Risk of Adverse Pregnancy Outcomes in Women with CKD

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ABSTRACT

CKD is increasingly prevalent in pregnancy. In the Torino-Cagliari Observational Study (TOCOS), we assessed whether the risk for adverse pregnancy outcomes is associated with CKD by comparing pregnancy outcomes of 504 pregnancies in women with CKD to outcomes of 836 low-risk pregnancies in women without CKD. The presence of hypertension, proteinuria (>1 g/d), systemic disease, and CKD stage (at referral) were assessed at baseline. The following outcomes were studied: cesarean section, preterm delivery, and early preterm delivery; small for gestational age (SGA); need for neonatal intensive care unit (NICU); new onset of hypertension; new onset/doubling of proteinuria; CKD stage shift; "general" combined outcome (preterm delivery, NICU, SGA); and "severe" combined outcome (early preterm delivery, NICU, SGA). The risk for adverse outcomes increased across stages (for stage 1 versus stages 4–5: "general" combined outcome, 34.1% versus 90.0%; "severe" combined outcome, 21.4% versus 80.0%; $P<0.001$). In women with stage 1 CKD, preterm delivery was associated with baseline hypertension (odds ratio [OR], 3.42; 95% confidence interval [95% CI], 1.87 to 6.21), systemic disease (OR, 3.13; 95% CI, 1.51 to 6.50), and proteinuria (OR, 3.69; 95% CI, 1.63 to 8.36). However, stage 1 CKD remained associated with adverse pregnancy outcomes (general combined outcome) in women without baseline hypertension, proteinuria, or systemic disease (OR, 1.88; 95% CI, 1.27 to 2.79). The risk of intrauterine death did not differ between patients and controls. Findings from this prospective study suggest a "baseline risk" for adverse pregnancy-related outcomes linked to CKD.

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CKD is increasingly encountered in pregnancy.[1,2] Several studies suggest that even in the early stages, CKD is a relevant risk factor for adverse pregnancy outcomes.[3–5] These data partially contrast with one population-based study that did not find an additive risk for mild GFR reduction, thus suggesting that the clinical definition of CKD is more complex than the mere evaluation of GFR.[6]

Overall, quantifying the risks of CKD in pregnancy is also difficult because of the high heterogeneity of kidney diseases, stages, and clinical presentations.[4,7–11] A few points are clear: The risk of adverse pregnancy-related outcomes is high in advanced CKD, and the disease may progress during pregnancy.[2,11,12] The increase in risk was clearly described in previous articles in which kidney diseases were "graded" in severity according to serum

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creatinine levels, thus strengthening the importance of renal function reduction, however assessed.[13–15]

Specific diseases such as SLE or diabetic nephropathy may bear higher risks, even if no comparative data analyzing various kidney diseases in different stages are available to date.[13–16] Other diseases such as IgA or reflux nephropathy usually display a good prognosis, at least in the presence of normal kidney function.[17–23]

Despite rising interest, few large cohorts of nonselected patients with CKD encompassing the most frequently encountered disorders in clinical practice are available.

The Torino-Cagliari Observational Study (TOCOS) merges the two largest Italian cohorts of CKD patients followed-up in pregnancy between 2000 and 2013. We analyzed data concerning 508 singleton deliveries (504 live births) from 731 referred pregnancies and compared them with a low-risk, homogeneously followed-up population (839 singletons, 836 live births). Our aim was to identify the main determinants of risk for adverse pregnancy-related outcomes in the CKD population, with particular attention to the large stage 1 CKD subset of patients, in whom pregnancy-related risks are already higher than in the overall population, but whose kidney function is still within the normal range.

RESULTS

Baseline Data

Baseline data of the patients and of the controls are reported in Table 1 and in Figures 1 and 2.

The two cohorts in Turin and Cagliari reflect the demographic composition of the two Italian regions, Piedmont and Sardinia, according to Ministry of Health data from the Italian National Institute of Statistics (ISTAT) (Table 1).

No significant differences were observed between the two control groups referring to the Turin Maternal-Fetal Unit. Conversely, the significant difference in age at pregnancy in the Cagliari cohort reflects a tendency to postpone pregnancy, which is characteristic for the whole Sardinia region.[24,25]

No significant differences were observed with regard to body mass index (BMI) and educational levels across patients and controls. The BMI range was higher among the patients because morbid obesity was considered a hallmark of "high-risk" pregnancies and was not present in controls. The prevalence of non-Caucasian mothers was higher among patients and controls that reside in the large multiethnic city of Turin compared with Cagliari, in keeping with the low migration flows of the Sardinian population.[26]

Table 2 summarizes the main baseline clinical data of the two patient populations followed-up in Turin and Cagliari.

In both cohorts, patients in early CKD stages accounted for the majority of the observed cases, in keeping with the distribution of CKD in the childbearing age groups. The higher prevalence of glomerular diseases in the Cagliari group and of interstitial diseases in the Turin group are in keeping with the main referral characteristics of the two nephrology units: The Turin unit is linked with a large Urology ward, whereas the Cagliari unit is a regional referral center for glomerular diseases. The higher prevalence of diabetic nephropathy is consistent with the high prevalence of type 1 diabetes in Sardinia. These differences in the distribution of baseline diseases explain the higher prevalence of hypertension (higher in glomerular diseases and diabetic nephropathy) and of stage 2 CKD in Cagliari.

Maternal-Fetal Outcomes in Patients and Controls

Table 3 reports the main outcomes of patients and controls, considering the pregnancies that resulted in a live-born baby. In the control groups, the prevalence of cesarean sections was lower than the national average (38.8% in Italy in 2009[24–26]). Piedmont and Sardinia are regions of average-high and average-low incidence with respect to Italy (37.1% in Sardinia and 29.9% in Piedmont, according to ISTAT 2010 data).[25,26] The incidence of "late preterm" deliveries (34–37 weeks) is higher in Cagliari, likely as a reflection of a more "aggressive" policy toward cesarean sections, whereas the incidence of early preterm deliveries, a harder outcome that is less affected by standard policies, is not statistically different in the two settings (Table 3).

