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Original Article

ORIGINAL ARTICLE

Twenty-four-hour proteinuria levels are associated with adverse pregnancy outcomes among women with CKD

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ABSTRACT

Background. Proteinuria is commonly measured to assess the renal status of chronic kidney disease (CKD) patients before the 20th week of gestation during pregnancy. High levels of proteiuria have been associated with adverse pregnancy outcomes. However, researchers have not clearly determined what baseline proteinuria levels would be associated with adverse pregnancy outcomes. This study aimed to analyse associations between proteinuria levels and adverse pregnancy outcomes among CKD patients treated with or without steroids/immunosuppressive therapy in early pregnancy.

Methods. This retrospective study included the clinical information of 557 pregnant patients with CKD from 1 January 2009 to 31 December 2021. A multivariable logistic regression analysis was conducted to evaluate the risk of adverse pregnancy outcomes across various proteinuria ranges, which were further stratified by whether the patients were receiving steroids/immunosuppressive therapy.

Results. (i) Proteinuria was assessed on 24-h urine collection. The median (quartile) baseline proteinuria levels were 0.83 g (0.20, 1.92) and 0.25 g (0.06, 0.80) in the steroids/immunosuppressive therapy and therapy-free groups, respectively. (ii) CKD patients with adverse pregnancy outcomes had significantly higher proteinuria levels in the first trimester than patients without adverse pregnancy outcomes. (iii) The risk of adverse pregnancy outcomes increased with increasing baseline proteinuria levels ($P < .001$). (iv) In the early-pregnancy steroids/immunosuppressive therapy group, the risk of severe preeclampsia was higher in patients with higher baseline proteinuria levels ($P < .007$) [odds ratio (OR) 30.86 for proteinuria ≥5.00 g/24 h]; in the therapy-free group, the risks of severe preeclampsia, very-low-birth-weight infants, early preterm birth and foetal–neonatal death were higher in patients with higher baseline proteinuria levels (OR 53.16 for proteinuria ≥5.00 g/24 h; OR 37.83 for proteinuria ≥5.00 g/24 h; OR 15.30 for proteinuria ≥5.00 g/24 h; and OR 18.83 for proteinuria ≥5.00 g/24 h, respectively; $P < .001$, $P < .001$, $P < .001$ and $P = .006$, respectively).

Conclusions. As shown in the present study, a baseline 24-h proteinuria level >1.00 g was associated with adverse maternal outcomes. Furthermore, a 24-h proteinuria level >2.00 g increased the incidence of adverse foetal events among CKD patients.

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Keywords: 24-hour proteinuria, adverse pregnancy outcomes, chronic kidney disease, steroids/immunosuppressive therapy in early pregnancy

INTRODUCTION

Chronic kidney disease (CKD) is a heterogeneous disease characterized by changes in kidney morphology, imaging characteristics or function. Approximately 0.10%–4.00% of women of childbearing age suffer from CKD [1]. CKD increases the risk of adverse pregnancy outcomes, while pregnancy itself may exacerbate renal disease progression [2–4].

The measurement of proteinuria levels is commonly used to assess the renal status of CKD patients during pregnancy [5]. The degree of proteinuria has been associated with the progression of underlying kidney disease during pregnancy [3] and adverse pregnancy outcomes [6]. Ideally, better control of baseline proteinuria before conception is beneficial for optimizing pregnancy outcomes. In some patients with CKD, steroids/immunosuppressive therapy may be applied before pregnancy to control disease activity. Compared with patients who discontinue therapy before pregnancy, patients who still continue steroids/immunosuppressive therapy during pregnancy may have more severe kidney disease, and thus the risk of adverse pregnancy outcomes may be higher even if they have the same proteinuria levels.

In 2013, proteinuria was deemed to be an adequate but unnecessary clinical manifestation for the diagnosis of preeclampsia [7]. Although the role of proteinuria level in the development of adverse pregnancy outcomes in patients with preeclampsia is controversial, the baseline proteinuria levels played an important role in predicting adverse pregnancy outcomes among women with CKD. In pregnant CKD patients, elevated proteinuria levels are independently associated with adverse maternal–foetal outcomes in the short and long terms [6, 8]. Additionally, studies on the relationship between different baseline proteinuria profiles and adverse obstetric outcomes are scant and inconsistent. For women with glomerular disease, immunosuppressive therapy may be recommended depending on the diagnosis and activity of the disease, and these therapies may be continued during pregnancy if necessary. Currently, joint analyses of the effects of proteinuria and steroids/immunosuppressive therapy in the first trimester on the occurrence of adverse pregnancy outcomes among CKD patients have not been conducted.

This study aimed to evaluate adverse pregnancy outcomes among CKD patients with various proteinuria profiles; importantly, we sought to reveal the effect of the interaction between steroids/immunosuppressive therapy in early pregnancy and proteinuria levels on pregnancy outcomes.

MATERIALS AND METHODS

Study design and participants

The medical information of 652 women diagnosed with CKD between January 2009 and December 2021 was collected retrospectively. The inclusion criteria were as follows: (i) pre-existing CKD, (ii) 24-h proteinuria levels recorded before the 20th week of gestation and (iii) gestation that proceeded up to the 12th week with complete maternal and infant records. The exclusion criteria were pregnancies that ended spontaneously or by therapeutic termination of pregnancy in the first trimester or patients with kidney disease diagnosed during pregnancy. Eleven patients underwent abortion due to CKD or for personal reasons, 61 patients were transferred to our hospital in the second or third trimester, 15 patients delivered in other hospitals and 8 patients underwent therapeutic termination of pregnancy in the second trimester. The participants were screened based on the inclusion and exclusion criteria (Fig. 1). A total of 557 women with CKD and their 570 pregnancies with complete pregnancy and childbirth data were enrolled. If one patient had multiple occurrences of pregnancy and childbirth, each pregnancy was regarded as one case.

