Any reduction in maternal kidney mass makes a difference during pregnancy in gestational and fetal outcome

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Little is known about the effect tubulointerstitial nephropathies have in modulating maternal-fetal outcomes in pregnancy. Therefore, we analyzed the main outcomes of pregnancy in these women to gain a better understanding of the role of a reduction in maternal kidney mass. From the Torino Cagliari Observational Study (TOCOS) cohort, we selected 529 patients with a diagnosis of tubulointerstitial disease and focused on 421 patients with chronic kidney disease (CKD) stage 1, without hypertension but with proteinuria less than 0.5 g/day at referral. From a cohort of 2969 singleton deliveries from low-risk pregnancies followed in the same settings we selected a propensity score matched control cohort of 842 pregnancies match 2:1 for age, parity, body mass index, ethnicity, and origin. Time to delivery was significantly shorter in the study cohort 38.0 (Quartile 1-Quartile 3: 37.0-39.0) versus 39.0 (Q1-Q3 38.0-40.0) weeks, with respect to controls. Incidence of delivery of less than 37 gestational weeks significantly increased from controls (7.4%) to women with previous acute pyelonephritis (10.8%), other tubulointerstitial diseases (9.7%) and was the highest in patients with a single kidney (31.1%). Similarly, neonatal birthweight significantly and progressively decreased from controls (3260 g [Q1-Q3: 2980-3530]), previous acute pyelonephritis (3090 g [Q1-Q3: 2868-3405], other tubulointerstitial diseases (3110 g [Q1-Q3: 2840-3417]), and to solitary kidney (2910 g [Q1-Q3: 2480-3240]). Risk of developing preeclampsia was significantly higher in the CKD cohort (3.6% vs 1.7% in low-risk controls). Thus, even a small reduction in functional kidney mass, such as a pyelonephritic scar, is associated with a shorter duration of pregnancy and an increased risk of preterm delivery. The risk is proportional to the extent of parenchymal reduction and is highest in cases with a solitary kidney.

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Lay Summary

Chronic kidney disease (CKD) is a risk factor for unfavorable pregnancy outcomes. To get more insights into the role of a reduction in the kidney tissue on pregnancy outcomes, we selected a large cohort of pregnant patients with stage 1 CKD with tubulointerstitial nephropathies, without hypertension or proteinuria (421 cases), and compared it with 842 low-risk pregnancies without CKD. We found that the risk of preterm delivery and giving birth to small babies constantly increased proportionally to the amount of kidney tissue lost, from a simple kidney scar to a solitary kidney (i.e., the loss of 50% of renal mass). The risk of delivery of <37 gestational weeks increased from controls (7.4%) to previous acute pyelonephritis (10.8%) and other tubulointerstitial diseases (9.7%) and was the highest in patients with a single kidney (31.1%). Likewise, the risk of developing preeclampsia was significantly higher in the CKD cohort (3.6% vs. 1.7% in low-risk controls; $P = 0.034$). Our findings suggest that the threshold of kidney damage that has a significant role in shortening pregnancy duration, potentially leading to adverse pregnancy outcomes, is very low and highlights the importance of being particularly attentive to all patients with CKD in pregnancy.

Pregnancy is a unique condition from an immunologic standpoint and in terms of hemodynamic state. A combination of physiological mechanisms is put in place in response to the new needs of the woman who must enable the fetus to develop. A reduction in blood pressure and

an increase in cardiac output, plasma volume, renal plasma flow, and glomerular filtration rate are required for a physiological pregnancy.[1] These modifications are supported by pre- and postglomerular arteriolar vasodilation.[1] Despite the expansion of plasma volume, tubuloglomerular feedback is not suppressed, and the other regulators of blood volume are not activated, almost as if the regulatory system recognized the increased plasma volume as normal.[1]

Any renal alteration is associated with adverse maternal-fetal outcomes.[2–5] In this regard, studies on pregnancy in women with kidney disease led to the conclusion that the reduction in the kidney function, or the presence of proteinuria, and hypertension are independent risk factors for preterm birth, preeclampsia (PE), hypertensive pregnancy disorders, and delivery of a small for gestational age (SGA) baby; the risks are proportional to the severity of the alterations.[4–6]

Regardless of the presence of hypertension, proteinuria, and kidney function impairment, a history of kidney damage (as in the case of patients with kidney stones or with previous acute renal injury) or a "healthy" reduction in the renal parenchyma (as in kidney donor patients) is associated with adverse maternal-fetal outcomes.[3,5,7–14]

Although these concepts are acknowledged, the fine-tuning of the risks by type of disease is less known. More data are available on glomerulonephritis than on other kidney diseases, in particular in their early stages. The range of tubulointerstitial kidney disease, congenital anomalies of the kidney and the urinary tract, previous acute pyelonephritis (APN), and solitary kidney has been little studied.[10,12–16] An analysis of these diseases can highlight the effect of kidney damage without active disease (as in the case of previous APN or solitary kidney), focusing on cases with blood pressure, renal function, and proteinuria in the normal range.

With this aim, we analyzed the data on tubulointerstitial kidney diseases from a large observational prospective cohort, the TOCOS cohort (an acronym derived from the Torino Cagliari Observational Study), focusing, in particular, on the cases with normal kidney function, no or low-grade proteinuria (<0.5 g/d), and normal blood pressure levels.

METHODS

Setting of study

This study was conducted in 2 Italian settings, the Maternal-Fetal Medicine Unit of the Sant'Anna Hospital in Turin, northern Italy, and the Azienda di Rilievo Nazionale ed Alta Specializzazione G. Brotzu in Cagliari, Sardinia. Both teams include nephrologists and obstetricians.

The Turin Metropolitan Area has approximately 1,500,000 inhabitants. There are overall 7 nephrology units in the city, 7 nephrology units in the surrounding areas, and 6 departments of obstetrics. In the largest maternity hospital (Sant'Anna), there are approximately 6700 deliveries per year. The outpatient unit for kidney diseases in pregnancy was established in 2000 in a maternal-fetal unit dedicated to the care of high-risk pregnancies. Patients are referred to Sant'Anna's obstetric-nephrology team by regional nephrology, urology, and obstetrics units and by family physicians.

Cagliari and its surroundings have approximately 560,000 inhabitants, 1 nephrology department, and 3 obstetrics departments; the Brotzu hospital is the largest in the Sardinia region. A joint nephrology-obstetrics outpatient service has been operating in the nephrology department since 1989. The hospital's nephrology and obstetrics departments (800–1000 deliveries per year) are the main source of referral, followed by other obstetrics and outpatient units, family physicians, and other regional nephrology centers.

