were prescribed weekly after 20 GW.

The placental biomarkers soluble FMS-like tyrosine kinase-1 (Sflt1) and placental growth factor (PlGF) were routinely checked monthly after 20 GW. Samples were assessed using the Elecsys® sFlt-1/PlGF immunoassay (Roche Diagnostics GmbH); the results of the tests were not considered in planning delivery, nor did they affect the obstetrical work-up. The median delay time between testing and availability of the results was 4 days. However, if nephrologists were aware of a high or increasing ratio, blood pressure, proteinuria, and clinical checks were more frequent.

All women were taught how to self-monitor blood pressure at home, and this was our preferred monitoring policy; women were asked to self-monitor blood pressure at home if they showed 'normal-high' blood pressure levels (130/80 mmHg) at clinical visits [42]. We also prescribed 24-hour blood pressure monitoring in cases of discrepancy between home and in-office monitoring, in cases in which blood pressure showed wide variations in self-monitoring, and in cases in which self-monitoring was not performed. Due to the fact that the procedure was not universally accepted by the patients, we tried to optimize monitoring according to their preferences.

Blood pressure targets under treatment followed the indications agreed on in CKD pregnancies by the Italian Society of Nephrology (target <130/80 mmHg); target blood pressure levels at which treatment was started were likewise individualized, but were mainly >140/90 mmHg as recommended in the current nephrology guidelines [43, 44].

Delivery was planned by the obstetricians, and advanced if the ACOG criteria for the definition of PE-HELLP were met, especially after term; otherwise a conservative approach was chosen with regard to the appearance of edema, weight gain, or isolated low-grade proteinuria and hypertension.

Study design and statistical analysis

From 108 pregnancies followed after an episode of PE or other severe HDP in our nephrology outpatient clinic between March 2018 and February 2024 (Fig. 1), we selected 77 singleton pregnancies; we excluded the 14 cases who had undergone termination or had a miscarriage, 10 ongoing pregnancies, 3 twin pregnancies, and 1 patient lost to follow-up during pregnancy. Patients were divided into three groups defined by the occurrence of pregnancy complications (PE, non-complicated, other complications). A dichotomous analysis (PE, all others) was performed for the main outcomes. Data are presented as absolute numbers and percentages for prevalence, mean and standard deviation (SD) for normally distributed variables, and median and first and third quartiles for non-normally distributed ones.

Multivariable logistic regression analysis was performed to determine which variables were associated with recurrence of PE: age at the beginning of the index pregnancy (as a continuous variable), BMI (dichotomized as $<$ or $\geq$30 kg/m^2), presence of chronic hypertension before the index pregnancy (dichotomized as yes or no), presence of CKD (dichotomized as yes or no), GW at delivery during the previous complicated pregnancy (dichotomized at 35 GW), and baby's centile in the previous complicated pregnancy (dichotomized at the 10th centile).

Each woman was her own control, as the results of the index pregnancy were compared with those of the previous complicated pregnancy.

In fact, while randomization was not proposed for ethical reasons, since women should be systematically offered follow-up without charge in our area, choosing as controls those who were not followed would have introduced a referral and a compliance bias. Hence, acknowledging these limits, we compared the outcomes of the pregnancy followed up in our unit (index pregnancy) with the outcomes in the previous pregnancy (the one that led to referral to our unit).

Reverse Kaplan–Meier curves (time to event) were used to assess the time to delivery starting from the viability zone (20 GW) in the overall cohort, and in keeping with the outcomes and the major risk factors, reported below. Cox regression analysis was performed to assess the effect on delivery week of the same independent variables used for the analysis of recurrences.

Longitudinal analysis using mixed-effect models and locally estimated scatterplot smoothing (LOESS) was used to explore the trends and variations in creatinine, uric acid, and sFlt1/PlGF levels.

Statistical analyses were performed with RStudio software version 2023.09.1+494 (Posit Software, Boston, MA). The two-sided α risk was set at 5%.

Ethical issues

The study was performed in accordance with the Declaration of Helsinki. Women signed an informed consent authorizing retrieval of their clinical data. Women who experienced an episode of PE are enrolled in the PRECEDE Study (Clinicaltrials.org NCT05056701, CPP 21.05200.210642, 5 July 2021, revised on 24 June 2024).

