

Multifetal Pregnancies in Women with CKD Risk Assessment and Indications for Counseling

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Key Points

- CKD carries an increased risk for developing hypertensive disorders of pregnancy in multifetal pregnancies.
- CKD in multifetal pregnancies is associated with a shorter duration of gestation and an increased risk of having a baby small for gestational age.
- Multifetal pregnancies are a risk factor for hypertensive disorders of pregnancy compared with singleton gestations in patients living with CKD.

Abstract

Background CKD is a risk factor for adverse pregnancy outcomes in singleton pregnancies. Little is known about multifetal pregnancies in women with CKD. Owing to higher maternal age and the wider use of medically assisted fertilization, multifetal pregnancies are increasing. We aimed to review pregnancy outcomes in the largest multicenter series of multifetal pregnancies in women affected by CKD.

Methods This retrospective study gathered data from three Italian units with long-standing experience in the follow-up of pregnancy in women with CKD (2000–2023). Propensity score-matched (age, parity, body mass index, year of delivery) multifetal low-risk pregnancies and singleton pregnancies served as controls; multifetal pregnancies were also matched for chorionicity, amnionity, and mode of conception. Intrauterine death of at least one fetus, given the low number of events, was explored in the overall multifetal cohorts.

Results In this propensity score matched-cohort study, 52 multifetal pregnancies in women with CKD were associated with a significantly lower gestational age compared with 104 low-risk non-CKD controls (median 34.0 versus 36.0 gestational weeks [GWs]) and with lower-term delivery rate (9.6% versus 28.8%). Neonatal intensive care unit admission was more frequent in multifetal pregnancies with CKD (50.9% versus 25.2%, $P = 0.003$). Cox regression and Kaplan–Meier analyses confirmed the independent effect of CKD on gestation duration. In women with CKD, multifetal pregnancies had a markedly shorter gestation than singletons (median 34 versus 39 GW, $P < 0.00001$), with significantly higher risk of preterm birth <34 GW (odds ratio [OR], 9.733), small for gestational age (OR, 5.155), and neonatal intensive care unit admission (OR, 8.033). The difference was sharper than in low-risk non-CKD pregnancies (35 and 39 GW, respectively).

Conclusions This study, the largest assessing the risks of adverse pregnancy outcomes in women with CKD carrying more than one fetus, suggests that multifetal gestation is a strong additional risk. These findings highlight the need for further investigation and demonstrate the importance of careful counseling, particularly in medically assisted reproduction.

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Introduction

CKD is an acknowledged risk factor for adverse pregnancy outcomes (APOs).^{1,2} The risk increases starting in the early CKD stages, and even cases with normal kidney function, no proteinuria (PTU), and normotension have a higher risk of APOs³ which increases with kidney function reduction, hypertension, and PTU.⁴ The risk is consistent in different kidney diseases, including kidney stones, in kidney donors and after an episode of AKI.^{5–7}

However, quantifying the risk is difficult, since, besides CKD, all the situations in which incidence of APOs is augmented (obesity, teenage pregnancy, older age, and previous APOs) need to be considered. Among these non-CKD-related risk factors, multifetal pregnancies are a growing challenge. An increase has been widely described in the western world: since the 1980s, the global twinning rate has increased from 9.1 to 12.0 twin deliveries per 1000 deliveries; about 1.6 million twin pairs are now being born every year.⁸ This trend has been attributed to the progressive rise in maternal age and the widespread use of medically assisted reproductive technologies (MART): in the United States and in Europe, the rate ranges between 1.5% and 4% of all births.^{9,10} In Italy, the rate of multifetal births rose from 1.5% in 2010 to 1.7% in 2015, before slightly decreasing in 2019.^{10,11} The incidence of multifetal pregnancies is influenced by genetic factors and differs in ethnic groups.¹² According to a study conducted in Lombardy, Italy, approximately 70% of twin pregnancies are dizygotic.¹³