Definitions

Chronic kidney disease (CKD) was classified according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) classification and stratification.[17]

Because in many cases there were no prepregnancy data on patients, estimated glomerular filtration rate calculation was based on data at the first checkup in pregnancy; the calculation was performed using the Chronic Kidney Disease Epidemiology Collaboration formula.[18]

A patient was considered hypertensive in the presence of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or if she was on chronic antihypertensive therapy before pregnancy. Patients on antihypertensive therapy before conception were considered "hypertensive" even if antihypertensive treatment was discontinued during pregnancy.

PE was defined according to the American College of Obstetricians and Gynecologists guidelines.[19]

Because the definition of "superimposed PE" (PE superimposed on hypertension or proteinuria already present at baseline) is not unequivocal, we did not use it in this study, and we limited the definition of PE to previously normotensive patients without proteinuria.

Babies below the 5th and 10th centiles, following INTERGROWTH curves, were defined as SGA.[20,21]

Parity was conventionally defined as "the state or fact of having borne offspring" or "the number of children previously borne." Because, by the discussed criteria, all cases included in the analysis had delivered, parity was dichotomized as primiparous versus multiparous.

Preterm birth was defined as a live birth that occurs before 37 completed weeks of pregnancy, early preterm was considered before 34 completed gestational weeks, and very early preterm delivery before 28 gestational weeks.[22–24]

Obesity, overweight, and underweight were defined on the basis of pregestational body mass index (BMI). The main definitions used in this study are summarized in Supplementary Table S1.

Selection of the patients

This study included patients with a diagnosis of tubulointerstitial kidney disease and with singleton live-born offspring. Consequently, miscarriages and pregnancy terminations were excluded (<24 gestational weeks and/or weight <500 g). Further reasons for exclusion were ongoing pregnancy, multiple pregnancies, patients only evaluated preconception, and patients with recurrent lower urinary tract infections without evidence of present or past kidney involvement. This study is focused on patients with stage 1 CKD with tubulointerstitial nephropathies, without hypertension, whose proteinuria was <0.5 g/d at referral (main study group).

Starting from 1445 referred pregnancies and 918 singleton live births, of 529 patients with a diagnosis of tubulointerstitial diseases, we selected 421 patients with stage 1 CKD, without hypertension and with proteinuria <0.5 g/d, and with complete data on pregnancy

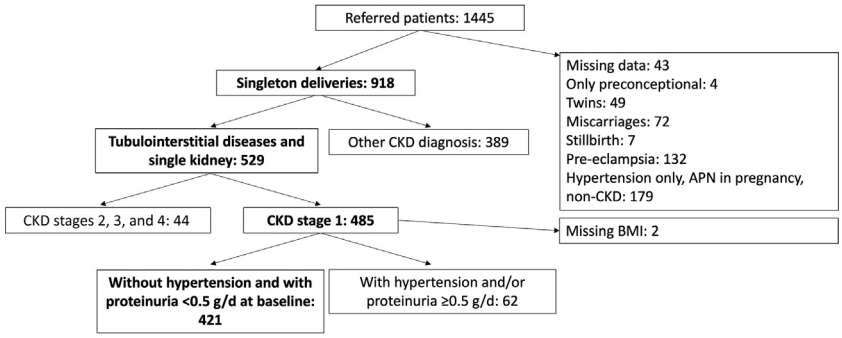

Figure 1 | Flowchart of the patients included. APN, acute pyelonephritis; BMI, body mass index; CKD, chronic kidney disease.

outcomes, ethnicity, BMI, age, and parity (Figure 1). A separate analysis included further 106 patients with either hypertension or proteinuria in CKD stage 1 or with more advanced CKD stages.

Diagnostic criteria

The definitions of CKD were reviewed by the senior nephrologist, in both settings. Only cases in which the kidney alteration was known or considered to have been present before pregnancy were included.

As for previous pyelonephritis, this series includes patients with documented previous APN, with demonstrated parenchymal involvement occurring before pregnancy, in which there was evidence at imaging, or in the clinical history, of kidney scars, regardless of their size. These definitions were made possible by the local policy of performing renal imaging in all upper urinary tract infections, as described in detail elsewhere.[25] Patients referred for an acute episode of pyelonephritis in pregnancy were not considered in the absence of scars from a previous episode.

Of note, because of the policy of strict controls and timely treatment of urinary tract infections, recurrence of APN was found in only 5 of the cases referred because of previous APN (3 in the matched cohort without hypertension and proteinuria).

The diagnosis of solitary kidney rested on the demonstration of either a single kidney (congenital or acquired) or a reduction to less than 10% of the overall functional contribution at renal scintigraphy of the separate kidney function (either mercaptoacetyltriglycine or dimercaptosuccinic acid).

The diagnosis of other tubulointerstitial diseases included reflux nephropathy, congenital anomalies of the kidney and the urinary tract with separate kidney function not falling into the above definition, kidney stones, nephrocalcinosis, ureteropelvic junction obstruction, and other known interstitial disorders (such as Gitelman syndrome or medullary sponge kidney).

Biochemical data

As we frequently lacked prepregnancy biochemical data on patients, kidney function and proteinuria were considered at referral.

In case of traces of proteinuria at urinalysis (proteinuria on a spot urine sample; alteration of the albuminuria-to-creatininuria or proteinuria-to-creatininuria ratio), proteinuria was quantified on a 24-hour urine collection.

Control group

The control group consisted of women with low-risk pregnancies, defined as pregnancies without any disease or condition likely to affect pregnancy outcomes. The only exceptions were previous thyroid diseases and obesity; the latter was not considered a risk factor in itself.

Participants in the Turin control group were selected from Sant'Anna Hospital's files of patients followed in the obstetrics outpatient unit between 2000 and 2021.

The selection procedure was the same in Cagliari; participants in the control group were women with low-risk pregnancies who were followed up in the obstetrics outpatient unit of the Brotzu Hospital between 2000 and 2021.

To adjust for potential confounders, controls were matched to cases in a 1:2 ratio according to age, parity (dichotomized as primiparous or multiparous), BMI, ethnicity (Caucasian or not), and setting of care (Torino or Cagliari).

Pregnancy and intrapartum care

Clinical policies in the 2 settings of study are similar. They follow the Italian best practices for the care of CKD in pregnancy and the guidelines of the Piemonte region for the prevention and treatment of infectious diseases in pregnancy.[26,27]

The frequency of follow-up was tailored to the patient's needs but, overall, consisted of 1 conjoint obstetrical and nephrological examination with blood and urine tests every 4 to 6 weeks. However, for patients who were stable and did not present further risk factors (such as obesity, low or high maternal age, or a history of a hypertensive disorder of pregnancy or preterm birth), follow-up was alternated with peripheral hospitals or outpatient facilities ("consultori").