RESULTS

Baseline data

The baseline data of the 77 cases with singleton delivery are summarized in Table 1 (selection in Fig. 1). The data identify a cohort with a high prevalence of overweight-obesity, and in line with expected standards in terms of age and ethnicity. Median referral occurred early, since most of the patients (67.5%) were already on follow-up in the nephrology unit. Outcomes

Table 1: Baseline data of the index pregnancy of women with singleton deliveries divided into three groups defined by the occurrence of pregnancy complications (PE/HELLP, non-complicated, other complications).

	All cases ($n = 77$)	Recurrence of PE/HELLP ($n = 33$)	Non-complicated ($n = 29$)	Other complications ($n = 15$)
Age at referral (years), median [Q1–Q3]	31.6 [27.2–39.6]	32 [28.6–35.5]	28.7 [29.2–33.4]	33.5 [29.9–36.3]
Week at referral (weeks), median [Q1–Q3]	9.9 [6.7–16.4]	10 [6.7–16]	8 [6.4–16]	12.7 [8.3–18.4]
Parity = 1, *n* (%)	48 (62.3)	20 (60.6)	20 (68.9)	8 (53.3)
Parity ≥ 2, *n* (%)	29 (37.7)	13 (39.4)	9 (31.1)	7 (46.7)
Ethnicity (white), *n* (%)	56 (72.7)	23 (69.7)	23 (79.3)	10 (66.7)
BMI before pregnancy (kg/m^2), median [Q1–Q3]	27.6 [22.1–33.5]	29.3 [22.1–34.4]	26.9 [22.5–32.2]	29.0 [23.5–33.3]
BMI <20 kg/m^2, *n* (%)	11 (14.3)	5 (15.1)	4 (13.8)	2 (13.3)
BMI >30 kg/m^2, *n* (%)	31 (40.2)	14 (42.4)	10 (34.4)	7 (46.6)
Only 1 previous complicated pregnancy, *n* (%)	62 (80.5)	25 (75.7)	24 (82.7)	13 (86.7)
≥2 previous complicated pregnancies, *n* (%)	15 (19.5)	8 (24.3)	5 (17.3)	2 (13.3)
Birth weight of the woman (g), median [Q1–Q3]	3250 [3000–3525] (missing: 39)	3250 [3000–3600] (missing: 18)	3200 [2915–3500] (missing: 12)	3500 [2150–3757.5] (missing: 9)
Profession: unemployed, *n* (%)	7 (10.8) (missing: 12)	2 (6.45) (missing: 2)	3 (13.6) (missing: 7)	2 (16.7) (missing: 3)
Hypertension before pregnancy, *n* (%)	27 (35.1)	17 (51.5)	2 (6.9)	8 (53.3)
Diabetes mellitus before pregnancy, *n* (%)	4 (5.2)	3 (9.1)	0 (0)	1 (6.7)
CKD diagnosed after a previous complicated pregnancy, *n* (%)	22 (28.6)	9 (27.3)	7 (24.1)	6 (40.0)

Table 2: Main characteristics of the index pregnancy in women with singleton deliveries divided into three groups defined by the occurrence of pregnancy complications (PE/HELLP, non-complicated, other complications).

	All cases ($n = 77$)	Recurrence of PE—HELLP ($n = 33$)	Non-complicated ($n = 29$)	Other complications ($n = 15$)
Acetylsalicylic acid, *n* (%)	71 (92.2)	32 (96.9)	27 (93.1)	12 (80)
Antihypertensive medications, *n* (%)	24 (31.2)	21 (63.6)	1 (3.4)[a]	2 (13.3)
Gestational diabetes, *n* (%)	6 (7.8)	4 (12.1)	0 (0)	2 (13.3)
Creatinine max (mg/dL), median [Q1–Q3]	58 [52–69]	60 [50.5–77]	57 [51–64]	62 [54–67]
Week of delivery, median [Q1–Q3]	38.0 [37.0–39.0]	38.0 [35.0–39.0]	39.0 [38.0–40.0]	38.0 [37.0–39.0]
Weight gain (kg), median [Q1–Q3]	11.4 [7–15]	10 [5.5–14]	11.5 [6.25–16.4]	14 [10–17]
Cesarean section, *n* (%)	34 (44.2)	20 (60.6)	9 (31.0)	5 (33.3)
Baby's weight (g), median [Q1–Q3]	2180 [2560–3430]	2615 [2057–3300]	3330 [3127–3677]	3255 [2935–3565]
Centile, median [Q1–Q3]	47.3 [18.4–84.1]	18.9 [2.1–74.1]	60.4 [32.3–88.9]	61.9 [29–85.2]
Baby's sex: male, *n* (%)	41 (53.2)	17 (51.1)	14 (48.3)	10 (66.6)