Women carrying multiple fetuses have a greater likelihood of developing hypertensive disorders of pregnancy (HDP) and gestational diabetes and delivering by caesarean section. Preterm birth occurs in up to 50% of cases.¹⁴ Moreover, the risks of stillbirth, perinatal mortality, low birth weight, congenital anomalies, and cerebral palsy are also substantially higher.^{15,16} The risk of APOs is higher in monozygotic pregnancies, including twin-to-twin transfusion syndrome, neurologic impairment, discordant growth, and stillbirth.¹⁷

Having CKD and a multifetal pregnancy was previously considered an ominous combination; however, the evidence is scant: the largest series, published in 2012, involved 18 multifetal pregnancies in women with CKD, observed in the period 2000–2011.¹⁸

With the aim of updating the evidence, we analyzed the data of 54 multifetal pregnancies in women with CKD (52 deliveries of at least one live-born baby, two complete stillbirths), in comparison with a propensity-matched cohort of low-risk multifetal pregnancies, and of singletons, both from mothers with CKD and low-risk mothers.

Methods

Study Settings and Databases

The data were obtained from TORINO Cagliari Observational Study (TOCOS-I, established in 2000) a multicenter cohort of pregnancies in women with CKD. The I stands for international, acknowledging the recent inclusion of data from Rome (Italy) and Le Mans (France). Since no multifetal pregnancy was referred because of CKD in the Le Mans, this study was limited to the other three participating units.

Patients with CKD

- Torino: the outpatient unit dedicated to kidney disease and pregnancy started regular activity in 2000 in the obstetrics clinic and is run by a multidisciplinary team of obstetricians and nephrologists; the last update was completed in December 2023.
- Cagliari: the outpatient unit at Azienda Ospedaliera G. Brotzu was the first one dedicated to kidney disease and pregnancy in Italy. It started regular activity in 1990, and since 2000, it has participated in the TOCOS database. It is part of the nephrology clinic and is run by a nephrologist working in close collaboration with the obstetricians.
- Rome: the unit at Policlinico Umberto I started regular activity in 2000 in the nephrology clinic and is managed by a nephrologist working with the obstetricians' team. Data have been prospectively gathered since 2007.

Control Groups

Low-risk multifetal pregnancies were selected as controls from the outpatient unit dedicated to multifetal pregnancies in Torino, one of the largest in Italy. It started regular activity in September 2004 and is run by a multidisciplinary team of obstetricians, psychologists, and neonatologists. At the most recent update, about 650 multifetal pregnancies were on file.

Singletons

The data on singleton pregnancies in women with CKD and on low-risk pregnancies were obtained from the TOCOS cohort. Since most of the multifetal pregnancies (48/54) were observed in Torino, we selected control singletons from this setting.

Definitions Used

The definitions used in this study are available in the [Supplemental Methods](#).

Prenatal and Intrapartum Care

Multifetal Pregnancies with CKD

Once chorionicity is determined (ideally by 12 gestational week [GW]), women are carefully monitored.¹⁹ This includes at least one control with a dietician, being taught how to recognize the common signs of preterm delivery, and, when deemed necessary, a consultation with a psychologist.²⁰ Women are seen at least once a month; blood tests are those indicated for patients with CKD, with the addition, for multifetal pregnancies, of a vaginal swab during the first trimester and screening for gestational diabetes at 24–28 weeks. In patients at risk for urinary infections, urinalysis and urine cultures are performed weekly or every 2 weeks.

Starting in 2019, aspirin has been prescribed in all multifetal pregnancies and, since 2023, in all CKD pregnancies referred within 16 GW.²¹ All women are taught how to self-measure their BP at home (if hypertensive, two to three measurements/d). Monochorionic pregnancies undergo ultrasound assessments every 2 weeks starting from the 16th GW (biometry, Doppler assessment of the umbilical artery and middle cerebral artery, deepest vertical pocket, and bladder filling).¹⁹ Dichorionic pregnancies are monitored every 4 weeks starting from the 20th GW.

Cardiotocography is performed in dichorionic pregnancies on alternate days starting from the 36th GW and in monochorionic diamniotic pregnancies starting from the 35th GW.