In patients at high risk for urinary infections, such as those with previous APN or reflux nephropathy, a urine culture was performed every 1 to 2 weeks. All positive cultures were treated according to the antibiogram. When more than 3 positive urinary cultures were recorded, prophylaxis with 100 mg of nitrofurantoin (1 tablet at bedtime) was considered. If prescribed, treatment with nitrofurantoin usually started in the second trimester of pregnancy and continued until 35 to 36 gestational weeks, after which it was discontinued because of the risk of anemia in the case where the fetus exhibited glucose 6 phosphate dehydrogenase deficiency.[28,29]

At each clinical consultation, weight was recorded, and blood pressure was measured at least twice.

The therapeutic blood pressure goal was ≤130/80 mm Hg; this relatively low target has characterized the policy of the Italian Society of Nephrology with respect to pregnancy since the start of the study, as elsewhere reported.[3,5,26] The drugs of choice were α-methyldopa or nifedipine.[26,30] In case of unsatisfactory response or side effects, β-blockers or doxazosin was employed, further treatment being tailored on a case-by-case basis.[26,30]

Serial measurements of symphysis fundal height were employed to check fetal growth. In addition, ultrasound biometry and Doppler study of the uterine and umbilical arteries were routinely performed.

In singleton pregnancies, the aim was to delay delivery at least until term (≥37 completed gestational weeks); indications for early delivery included severe worsening of maternal and/or fetal conditions up to the 32nd week of gestational age and less severe worsening after 32 weeks. Conditions considered to be a risk to maternal health included PE), HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, poorly controlled hypertension, rapidly increasing nephrotic proteinuria, and increased serum creatinine, alone or in combination.

Indications for cesarean section were unfavorable conditions, both maternal (such as PE) and fetal (such as fetal suffering).

In case of birth weight <1800 g, gestational age <34 weeks, sepsis, or other serious diseases that required continuous monitoring, newborns were hospitalized in the neonatal intensive care unit.

The database

The TOCOS combines the 2 largest Italian cohorts of patients with CKD followed up during pregnancy. Since 2000, both units have prospectively collected data on CKD characteristics and pregnancy outcomes.

The databases were updated and merged for the current analysis on July 31, 2021.

A senior nephrologist and a trained statistician performed the final coherence control. The following data were gathered and/or calculated for patients and controls: center and date of referral and delivery; mother's educational level, age, parity, ethnicity, and BMI; gestational age at delivery, type of delivery, and clinical complications; baby's sex, fetal weight, centile, and Apgar scores; and need for admission to the neonatal intensive care unit and outcome. Data collection for patients with CKD included serum creatinine, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, and CKD stage, defined in accordance with KDIGO guidelines.[17,18] Whenever available, prepregnancy data were also gathered.

Statistical analysis

Statistical analyses were performed using JASP (version 0.16.1; JASP Team, 2022) and RStudio (R Core Team, 2021).

Bipartite propensity score matching through the greedy nearest-neighbor matching algorithm was used to produce a control-matched sample from the overall 2969 available controls, with a 1:2 ratio.[31,32] Matching was performed using the "Matchit" R package version 4.2.0.33.

The ordinary (i.e., bipartite) propensity score was calculated by a logistic regression analysis having as a dependent variable a binary variable codified as follows: group 0 = for the pregnancies used as source population for the control group and group 1 = for the patients with stage 1 CKD, without hypertension and with proteinuria <0.5 g/d at referral. As independent variables, we considered age (as a continuous variable), parity (dichotomized as primiparous or not), BMI, ethnicity (Caucasian or not), and origin (Torino or Cagliari).

After fitting the multiple logistic model, an estimated probability of belonging to group 1 was calculated on individual basis, conditional to the variables introduced into the logistic model. As described by Austin,[31,32] greedy nearest-neighbor matching selects a patient of group 1 and then selects as a matched control patient the patient of group 0 whose propensity score is closest to that of the patient of group 1 (if multiple patients of group 0 are equally close to the subject of group 1, one of the patients of group 0 is selected at random). Given the fact that matched patients have an identical propensity score, the logical consequence is that the 2 matched groups will be similar as for the variables used to calculate the propensity score.[33]

Supplementary Table S2 reports the main baseline data and pregnancy outcomes in all controls and in the matched cohort.

The continuous series were tested for normality using the Shapiro-Wilk test and the homoscedasticity hypotheses between cases and controls with Levene's tests.

According to their distribution, the results were expressed with mean and standard deviation or median and Q1–Q3 intervals. Categories were presented as numbers and percentages.

In the case of normal distribution, 2 groups were compared using the Student t test, whereas analysis of variance was performed to compare 3 groups; otherwise, the Wilcoxon rank-sum test or the Kruskal-Wallis test was preferred. Categorical data were compared using the χ^2 or Fisher exact test according to the size of the subsample involved. The significant P value was set at 0.05 for 2-sided tests.

Multivariable logistic regression analysis, using the backward deletion method with a P threshold of 0.1, was used to explain the following outcomes: cesarean section, preterm delivery (considering the following cut-points: <34 and <37 gestational weeks), SGA baby (<10th centile), and need for the neonatal intensive care unit. The covariates were chosen based on statistical significance in univariable analysis or widely accepted clinical criteria: age (dichotomized at the median, 32 years), parity (dichotomized at primiparous vs. multiparous), BMI before pregnancy (dichotomized at 25 kg/m^2), presence of tubulointerstitial diseases (CKD group). The odds ratio (OR) for preterm delivery was also calculated for each week of gestation with the same method.

Temporal series (i.e., week of delivery) were visually analyzed with the reversed Kaplan-Meier curves, and differences were tested using the log-rank test.

Because we included only live births, we considered only pregnancies that went beyond the term considered as the viability limit, which is classically set at 24 gestational weeks. As a consequence, we are showing Kaplan-Meier curves starting at 24 weeks of gestation. Although some authors now suggest starting observation at 20 or 22 gestational weeks due to the recent extension of the viability zone, considering the time span of our series, we maintained the classical cut-point. However, no difference would have been found with a different selection because no fetal loss occurred between 20 and 24 weeks of gestation. No intrauterine death (after 24 weeks of gestation) and no maternal death were present in our population.

All patients delivered within 42 weeks of gestation.

RESULTS

Baseline data in patients with tubulointerstitial diseases and controls

The 421 pregnancies considered in the main study cohort consisted of 102 pregnancies in patients with previous APN, 258 in patients with "other" tubulointerstitial diseases (27 reflux nephropathies, 10 chronic pyelonephritis, 21 tubular acidosis and other tubulopathies, 111 recurrent kidney stones, 47 hydronephrosis and ureteropelvic junction pathologies, and 42 other malformations), and 61 with a solitary kidney (diagnostic details are available in Supplementary Table S3).