In all of the control cohorts, the incidence of hypertensive disorders of pregnancy was lower than in the general Italian population (overall 12%), thus supporting the definition of "low-risk" cohorts (Table 3). Within this frame, the incidence of hypertensive disorders of pregnancy was higher in the

Table 1. Main baseline data in the patients and in the controls (live births, singleton deliveries)

Characteristic	Controls				Patients				*P* Value for Patients versus Controls
	Turin	Cagliari	All	*P* Value	Turin	Cagliari	All	*P* Value	
Pregnancies (*n*)	559	277	836		336	168	504		
Age at pregnancy (yr)	28.9±4.8	32.1±5.7	29.9±5.3	<0.001	30.9±5.5	33.7±5.0	31.9±5.4	<0.001	<0.001
Parity (nulliparous)	61.2	52.0	58.1	0.01	58.6	51.2	56.2	0.14	0.48
BMI	22.6±3.3	21.9±3.3	22.4±3.3	0.01	23.1±4.8	23.6±5.1	23.3±4.9	0.35	0.001
Caucasian	80.1	97.8	86.0	<0.001	87.5	99.4	91.5	<0.001	0.004
Education level (>8th grade)	60.9	73.3	63.8	0.01	66.0	66.2	66.1	1.00	0.48

Data are presented as the mean±SD or percentage, unless otherwise indicated. The prevalence of Italian patients is 73.99% for Turin and 94.56% for Cagliari. According to ISTAT data, median age at delivery is 32.6 years for Italian mothers and 29.3 years for foreign mothers. In Italy, Caucasian mothers make up 92.7% of the cohort; 66.7% of the mothers have an educational level >8th grade. Age at pregnancy is 1 year higher in Sardinia versus the rest of Italy (ISTAT 2008).

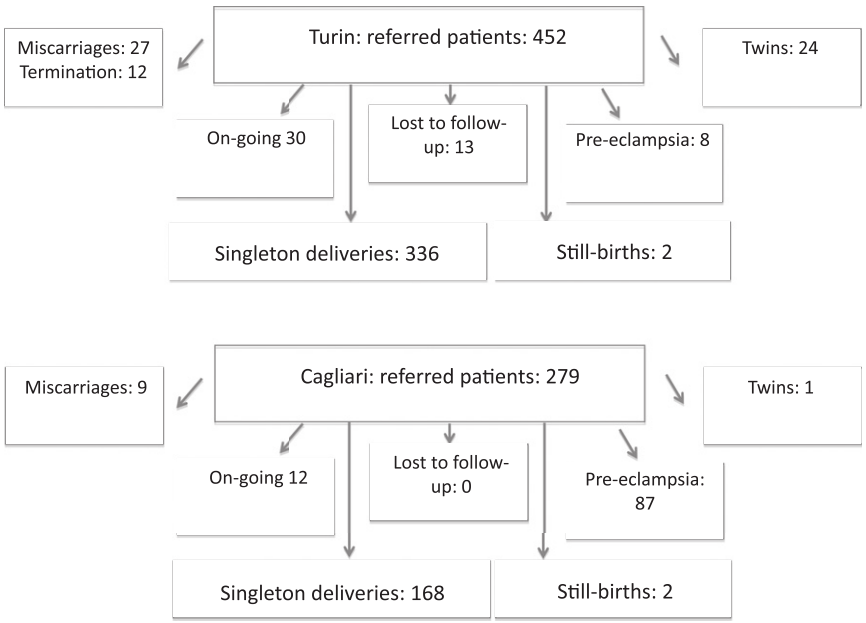

Figure 1. Flow chart of the cases reported in the two study settings.

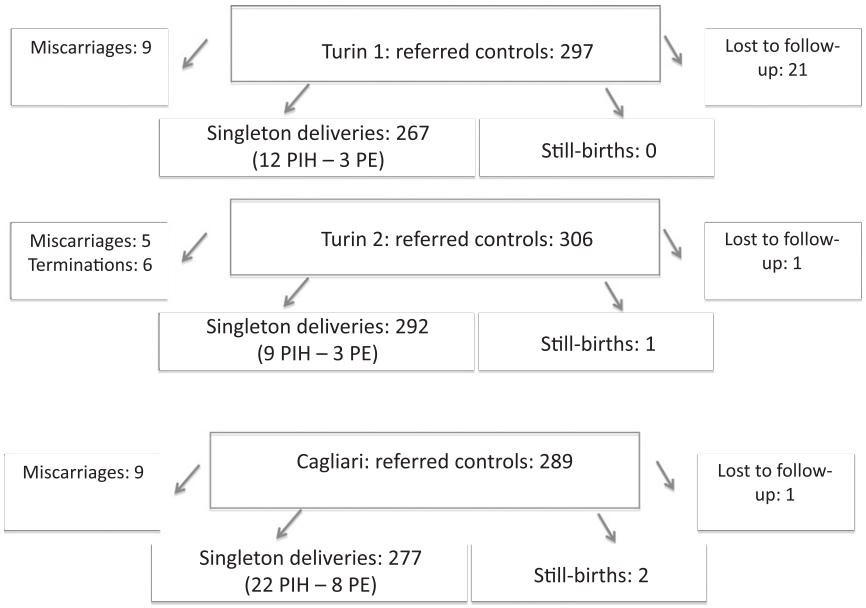

Figure 2. Flow chart of the controls. PE, preeclampsia; PIH, pregnancy induced hypertension.

Cagliari controls compared with the Turin controls, in keeping with the older age at pregnancy and a greater predisposition to juvenile hypertension in this region (Sardinia)[27] (Tables 1 and 3).

As expected, most of the tested outcomes, with the exception of small for gestational age (SGA) babies, are different in the overall populations of patients versus controls, regardless of the chosen scale (Parazzini versus INeS charts[28,29]).

For the hard outcome of intrauterine death, seven deaths were recorded overall, of which three occurred in the control group and four occurred in patients (P=0.44). Three of the four intrauterine deaths in CKD occurred in patients affected by SLE, and one occurred in a patient with a single kidney and normal renal function.

None of the live-born singletons born after the 28th week died within the first 3 months after delivery. One male child, born at 25 weeks, died of respiratory distress after 4 days (weight 500 g, Apgar scores of 3–5 at birth); his mother was affected by SLE, with baseline kidney function impairment (serum creatinine of 2.2 mg/dl at the start of pregnancy).

Pregnancy-Related Outcomes: CKD Stage

Table 4 summarizes the main outcomes recorded across CKD stages.

The progressive worsening of outcomes observed from CKD stage 1 to CKD stages 4–5 is significant for most of the maternal-fetal outcomes, with the exception of the incidence of SGA babies (significant only for babies below the 10th centile: P=0.02). This outcome is partially modified by the medical policy, because intrauterine growth restriction is one of the indications for preterm delivery and for cesarean section (reaching 70% in CKD stage 2) (Table 4).

As for maternal renal outcomes, across the functional stages there is a trend toward a higher risk of onset of hypertension (considering only the normotensive cases at baseline: 7.9% in stage 1 to 50% in stages 4–5), development or doubling of proteinuria (20.5% in stage 1 to 86.5% in stage 3 and 70% in stages 4–5) and shift of at least one functional stage or start of dialysis. One patient alone (in Cagliari), already in stage 5 at referral, started dialysis in pregnancy, whereas three patients shifted by two stages (two in Torino and one in Cagliari, all in stage 2 at the start of pregnancy). The differences reach statistical significance for hypertension and proteinuria; however, in spite of an increasing trend, they are not statistically significant in the case of stage shift and start of dialysis, whose risk is considerably lower compared with the other renal outcomes (7.6% in stage 1% to 20% in stages 4–5) (Table 4).