Indications for Delivery

Multifetal Pregnancies

Based on the woman's clinical status, delivery is planned between 37 and 38 GW in dichorionic pregnancies and between 35 and 36 weeks in monochorionic ones. Follow-up of triplets follows the same indications, in accordance with chorionicity.²⁰

Women with CKD

Indications for delivery are severe worsening of maternal and/or fetal conditions until 32 GW or less severe worsening after 32 GW. In addition to the classic hallmarks of preeclampsia or hemolysis, elevated liver enzymes, and low platelet count (hemolysis-elevated liver enzyme-low platelet) syndrome, worsening of the maternal conditions includes poorly controlled hypertension, rapidly increasing PTU or serum creatinine, alone or in combination. Fetal worsening includes abnormal fetal heart rate tracings at any gestational age and no fetal growth for over 2 weeks at later gestational ages.²² The BP therapeutic goal was $\leq 130/80$ mm Hg. Drugs of choice are nifedipine or α -methyldopa, while β -blockers (Trandate) or doxazosin are used in cases of insufficient response or side effects.²³

In all cohorts, the main indications for admission to a neonatal intensive care unit (NICU) were birth weight <1500 g, gestational age <32 weeks, Apgar Score below seven at 5 minutes after birth, and need for intubation.²²

Selection of Cases for the Study

From the 62 multifetal pregnancies in women with CKD referred to the three centers, we excluded four cases with incomplete data and four miscarriages/pregnancy terminations, thus leaving us with 52 live births of at least one twin and two complete stillbirths. The two multifetal pregnancies resulting in complete stillbirth (at 32 and 22 GW) were excluded from the maternal and fetal outcome analysis because of the lack of information on delivery. However, they were kept for the fetal death analysis, thus leaving us with a total of 52 multifetal pregnancies for the materno-fetal outcome analysis and 54 multifetal pregnancies for the fetal death analysis. The same selection criteria were applied to the control group of multifetal pregnancies. The singleton pregnancies, both with stage 1 CKD and low-risk pregnancies, were selected from the Torino cohort files (Figure 1). All cases and matched controls were included in the outcome analyses, but women with missing data on a specific information were excluded from that specific analysis. The number of missing data for any given information is included in the table footnotes.

Statistical Analysis

Descriptive analysis was performed as appropriate (mean and SD for normally and median and Q1–Q3 for non-normally distributed data). Continuous variables were compared using a Student *t*-test or a Wilcoxon rank-sum test and categorical variables using a chi-square test or a Fisher exact test in case of low subsample size. Owing to

the low number of events, intrauterine death of at least one fetus was explored in the overall cohorts of multifetal pregnancies, both including and excluding selective pregnancy termination of one fetus.

The main outcomes analyzed were preterm delivery (<34 GW), GW at delivery, prevalence of babies born small for gestational age (SGA) (<10 th centile), and need for hospitalization in NICU.

Our first analysis considered all multifetal pregnancies, regardless of CKD stage and number of fetuses. These cases were matched with a propensity score to low-risk multifetal pregnancies, using a nearest neighbor algorithm (MatchIt package) with a 1:2 ratio, considering the number of fetuses, chorionicity, amnionicity (bichorionic-biamniotic versus all other), parity, body mass index (BMI), mother's age at the beginning of pregnancy, year of delivery, and mode of conception (Figure 1A). To limit heterogeneity, a second analysis considered only cases from the largest contributing center (Torino, 46/52) and focused on twin pregnancies (excluding three sets of triplets), in women with stage 1 CKD (excluding four cases with stage 2–3 CKD), leaving us with 41 cases with at least one live-born baby, propensity score-matched with low-risk multifetal pregnancies (Figure 1B; data on excluded case available in Supplemental Tables 1.1 and 1.2). Matching (1:2 ratio) with singleton mothers with CKD stage 1 considered parity, BMI, age, and year of delivery (Figure 1C). These 82 singletons from mothers with CKD were in turn matched with singleton low-risk pregnancies (same criteria, 1:2 ratio; Figure 1D). Supplemental Figure 1 shows the selection of case hierarchy charts. The standardized mean differences between groups were computed for each variable of each matching to quantify the covariance reduction caused by the propensity score matching (Supplemental Figure 2). Finally, low-risk multifetal and singleton pregnancies were compared (Figure 1E).