Table 1 | Baseline data in patients with singleton live-born deliveries in CKD stage 1, proteinuria <0.5 g/d, no hypertension, and tubulointerstitial diseases versus controls

Overall data	Matched controls (n = 842)	Nephropathies (all interstitial disease included) (n = 421)	*P* value all cases vs. matched controls	Previous acute pyelonephritis (n = 102)	Other tubulointerstital diseases (n = 258)	Single kidney (n = 61)	*P* value
Baseline data							
Age, yr, median [Q1–Q3]	32.0 [28.0–35.4]	32.0 [28.0–36.0]	0.656	31.0 [27.0–35.0]	31.0 [28.0–35.0]	34.0 [31.0–38.0]	**<0.001**
Parity (primiparous), n (%)	462 (54.9)	236 (56.1)	0.689	62 (60.8)	139 (53.9)	35 (57.4)	0.480
BMI, kg/m^2, median [Q1–Q3]	21.8 [19.9–24.6]	21.7 [19.5–24.6]	0.990	21.7 [19.7–24.7]	21.7 [19.4–24.8]	21.8 [20.3–26.2]	0.230
BMI ⩾25 kg/m^2, n (%)	200 (23.8)	104 (24.7)	0.710	25 (24.5)	62 (24.0)	17 (24.7)	0.821
Ethnicity (non-Caucasian), n (%)	81 (90.4)	37 (8.8)	0.632	11 (10.8)	21 (8.1)	5 (8.2)	0.716
Baseline kidney function data, median [Q1–Q3]							
Serum creatinine	–	0.57 [0.50–0.65]	–	0.58 [0.50–0.64]	0.55 [0.49–0.64]	0.63 [0.54–0.72]	**<0.001**
eGFR CKD-EPI, ml/min per 1.73 m^2	–	123 [117–132]	–	124 [118–132]	126 [118–134]	119 [111–125]	**<0.001**
Proteinuria, g/24 h	–	0.10 [0.05–0.13]	–	0.10 [0.05–0.10]	0.10 [0.06–0.14]	0.10 [0.05–0.14]	0.326
Timing of referral							
Week of referral, median [Q1–Q3]	–	15.0 [9.0–24.0]	–	13.0 [8.0–20.0]	17.0 [10.0–25.0]	13.0 [9.0–21.0]	**0.002**
<12 gestational weeks, n (%)	–	142 (33.7)	–	40 (39.2)	78 (30.2)	24 (39.3)	0.063
12–23 gestational weeks, n (%)	–	169 (40.1)	–	44 (43.1)	100 (38.8)	25 (41.0)	–
⩾24 gestational weeks, n (%)	–	110 (26.1)	–	18 (17.7)	80 (31.0)	12 (19.7)	–

BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.
Bold values indicate statistical significance.

The main baseline data for patients and controls are reported in Table 1.

No significant differences in age, BMI, parity, and ethnicity were found between the group with tubulointerstitial diseases and the matched controls; in the study cohort, women with a solitary kidney had a higher age (34 vs. 31 years) and a higher serum creatinine (0.63 mg/dl vs. 0.58 and 0.55 mg/dl in patients with previous pyelonephritis and other tubulointerstitial diseases) and consequently a lower estimated glomerular filtration rate than patients with previous APN and other interstitial diseases; although statistically significant, the latter difference is within the normal range and of minor clinical relevance (119 ml/min per 1.73 m^2, 124 ml/min per 1.73 m^2, and 126 ml/min per 1.73 m^2, respectively).

Educational level was not systematically gathered, especially in the first period of the database; according to the data available in a subset of patients, no difference was found between cases and controls: compulsory education, up to the eighth grade 33% versus 32% and higher education 67% versus 68%, respectively, in cases (265) and all controls (826), with available information.

Main outcomes in patients with CKD versus controls

When patients with stage 1 CKD with a tubulointerstitial disease, without relevant proteinuria and hypertension, were compared with the matched controls, the crude data differed for most of the outcomes considered, with an overall shorter gestation and lower birth weight in patients with CKD versus matched controls; conversely, no difference in centiles at birth and the prevalence of SGA babies was observed (Table 2). Of note, the incidence of cesarean sections was similar in the matched controls and in the cases (24.8% vs. 29.7%); both were in the usual Italian range (31.2%).[34]

The stratification for the main types of interstitial disease allowed us to identify a progressive increase in the incidence of preterm delivery from controls (7.4%) to previous APN and other interstitial diseases (10.8% and 9.7%), with the highest prevalence found in patients with a solitary kidney (31.1%; Table 2). The same trend, but with a progressive decrease, was found in birth weight (3260 g in controls, 3090 g in women with previous pyelonephritis, 3110 g in those with other interstitial nephropathies, and 2910 g in those with a solitary kidney; Table 2). Delivery of SGA babies (<10th centile) did not differ between patient subgroups (Table 2). The incidence of PE was significantly higher in patients than in matched controls (Table 2: all cases 3.6% vs. matched controls 1.7%; $P = 0.034$).

Multivariable logistic regression analysis

Table 3 reports the results of the multivariable logistic regression analysis considering the main maternal-fetal outcomes in women with interstitial nephropathies compared with the low-risk matched population. The univariable analyses are shown in Supplementary Table S4.

Preterm delivery was significantly associated with the presence of all interstitial nephropathies (OR: 1.891, 95%

Table 2| Main outcomes in patients with singleton live-born deliveries in CKD stage 1, proteinuria <0.5 g/d, no hypertension, and interstitial diseases versus controls