Table 2. Main baseline clinical data in the Turin and Cagliari patient cohorts

Characteristic	Turin	Cagliari	All Patients	*P* Value for Turin versus Cagliari
Pregnancies (*n*)	336	168	504	
Baseline hypertension (%)	19.6 (66)	42.9 (72)	27.4 (138)	<0.001
Baseline proteinuria (g/d)	0.13 (0.01–14.6)	0.14 (0.01–5.38)	0.13 (0.01–14.6)	0.11
Proteinuria (class)				0.84
<0.3	71.1 (239)	73.1 (117)	71.8 (356)	
≥0.3 to <0.5	8.0 (27)	7.5 (12)	7.9 (39)	
0.5–1	8.9 (30)	6.9 (11)	8.3 (41)	
1–3	8.3 (28)	10.0 (16)	8.9 (44)	
≥3	3.6 (12)	2.5 (4)	3.2 (16)	
Median GFR (ml/min)				
CKD-EPI	120 (15–186)	112 (6–145)	118 (6–186)	<0.001
Cockcroft–Gault	121 (19–396)	102 (14–302)	114 (14–396)	<0.001
Median serum creatinine (mg/dl)	0.62 (0.3–3.80)	0.70 (0.38–7.9)	0.64 (0.3–7.9)	<0.001
CKD stage				<0.001
1	78.9 (265)	62.5 (105)	73.4 (370)	
2	12.8 (43)	26.2 (44)	17.3 (87)	
3	6.8 (23)	8.3 (14)	7.3 (37)	
4–5	1.5 (5)	3 (5)	2 (10)	
Main cause of CKD (%)				<0.001
Glomerular	15.5	17.9	16.3	
Interstitial	52.7	9	38.1	
ADPKD	4.5	6.5	5.2	
Systemic disease (%)				<0.001
SLE-collagen diseases	4.7	19	9.5	
Diabetic nephropathy (type 1)	3.3	10.1	5.6	
Kidney graft	3.6	3.6	3.6	

Data are presented as % (*n*) or median (range) unless otherwise specified. CKD-EPI, Chronic Kidney Disease in Epidemiology Collaboration; ADPKD, autosomic dominant polycystic kidney disease.

Pregnancy-Related Outcomes: Logistic Regression Analyses within CKD Stage 1

In an effort to identify which factors besides kidney function and CKD stage modulate the outcomes of patients with CKD, we focused on the first CKD stage because of the normal renal function. We felt that this would allow us to more easily identify the effect that other factors such as proteinuria, hypertension, and systemic disease may exert. Table 5 reports the results of the logistic regression analysis in patients with stage 1 CKD.

In the overall cohort of patients with stage 1 CKD, the effects of parity, maternal age, and setting of care (with the exception of cesarean section) are no longer significant, whereas baseline hypertension, baseline proteinuria (≥1 g/d), and the presence of systemic disease are confirmed as significant predictors of adverse outcomes in this cohort with normal kidney function.

Once more, SGA escapes from this rule, presumably because the onset of intrauterine growth restriction is an indication for delivery, ideally before the baby becomes "small for gestational age." After adjustment for proteinuria and hypertension, the presence of a systemic disease is an independent risk for preterm delivery, new onset or doubling of proteinuria, and cesarean section. There is also a trend toward an association of systemic disease with increased risk for early preterm delivery, need for the neonatal intensive care unit (NICU), and stage shift of CKD.

Interestingly, in spite of the baseline differences in obstetric policies, the risks of the combined outcomes are not significantly different in the two settings, suggesting common indications to delivery, within a different policy toward its modality (Table 5).

Comparison between Controls and Patients with Stage 1 CKD

Figures 3 and 4 report a stepwise comparison between controls and patients with stage 1 CKD.

The increase in risk for adverse pregnancy-related outcomes persists in patients with stage 1 CKD even when the patients with the main risk factors concomitant with CKD are excluded (hypertension, baseline proteinuria, and systemic diseases) and when only patients who are referred early are considered (excluding patients in whom a clinical problem may have led to a *post hoc* diagnosis of CKD).

The increase is significant for the general combined outcome (odds ratio [OR], 1.88; 95% confidence interval, 1.27 to 2.80), suggesting the presence of a baseline risk linked to the presence of stage 1 CKD (Figure 3).

DISCUSSION

This study aimed to identify the characteristics associated with risk for adverse pregnancy-related outcomes in women with

Table 3. Main maternal-fetal outcomes in patients and controls

Outcome	Controls				Patients				*P* Value for Patients versus Controls
	Turin	Cagliari	All	*P* Value	Turin	Cagliari	All	*P* Value	
Pregnancies (*n*)	559	277	836		336	168	504		
Cesarean sections	23.1	35.4	27.2	<0.001	42.9	78.6	54.8	<0.001	<0.001
Gestational week	39.2±1.7	38.7±1.8	39.0±1.7	<0.001	37.3±2.8	36.1±3.1	36.9±2.9	<0.001	<0.001
Preterm (<37 wk)	4.7	9.0	6.1	0.02	27.1	46.1	33.4	<0.001	<0.001
Early preterm (<34 wk)	0.7	1.4	1.0	0.45	10.4	16.8	12.5	0.06	<0.001
Weight at birth (g)	3289.3±481	3145.4±465	3241.6±480	<0.001	2869.2±705	2669.4±758	2802.6±728	0.004	<0.001
SGA score									
Parazzini									
<10%	9.5	12.0	10.3	0.34	15.8	13.5	15.1	0.58	0.01
<5%	4.0	5.4	4.5	0.43	6.6	3.7	5.6	0.27	0.41
INeS									
<10%	7.8	10.8	8.8	0.18	13.1	12.0	12.7	0.83	0.03
<5%	3.1	3.6	3.2	0.84	5.1	1.2	3.8	0.06	0.72
Need for NICU	1.3	2.9	1.8	0.18	16.1	18.7	16.9	0.55	<0.001
General combined outcome	13.6	20.3	15.9	0.02	38.7	54.5	43.9	0.001	<0.001
Severe combined outcome	10.6	14.5	11.9	0.13	27.7	32.9	29.4	0.27	<0.001
New-onset hypertension	4.3	7.9	5.5	0.05	12.2	11.5	12.0	0.99	
New-onset or doubling of proteinuria					28.3	31.5	29.4	0.51	
CKD stage shift					9.8	8.3	9.3	0.71	

Data are presented as the mean±SD or percentage unless otherwise specified. ISTAT data (2010) show the following rates for cesarean sections: 37.5% in Italy, 29.9% in Piedmont, and 37.1% in Sardinia.[26] The rate for preterm delivery in Italy was 6.6%. There was one case with nondetermined gestational age. SGA was not assessed in the child with uncertain gestational age. Parazzini scores were not assessable in children born before the 28th gestational week. For new-onset hypertension, only normotensive cases at baseline are considered. Doubling of serum creatinine occurred in three patients in the Turin cohort (diabetic nephropathy; pancreas-kidney graft; polycystic nephropathy) and in two patients in the Cagliari cohort (one patient with GN as well as one patient who started peritoneal dialysis in pregnancy) (*P*=NS). Diagnosis of preeclampsia (only controls are considered) was as follows: 1.2% in Torino-1, 1.0% in Torino-2, 2.9% in Cagliari, and 1.7% in all controls (*P*=NS).