Time to delivery was analyzed using time to event Kaplan–Meier curves, and the time-dependent delivery probability was assessed using Cox proportional hazard analysis. The covariates were chosen on the basis of their clinical relevance; they included the presence of CKD, age (≥ 35 years old), parity (parous versus nulliparous), BMI (≥ 25 kg/m²), year of delivery (≥ 2013), chorionicity and amnionicity (bichorionic-biamniotic versus all others), and mode of conception (assisted versus spontaneous).

Incidence of early preterm delivery (<34 GW), small for gestational age baby (<10 th centile), and need for NICU admission were analyzed by multivariable logistic regression analysis, considering the covariates described above. Variance inflation factor was calculated to quantify collinearity among independent variables.

The statistical analysis was conducted using R v.4.3.1 (Foundation for Statistical Computing, Vienna, Austria) with the RStudio interface v.2024.12.0 (Posit Software, Boston). Significance was set at <0.05 .

Results

Baseline and Delivery Data

The flow chart of the study cohorts is presented in Figure 1.

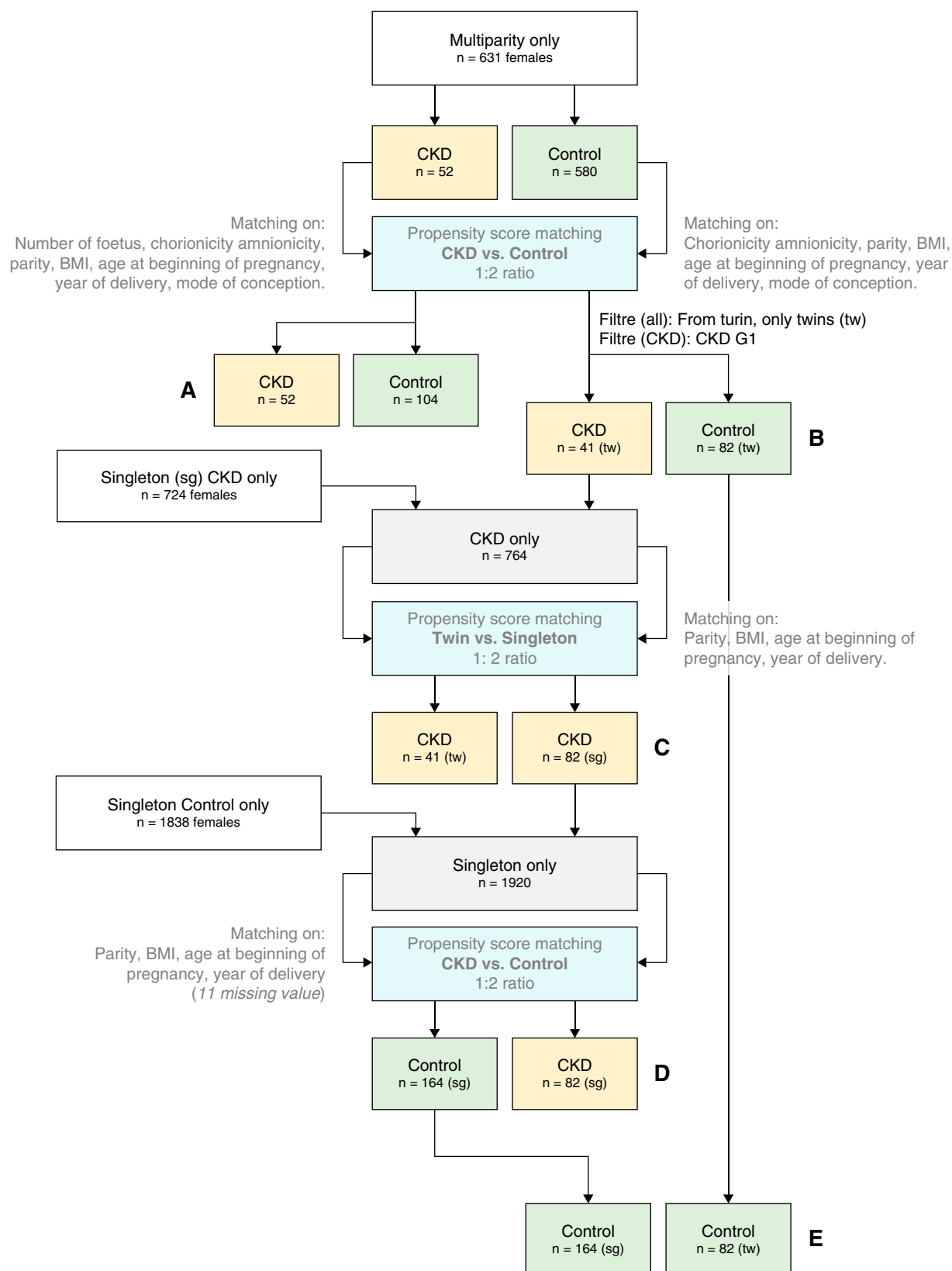


Figure 1. Flow chart of the study. BMI, body mass index.

Table 1 presents the main clinical characteristics of the 52 multifetal pregnancies recorded in women with CKD. The vast majority was in stage 1 CKD (48/52); of note, in none of the participating units was pregnancy interruption advised because of the presence of CKD. Data from the 104 propensity score-matched low-risk multifetal pregnancies are reported in the same table. Baseline matching was consistent for age, parity, and BMI, and the incidence of gestational diabetes was similar (20.4% versus 17.5%).

Only 9.6% of the pregnancies in women with CKD reached term (37 GW) versus 28.8% in the matched group (Fisher exact $P = 0.009$); the difference in median gestational age at delivery was 34.0 versus 36.0 weeks (Mann-Whitney U test P value = 0.006).