Overall data	Matched controls (n = 842)	Nephropathies (all interstitial disease included) (n = 421)	*P* value all cases vs. matched controls	Previous acute pyelonephritis (n = 102)	Other tubulointerstital diseases (n = 258)	Single kidney (n = 61)	*P* value
Delivery data							
Cesarean section, n (%)	231 (24.8)	125 (29.7)	0.401	35 (34.0)	69 (26.7)	21 (34.4)	0.250
Term, wk, median [Q1–Q3]	39.0 [38.0–40.0]	38.0 [37.0–39.0]	**<0.001**	39.0 [37.0–40.0]	38.5 [37.0–39.0]	38.0 [36.0–39.0]	**0.001**
Term <37 gw, n (%)	62 (7.4)	55 (13.1)	**<0.001**	11 (10.8)	25 (9.7)	19 (31.1)	**<0.001**
Term <34 gw, n (%)	16 (1.9)	10 (2.4)	0.575	2 (2.0)	5 (1.9)	3 (4.9)	0.370
Term <32 gw, n (%)	5 (0.6)	5 (1.2)	0.262	1 (1.0)	3 (1.2)	1 (1.6)	0.432
Term <28 gw, n (%)	0 (0.0)	2 (0.5)	–	0 (0.0)	2 (0.8)	0 (0.0)	0.999
Offspring data							
Weight at delivery, median [Q1–Q3]	3260 [2980–3530]	3080 [2800–3400]	**<0.001**	3090 [2868–3405]	3110 [2840–3417]	2910 [2480–3240]	**0.012**
Weight <2500 g, n (%)	47 (5.6)	50 (11.9)	**<0.001**	10 (9.8)	24 (9.3)	16 (26.2)	**<0.001**
Weight <1500 g, n (%)	8 (1.0)	7 (1.7)	0.270	2 (2.0)	5 (1.9)	0 (0.0)	–
Centile, median [Q1–Q3]	48.6 [25.8–73.3]	48.4 [23.6–70.7]	0.390	46.7 [25.4–67.6]	50.8 [23.7–72.0]	42.6 [21.9–64.2]	0.408
Centile <10, n (%)	78 (9.3)	40 (9.5)	0.891	10 (9.8)	24 (9.3)	6 (9.8)	0.985
Centile <5, n (%)	41 (4.9)	29 (6.9)	0.139	8 (7.8)	18 (7.0)	3 (4.9)	0.772
Hospitalization in NICU, n (%)	29 (3.7)	18 (6.1)	0.084	5 (6.4)	8 (4.6)	5 (10.9)	0.285
Other pregnancy-related outcome							
Preeclampsia, n (%)	14 (1.7)	15 (3.6)	**0.034**	1 (1.0)	11 (4.3)	3 (4.9)	0.263

CKD, chronic kidney disease; gw, gestational week; NICU, neonatal intensive care unit.
Bold values indicate statistical significance.

confidence interval: 1.288–2.775; $P = 0.001$), whereas cesarean section was associated with multiparity (OR: 0.609, 95% confidence interval: 0.468–0.793; $P < 0.001$) and age (OR: 1.380, 95% confidence interval: 1.065–1.790; $P = 0.015$; Table 3). The cesarean section in the 125 patients with CKD (at a median of 38 weeks) was classified as elective in 72% (week of delivery: minimum 36 and maximum 41 weeks) and urgent in 28% (minimum 27 and maximum 41 weeks) of the cases. Previous cesarean section was the main cause of both elective (68 of 90 cases) and urgent cesarean deliveries (31 of 35 cases). The data relative to the different causes of CKD are reported in Supplementary Tables S5–S7. Figure 2 shows the OR for delivery at each gestational week.

Delivery curves

The Kaplan-Meier curves describing time to delivery showed a significant difference between cases and controls. The difference versus the matched controls is significant in all subgroups, with a progressive reduction of gestational time from patients with previous APN to patients with a solitary kidney (Figure 3; Supplementary Figure S1).

Further analyses: other CKD stages and setting of care

Table 4 reports the main data of the 106 patients with either stage 1 CKD and hypertension and/or proteinuria or more advanced CKD stages. As expected, pregnancy duration and complications increased across the CKD stages and in the presence of hypertension and proteinuria, with respect to cases with tubulointerstitial diseases with normal kidney function and without hypertension and proteinuria (Figure 4).

Supplementary Table S8 shows the baseline characteristics of the cases in Turin (389 patients) and Cagliari (32 patients); patients in Cagliari were older and had a higher serum creatinine (0.7 vs. 0.6), a statistically significant difference but probably of limited clinical value.

There were more cesarean sections in Cagliari, as well as a higher incidence of preterm delivery (Supplementary Table S9). The analysis of the Kaplan-Meier curves in each setting confirms the overall results, but the difference between cases with previous APN and controls did not reach statistical significance in Cagliari, presumably due to the very low number of cases in this subset (Supplementary Figures S2 and S3).

DISCUSSION

Considering the crucial role of the kidney-placenta crosstalk in pregnancy, it is not surprising that kidney function impairment and immunologic diseases are associated with adverse pregnancy outcomes.[3–5,7,8,35–44] However, why stage 1 kidney disease, even in the absence of proteinuria or hypertension, is associated with adverse pregnancy outcomes is still not clear.[5,9–12,14–16,45–56] Recent insights come from a study on nephrectomized mice, a model that could be seen as resembling kidney donation, suggesting that a drastic reduction in kidney tissue is associated with a lack of adaptive mechanisms, ultimately resulting in placental hypoperfusion.[57] The authors studied the plasma metabolite signatures that intervene in this process, identifying the role of

Table 3 | Mutivariable logistic regression: patients with CKD (stage 1 CKD, proteinuria <0.5 g/d, no hypertension):matched controls (1:2)

Steps	Outcomes	OR	95% CI		*P* value
			Lower	Higher	
	Cesarian section				
1	Age ≥32 yr	**1.394**	**1.074**	**1.810**	**0.012**
	Parity (nonprimiparous)	**0.606**	**0.465**	**0.790**	**<0.001**
	BMI ≥25 kg/m^2	1.095	0.814	1.472	0.549
	CKD	1.186	0.911	1.545	0.205
2	Age ≥32 yr	**1.387**	**1.069**	**1.799**	**0.014**
	Parity (nonprimiparous)	**0.610**	**0.468**	**0.794**	**<0.001**
	CKD	1.186	0.911	1.545	0.205
3	Age ≥32 yr	**1.380**	**1.065**	**1.790**	**0.015**
	Parity (nonprimiparous)	**0.609**	**0.468**	**0.793**	**<0.001**
	Term <34 wk				
1	Age ≥32 yr	**2.539**	**1.085**	**5.943**	**0.032**
	Parity (nonprimiparous)	**0.243**	**0.090**	**0.656**	**0.005**
	BMI ≥25 kg/m^2	1.324	0.547	3.206	0.533
	CKD	1.263	0.565	2.822	0.569
2	Age ≥32 yr	**2.530**	**1.081**	**5.923**	**0.032**
	Parity (nonprimiparous)	**0.242**	**0.090**	**0.654**	**0.005**
	BMI ≥25 kg/m^2	1.323	0.547	3.202	0.535
3	Age ≥32 years	**2.501**	**1.069**	**5.849**	**0.034**
	Parity (nonprimiparous)	**0.246**	**0.091**	**0.663**	**0.006**
	Term <37 wk				
1	Age ≥32 yr	1.182	0.799	1.750	0.403
	Parity (nonprimiparous)	1.075	0.728	1.588	0.717
	BMI ≥25 kg/m^2	1.150	0.743	1.779	0.531
	CKD	**1.903**	**1.296**	**2.794**	**0.001**
2	Age ≥32 yr	1.197	0.814	1.761	0.361
	BMI ≥25 kg/m^2	1.157	0.749	1.788	0.511
	CKD	**1.902**	**1.295**	**2.793**	**0.001**
3	Age ≥32 yr	1.190	0.809	1.749	0.377
	CKD	**1.903**	**1.296**	**2.795**	**0.001**
4	CKD	**1.891**	**1.288**	**2.775**	**0.001**
	Centile <10				
1	Age ≥32 yr	0.888	0.603	1.308	0.549
	Parity (nonprimiparous)	**0.574**	**0.381**	**0.865**	**0.008**
	BMI ≥25 kg/m^2	0.860	0.540	1.368	0.524
	CKD	1.019	0.682	1.523	0.927
2	Age ≥32 yr	0.888	0.603	1.307	0.547
	Parity (nonprimiparous)	**0.574**	**0.381**	**0.865**	**0.008**
	BMI ≥25 kg/m^2	0.860	0.540	1.368	0.524
3	Parity (nonprimiparous)	**0.561**	**0.375**	**0.840**	**0.005**
	BMI ≥25 kg/m^2	0.866	0.545	1.378	0.545
4	Parity (nonprimiparous)	**0.557**	**0.372**	**0.834**	**0.004**
	Hospitalization in NICU				
1	Age ≥32 yr	**1.981**	**1.059**	**3.707**	**0.033**
	Parity (nonprimiparous)	1.555	0.587	2.270	0.061
	BMI ≥25 kg/m^2	0.549	0.293	1.027	0.677
	CKD	1.716	0.935	3.147	0.081
2	Age ≥32 yr	**1.967**	**1.052**	**3.678**	**0.034**
	Parity (nonprimiparous)	0.553	0.296	1.033	0.063
	CKD	1.715	0.935	3.146	0.081