CKD, with particular emphasis on stage 1 CKD. We sought to determine whether adverse pregnancy outcomes in women with stage 1 CKD were due to hypertension, proteinuria, presence of systemic disease, or other factors associated with CKD that are not clinically identified.

The TOCOS cohort collects patients who were followed-up on the basis of similar nephrologic policies in the two largest units following CKD in pregnancy in Italy.

The differences between the control populations in the two settings reflect the well known widespread differences in epidemiology and obstetric management and underline the need to contextualize the data regarding pregnancy outcomes.[30–32] Cesarean section is a main marker of such differences, and the variability is enormous even within the same country. In a recent study in 593 US hospitals, rates varied almost 10-fold across hospitals.[32] Hence, the variations found in our study (1.5-fold to 2-fold) are within the variability expected in multicenter studies.[30–33]

Analysis of the TOCOS cohort led to three main results that could be used as a guide for prenatal counseling and for tailoring clinical surveillance in pregnancy (Figures 3 and 4, Tables 3–5). The first result is confirmatory, on a much larger scale, of previously reported data. Renal function matters, and its effect is likely to be continuous. Considering only the patients with a live-born baby, our data confirm a stepwise increase in pregnancy-related risks from stage 1 to stages 4–5 (Table 3). Interestingly, there is a significant increase in risk from stage 1 to stage 2 CKD, which represents a sort of "gray" area with regard to kidney function.[12–15]

The increase in risk is observed both for maternal-fetal outcomes, particularly prematurity, and for renal outcomes, including the development of hypertension, proteinuria, and shift toward a higher functional CKD stage or to dialysis. Of note, however, even in the higher stages, a stage shift was observed in only about 20% of patients. With the limit of the small number of cases, this may suggest that worsening of kidney function is not an absolute rule and the presence of advanced CKD should not be the only reason for counseling pregnancy termination (Table 4).

The second point specifically regards the population with stage 1 CKD. With 370 singleton deliveries, this is probably the

Table 4. Comparisons across CKD stages

Characteristic	CKD Stage				*P* Value across Stages
	1 (*n*=370)	2 (*n*=87)	3 (*n*=37)	4–5 (*n*=10)	
Baseline data					
Maternal age (yr)	31.3±5.5	33.8±4.5	33.5±4.1	32.3±5.2	<0.001
Parity (% nulliparous)	54.6	57.5	64.9	70.0	0.50
Referral week	15.0 (4–39)	11.0 (4–38)	8.0 (5–33)	8.0 (4–28)	<0.001
Systemic disease (%)	11.6 (43/370)	35.6 (31/87)	43.2 (16/37)	40.0 (4/10)	<0.001
Hypertension (%)	21.6 (80/370)	41.4 (36/87)	54.1 (20/37)	20.0% (2/10)	<0.001
Proteinuria (g/d)					
Baseline	0.12 (0–14.6)	0.15 (0–6.8)	0.50 (0–2.8)	0.63 (0.10–3.44)	<0.001
<0.3	78.4 (286/370)	65.1 (56/86)	33.3 (12/36)	22.2 (2/9)	
≥0.3 to <0.5	7.9 (29/370)	5.8 (5/86)	11.1 (4/36)	11.1 (1/9)	
≥0.5 to <1.0	5.2 (19/370)	8.1 (7/86)	33.3 (12/36)	33.3 (3/9)	
≥1.0 to <3.0	6.0 (22/370)	14.0 (12/86)	22.2 (8/36)	22.2 (2/9)	
≥3.0	2.5 (9/370)	7.0 (6/86)	—	11.1 (1/9)	
Maternal-fetal outcomes					
Cesarean sections	48.4	70.1	78.4	70.0	<0.001
Gestational week	37.6±2.6	35.7±3.2	34.4±2.4	32.6±4.2	<0.001
Preterm delivery (<37 wk)	23.5	50.6	78.4	88.9	<0.001
Early preterm (<34 wk)	7.3	20.7	37.8	44.4	<0.001
Birth weight (g)	2966.5±659	2484±707	2226.3±582	1639±870	<0.001
SGA score (Parazzini)					
<10%	13.3	17.9	18.9	50.0	0.02
<5%	5.1	6.0	5.4	25.0	0.12
Need for NICU	10.3	27.6	44.4	70.0	<0.001
General combined outcome	34.1	63.2	83.8	90.0	<0.001
Severe combined outcome	21.4	44.8	59.5	80.0	<0.001
New-onset hypertension (%)	7.9 (23/290)	17.6 (9/51)	47.1 (8/17)	50.0 (4/8)	<0.001
New-onset or doubling of proteinuria	20.5 (76/370)	37.9 (33/87)	86.5 (32/37)	70.0 (7/10)	<0.001
CKD stage shift or RRT start	7.6 (28/370)	12.6 (1/87)	16.2 (6/37)	20.0 (2/10)	0.12

Data are presented as the mean±SD, percentage (proportion), or median (range), unless otherwise indicated. CKD stage shift indicates an increase of at least 1 CKD stage. New-onset proteinuria is defined as proteinuria increasing from a baseline level <0.3 to ≥0.3 g/d (calculated in patients with proteinuria <0.3 g/d). *P* values through CKD stages (P1, stage 1 versus stage 2; P2, stage 2 versus stage 3; P3, stage 3 versus stages 4–5) are illustrated: Maternal age: P1<0.001; P2=1.0; P3=1.0. Parity: P1=0.71; P2=0.57; P3=1.0. Week of referral: P1<0.001; P2=0.17; P3=0.72. Systemic disease: P1<0.001; P2=0.55; P3=1.0. Hypertension: P1<0.001; P2=0.27; P3=0.07. Baseline proteinuria: P1=0.01; P2<0.001; P3=0.36. Cesarean section: P1<0.001; P2=0.46; P3=0.67. Gestational age: P1<0.001; P2=0.08; P3=0.40. Preterm delivery (<37 weeks): P1<0.001; P2=0.007; P3=0.66. Early preterm (<34 weeks): P1<0.001; P2=0.007; P3=0.72. Weight at birth: P1<0.001; P2=0.29; P3=0.08. SGA 10% (Parazzini): P1=0.36; P2=1.0; P3=0.08. SGA 5% (Parazzini): P1=0.99; P2=1.0; P3=0.05. Need for NICU: P1<0.001; P2=0.05; P3=0.30. New-onset hypertension: P1=0.03; P2=0.02; P3=1.0. New-onset or doubling of proteinuria: P1<0.001; P2<0.001; P3=0.34.
P values stage 1 versus controls are illustrated: Maternal age: P<0.001. Parity: P=0.28. Cesarean sections, gestational age, preterm delivery (<37 weeks), early preterm delivery (<34 weeks), birth weight, and need for NICU: P<0.001; SGA 10% (Parazzini): 0.16; SGA 5% (Parazzini): 0.70; new-onset hypertension P=0.19. *P* values for combined outcomes through stages are illustrated: General combined outcome: P1<0.001; P2=0.039; P3=1.0. Severe combined outcome: P1<0.001; P2=0.195; P3=0.289.

largest currently available cohort. By definition, patients with stage 1 CKD have normal kidney function; therefore, the significant differences compared with the low-risk control population demonstrate that kidney function impairment is not the only element to be taken into consideration for risk assessment in CKD pregnancy (Figures 3 and 4, Tables 3 and 5).