Table 2 presents the baseline and delivery data of 41 women with stage 1 CKD and multifetal pregnancies and three matched control groups: low-risk multifetal pregnancies without CKD, singleton pregnancies in women with stage 1 CKD, and low-risk singleton pregnancies without CKD, from the same setting (Torino). Only a minority of multifetal pregnancies in mothers with CKD reached term (12.2% versus 25.6%). Birth weight discordance of at least 20% was more frequent in CKD multifetal pregnancies compared with non-CKD multifetal matched controls (24.3% versus 13.6%), although the difference did not reach statistical significance. Multifetal gestations had a shorter pregnancy duration compared with singleton pregnancies in both women with CKD and non-CKD multifetal matched controls. The proportion of preterm births (<37 GW) was markedly higher in CKD multifetal pregnancies versus CKD singletons (87.8% versus 15.9%, Fisher exact $P < 0.001$), translating into a greater need for neonatal intensive care (multifetal 50.9% versus singletons 11.5%, Fisher exact $P < 0.001$; **Table 2**).

At-term deliveries were more frequent in singleton pregnancies without CKD than singleton pregnancies in women suffering from CKD (97.6% versus 84.1%, Fisher exact $P < 0.001$; **Table 2**). The inclusion of the four women with more advanced CKD (stage 2 or 3a) did not affect any of the outcome analyses.

Duration of Pregnancy

The duration of multifetal pregnancies was significantly shorter in women with CKD (34 GW) than non-CKD multifetal matched controls (35–36 GW; **Tables 1** and **2**).

Time to event analysis showed that delivery occurred significantly earlier in women with CKD compared with controls, in both all multifetal pregnancies ($P < 0.001$, **Figure 2A**) and the subgroup from Torino of women with stage 1 CKD and a multifetal pregnancy ($P = 0.006$, **Figure 2B**).

Cox analysis confirmed the role of CKD in determining the duration of pregnancy in multifetal gestations, while the differences linked to the other covariates (mode of conception, period of delivery, age, parity, and chorionicity/amnionicity) did not reach statistical significance (**Supplemental Table 2**; all cases in **Supplemental Table 3**). In women affected by CKD, multifetal pregnancy resulted in a higher risk of shorter pregnancy duration (**Supplemental Table 4**).