[a]Occasional need.

were not affected by referral week (Table 1). Women with non-complicated pregnancies were significantly younger than women whose pregnancies were complicated by PE-HELLP or other conditions (29 vs 32 and 33 years, respectively; $P < .01$), and BMI was lower at baseline in non-complicated versus complicated pregnancies, albeit not significantly.

Twenty-two of the 77 women (28.6%) had been diagnosed with CKD during the follow-up after their previous PE; all were in CKD G1, and none had kidney failure (Supplementary Table 1). This proportion was non-significantly different in complicated and non-complicated pregnancies.

Main outcomes

The index pregnancy was uneventful in 29 cases, recurrence was observed in 33 pregnancies, and 15 women experienced complications, including isolated hypertension or worsening of chronic hypertension (10), intrapartum hemorrhage (3), and new-onset gestational diabetes mellitus (3) (one patient developed both hypertension and gestational diabetes).

Data on the three twin pregnancies are reported in Supplementary Table 2.

Overall, 92.2% of the women in the study received low-dose acetylsalicylic acid (ASA) during the index pregnancy (Table 2). The few patients who did not start ASA were referred after the 16th GW, when the benefits of ASA are not demonstrated. All women had normal kidney function at referral (Table 2, Supplementary Fig. 1).

As expected, delivery by cesarean section was more frequent in women who experienced a recurrence than in the other outcome groups, and the group with recurrence gave birth to smaller babies compared with women who had an uneventful pregnancy or developed other complications (Table 2).

Timing of delivery and of recurrences

The median gestational week at delivery was, as expected, higher in non-complicated pregnancies than in the presence of recurrent PE-HELLP or other complications (39, 37, and 38 GW, respectively) (Fig. 2). Of note, 60.6% of recurrences occurred after

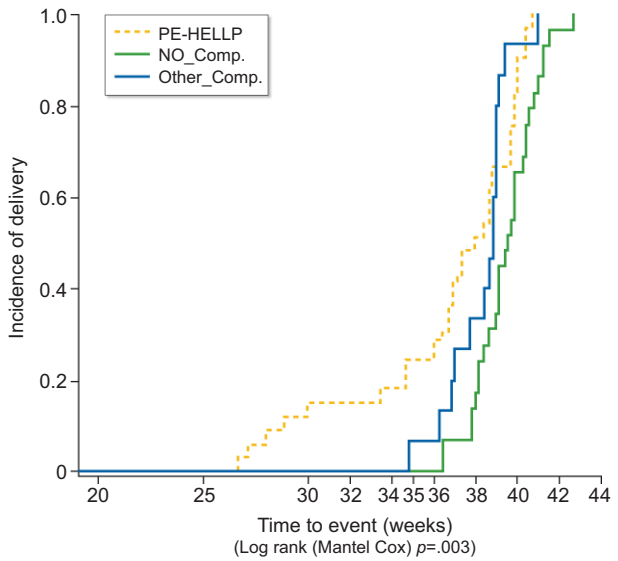

Figure 2: Week of delivery in the index pregnancy according to pregnancy complications: preeclampsia or hemolysis, elevated liver enzymes and low platelet count (PE-HELLP), no complication (NO_Comp) or other complications (OTHER_Comp).