In an effort to understand whether there was a baseline risk linked to CKD *per se*, we first analyzed the effect of the classic risk factors (proteinuria, hypertension, and systemic diseases) in a logistic analysis including only patients with stage 1 CKD. Because the different outcomes are interrelated, we also analyzed two combined outcomes: a general outcome, including preterm delivery, need for NICU, and SGA; and a severe outcome, combining early preterm delivery with need for NICU and SGA (Table 5).

Second, we performed a comparison with the low-risk controls, progressively excluding the patients with systemic diseases, hypertension, or proteinuria, or who were referred late (Figures 3 and 4).

As expected, the presence of the "classic" risk factors increases the odds of negative outcomes, single or combined. However, a significant risk of general adverse outcomes persists (in spite of the lower number of patients) after excluding all of the participants with other unfavorable prognostic markers and considering only the patients referred before the 20th gestational week in order to avoid biases due to the *post hoc* identification of CKD in patients studied for clinical problems (Figures 3 and 4).

These data support the hypothesis that any persistent renal damage, even when associated with preserved kidney function,

Table 5. Multivariate logistic regression analysis: Effect of risk predictors on the different outcomes (patients with stage 1 CKD)

Patients with Stage 1 CKD	Cesarean Section	Preterm Delivery <34 wk	Preterm Delivery <37 wk	SGA Parazzini <10th Centile	Need for NICU	Stage Shift (or RRT Start)	Doubling of or New-Onset Proteinuria	General Combined Outcome	Severe Combined Outcome
Torino cohort (*n*=265)									
Age (≥30 versus <30 yr)	0.93 (0.54 to 1.62)	1.18 (0.32 to 4.33)	1.63 (0.78 to 3.38)	1.12 (0.52 to 2.40)	1.37 (0.53 to 3.56)	1.15 (0.40 to 3.29)	1.29 (0.66 to 2.52)	1.39 (0.77 to 2.50)	1.20 (0.61 to 2.34)
Multi- versus nulliparous	0.80 (0.46 to 1.40)	0.49 (0.13 to 1.91)	0.86 (0.42 to 1.76)	0.72 (0.33 to 1.58)	0.80 (0.31 to 2.09)	2.13 (0.75 to 6.02)	0.98 (0.51 to 1.91)	0.89 (0.49 to 1.59)	0.73 (0.37 to 1.43)
Baseline hypertension	3.62 (1.65 to 7.94)	11.99 (3.35 to 42.83)	3.46 (1.52 to 7.87)	2.07 (0.80 to 5.31)	1.88 (0.63 to 5.57)	1.30 (0.36 to 4.73)	2.84 (1.27 to 6.35)	2.84 (1.32 to 6.11)	2.55 (1.13 to 5.77)
Baseline proteinuria ≥1 g/d	1.69 (0.68 to 4.19)	3.07 (0.72 to 13.03)	3.64 (1.42 to 9.27)	1.66 (0.56 to 4.93)	2.35 (0.73 to 7.60)	2.91 (0.83 to 10.15)	0.95 (0.33 to 2.75)	3.14 (1.28 to 7.68)	2.21 (0.87 to 5.63)
Systemic disease	3.75 (1.23 to 11.45)	3.87 (0.95 to 15.82)	3.71 (1.29 to 10.64)	1.31 (0.38 to 4.56)	5.61 (1.79 to 17.60)	1.59 (0.29 to 8.66)	3.92 (1.40 to 10.99)	2.32 (0.83 to 6.49)	2.77 (0.99 to 7.73)
Cagliari cohort (*n*=105)									
Age (≥30 versus <30 yr)	1.11 (0.33 to 3.64)	0.91 (0.15 to 5.67)	1.20 (0.40 to 3.57)	5.35 (0.61 to 46.46)	1.55 (0.22 to 10.98)	—	1.01 (0.26 to 3.84)	1.72 (0.60 to 4.95)	1.86 (0.50 to 6.92)
Multi- versus nulliparous	0.66 (0.24 to 1.81)	0.61 (0.14 to 2.62)	1.08 (0.44 to 2.66)	0.53 (0.16 to 1.75)	1.21 (0.27 to 5.41)	0.16 (0.03 to 0.83)	0.74 (0.25 to 2.22)	0.90 (0.38 to 2.15)	0.83 (0.31 to 2.23)
Baseline hypertension	1.48 (0.54 to 4.03)	13.48 (1.53 to 118.76)	3.25 (1.28 to 8.24)	1.46 (0.43 to 4.95)	10.41 (1.22 to 88.81)	0.51 (0.11 to 2.27)	5.65 (1.74 to 18.31)	2.56 (1.06 to 6.20)	2.26 (0.81 to 6.33)
Baseline proteinuria ≥1 g/d	—	22.05 (1.41 to 345.35)	3.43 (0.63 to 18.65)	5.61 (0.71 to 44.11)	49.85 (3.21 to 775.04)	—	—	4.83 (0.76 to 30.85)	9.69 (1.56 to 60.07)
Systemic disease	2.02 (0.53 to 7.78)	0.36 (0.04 to 3.51)	2.59 (0.92 to 7.3)	0.46 (0.08 to 2.56)	0.22 (0.02 to 2.43)	2.16 (0.43 to 10.92)	3.38 (0.99 to 11.41)	2.39 (0.86 to 6.66)	0.54 (0.14 to 2.02)
All patients (*n*=370)									
Age (≥30 versus <30 yr)	0.95 (0.58 to 1.56)	0.99 (0.35 to 2.79)	1.48 (0.81 to 2.70)	1.44 (0.72 to 2.87)	1.32 (0.58 to 3.01)	2.11 (0.81 to 5.48)	1.25 (0.69 to 2.70)	1.45 (0.87 to 2.41)	1.29 (0.72 to 2.31)
Multi- versus nulliparous	0.78 (0.48 to 1.25)	0.51 (0.20 to 1.32)	0.93 (0.54 to 1.62)	0.64 (0.33 to 1.21)	0.82 (0.39 to 1.74)	0.90 (0.40 to 2.00)	0.90 (0.52 to 1.58)	0.90 (0.56 to 1.45)	0.74 (0.43 to 1.27)
Cagliari versus Turin	4.45 (2.52 to 7.84)	1.14 (0.43 to 3.05)	1.47 (0.81 to 2.65)	0.94 (0.45 to 1.95)	0.84 (0.36 to 1.93)	1.33 (0.55 to 3.19)	0.54 (0.28 to 1.05)	1.24 (0.72 to 2.11)	0.96 (0.52 to 1.76)
Baseline hypertension	2.55 (1.38 to 4.70)	12.22 (4.45 to 33.60)	3.44 (1.89 to 6.26)	1.91 (0.93 to 3.96)	3.07 (1.39 to 6.76)	0.98 (0.38 to 2.54)	3.80 (2.03 to 7.11)	2.68 (1.53 to 4.72)	2.53 (1.37 to 4.67)
Baseline proteinuria ≥1 g/d	2.16 (0.94 to 4.96)	4.81 (1.48 to 15.66)	3.65 (1.61 to 8.24)	2.12 (0.84 to 5.36)	3.67 (1.43 to 9.41)	1.94 (0.61 to 6.15)	0.69 (0.25 to 1.89)	3.42 (1.55 to 7.57)	3.05 (1.38 to 6.75)
Systemic disease	3.20 (1.35 to 7.55)	1.70 (0.57 to 5.09)	3.16 (1.52 to 6.54)	0.90 (0.34 to 2.37)	2.00 (0.79 to 5.08)	1.51 (0.51 to 4.43)	3.33 (1.56 to 7.11)	2.38 (1.17 to 4.85)	1.45 (0.68 to 3.11)
P value (H&L)	0.89	0.56	0.79	0.84	0.29	0.13	0.95	0.75	0.59