Ethical approval

The study was undertaken in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Peking University First Hospital [No. 2022 (233)]. The data were anonymous, and the requirement for informed consent was therefore waived.

Data collection

Clinical and pathological data were extracted for all patients at their first visit to our hospital during pregnancy. All patients were followed up every 2–4 weeks per routine clinical practice, and clinical information for every visit was obtained from the medical records.

The following baseline information was collected: age, immunosuppressive therapy (cyclosporine, tacrolimus, prednisone and so on), pathological results of renal biopsy, type of CKD, mean arterial pressure (MAP), body weight, body height, serum creatinine (Scr) and 24-h proteinuria levels. Body mass index (BMI) was calculated as the body weight in kilograms during

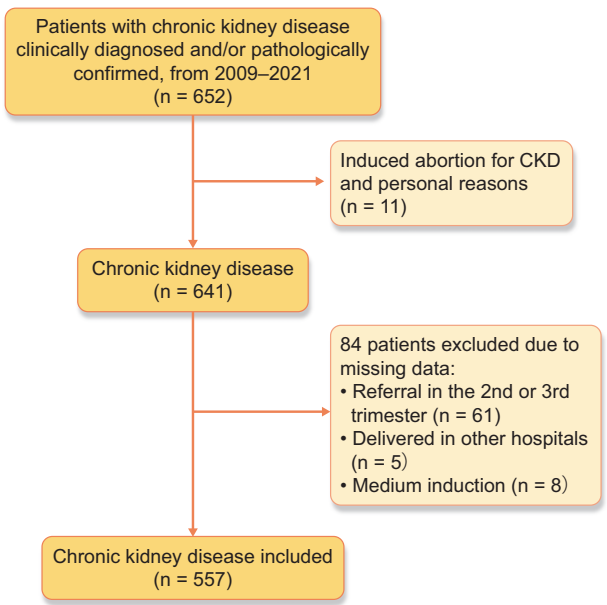

Figure 1: Flow chart of study cohort.

the first exam divided by height in metres squared (kg/m^2). According to age and Scr levels, the estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) equation [9]. For the patients who had undergone renal biopsy, the type of CKD was determined based on the biopsy results; for the other patients, the CKD type was determined based on the clinical diagnosis. The staging of kidney disease was classified based on the preconception eGFR as follows: Stage 1: eGFR ≥90.00 mL/min/1.73 m^2; Stage 2: eGFR 60.00–89.00 mL/min/1.73 m^2; Stage 3: eGFR 30.00–59.00 mL/min/1.73 m^2; Stage 4: eGFR 15.00–29.00 mL/min/1.73 m^2; and Stage 5: eGFR <15.00 mL/min/1.73 m^2 [9].

Pregnancy outcomes

The adverse pregnancy outcomes included severe preeclampsia, early preterm birth, stillbirth, foetal–neonatal death, very-low-birth-weight infants (VLBWIs) and small for gestational age (SGA). The diagnoses of severe preeclampsia in patients enrolled between 2009 and 2013 were reviewed according to the 2013 guidelines.

Definitions

(i) CKD was defined as either kidney damage (an albumin-to-creatinine ratio >30.00 mg/24 h for two of three urine specimens, urine sediment abnormalities, tubular disorders, histologically diagnosed abnormalities, structural abnormalities detected by scanning) or GFR <60.00 mL/min/1.73 m^2 for 3 months defined by the Kidney Disease: Improving Global Outcomes guidelines [9].

(ii) Preterm birth was defined according to the World Health Organization criteria as all births before 37 completed weeks. The diagnostic criterion for early preterm birth was a gestational age at birth of <34 weeks [2, 10, 11].

(iii) The diagnostic criteria for severe preeclampsia in patients with normal blood pressure and no proteinuria were based on the 2013 Hypertension in Pregnancy Guidelines of the American College of Obstetricians and Gynecologists [8]. For women who had proteinuria but no hypertension in early pregnancy, the diagnosis of severe preeclampsia required the presence of thrombocytopenia, a sudden increase in proteinuria (either five times the baseline value or twice the baseline value if the baseline value exceeded 2.00 g/24 h), hypertension accompanied by severe headaches, epigastric pain or a serum aspartate aminotransferase concentration >70.00 U/L. For women who had both hypertension and proteinuria in early pregnancy, the diagnosis of severe preeclampsia required any one of the following criteria: an elevated serum aspartate aminotransferase concentration (>70.00 U/L), thrombocytopenia or worsening hypertension (systolic blood pressure ≥140.00 mmHg with an increase of at least 30.00 mmHg or a diastolic blood pressure ≥90.00 mmHg with an increase of at least 15.00 mmHg) accompanied by severe headaches or epigastric pain [12, 13].

(iv) SGA was defined as a birth weight under the 10th percentile based on gestational age [2, 10, 11].

(v) VLBWIs were defined as neonates with birth weights <1500.00 g [2, 10, 11].