37 GW and 48.5% after 38 GW. No intrauterine deaths occurred in the index pregnancy. Overall, we observed an increase in GW at delivery in the index pregnancy compared with the previous one (Fig. 3A). In cases in which there was a recurrence, the median GW at delivery was significantly higher (38 weeks) than in their previous complicated pregnancy (35 weeks) (Tables 2 and 3 and Fig. 3B). Previous complicated pregnancies were characterized by 23 HELLP/intrauterine deaths, 53 PE and 1 isolated IUGR. Before the index pregnancy, 67.5% of women were already followed up in our outpatient clinic.

Serum creatinine, uric acid, and sFLT1 to PlGF ratio during pregnancy

Supplementary Figs 1 and 2 and Fig. 4 show the longitudinal patterns of serum creatinine, uric acid, and sFLT1 to PlGF ratio, respectively, during pregnancy.

The trajectory of serum creatinine was quite flat in this population, suggesting a lack of decrease in serum creatinine in mid-pregnancy in women who had already experienced a PE episode (Supplementary Fig. 1). Uric acid patterns were likewise not different in the three groups (Supplementary Fig. 2).

Conversely, although the sFLT1 to PlGF ratio increased at the end of all pregnancies, the pattern differed in pregnancies with recurrences, with earlier recurrences showing the highest values (Fig. 4).

Predictors of recurrences

In the logistic regression analyzing the outcome of PE in the index pregnancy, the two covariates significantly associated with the risk of a recurrence were baseline hypertension and the birth of a baby below the 10th centile in the previous pregnancy (Table 4). Cox analysis on time to event confirmed a significant role of baseline hypertension and of age at the start of pregnancy in predicting a shorter duration of pregnancy, while centile and CKD did not reach statistical significance (Table 5).

DISCUSSION

PE is a well-acknowledged risk factor for having or developing CKD, and recurrent PE is associated with an even higher incidence of kidney failure during the patient's lifetime [7]. Dedicated multidisciplinary follow-up is advocated by some experts and scientific societies, but seldom performed [20]. Hence, the present study offers some insights into the results of pilot multidisciplinary obstetric–nephrology management, characterized by a longitudinal follow-up in nephrology of women who

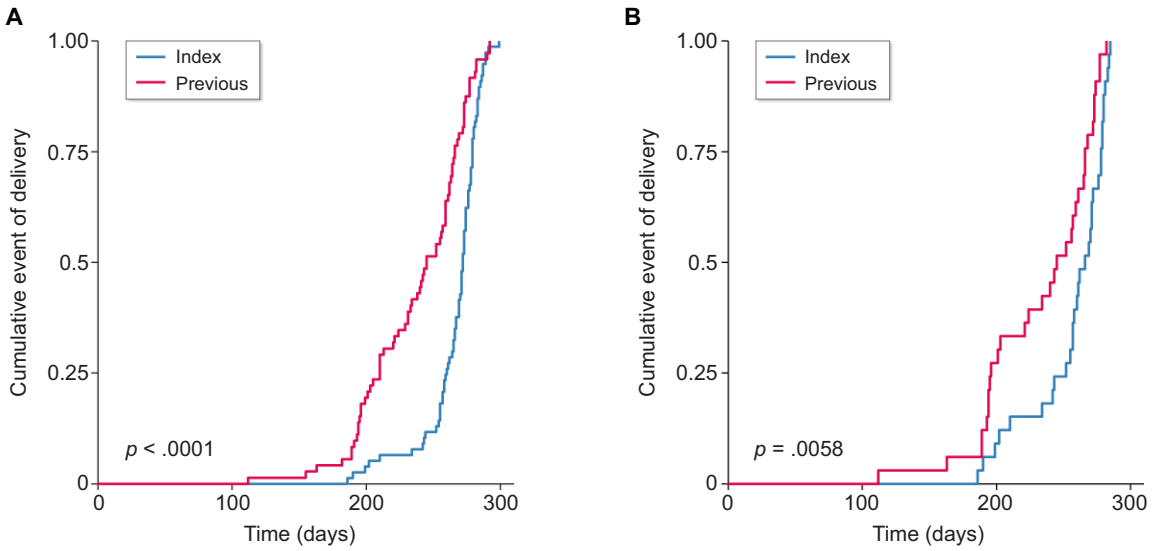

Figure 3: Comparison between the week of delivery in the index pregnancy (Index) and the previous pregnancy (Previous) in the overall cohort (A) and in recurrences (B).