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; NICU, neonatal intensive care unit; OR, odds ratio.
Bold values indicate statistical significance.

the l-tryptophan/l-kynurenine pathway.[57,58] The suggestion that tryptophan supplementation may improve outcomes opens new therapeutic possibilities.[57,58]

The threshold that could support the definition of the minimum clinically significant level of kidney damage to be considered relevant for pregnancy outcomes is unknown.

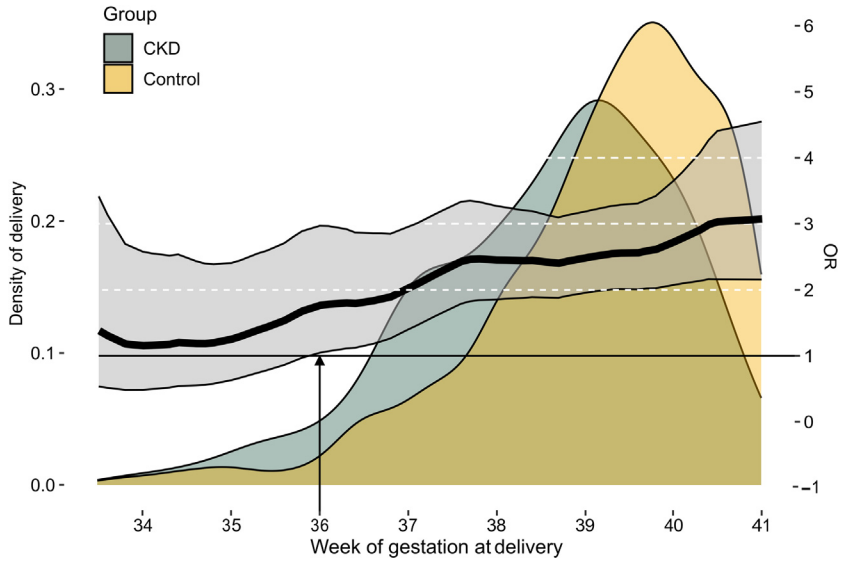

Figure 2 | Density of delivery according to week of delivery (left axis); odds ratio (OR) testing the event delivery in patients with chronic kidney disease (CKD) with respect to matched controls in the different weeks of gestation (right axis), adjusted on the following variables: age (dichotomized at the median, ≥32 years), primiparous (nonprimiparous), and BMI (dichotomized at ≥25 kg/m^2). The vertical arrow indicates the week after which the difference becomes statistically significant.

In this study focused on a cohort of 421 patients with previous APN, other tubulointerstitial diseases, or solitary kidney, in the absence of hypertension and proteinuria <0.5 g/d, we analyzed cases with progressive degrees of reduced renal tissue, ranging from simple kidney scars from previous APN to solitary kidney, followed up in the same settings (Table 1, Figure 1).

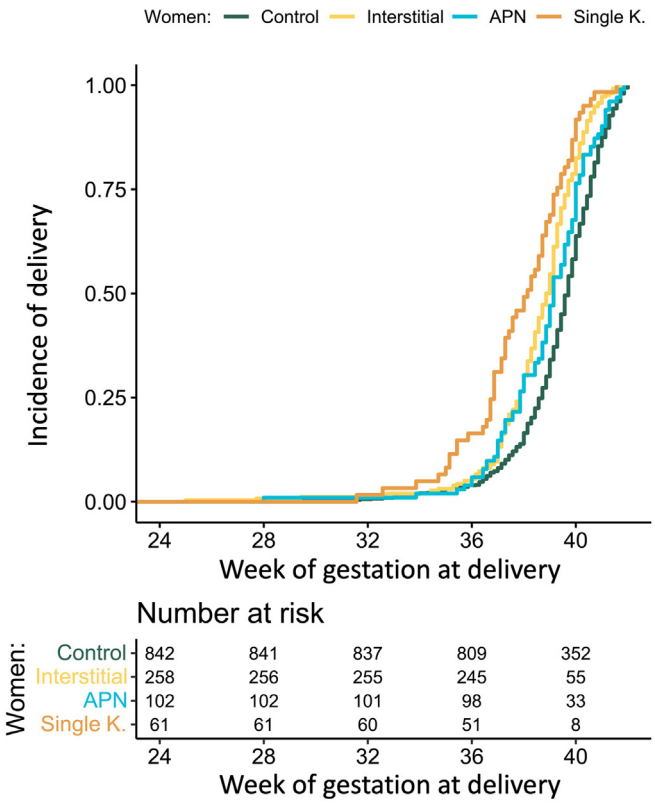

Figure 3 | Kaplan-Meier curves. Time to delivery in the different subsets of patients with chronic kidney disease and controls. APN, previous acute pyelonephritis; Interstitial, other tubulointerstitial diseases; Single K., solitary kidney.

The 2 main findings of our study are the association between an even minimal reduction of the kidney tissue (kidney scar) with pregnancy duration and the observation that the extent of the reduction in kidney parenchyma further modulates pregnancy outcomes. A significant difference in the duration of pregnancy was observed in all cases, including those with "only" a history of previous APN ($P = 0.011$; Figure 3, Table 2), with a progressive increase in risk accompanying the reduction in kidney tissue, reaching a peak in cases of solitary kidney.