(vi) Stillbirth was defined as the absence of signs of life at or after birth.

(vii) Neonatal death was defined as death of a live-born neonate during the first 7 days after birth.

(viii) Proteinuria groups: according to the median proteinuria level in our study (0.38 g) and the definition of proteinuria during pregnancy (proteinuria ≥0.30 g/24 h), proteinuria was divided into five groups according to the first-trimester quantitative measurements of 24-h proteinuria: Group 1 (non-proteinuria as the control group): proteinuria <0.30 g/24 h; Group 2: 0.30 g/24 h ≤ proteinuria < 1.00 g/24 h; Group 3: 1.00 g/24 h ≤ proteinuria < 2.00 g/24 h; Group 4: 2.00 g/24 h ≤ proteinuria < 5.00 g/24 h; and Group 5: proteinuria ≥5.00 g/24 h. Furthermore, subgrouping was performed according to immunosuppressive therapy in early pregnancy.

Statistical analysis

All statistical analyses were conducted with SPSS version 23.0 (IBM, Chicago, IL, USA) software. Continuous variables are expressed as the mean ± standard deviation or the median and interquartile range, and categorical variables are expressed numerically and as percentages. The mean arterial pressure was evaluated as a dichotomous variable according to the Jorden index. Differences in the means between the groups were assessed using the independent samples *t*-test, analysis of variance (ANOVA) and Kruskal–Wallis *H* test/Wilcoxon's rank-sum test for continuous variables, whereas Pearson's chi-square test or Fisher's exact test was used for categorical variables. The relevant variables that were significantly associated with adverse pregnancy outcomes in the univariable analysis were included in the multivariable models. A multivariable binary logistic regression analysis was conducted to evaluate the relative risk by generating the odds ratios (ORs) and 95% confidence intervals (CIs) for adverse pregnancy outcomes. A two-sided *P*-value <.05 was considered significant. The Bonferroni correction for multiple comparisons was used.

RESULTS

Baseline clinical characteristics

There were 557 CKD patients with 570 pregnancies included in this study, with a median maternal age of 31.00 years (29.00, 35.00). The median quantified 24-h proteinuria levels during early pregnancy were 0.38 g (0.10,1.24), with levels of 0.09 g (0.03, 0.18), 0.59 g (0.42, 0.75), 1.41 g (1.18, 1.60), 2.78 g (2.46, 3.45) and 5.81 g (5.33, 6.71) in Groups 1, 2, 3, 4 and 5, respectively.Twenty-two participants (3.9%) had proteinuria greater than 5.00 g/24 h, and one patient (0.18%) had proteinuria greater than 10.00 g/24 h. We found that 16 patients presented with nephrotic syndrome among patients with proteinuria ≥2.00 g/24 h in the first trimester. One hundred and six (19.03%) patients had chronic hypertension. Ninety-one (16.34%) patients were receiving steroids/immunosuppressive therapy, 28 of whom had chronic hypertension, and the prevalence of severe preeclampsia was 20.88% (19/91). Four hundred and sixty-six patients did not receive steroids/immunosuppressive therapy, 78 of whom had chronic hypertension, and the prevalence of severe preeclampsia was 12.23% (57/466). The baseline clinical information is shown in Tables 1 and 2. The proportion of patients with steroids/immunosuppressant administration was higher in patients with higher baseline proteinuria levels. Furthermore, we found that the women in

Table 1: Baseline characteristics of pregnant women with CKD.

	Total ($n = 557$)	Group 1 ($n = 257$)	Group 2 ($n = 131$)	Group 3 ($n = 91$)	Group 4 ($n = 56$)	Group 5 ($n = 22$)	*P*
Gestational age at baseline (weeks)	7.00 (6.00, 10.00)	7.00 (6.00, 10.00)	7.00 (6.00, 10.00)	8.00 (6.00, 11.00)	8.00 (7.00, 11.00)	7.50 (6.00, 13.25)	.11
Age (years)	31.00 (29.00, 35.00)	31.00 (29.00, 35.00)	31.00 (29.00, 34.00)	32.00 (30.00, 34.00)	32.00 (29.00, 35.00)	31.00 (26.75, 34.00)	.37
BMI (kg/m^2)	22.78 (20.68, 25.26)	22.48 (20.32, 24.64)	22.90 (21.08, 25.34)	23.05 (21.56, 26.67)	23.28 (21.02, 27.21)	23.00 (21.32, 26.68)	.03
Scr (μmol/L)	61.20 (52.80, 75.00)	57.70 (51.00, 66.00)	66.00 (54.00, 81.00)	70.00 (54.00, 84.60)	65.50 (53.00, 93.90)	66.50 (53.85, 133.50)	<.001
eGFR ($mL/min/1.73\ m^2$)	112.00 (88.00, 139.30)	119.00 (99.00, 156.00)	105.21 (80.0 126.00)	98.72 (77.00, 130.00)	106.21 (67.80, 129.18)	99.63 (48.08, 138.01)	<.001
MAP (mmHg)	84.7 (79.00, 93.00)	83.33 (76.67, 88.67)	89.00 (80.00, 96.67)	86.67 (81.67, 93.33)	86.67 (80.42, 94.33)	85.66 (79.67, 98.42)	<.001
Stage							<.001
1 [*n* (%)][a]	401 (71.99)	222 (86.38)	83 (63.36)	52 (57.14)	31 (55.36)	13 (59.09)	
2 [*n* (%)][a]	105 (18.85)	27 (10.51)	37 (28.24)	25 (27.47)	15 (26.79)	1 (4.55)	
3 [*n* (%)][a]	40 (7.18)	8 (3.11)	7 (5.34)	13 (14.29)	8 (14.29)	4 (18.18)	
4 [*n* (%)][a]	9 (1.62)	0 (0.00)	3 (2.29)	1 (1.10)	2 (3.57)	3 (13.64)	
5 [*n* (%)][a]	2 (0.36)	0 (0.00)	1 (0.76)	0 (0.00)	0 (0.00)	1 (4.55)	
Chronic hypertension [*n* (%)][a]	106 (19.03)	37 (14.40)	27 (20.61)	23 (25.27)	12 (21.43)	7 (31.82)	.02
Steroids/immunosuppressive therapy in early pregnancy [*n* (%)][a]	91 (16.34)	27 (10.51)	19 (14.50)	16 (17.58)	19 (33.93)	10 (45.45)	<.001
DM [*n* (%)][a]	6 (1.08)	0 (0.00)	1 (0.76)	3 (3.30)	0 (0.00)	2 (9.09)	.03
SLE [*n* (%)][a]	21 (3.77)	13 (5.06)	4 (3.05)	3 (3.30)	0 (0.00)	1 (4.55)	.38