Data are presented as ORs (95% confidence intervals). General combined outcome includes preterm <37 weeks and/or NICU and/or SGA. Severe combined outcome includes early preterm <34 weeks and/or NICU and/or SGA. Models for which expected and observed event rates in subgroups are similar (*P*=NS) are well calibrated. H&L, Hosmer–Lemeshow goodness of fit test.

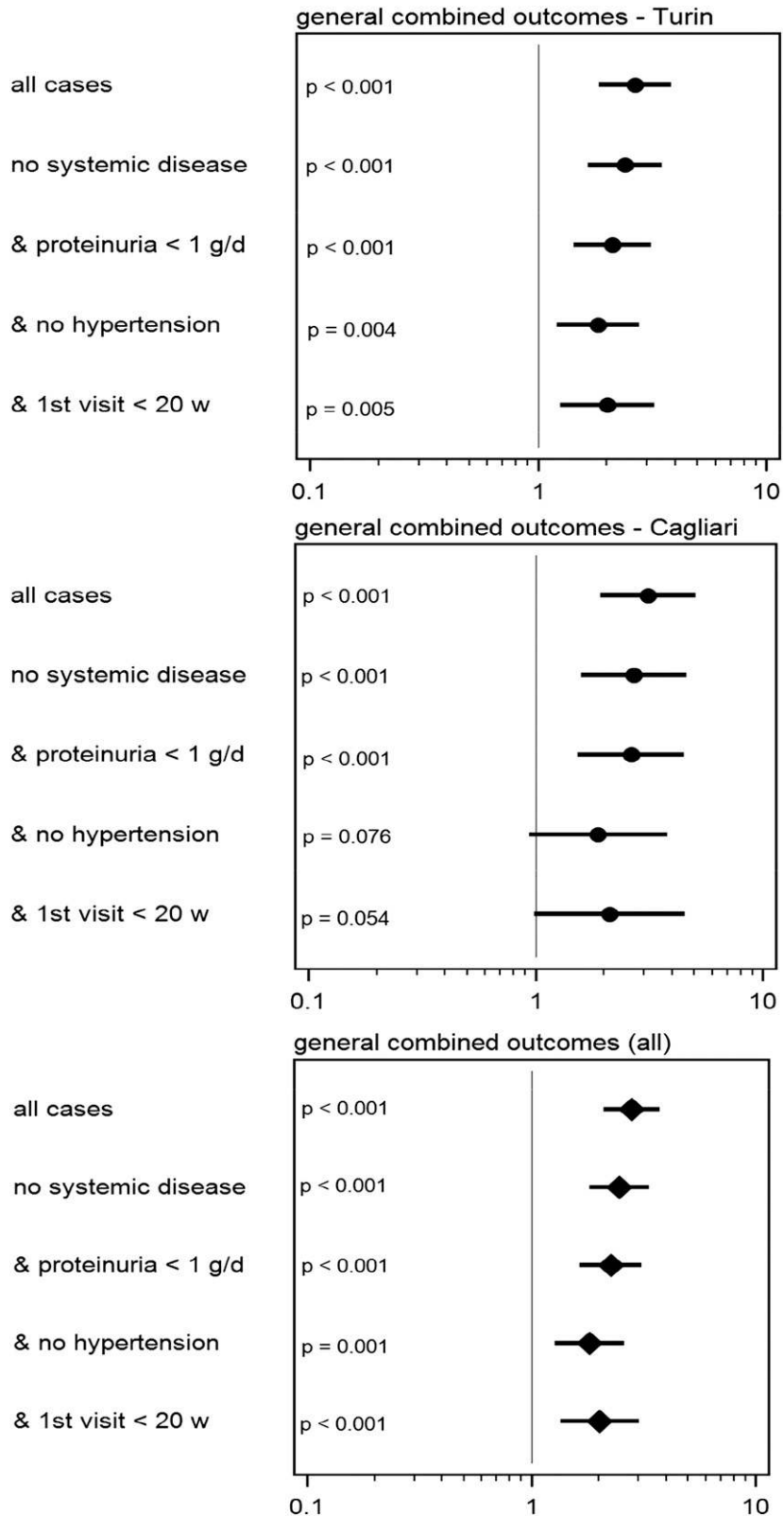

Figure 3. Forest plot and random-effects meta-analysis of the general combined outcome (preterm delivery, SGA, NICU) in different selections of CKD stage 1 versus low-risk pregnancies. Results for Turin are presented as follows: all cases (OR, 2.66; 95% CI, 1.85 to 3.83), no systemic disease (OR, 2.40; 95% CI, 1.65 to 3.50), no systemic disease and proteinuria <1 g/d (OR, 2.12; 95% CI, 1.43 to 3.13), no systemic disease and proteinuria <1 g/d and normotension (OR, 1.84; 95% CI, 1.21 to 2.78), and no systemic disease and proteinuria <1 g/d and normotension and referral within 20 gestational weeks (OR, 2.01; 95% CI, 1.25 to 3.23). Results for Cagliari are presented as follows: all cases (OR, 3.12; 95% CI, 1.13 to 5.01), no systemic disease (OR, 2.71; 95% CI, 1.59 to 4.61), no systemic disease and proteinuria <1 g/d (OR, 2.63; 95% CI, 1.53 to 4.53), no systemic disease and proteinuria <1 g/d and normotension (OR, 1.89; 95% CI, 0.94 to 3.80), and no systemic disease and proteinuria <1 g/d and normotension and referral within 20 gestational weeks (OR, 2.11; 95% CI, 0.99 to 4.53). Results for both Turin and Cagliari are presented as follows: all cases (OR, 2.67; 95% CI, 2.00 to 3.55), no systemic disease (OR, 2.33; 95% CI, 1.72 to 3.14), no systemic disease and proteinuria <1 g/d (OR, 2.13; 95% CI, 1.56 to 2.91), no systemic disease and proteinuria <1 g/d and normotension (OR, 1.68; 95% CI, 1.19 to 2.38), and no systemic disease and proteinuria <1 g/d and normotension and referral within 20 gestational weeks (OR, 1.88; 95% CI, 1.27 to 2.79). 95% CI, 95% confidence interval.

in the absence of hypertension, significant proteinuria or systemic disease, increases the risk for adverse pregnancy outcomes. The presence of such a baseline risk should lead to the search for other markers and disease modulators.