In addition, we found that birth weight consistently and progressively decreased from a median of 3260 g in controls to 2910 g in mothers with a solitary kidney (Table 2). These 2 outcomes are clearly associated as, overall, birth weight increases rapidly in the late phases of gestation. Their consistency stresses the importance of even small decreases in pregnancy duration (Table 2). Of note, the incidence of cesarean delivery was similar in the study cohort and in the low-risk controls (29.7% vs. 24.8%) and both are in the usual Italian range (approximately 31%),[34] thus making highly unlikely the explanation that the difference in pregnancy duration is due to a iatrogenic interference (Table 2).

The clinical relevance of these findings is confirmed by an overall increase in the incidence of PE in women with tubulointerstitial nephropathies versus low-risk controls (3.6% vs. 1.7%, notably even lower in APN, and higher, 4.3% and 4.9%, in other tubulointerstitial diseases and single kidney, respectively; Table 2).

Of note, the incidence of PE is very low in this matched-control cohort and is similar to that observed in patients with previous APN (Table 2). Moreover, in the overall control

Table 4 | Baseline data and main outcomes in patients with singleton live-born deliveries in CKD stage 1 with either proteinuria ≥0.5 g/d or hypertension (or both) or CKD stages 2, 3, and 4

Overall data	CKD stage 1, PTO ≥0.5 g/d; hypertension (n = 62)	CKD stages 2, 3, and 4 (n = 44)	*P* value
Baseline data			
Age, yr, median [Q1–Q3]	32.0 [29.0–36.0]	34.0 [28.0-37.0]	0.700
Parity (primiparous), n (%)	33 (53.2)	26 (59.1%)	0.549
BMI, kg/m^2, median [Q1–Q3]	24.3 [20.2–27.0]	22.2 [19.5-23.7]	0.055
BMI ≥25 kg/m^2, n (%)	26 (41.9)	10 (23.3%)	**0.047**
Ethnicity (non-Caucasian), n (%)	5 (8.1)	2 (4.6%)	0.472
Baseline kidney function data, median [Q1–Q3]			
Serum creatinine, μmol/l	0.6 [0.5–0.7]	1.0 [0.9–1.4]	**<0.001**
eGFR CKD-EPI, ml/min per 1.73 m^2	119.7 [112.1–130.9]	66.4 [50.6–82.0]	**<0.001**
Proteinuria, g/24 h	0.56 [0.12–1.17]	0.23 [0.10–0.50]	**0.009**
Timing of referral			
Week of referral, median [Q1-Q3]	17.0 [11.0–27.0]	8.0 [6.0–13.0]	**<0.001**
<12 gestational weeks, n (%)	5 (8.1)	2 (4.6)	0.472
12–23 gestational weeks, n (%)	22 (35.5)	7 (15.9)	**0.026**
≥24 gestational weeks, n (%)	22 (35.5)	5 (11.4)	**0.005**
Delivery data			
Cesarean section, n (%)	32 (51.6)	22 (50.0)	0.870
Term, wk, median [Q1–Q3]	37.9 [37.0–39.3]	37.4 [35.0–37.9]	**0.019**
Term <37 gestational weeks, n (%)	15 (24.2)	20 (45.5)	**0.022**
Term <34 gestational weeks, n (%)	8 (12.9)	8 (18.2)	0.454
Term <32 gestational weeks, n (%)	4 (6.5)	3 (6.8)	0.999
Term <28 gestational weeks, n (%)	1 (1.6)	0 (0.0)	0.999
Offspring data			
Weight at delivery, g, median [Q1–Q3]	2895 [2620–3202]	2675 [1892–2993]	**0.006**
Weight <2500 g, n (%)	13 (21.0)	18 (40.9)	**0.026**
Weight <1500 g, n (%)	4 (6.5)	6 (13.6)	0.212
Centile, median [Q1–Q3]	36.1 [15.7–71.1]	30.7 [7.3–53.3]	**0.026**
Centile <10, n (%)	12 (19.4)	15 (34.1)	0.086
Centile <5, n (%)	7 (11.3)	10 (22.7)	0.114
Hospitalization in NICU, n (%)	7 (16.7)	12 (32.4)	0.102

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; NICU, neonatal intensive care unit; PTO, proteinuria.
Bold values indicate statistical significance.

group, the incidence of PE was 2% (Supplementary Table S2), in line with what was described in other selected low-risk populations (for instance, 3% in the matched low-risk population in the study by Garg *et al.*,[12] 1%–3% predonation in the recent review by Pippias *et al.*[59]).

Overall, our findings support the hypothesis that the threshold for a "significant" kidney tissue reduction with respect to pregnancy outcomes is very low, because even the presence of a kidney scar was found to modulate the duration of pregnancy. In the cohort with stage 1 CKD, preterm delivery is mainly identifiable as "late preterm," and the OR for delivery becomes significant at 36 gestational weeks (Figure 2), in keeping with previous studies addressed at kidney donors or at patients with early-stage CKD.[10–14] In further accordance with these findings, previous studies on women with borderline hypertension or previous acute kidney injury suggest that when the kidney functional reserve is presumably not intact, this can affect pregnancy-related outcomes.[60–63]

A more important reduction in kidney tissue, witnessed by higher CKD stages, was associated with a shorter duration of gestation and a significantly higher risk of preterm delivery, and PE, in keeping with previous reports[5,6] (Tables 3 and 4; Supplementary Tables S5–S7).

Our study has some limitations that may stimulate future research. The first one is the number of cases involved; although, to the best of our knowledge, this is the largest series of women with normal kidney function and tubulointerstitial diseases described in pregnancy, the numbers are still limited and confidence intervals are wide due to the low incidence of each adverse outcome. A more precise assessment will only be possible by gathering additional multicenter series together.

The second limitation is that our series mostly regards White European women, thus calling for similar studies in cohorts of women of Asian or African descent.

The third limitation is that we do not have data on the hyperfiltration response in the study cohort, a response that has been associated with better pregnancy outcomes in patients with more advanced CKD or with kidney transplantation.[61–63] However, in a previous study on the TOCOS cohort, we failed to demonstrate that hyperfiltration (or lack of it), specifically in patients with CKD stage 1, normal blood pressure, and no relevant proteinuria, was associated with adverse pregnancy outcomes, thus suggesting that the presence of a hyperfiltration response may be a better prognostic marker in cases with a baseline reduction in kidney function.[64] Once more, this issue should be the focus of future research.