Statistically significant at $P = .0125$ after the Bonferroni correction for multiple comparisons.

Values are presented as the means ± standard deviations, medians and quartiles or numbers and percentages.

DM, diabetes mellitus; SLE, systemic lupus erythematosus.

[a]Ratio of CKD patients in the corresponding group.

The *P*-values refer to the overall differences observed across the proteinuria groups using ANOVA, Kruskal–Wallis *H* test or χ^2 tests.

Group 1: proteinuria <0.30 g/24 h; Group 2: 0.30 g/24 h ≤ proteinuria < 1.00 g/24 h; Group 3: 1.00 g/24 h ≤ proteinuria < 2.00 g/24 h; Group 4: 2.00 g/24 h ≤ proteinuria < 5.00 g/24 h; and Group 5: proteinuria ≥5.00 g/24 h.

Table 2: Pregnancy outcomes of patients stratified according to the proteinuria level.

	Total ($n = 557$)	Group 1 ($n = 257$)	Group 2 ($n = 131$)	Group 3 ($n = 91$)	Group 4 ($n = 56$)	Group 5 ($n = 22$)	P	P^a	P^b	P^c	P^d
Twin pregnancy [*n* (%)][a]	13 (2.33)	6 (2.33)	4 (3.05)	2 (2.20)	0 (0.00)	1 (4.55)	.67	1.00	1.00	.60	.44
Live birth [*n* (%)][a]	531 (95.33)	251 (97.67)	127 (96.95)	87 (95.60)	50 (89.29)	16 (72.73)	<.001	.34	1.00	.001	<.001
Live-born infants [*n* (%)][b]	544 (95.44)	257 (97.72)	131(97.04)	89 (95.70)	50 (89.29)	17 (73.91)	<.001	.74	.01	.01	<.001
Weeks of pregnancy[c]	38.00 (37.00, 39.00)	38.00 (37.00, 39.00)	38.00 (37.00, 39.00)	37.00 (36.00, 38.00)	36.00 (33.00, 38.00)	30.50 (26.00, 36.00)	<.001	.60	<.001	<.001	<.001
Mean birth weight (g)[c]	3045.00 (2550.00, 3395.00)	3142.50 (2800.00, 3443.75)	3070.00 (2660.00, 3430.00)	2950.00 (2440.00, 3235.00)	2500.00 (2100.00, 3160.00)	1505.00 (800.00, 2447.50)	<.001	1.00	.01	<.001	<.001
Delivery by CS [*n* (%)][c]	328 (61.77)	141 (56.18)	70 (55.12)	63 (72.41)	38 (76.00)	16 (100.00)	.03	.83	.02	.10	.11
HTD in pregnancy [*n* (%)][a]	122 (21.90)	22 (8.56)	42 (32.06)	23 (25.27)	20 (35.71)	15 (68.18)	<.001	<.001	.001	<.001	<.001
GH [*n* (%)][a]	27(4.85)	8 (3.11)	10 (7.63)	4 (4.40)	4 (7.14)	1 (4.55)	.26	.09	.93	.67	1.00
PE [*n* (%)][a]	19 (3.41)	5 (1.95)	9 (6.87)	5 (5.50)	0 (0.00)	0 (0.00)	.04	.03	.17	.59	1.00
Severe preeclampsia [*n* (%)][a]	76 (13.64)	9 (3.50)	23 (17.56)	14 (15.38)	16 (28.57)	14(63.64)	<.001	<.001	<.001	<.001	<.001
Perinatal death [*n* (%)][a]	26 (4.67)	6 (2.33)	4 (3.05)	4 (4.40)	6 (10.71)	6 (27.27)	<0.001	1.00	0.65	0.21	0.002
Preterm birth [*n* (%)][c]	116 (21.85)	31 (12.35)	19 (14.96)	26 (29.89)	27 (54.00)	13(81.25)	<0.001	0.74	0.001	<0.001	<0.001
28–32 weeks [*n* (%)]	23 (4.33)	5 (1.99)	3 (2.36)	5 (5.75)	4 (8.00)	6 (37.50)	<0.001	1.00	0.17	0.32	<0.001
32–34 weeks [*n* (%)]	36 (6.78)	10 (3.98)	5 (3.94)	10 (11.49)	10 (20.00)	1(6.25)	0.002	1.00	0.02	<0.001	0.60
LBWIs [*n* (%)][d]	100 (18.38)	32(12.45)	20 (15.27)	22 (24.72)	19 (38.00)	7 (41.18)	0.002	0.42	0.02	0.001	0.07
VLBWIs [*n* (%)][d]	27 (4.96)	6 (2.33)	4 (3.05)	5 (5.62)	6 (12.00)	6(35.29)	<0.001	1.00	0.17	0.005	<0.001
SGA [*n* (%)][d]	37 (6.80)	13 (5.06)	6 (4.58)	10 (11.24)	6 (12.00)	2(11.76)	0.20	0.67	0.05	0.19	0.76
Data from twin pregnancies											
	Group 1	Group 2	Group 3	Group 4	Group 5						
Twin pregnancy [*n* (%)]	6 (2.33)	4 (3.05)	2 (2.20)	0 (0.00)	1 (4.55)						
Weeks of pregnancy	37.00 (32.25, 37.25)	37.00 (36.00, 37.00)	33.50 (30.00, 37.00)	0 (0.00)	31.00						
Mean birth weight, g	2428.50 (1558.75, 2587.50)	2440.00 (2235.00, 2615.00)	1670.00 (1365.00, 1975.00)	0 (0.00)	1750.00/1770.00 g						
Delivery by CS [*n* (%)]	6 (100.00)	4 (100.00)	2 (100.00)	0 (0.00)	1 (100.00)						
Preterm birth [*n* (%)]	2 (33.33)	1 (25.00)	1 (50.00)	0 (0.00)	1 (100.00)						
Severe preeclampsia [*n* (%)]	1 (16.67)	1 (25.00)	0 (0.00)	0 (0.00)	0 (0.00)						