Finally, the third result concerns the risk of stillbirth. We observed four cases in the CKD population and three among the controls. Although the prevalence is slightly higher in patients with CKD, the difference is not statistically significant. Of note, three of four patients with CKD were affected by SLE. This observation should not lead us to underestimate the risk in patients with CKD, but may scale it down, at least within the "standard" kidney diseases.[16–19]

Our study has weaknesses and strengths, in part shared by other clinical studies on CKD and pregnancy. This study is based on the data collected by two centers alone. However, according to the Italian Study Group on Kidney and Pregnancy, these are the only ones with prospective data collection and with >100 pregnancies followed-up since 2000.

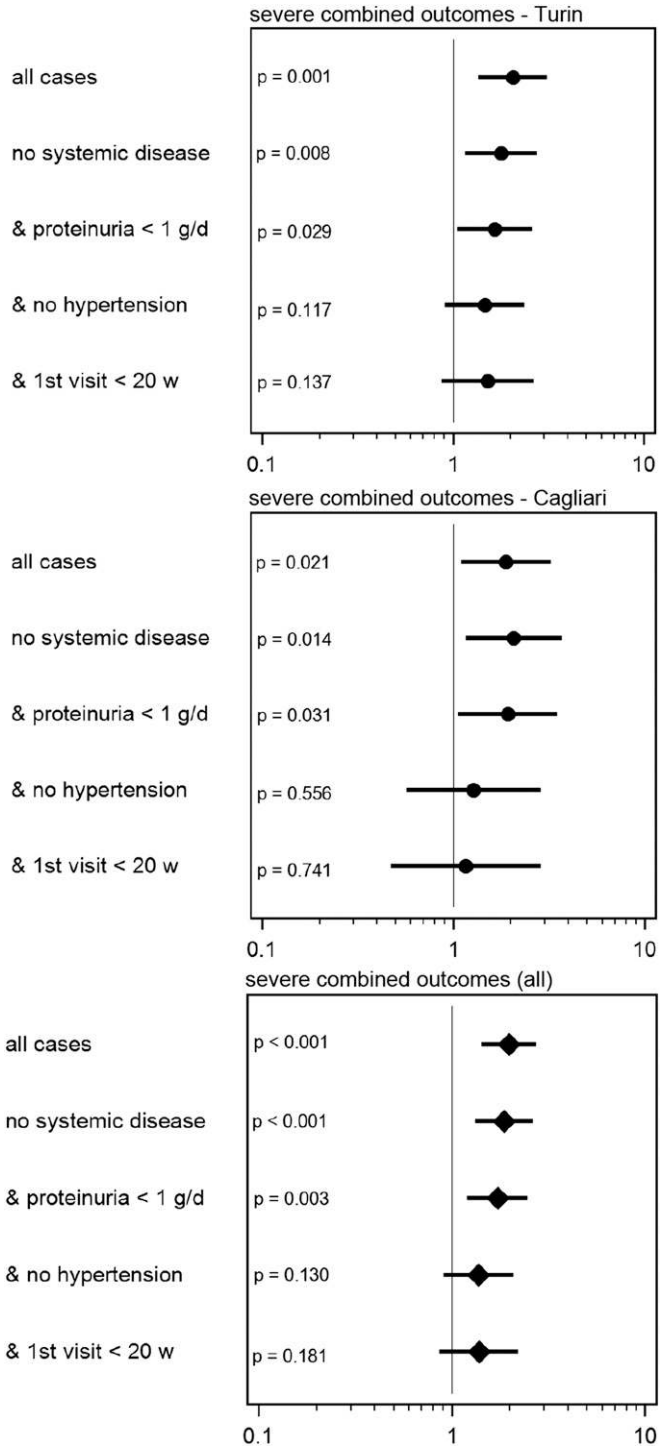

Figure 4. Forest plot and random-effects meta-analysis of the "severe" combined outcome (early preterm delivery, SGA, NICU) in different selections of CKD stage 1 versus low-risk pregnancies. Results for Turin are presented as follows: all cases (OR, 2.06; 95% CI, 1.37 to 3.12), no systemic disease (OR, 1.79; 95% CI, 1.64 to 2.76), no systemic disease and proteinuria <1 g/d (OR, 1.65; 95% CI, 1.05 to 2.59), no systemic disease and proteinuria <1 g/d and normotension (OR, 1.47; 95% CI, 0.91 to 2.36), and no systemic disease and proteinuria <1 g/d and normotension and referral within 20 gestational weeks (OR, 1.53; 95% CI, 0.87 to 2.66). Results for Cagliari are presented as follows: all cases (OR, 1.89; 95% CI, 2.00 to 3.24), no systemic disease (OR, 2.10; 95% CI, 1.16 to 3.70), no systemic disease and proteinuria <1 g/d (OR, 1.93; 95% CI, 1.06 to 3.50), no systemic disease and proteinuria <1 g/d and normotension (OR, 1.28; 95% CI, 0.57 to 2.88), and no systemic disease and proteinuria <1 g/d and normotension and referral within 20 gestational weeks (OR, 1.17; (95% CI, 0.47 to 2.87). Results for both Turin and Cagliari are presented as follows: all cases (OR, 1.93; 95% CI, 1.39 to 2.66), no systemic disease (OR, 1.77; 95% CI, 1.26 to 2.50), no systemic disease and proteinuria <1 g/d (OR, 1.66; 95% CI, 1.16 to 2.36), no systemic disease and proteinuria <1 g/d and normotension (OR, 1.31; 95% CI, 0.88–1.96), and no systemic disease and proteinuria <1 g/d and normotension and referral within 20 gestational weeks (OR, 1.33; 95% CI, 0.84 to 2.13).

A second limitation is the assessment of kidney function. There are currently no validated formulas in pregnancy, and the frequent lack of preconception data prevents precise staging of baseline CKD. However, this limitation is attributable to the frequently late referral of patients with CKD, which is likely a worldwide problem. However, in a clinical context, the advantage of our data is that they take into consideration commonly assessed, low-cost parameters that are readily available worldwide.