Among women with CKD, gestational age at delivery was lower in multifetal pregnancies compared with CKD

singletons, with a median of 34.0 versus 39.0 weeks ($P < 0.001$; **Figure 3A**). The difference between multifetal and singleton pregnancies in women with CKD (34 versus 39 GW) was higher than the difference between low-risk non-CKD multifetal pregnancies and multifetal non-CKD controls (35–36 versus 39 GW, respectively; **Table 2**). Of note, in singleton gestations, duration of pregnancy was significantly shorter in women with stage 1 CKD than in low-risk non-CKD controls (**Figure 3B** and **Supplemental Table 5**). Multifetal pregnancies in non-CKD patients were shorter than non-CKD singleton controls (**Supplemental Table 6**).

Other Outcomes: Preterm Delivery, Being Small for Gestational Age, and Admission to a NICU

Neonates born to women with stage 1 CKD multifetal pregnancy were more frequently admitted to an NICU (50.9%) compared with low-risk non-CKD multifetal matched controls (25.2%, Fisher exact $P = 0.001$). The prevalence of SGA newborns was similar in both groups (29.1% versus 31.3%), as was the proportion of infants below the fifth percentile (22.8% versus 20.2%; **Table 2**).

Table 3 presents the results of multivariable logistic regression analyses (**Figure 1B**), employing as outcomes the classic cut-points of early preterm delivery before 34 GW, SGA babies (<10th centile) and need for NICU admission. CKD status did not reach significance as an independent predictor of preterm delivery before 34 weeks ($P = 0.086$) and was not associated with increased odds of SGA or NICU admission after adjusting for maternal and pregnancy-related covariates (data on the overall cohort of multifetal pregnancies and CKD available in **Supplemental Table 7**; singletons in **Supplemental Table 8**; non-CKD patients in **Supplemental Table 9**).

Notably, dichorionic-diamniotic twins were confirmed as having a lower risk for delivery <34 GW (odds ratio [OR], 0.232; 95% confidence interval [CI], 0.050 to 0.774; $P = 0.031$), while maternal BMI ≥ 25 kg/m² was independently associated with increased odds of NICU admission (OR, 3.694; 95% CI, 1.322 to 11.058; $P = 0.015$). Recent period of delivery (2013–2023) was associated with a lower risk of SGA (OR, 0.308; 95% CI, 0.132 to 0.692; $P = 0.005$).

Mothers with multifetal stage 1 CKD had a higher risk of newborns being below the tenth centile compared with mothers with CKD and singleton pregnancies (in CKD: 29.1% versus 4.9% Fisher exact $P < 0.001$; **Table 2**).

Among women with stage 1 CKD, a multifetal pregnancy was independently associated with an increased risk of delivery before 34 weeks (OR, 9.733; 95% CI, 3.260 to 33.567; $P < 0.001$), having at least one SGA infant (OR, 5.155; 95% CI, 2.048 to 13.683; $P = 0.001$), and requiring NICU admission for at least one newborn (OR, 8.033; 95% CI, 2.789 to 25.989; $P < 0.001$; **Table 4**).

Other Outcomes: Intrauterine Death of At Least One Twin

Owing to the low incidence of intrauterine fetal death in women with CKD and in controls, we included all multifetal pregnancies in cases and controls in the analysis. The occurrence of intrauterine fetal death of at least one twin was significantly higher in women with CKD compared with those without (seven pregnancies: in two both twins died, in five one survived; 12.96% versus

Table 1. Baseline and delivery data of women with CKD and multifetal pregnancies (all cases) versus propensity-matched controls without CKD