Table 3: Main outcomes of the previous pregnancies in women with singleton deliveries divided into three groups defined by the occurrence of pregnancy complications (PE/HELLP, non-complicated, other complications).

	All cases ($n = 77$)	Recurrence of PE—HELLP ($n = 33$)	Non-complicated ($n = 29$)	Other complications ($n = 15$)
Week of delivery in the previous complicated pregnancy, median [Q1–Q3][a]	35.0 [30.0–38.0] (missing: 4)	35.0 [27.5–38.0]	35.0 [31.5–37.0] (missing: 1)	35.0 [30–39.0] (missing: 3)
Week <28, *n* (%)	10 (14.5)	8 (24.2)	2 (8.3)	0 (-)
Week <32, *n* (%)	19 (27.5)	12 (36.4)	6 (25.0)	1 (8,3)
Week <37, *n* (%)	37 (53.6)	20 (60.6)	14 (58.3)	3 (25)
Baby's weight in the previous complicated pregnancy (g), median [Q1–Q3][a]	2480.0 [1425.0–3145.0] (missing: 1)	1927 [902.5–3048.7] (missing: 1)	2480.0 [1615.0–3055.0]	2952.2 [2250.0–3583.7]
Intrauterine death in the previous complicated pregnancy, *n* (%)	7 (10.1)	0 (–)	4 (12.5)	3 (20.0)
Centile in the previous complicated pregnancy, median [Q1–Q3][a]	18.9 [1.3–59.1] (missing: 5)	12.4 [0.2–68.7] (missing: 1)	24.8 [5.4–55.2] (missing: 1)	17.9 [7.6–77.3] (missing: 3)

[a]Excluding missing data.

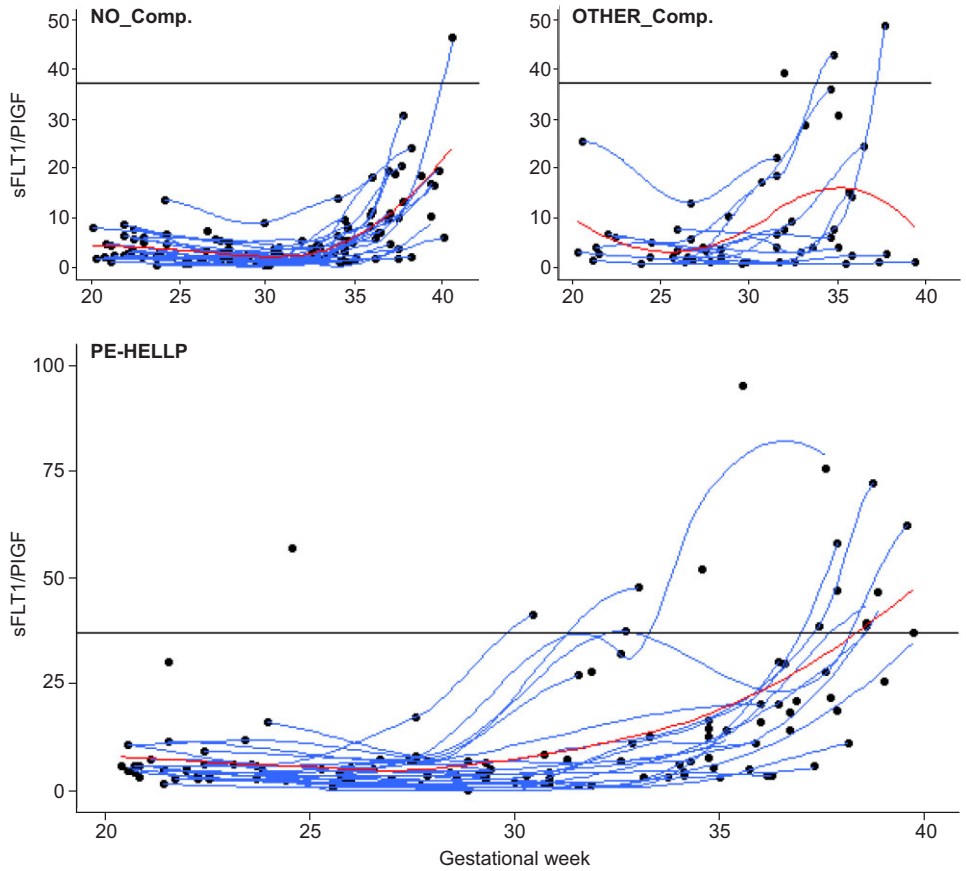

Figure 4: sFLT1 to PlGF ratio trend based on pregnancy complications: preeclampsia or hemolysis, elevated liver enzymes and low platelet count (PE-HELLP), no complication (NO_Comp) or other complications (OTHER_Comp).