Statistically significant at $P = .005$ after the Bonferroni correction for multiple comparisons.
Values are presented as the means ± standard deviations, medians and quartiles or numbers and percentages.
HTD, hypertension disease; GH, gestational hypertension; PE, preeclampsia; LBWIs, low-birth-weight infants; CS, Cesarian section.
[a]Ratio of CKD patients in the corresponding group
[b]Ratio of foetuses in the corresponding group
[c]Data were available only for patients with live births.
[d]Data were available only for live-born infants.
The *P*-values refer to the overall differences observed across the proteinuria groups using ANOVA, Kruskal–Wallis *H* test or χ^2 tests.
[α]Group 2 compared with Group 1
[β]Group 3 compared with Group 1
[γ]Group 4 compared with Group 1
[δ]Group 5 compared with Group 1
Group 1: proteinuria <0.30 g/24 h; Group 2: 0.30 g/24 h ≤ proteinuria < 1.00 g/24 h; Group 3: 1.00 g/24 h ≤ proteinuria < 2.00 g/24 h; Group 4: 2.00 g/24 h ≤ proteinuria < 5.00 g/24 h; and Group 5: proteinuria ≥5.00 g/24 h.

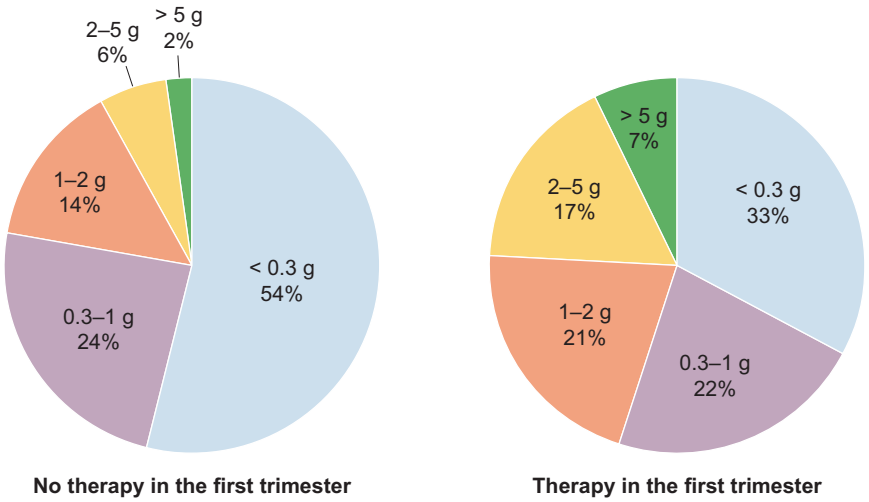

Figure 2: The proportion of proteinuria values in women with steroids/immunosuppressive therapies in early pregnancy categories.

the steroids/immunosuppressive therapy group had significantly higher levels of proteinuria than those in the no steroids/immunosuppressive therapy group [therapy group vs therapy-free in early pregnancy group: 0.83 g (0.20, 1.92) vs 0.25 g (0.06, 0.80); $P < .001$]. The distribution of proteinuria levels in the first trimester based on steroids/immunosuppressive therapy in early pregnancy is shown in Fig. 2.