Characteristic	Women with CKD and Multifetal Pregnancies (All Cases)	Women without CKD and Multifetal Pregnancies (Matched Controls)
N	52	104
Age at the start of pregnancy (yr), median (Q1–Q3)	33 (30–35)	32 (29–36)
Ethnicity (White), <i>n</i> (%)	49 (94.2)	87 (84.5) ^b
BMI before pregnancy (kg/m ²), median (Q1–Q3)	22.15 (19.05–25.28)	21.9 (20.1–25.1)
Nulliparous, <i>n</i> (%)	34 (65.4)	73 (70.2)
CKD stage at the beginning of pregnancy (1/2/3a/3b), <i>n</i> (%)	48/1/2/1 (92.3/1.9/3.9/1.9)	
CKD: interstitial ^a , <i>n</i> (%)	24 (46.2)	
CKD: CAKUT-single kidney, <i>n</i> (%)	14 (26.9)	
CKD: ADPKD, <i>n</i> (%)	6 (11.5)	
CKD: GN-DKD, <i>n</i> (%)	3 (5.8)	
CKD: other, <i>n</i> (%)	5 (9.6)	
Hypertension at the start of pregnancy, <i>n</i> (%)	10 (19.2)	
PTU at the start of pregnancy (≥ 0.5 g/24 h), <i>n</i> (%)	8 (15.4)	
Mode of conception: spontaneous, <i>n</i> (%)	37 (71.2)	70 (67.3)
Mode of conception: assisted, <i>n</i> (%)	11 (21.6)	29 (27.9)
Mode of conception: egg donation, <i>n</i> (%)	4 (7.7)	5 (4.8)
Number of fetuses at diagnosis of pregnancy (2/3), <i>n</i> (%)	49/3 (94.2/5.8)	99/5 (95.2/4.8)
Monochorionic-diamniotic/dichorionic-diamniotic/dichorionic-triamniotic/trichorionic-triamniotic, <i>n</i> (%)	10/39/2/1 (19.2/75.0/3.9/1.9)	20/79/4/1 (19.2/76.0/3.9/0.9)
HELLP, PE, PIH, <i>n</i> (%)	7 (14.9) ^c	18 (19.1) ^d
GDM, <i>n</i> (%)	10 (20.4) ^e	18 (17.5) ^b
Delivery year (2013–2023), <i>n</i> (%)	31 (59.6)	44 (42.3)
Delivery week, median (Q1–Q3)	34 (32–36)	36 (33–37)
Delivery: <28 GW, <i>n</i> (%)	1 (1.9)	3 (2.9)
Delivery: <32 GW, <i>n</i> (%)	5 (9.6)	12 (11.5)
Delivery: <34 GW, <i>n</i> (%)	19 (36.5)	28 (26.9)
Delivery: ≥ 37 GW, <i>n</i> (%)	5 (9.6)	30 (28.8)
Caesarean delivery, <i>n</i> (%)	43 (82.7)	81 (77.9)
Pregnancies with one fetal death, <i>n</i> (%)	5 (9.6)	0 (0.0)
Delivered live-born babies, <i>n</i>	101	213
Baby sex (F), <i>n</i> (%)	47(46.5)	101 (51.5) ^f
Baby percentile, median (Q1–Q3)	22.0 (6.0–54.0)	17.0 (6.0–39.0)
Baby percentile (<5), <i>n</i> (%)	21 (20.8)	37(17.4)
Baby percentile (<10), <i>n</i> (%)	29 (28.7)	73 (34.3)
Discordance of baby's weight $\geq 20\%$, <i>n</i> (%)	11 (23.4)	19 (22.6)
Need for NICU, <i>n</i> (%)	42 (55.3) ^g	66 (33.8) ^h
Perinatal death, <i>n</i> (%)	1 (0.9)	1 (0.7) ⁱ

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; DKD, diabetic kidney disease; GDM, gestational diabetes mellitus; GW, gestational week; HELLP, hemolysis-elevated liver enzyme low platelet; NICU, neonatal intensive care unit; PE, preeclampsia; PIH, pregnancy-induced hypertension; PTU, proteinuria.

^aNephrolithiasis-pyelonephritis.

^bOne missing data.

^cFive missing data.

^dTen missing data.

^eThree missing data.

^f17 missing data.

^g25 missing data.

^h18 missing data.

ⁱ68 missing data.