experienced an episode of PE, who are followed up whenever possible since the start of pregnancy with the same protocols that are used in CKD G1 [20].

In the context of expectant management in the obstetric setting, the first issue was that, despite intensive follow-up in nephrology (including timely start of ASA treatment, nutritional management, correction of vitamin deficits, and treatment of hypertension), the recurrence rate was high: 43% of the cases. Furthermore, 19.5% of the remaining pregnancies experienced other pregnancy-related complications and only 38% were non-complicated.

We can only speculate on the reasons why this prevalence is higher than the one reported in the largest meta-analysis [17–18]. While follow-up after a PE episode was offered to all women

Table 4: Multivariable regression analysis for the outcome recurrence of PE.

	95% CI			
	OR	Lower	Higher	*P*-value
Age at beginning of index pregnancy	1.114	0.997	1.264	.070
BMI (≥30 kg/m^2) at beginning of index pregnancy	1.187	0.356	3.917	.776
Presence of chronic hypertension before index pregnancy (yes)	7.662	2.122	33.379	**.003**
Diagnosis of CKD after previous complicated pregnancy (yes)	1.321	0.370	4.795	.666
Week of delivery in previous complicated pregnancy (≥35)[a]	0.546	0.139	1.979	.365
Baby's centile in previous complicated pregnancy (<10th)	7.049	1.566	41.027	**.018**

OR, odds ratio; CI, confidence interval.
Values written in bold achieved statistical significance.
[a]Dichotomization was performed at 35 GW, median GW in the previous complicated pregnancy.

Table 5: Cox proportional hazards model for the outcome shorter duration of pregnancy.

	95% CI			
	HR	Lower	Higher	*P*-value
Age at beginning of index pregnancy	1.086	1.025	1.150	**.005**
BMI (≥30 kg/m^2) at beginning of index pregnancy	0.958	0.555	1.654	.878
Presence of chronic hypertension before index pregnancy (yes)	2.103	1.218	3.629	**.008**
Diagnosis of CKD after previous complicated pregnancy (yes)	1.735	0.935	3.221	.081
Week of delivery in previous complicated pregnancy (≥35)[a]	1.005	0.562	1.796	.987
Baby's centile in previous complicated pregnancy (<10th)	1.835	0.962	3.499	.065

HR, hazard ratio; CI, confidence interval.
Values written in bold achieved statistical significance.
[a]Dichotomization was performed at 35 GW, median GW in the previous complicated pregnancy.

in our setting, the prevalence of pre-term PE was higher than in the analysis (in our series the previous delivery was at a median of 35 GW, whereas > 75% of previous episodes in the largest meta-analysis occurred after 37 GW). This difference is an indication of a negative selection bias that may be due both to the referral pattern in our tertiary care center and to the fact that women who experience a severe disease more often decide to undergo follow-up. In fact, our data are in line with smaller series selected on the basis of a severe previous PE episode [45–47]. Furthermore, milder, late PE cases might have been overlooked if clinical surveillance was less rigorous. Of note, most of the previous series were reported before aspirin use became the standard of care for PE prevention [48]. We were not able to compare data of women followed up in our unit with those of women who did not undergo this follow-up. Indeed, while randomization was not proposed for ethical reasons, since women should be systematically offered follow-up in our area, by means of the follow-up program which was agreed and is free of charge, choosing those who were not followed would have introduced a referral and probably also bias. Hence, acknowledging these limits, we compared the outcomes of the pregnancy followed up in our unit (index pregnancy) with the outcomes in the previous pregnancy (the one that led to referral to or unit).