Proteinuria levels and adverse pregnancy outcomes

Among the pregnant women with CKD, the median gestational age at birth was 38.00 weeks, and the median neonatal birth weight was 3045.00 g. The perinatal mortality rate was 1.40% (8/570). Moreover, the frequencies of live birth were lower in patients with higher baseline proteinuria ($P < .001$), and the incidences of severe preeclampsia, preterm birth, VLBWIs and perinatal deaths were significantly higher among the pregnant women with higher proteinuria levels ($P < .001$). The aetiology of CKD is reported in Supplementary data 4. The foetal outcomes of patients in Group 1 and Group 2 were not significantly different. In addition, the incidences of foetal and neonatal mortality and preterm birth (32–34 weeks) were significantly higher for patients in Group 5 than for patients in Group 1 ($P = .002$ and $P < .001$), and the VLBWIs rate was significantly higher in Group 4 than in Group 1 ($P = .005$). However, the incidence of severe preeclampsia was significantly higher in Group 2 than in Group 1 ($P < .01$). The pregnancy outcomes are shown in Table 2 for the overall cohort and were stratified according to various proteinuria levels.

Univariable and multivariable predictive models of adverse pregnancy outcomes

Univariable logistic regression was conducted to assess the relationship between each of the risk variables and adverse maternal outcomes, which revealed that proteinuria levels ($P < .001$), MAP (OR 3.07, 95% CI 1.83–5.15, $P < .001$), immunosuppressive therapy in early pregnancy (OR 1.89, 95% CI 1.06–3.37, $P = .03$), CKD stage ($P = .001$) and Scr levels (OR 1.40, 95% CI 1.14–1.72, $P = .002$) were related to severe preeclampsia. Relevant variables those $P < .05$ in the univariable analysis and well-recognized risk factors, such as age and BMI, even if not statistically significant in the univariate analysis, were included in the multivariable models. Multivariable analysis showed that the MAP (OR 2.78, 95% CI 1.58–4.90, $P < .001$) and proteinuria levels ($P < .001$) were risk factors for severe preeclampsia, as shown in Table 3. Furthermore, the MAP and proteinuria levels were associated with adverse pregnancy outcomes, including severe preeclampsia, early preterm birth, foetal–neonatal death and VLBWIs, as shown in Table 4. Interestingly, in multivariate analysis, immunosuppressive therapy was not associated with severe preeclampsia and foetal–neonatal death, but only with early preterm birth and VLBWIs. The univariable and multivariable logistic regression analyses of the factors at baseline influencing early preterm birth, VLBWIs and foetal–neonatal deaths are shown in Supplementary data 1–3. The risk of adverse pregnancy outcomes was higher in patients with higher baseline proteinuria levels, as shown in Fig. 3.

In the early-pregnancy steroids/immunosuppressive therapy group, the risk of severe preeclampsia was higher in patients with higher baseline proteinuria levels ($P < .007$) (OR 30.86 for proteinuria ≥5.00 g/24 h); however, in the therapy-free group, the risk of severe preeclampsia, VLBWIs, early preterm birth and foetal–neonatal death was higher in patients with higher baseline proteinuria levels (OR 53.16 for proteinuria ≥5.00 g/24 h; OR 37.83 for proteinuria ≥5.00 g/24 h; OR 15.30 for proteinuria ≥5.00 g/24 h; OR 18.83 for proteinuria ≥5.00 g/24 h; $P < .001$, $P < .001$, $P < .001$ and $P = .006$, respectively). Models were adjusted for maternal age, BMI, Scr, MAP and CKD stage to estimate the ORs for the associations between proteinuria levels and adverse pregnancy outcomes described above.

DISCUSSION

This study was the first to jointly analyse the effects of proteinuria and steroids/immunosuppressive therapy in the first trimester on the occurrence of adverse pregnancy outcomes among CKD patients, for which the sample size was large.

There are several methods to assess proteinuria levels, but since the levels of proteinuria fluctuate substantially over a 24-h period due to circadian changes in urinary albumin excretion, the most accurate measurement of proteinuria levels

Table 3: Univariable and multivariable logistic regression analyses of baseline factors influencing severe preeclampsia.

	Univariable			Multivariable		
Baseline characteristics	OR	95% CI	*P*	OR	95% CI	*P*
Age (per 1 standard deviation)	0.64	0.28–1.46	.29	0.56	0.22–1.43	.49
BMI (per 1 standard deviation)	1.25	0.99–1.56	.06	1.13	0.87–1.46	.48
CKD stage			.001			.14
Stage 1–2	1.00	Reference				
Stage 3–5	3.23	1.67–6.28	.001	2.07	0.73–5.83	.14
Proteinuria			<.001			<.001
Group 1	1.00	Reference				
Group 2	5.87	2.63–13.10	<.001	4.90	2.17–11.05	<.001
Group 3	5.01	2.09–12.03	<.001	4.41	1.82–10.69	.001
Group 4	11.02	4.56–26.64	<.001	9.90	4.05–24.23	<.001
Group 5	48.22	16.15–144.01	<.001	48.43	15.80–148.47	<.001
MAP			<.001			<.001
<86.5 mmHg	1.00	Reference				
≥86.5 mmHg	3.07	1.83–5.15	<.001	2.78	1.58–4.90	<.001
Steroids/immunosuppressive therapy in early pregnancy (yes or no)	1.89	1.06–3.37	.03	1.03	0.53–2.03	.78
Scr (per 1 standard deviation)	1.40	1.14–1.72	.002	0.95	0.71–1.28	.41

Group 1: proteinuria <0.30 g/24 h; Group 2: 0.30 g/24 h ≤ proteinuria < 1.00 g/24 h; Group 3: 1.00 g/24 h ≤ proteinuria < 2.00 g/24 h; Group 4: 2.00 g/24 h ≤ proteinuria < 5.00 g/24 h; and Group 5: proteinuria ≥5.00 g/24 h.