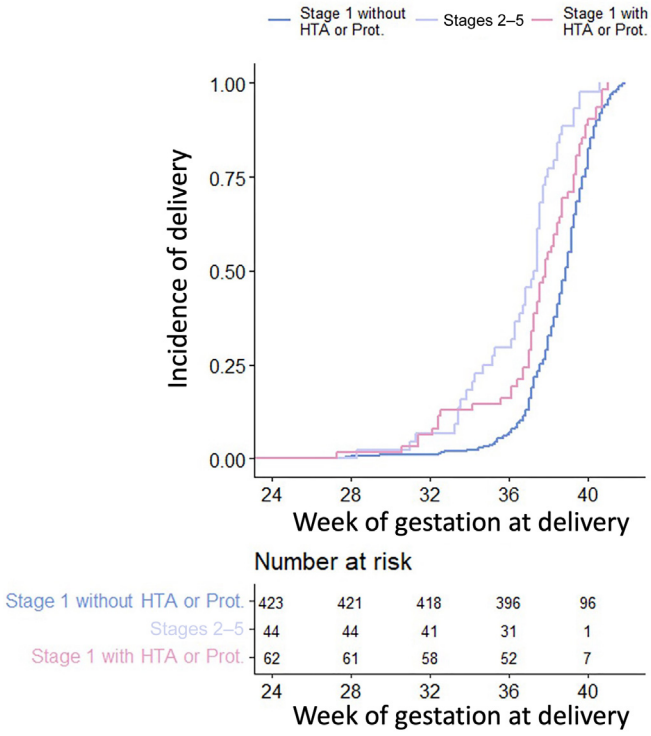

Figure 4| Kaplan-Meier curves. Time to delivery in the whole cohort of patients with tubulointerstial diseases: 106 patients with either chronic kidney disease (CKD) stage 1, hypertension (HTA) and/or proteinuria (Prot.) >0.5 g/d, or more advanced CKD stages, in comparison with the study cohort (CKD stage 1, no hypertension, and proteinuria <0.5 g/d).

Fourth, the study was performed in a setting where, in keeping with a shared policy, all women with previous kidney diseases, including previous APN, are followed with special attention, and for this reason, the risk of APN in pregnancy was low (in our study we found only 5 cases). The risk may be different, and presumably higher, where the control policy is less strict.

The fifth limitation is that we do not have a control of the kidney function in the control group. This problem is shared by all pregnancy cohorts at low risk because serum creatinine is not included in the basic tests to be performed in pregnancy, an issue that has been only recently addressed by some scientific societies, some of which advocate its systematic addition.[65] Likewise, we did not gather data on postdelivery kidney function in this population, which is characterized by normal kidney function, absence of proteinuria, and hypertension before pregnancy. Indeed, most of these patients, out of the pregnancy context, are followed up by their family physicians, and those with previous APN are instructed to seek medical attention in case of urinary tract infections, pregnancy, or onset of hypertension.

Lastly, we did not take into account some potential issues, including smoking and the socioeconomic status. Smoking is a risk factor for adverse pregnancy outcomes in large populations and is associated with an increased risk of being SGA as well as with a paradox reduction of PE.[66] However, because of the low prevalence of smoking in pregnancy in Italy, recently estimated as 6.5%, and because we have no hint to hypothesize that CKD women (more strictly followed and more frequently controlled) smoke more than low-risk women, it is unlikely that adding this information would change the patterns herein described.[67]

Furthermore, interest on socioeconomic status in CKD pregnancy is only relatively recent, and our database was structured more than 20 years ago; the Italian legislation does not allow asking patients information on income, and frequently used socioeconomic status proxies, such as the home address, are not reliable in Italy due to the complex and mixed social geometry of most Italian cities. Comparing educational level, the only proxy partially available in our database, did not show differences in the educational status (compulsory 34% vs. 32% and higher education 67% vs. 67% in cases and controls, respectively). Furthermore, in Italy, the access to health care is granted to all residents without restrictions, and in each city, the facilities for CKD in pregnancy are only in the public settings, thus making it unlikely that differences in socioeconomic status affected patient management and follow-up. Once more, these limitations will induce us to further refine our databases.

Beyond all these limitations, this study is the first one to clearly define an effect of even minor changes in kidney tissue on pregnancy duration. Even if an observational study is not able to show anything more than an association, and cannot identify a cause-effect relationships, identifying this association is the first step to moving forward and exploring it.

Conclusions

This study, performed in a large multicenter Italian cohort considering more than 400 pregnancies in women with tubulointerstitial diseases, normal kidney function, no hypertension, and no relevant proteinuria, suggests that the threshold of kidney damage that has a significant role in shortening pregnancy duration and potentially leading to adverse pregnancy outcomes is very low.

A significant difference in pregnancy duration can also result from the presence of a simple kidney scar. This finding, highlighting the importance of being particularly attentive to all patients with even early CKD in pregnancy, shows the need for bedside-to-bench studies that would investigate and explain the reasons for this early increased risk and lead to improvements in therapeutic approaches.

DISCLOSURE

All the authors declared no competing interests.

DATA STATEMENT

The study data will be deposited in a public repository upon publication. Inquiries should be made to the corresponding author.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. Main definition used.

Supplementary Table S2. Baseline data in overall controls and matched controls.

Supplementary Table S3. Detailed diagnoses of tubulointerstitial diseases.

Supplementary Table S4. Univariable analysis for different outcomes.

Supplementary Table S5. Multivariable logistic regression: patients with previous acute pyelonephritis (APN), stage 1 chronic kidney disease, proteinuria <0.5 g/d, and no hypertension versus controls.

Supplementary Table S6. Multivariable logistic regression: patients with other tubulointerstitial diseases, stage 1 chronic kidney disease, proteinuria <0.5 g/d, and no hypertension versus controls.

Supplementary Table S7. Multivariable logistic regression: patients with a solitary kidney, stage 1 chronic kidney disease, proteinuria <0.5 g/d, and no hypertension versus controls.

Supplementary Table S8. Baseline data in patients with chronic kidney disease (CKD) in Cagliari and Turin (stage 1 proteinuria <0.5 g and no hypertension at baseline).

Supplementary Table S9. Main outcome differences between Cagliari and Turin patients.

Supplementary Figure S1. Kaplan-Meier curves. Time to delivery in matched controls versus patients with (**A**) other tubulointerstitial diseases, (**B**) other acute pyelonephritis (APN), and (**C**) solitary kidney (Single K.).

Supplementary Figure S2. Kaplan-Meier curves in Turin. Time to delivery in matched controls versus patients with other tubulointerstitial diseases, previous acute pyelonephritis (APN), and solitary kidney (Single K.).

Supplementary Figure S3. Kaplan-Meier curves in Cagliari. Time to delivery in matched controls versus patients with other tubulointerstitial diseases, previous acute pyelonephritis (APN), and solitary kidney (Single K.).

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