The second issue is risk factors. In previous studies, obesity, overweight, being black, having chronic hypertension, and having had an early and severe PE episode, or more than one PE episode were associated with recurrences [18, 49–53]. We were only able to confirm a role for baseline hypertension and for severe previous PE (indicated by the birth of a baby below the 10th centile) in our series. However, the high prevalence of overweight and obesity and of early delivery in the previous pregnancy may have offset differences [54]. Furthermore, we should keep in mind the limitation of the relatively low number of cases, which may have been insufficient to highlight smaller but relevant differences in outcomes.

In this context, in the setting of a relatively high prevalence of initial CKD stages, diagnosed after the episode of PE that led to starting follow-up in our unit, the diagnosis of which would most probably have been missed in the absence of a dedicated diagnostic pathway, the presence of CKD was not associated with a higher risk of recurrence of PE. Of note, all cases were in early CKD stage, without kidney failure, and were often diagnosed by imaging (Supplementary Table 1). In fact, due to the changes occurring during pregnancy, eGFR is not the most reliable marker to diagnose CKD during gestation [55]. While CKD remains an acknowledged risk factor for PE, our data suggest that the presence of a previous PE may be more important in determining the recurrence rate than early CKD itself.

As a third point, the longitudinal analysis of biochemical data suggests that the expected reduction in serum creatinine during pregnancy is seldom observed, suggesting that the renal response to pregnancy may be blunted in women having experienced an episode of PE; the trajectories are similar in patients with and without complications (Supplementary Fig. 1). Whether this lack of mid-term hyperfiltration is the cause or the effect of the previous PE episode remains to be established. The same pattern holds true for uric acid (Supplementary Fig. 2). Conversely, the trajectory of the Sflt1/PlGF ratio may have potential interest in the longitudinal follow-up (Fig. 4), a novelty associated with our study.

The last issue is that >60% of the recurrences, in this cohort characterized by high prevalence of pre-term PE and high recurrence rate, occurred after 37 GW and 48% after 38 GW (Fig. 3). A history of PE is not considered an indication for favoring early-term delivery, unlike other conditions, such as pre-existing or poorly controlled diabetes. While inducing elective early-term delivery may increase the incidence of cesarean sections, it could reduce the long-term kidney damage extensively reported in women with recurrent PE and HDP episodes. Further larger studies are needed to test this hypothesis.

As previously mentioned, the limits of our study are the relatively small number of patients included, potentially too few to allow relevant clinical differences to reach statistical significance, and the single-center setting. The negative selection of the patients, with a high incidence of preterm delivery in the previous pregnancy, may be both a limit, as this series may be less representative of all PE episodes, and a strength, as it seems to show that women that seek nephrology follow-up encompass a high-risk group needing dedicated commitment.

The lack of a control group not exposed to the intensive follow-up herein described is another limitation, as discussed above. This limitation does not allow us to conclude that the strict follow-up was the main reason for the better pregnancy-related outcomes, and allows us only to describe the results as an association.

Within its limits, our study has the merit of reporting on one of the few experiences in multidisciplinary kidney-oriented follow-up of women after an episode of PE, and the strength of homogeneous follow-up. We report it as a hypothesis generator, and as evidence of the feasibility of multidisciplinary care to improve kidney health and the overall health of women experiencing HDP.

In conclusion, in this cohort of women mainly affected by pre-term PE, and referred for a conjoint nephrology and obstetric follow-up, the recurrence rate of PE was high (>40%). Recurrences were, however, delayed with respect to the previous episode, and mainly occurred at term, thus raising the question of whether a different approach to delivery, once the term of 37 weeks is reached, can help to preserve long-term maternal kidney health. The benefit of a multidisciplinary follow-up in high-risk pregnancy should be further investigated in larger studies comprising women under routine care.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

Conceptualization, G.B.P.; data curation, O.D.M., C.R., L.N., B.M., G.S., A.F., M.T.C.; statistical analysis, O.D.M., A.C., M.S.; writing—original draft preparation, G.B.P., M.T. All the authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was approved on 5 July 2021, revised on 24 June 2024; CPP number 21.05200.210642.

INFORMED CONSENT STATEMENT

All patients signed an informed consent before participating in the study.

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