One of the strengths of our study is the very low incidence of patients lost to follow-up, thus guaranteeing against attrition biases after referral. Another important point is the availability of a large low-risk control population, allowing contextualization of the data.

Further studies on different, large cohorts are needed both to confirm the presence of this baseline risk linked to stage 1 CKD in the absence of other classic risk factors, and to unravel its mystery.

A prediction model should probably be the next step in this field, analogous with what was recently developed for preeclampsia, as a valuable support for counseling and for identifying patients at higher risk before pregnancy or at referral during pregnancy.[34,35]

Our study, which to our knowledge is likely the largest cohort to date of prospectively collected patients with CKD, aimed to assess the main determinants of risk in pregnancy. Renal function matters, and a stepwise increase in the risk of adverse maternal-fetal outcomes is observed from stage 1 to stages 4–5. However, the risk is not merely linked to kidney function reduction because patients with stage 1 CKD and controls differ significantly. Furthermore, the differences are not fully explained by the classic risk factors (proteinuria, hypertension, and kidney disease), thus suggesting the presence of a baseline risk linked to CKD *per se*. This observation is of practical value because it recommends that clinicians must take special care when treating all CKD patients in pregnancy, even in the absence of known risk factors, and that researchers should collect more data and test novel markers to shed light on this fascinating mystery.

CONCISE METHODS

Study Settings and Referral Criteria

This study was conducted in the Maternal-Fetal Medicine Unit of the Sant'Anna University Hospital (150 beds for obstetric patients) in Turin, Italy,[36] and in the Nephrology Department of the Brotzu Hospital (30 beds for nephrology and transplantation, 25 beds in obstetrics) in Cagliari, Italy. These two settings have the broadest experience with CKD in pregnancy in Italy. In Turin, the outpatient unit dedicated to kidney diseases in pregnancy was established in 2000.[36] In Cagliari, a joint nephrology-obstetrics outpatient service has been active since 1989. Both units collected data prospectively. The databases were updated and merged on December 31, 2013, and data concerning all of the patients referred since January 1, 2000, were selected. Complete methods are available in the Supplemental Material.

Patient and Control Populations

This study included patients with CKD with singleton pregnancies and of gestational age >23 completed weeks. Reasons for exclusion were as follows: ongoing pregnancy, multiple pregnancies, or preeclampsia without evidence of underlying CKD. Only 13 patients were lost to follow-up, all of whom were in Turin.

Overall, 508 pregnancies of 731 referred pregnancies (including 4 intrauterine deaths and 504 singleton deliveries) were taken into consideration for the present analysis (Figure 1).

The controls include low-risk cases, defined as pregnancies occurring in the absence of hypertension, obesity, diabetes, CKD, cardiovascular diseases, or any other severe disease or condition potentially affecting pregnancy; well controlled hypothyroidism was not considered as relevant.[36–39]

Turin-1 and Turin-2 consist of low-risk singleton pregnancies referred in 1999–2007 and in 2011–2013, respectively. The Cagliari control cohort was selected from among the low-risk patients followed-up by the obstetrics unit between 2009 and 2013 (random selection of 3 sample months per year). Of 879 low-risk singleton pregnancies, excluding miscarriages and lost to follow-up, 839 cases were selected for comparison, including 3 intrauterine deaths and 836 deliveries (Figure 2).

Definitions and Main Clinical Indications

CKD was classified according to Kidney Disease Outcomes Quality Initiative guidelines.[35] eGFR was calculated on preconception data, when available within 3 months before conception (38% of the cases in Torino and 57% in Cagliari) or on data at first check-up in pregnancy, employing the Cockcroft–Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration formulas; the latter was chosen on account of its wider use.[36,40–42] After referral, creatinine clearance and proteinuria were assessed on 24-hour urine collection.

The diagnoses of CKD and of preeclampsia were classified as described elsewhere[36]; systemic diseases included diabetic nephropathy, SLE, collagen diseases or vasculitides, and kidney transplantation.

A newborn was defined as SGA when birth weight was below the 10th percentile according to Italian birth weight references (Parazzini scale and INeS charts).[28,29] The Parazzini scale was chosen for multivariate analysis because its use as a referral scale covers most of our study period.

Preterm delivery was defined as before 37 completed gestational weeks; early preterm delivery was defined as before 34 gestational weeks.[35]

Prenatal and intrapartum care of low-risk pregnancies followed the current guidelines.[43,44] The frequency of nephrologic and obstetric visits was tailored to patients with CKD, ranging from one visit every 4–6 weeks in nonhypertensive, nonproteinuric, nonsystemic patients with stage 1 CKD to one to two times weekly in patients with severe proteinuria or hypertension or stages 4–5 CKD, alone or combined.

Indications for early delivery included severe worsening of maternal and/or fetal conditions up to the 32nd week of gestational age or less severe worsening after 32 weeks. The indications for NICU were as follows: birth weight<1800 g, gestational age<34 weeks, need for intubation, or other severe or potentially severe disease or condition.

Statistical Analyses

The following data were gathered and/or calculated for patients and controls: center, date of referral and delivery, age, parity, race, educational level, BMI, gestational age at delivery, type of delivery, clinical complications, fetal weight, centile, Apgar index, sex of the baby, admission to the NICU, and outcome. For patients with CKD, data collection also included serum creatinine, GFR, eGFR, CKD stage, kidney disease, and previous follow-up.

Because no maternal or neonatal deaths and only seven intrauterine deaths were observed overall, we limited our analysis to preterm delivery (<37 and <34 weeks), SGA babies, NICU admission, and cesarean section.

Because the different outcomes are interrelated, we also analyzed two combined outcomes: a general outcome, including preterm delivery, NICU and SGA; and a severe outcome, combining early preterm delivery with NICU and SGA.

A descriptive analysis was performed as appropriate. Multivariate logistic regression analysis was used to check for simultaneous effects of covariates. Adjusted ORs and 95% confidence intervals were derived from the estimated regression coefficients.

The logistic regression analyses in CKD stage 1 included the following: systemic diseases, baseline hypertension, early versus late referral (dichotomized at 20 weeks), and baseline proteinuria ≥1 g/d (this latter cut-point was chosen because it is less likely to identify a pregnancy-related disorder when assessed at baseline).[45]

The ORs derived from the analysis of the combined outcomes in different subsets of patients with stage 1 CKD were plotted as a forest plot, according to the analysis performed separately for the two settings (Turin and Cagliari) and then combined according to a random-effects model.

The Hosmer–Lemeshow test was utilized as a measure of goodness of fit. Models for which expected and observed event rates in subgroups are similar are considered "well calibrated," and a lack of statistical significance confirms the good fit of the model.

Statistical analyses were performed with SPSS software (version 18.0 for Windows; (SPSS Inc., Chicago IL). Significance was set at <0.05.

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DISCLOSURES

None.

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