Table 4: Univariable and multivariable logistic regression analyses of baseline factors influencing adverse pregnancy outcomes.

	Univariable			Multivariable		
Baseline characteristics	OR	95% CI	*P*	OR	95% CI	*P*
Age (per 1 standard deviation)	0.97	0.92–1.02	.33	0.66	0.29–1.51	.32
BMI (per 1 standard deviation)	1.03	0.97–1.08	.37	0.97	0.77–1.23	.58
CKD stage			<.001			.09
Stage 1	1.00	Reference				
Stage 2	1.51	0.87–2.60	.14	0.99	0.51–1.93	.98
Stage 3	4.65	2.35–9.19	<.001	1.46	0.46–4.68	.52
Stage 4	45.47	5.59–370.13	<.001	2.99	1.49–60.16	.47
Stage 5	5.68	0.35–92.10	.22	0.02	0.001–4.85	.16
Proteinuria			<.001			<.001
Group 1	1.00	Reference				
Group 2	3.20	1.74–5.87	<.001	2.29	1.20–4.36	.01
Group 3	3.17	1.62–6.17	.001	2.27	1.11–4.63	.02
Group 4	7.27	3.62–14.61	<.001	5.22	2.46–11.07	<.001
Group 5	38.21	12.82–113.93	<.001	28.75	8.70–95.02	<.001
MAP			<.001			.002
<86.5 mmHg	1.00	Reference				
≥86.5 mmHg	2.52	1.64–3.89	<.001	2.19	1.34–3.59	.002
Steroids/immunosuppressive therapy in early pregnancy (yes or no)	2.26	1.37–3.73	.001	1.19	0.65–2.19	.58
Scr (per 1 standard deviation)	1.02	1.01–1.02	<.001	1.51	0.92–2.49	.10

Group 1: proteinuria <0.30 g/24 h; Group 2: 0.30 g/24 h ≤ proteinuria < 1.00 g/24 h; Group 3: 1.00 g/24 h ≤ proteinuria < 2.00 g/24 h; Group 4: 2.00 g/24 h ≤ proteinuria < 5.00 g/24 h; and Group 5: proteinuria ≥5.00 g/24 h.

remains collecting 24-h urine [14]. The more convenient methods used in practice include urinary dipstick tests or the urine protein/creatinine ratio (UPCR) measurement in a spot urine sample, which has been routinely used in nonpregnant women. However, the UPCR is not yet a reliable indicator of pathological proteinuria during pregnancy, as proteinuria is elevated (>0.30) in one-third of uncomplicated term pregnancies, increases during pregnancy and reaches its highest levels in the postpartum period [15]. In pregnancy, the UPCR matches well with 24-h proteinuria levels when proteinuria was <1.00 g but does not match well when proteinuria was >1.00 g [16, 17]. Thus, the 24-h urine test remains the 'gold standard' for evaluating proteinuria in pregnant women. Our Department of Obstetrics has been continuing this practice with the goal of improving the detection accuracy of proteinuria levels. Therefore, in this study, baseline proteinuria levels were determined by collecting 24-h urine samples. We informed the patients of the detailed urine collection procedure, which ensured the accuracy of the urine collection.

The threshold for the diagnosis of gestational proteinuria is widely known to be greater than 0.30 g/24 h [7]. The incidence

SPE	OR	95% CI	P
Group 1	1.00		
Group 2	4.90	(2.17-11.05)	<0.001
Group 3	4.41	(1.82-10.69)	0.001
Group 4	9.90	(4.05-24.23)	<0.001
Group 5	48.43	(15.80-148.47)	<0.001

VLBWI	OR	95% CI	P
Group 1	1.00		
Group 2	0.72	(0.16-3.34)	0.68
Group 3	2.11	(0.58-7.69)	0.26
Group 4	3.40	(0.93-12.50)	0.06
Group 5	12.44	(3.25-47.71)	<0.001

early preterm	OR	95% CI	P
Group 1	1.00		
Group 2	1.02	(0.41-2.50)	0.97
Group 3	1.86	(0.79-4.40)	0.16
Group 4	3.60	(1.50-8.62)	0. 004
Group 5	5.71	(1.84-17.76)	0. 003

perinatal death	OR	95% CI	P
Group 1	1.00		
Group 2	1.00	(0.17-5.86)	0.99
Group 3	1.48	(0.26-8.58)	0.66
Group 4	4.15	(0.85-20.32)	0.08
Group 5	14.99	(2.73-82.17)	0.002

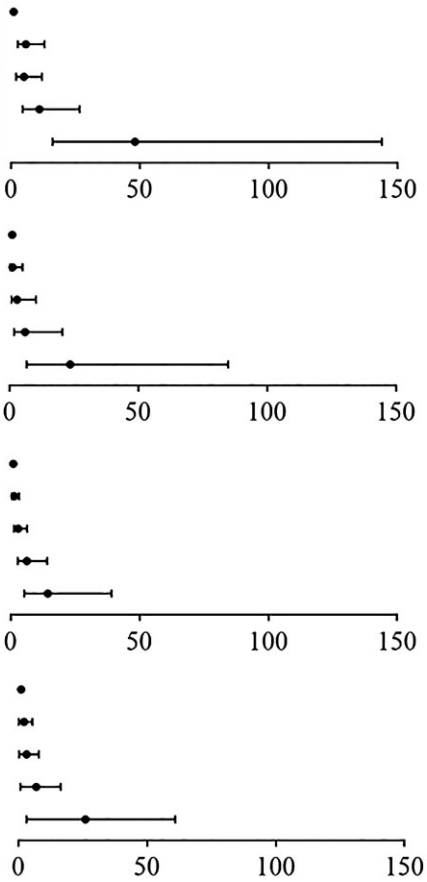

Figure 3: Effects of proteinuria values on severe preeclampsia, very low birth weight infants, early preterm and perinatal death.

of preeclampsia can reach 2%–8% according to this cut-off value [18, 19]. Nevertheless, this cut-off value was established based on several small studies [20–23], in which the level of evidence is not high or is controversial, and it is not applicable to patients with CKD. Indeed, the purpose of proteinuria assessment in the diagnosis of preeclampsia is different from that used to predict the pregnancy outcomes among CKD patients in early pregnancy. Several studies have shown that proteinuria levels are not associated with adverse maternal or perinatal outcomes in patients with preeclampsia [24–30], but Li *et al*. reported that a prenatal proteinuria level >3.50 g/day was an independent risk factor for adverse maternal outcomes in patients with gestational hypertension disease [31]. Although the role of proteinuria level in the development of adverse pregnancy outcomes in patients with preeclampsia is controversial, its effect on adverse pregnancy outcomes in patients with CKD is of significant importance. High baseline proteinuria levels have been shown to be an independent risk factor for adverse pregnancy outcomes, including severe hypertension, preterm birth, CS, SGA and perinatal mortality in women with CKD [6, 8]. However, it is unclear what baseline proteinuria levels would be associated with adverse pregnancy outcomes. Previous studies have shown that the severity of proteinuria affects foetal outcomes among CKD patients: proteinuria levels >1.00 g/day are associated with significantly higher risks of premature birth and VLBWIs even in the absence of preeclampsia [32]. Notably, we found that a 24-h proteinuria level >1.00 g was associated with adverse maternal outcomes including severe preeclampsia and early preterm birth, while a 24-h proteinuria level >2.00 g had significant association for adverse foetal events including VLBWIs and foetal–neonatal death. In particular, a 24-h proteinuria level >5.00 g was a high-risk factor for foetal–neonatal death.

Our study showed that the risk of severe preeclampsia and early preterm birth was significantly elevated in the therapy-free group when 24-h proteinuria levels exceeded 2.00 g. Furthermore, a 24-h proteinuria level >5.00 g was associated with adverse foetal events including VLBWIs and foetal–neonatal death. However, among CKD patients treated with steroids/immunosuppressive therapy during early pregnancy, the risk of severe preeclampsia increased significantly when proteinuria levels exceeded 1.00 g and the risk of perinatal death was significantly increased among patients without steroids/immunosuppressive therapy during the first trimester. Notably, the sample size of our study may still have been insufficient for some of the subgroups. In this study, significantly higher proteinuria levels were observed in the steroids/immunosuppressive therapy group than in the therapy-free group. This indicates that patients with CKD who received steroids/immunosuppressive therapy in the first trimester had a more severe underlying disease. Most of these patients planned to become pregnant after their proteinuria was controlled within an acceptable range, but their basal proteinuria levels were still higher than those of the patients who did not receive steroids/immunosuppressive therapy. We all know that better control of baseline proteinuria in CKD patients would significantly improve pregnancy outcomes, but standard

antiproteinuric treatments (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) are limited during pregnancy due to their teratogenic effects [33]. For some CKD patients, steroids/immunosuppressive therapy was critical for controlling disease activity, which may indirectly affect proteinuria levels. Based on the results of our study and other studies, exploring the link between steroids/immunosuppressive therapy and foetal outcomes may be a future direction of research and should be evaluated by more rigorously designed studies.

There were some limitations of this study. First, this was a retrospective study, which is inevitably affected by sample selection bias. For example, most patients enrolled in this study presented with early-stage CKD, and thus a prospective cohort study is needed for further validation. Second, this study did not analyse the effects of different types of kidney disease on pregnancy outcomes. Third, the assessment of renal function with the MDRD equation has not been validated in pregnant women [34].

CONCLUSIONS

In summary, we found that a baseline 24-h proteinuria level exceeding 1.00 g was associated with adverse maternal outcomes. Furthermore, a 24-h proteinuria level >2.00 g increased the incidence of adverse foetal events among CKD patients.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

Data curation: Z.L., Y.H. and S.C.; funding acquisition: Y.H.; investigation: Z.L. and Y.H.; methodology: Z.L. and Y.H.; resources: Y.H., Y.T. and J.L.; and supervision: J.L., Q.C. and M.Z. All the authors have read the manuscript and approved this submission.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest. This manuscript has not been published in whole nor is it being considered for publication elsewhere.

(See related article by Kervella and Torreggiani. Baseline proteinuria level and adverse outcomes in pregnant women with chronic kidney disease: new evidence and a note of caution. *Clin Kidney J* (2023) 16: 1550–1552.)

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