3.60% in controls [21 cases], OR, 3.99 [1.61 to 9.86], $P = 0.01241$). This difference was also confirmed as significant when excluding seven selective pregnancy terminations (one in cases and six in controls), with an OR of 4.78 (95% CI, 1.77 to 12.90; $P = 0.011$). Reasons

for selective pregnancy termination were trisomy 21 ($n=1$), Turner syndrome ($n=2$), severe fetal malformations ($n=2$) and were not specified in two cases. Details on the seven cases with complete or partial fetal loss are presented in [Supplemental Table 10](#).

Table 2. Baseline and delivery data of women with CKD G1 and multifetal pregnancies versus controls from the same setting (Torino)

Characteristic	Women with CKD and Multifetal Pregnancies (Torino, Multifetal, CKD G1)	Women without CKD and Multifetal Pregnancies (Matched Controls)	Women with CKD and Singleton Pregnancies (Matched Controls)	Women without CKD and Singleton Pregnancies (Matched Controls)
<i>n</i>	41	82	82	164
Age at the start of pregnancy (yr), median (Q1–Q3)	33 (30–35)	32 (29–36)	33 (29–36)	33 (29–36)
Ethnicity (White), <i>n</i> (%)	39 (95.1)	71 (87.7)	80 (97.6)	149 (92.5) ^a
BMI before pregnancy (kg/m ²), median (Q1–Q3)	21.5 (18.9–24.2)	21.0 (19.8–23.0)	20.9 (19.4–23.0)	21.0 (19.5–23.4)
Nulliparous, <i>n</i> (%)	28 (68.3)	62 (75.6)	56 (68.3)	117 (71.3)
CKD: interstitial ^b , <i>n</i> (%)	22 (53.7)		35 (42.7)	
CKD: CAKUT-single kidney, <i>n</i> (%)	10 (24.4)		20 (24.4)	
CKD: ADPKD, <i>n</i> (%)	5 (12.2)		4 (4.8)	
CKD: GN-DKD, <i>n</i> (%)	3 (7.3)		14 (17.1)	
CKD: other, <i>n</i> (%)	1 (2.4)		9 (11.0)	
Hypertension at the start of pregnancy, <i>n</i> (%)	6 (14.6)		7 (8.5)	
PTU at the start of pregnancy (≥0.5 g/24 h), <i>n</i> (%)	7 (17.1)		8 (9.8)	
Mode of conception: spontaneous, <i>n</i> (%)	30 (73.2)	62 (75.6)		
Mode of conception: assisted, <i>n</i> (%)	8 (19.5)	15 (18.3)		
Mode of conception: egg donation, <i>n</i> (%)	3 (7.3)	5 (6.1)		
Monochorionic-diamniotic/dichorionic-diamniotic, <i>n</i> (%)	9/32 (22.0/78.0)	21/61 (25.6/74.4)		
HELLP, PE, PIH, <i>n</i> (%)	6 (16.7) ^c	16 (20.8) ^d	2 (2.8) ^e	2 (1.2)
GDM, <i>n</i> (%)	7 (18.4) ^f	8 (9.8)	—	—
Delivery year (2013–2023), <i>n</i> (%)	24 (58.5)	32 (39.0)	47 (57.3)	102 (62.2)
Delivery week, median (Q1–Q3)	34 (32–36)	35 (34–37)	39 (37–40)	39 (38–40)
Delivery: <28 GW, <i>n</i> (%)	1 (2.4)	2 (2.4)	1 (1.2)	0 (0.0)
Delivery: <32 GW, <i>n</i> (%)	4 (9.8)	7 (8.5)	3 (3.7)	0 (0.0)
Delivery: <34 GW, <i>n</i> (%)	15 (36.6)	17 (20.7)	6 (7.3)	0 (0.0)
Delivery: ≥37 GW, <i>n</i> (%)	5 (12.2)	21 (25.6)	69 (84.1)	160 (97.6)
Caesarean delivery, <i>n</i> (%)	33 (80.5)	60 (73.2)	34 (42.5)	42 (25.6)
Pregnancies with one fetal death, <i>n</i> (%)	3 (7.3)	1 (1.2)		
Delivered live-born babies, <i>n</i>	79	163	82	164
Baby sex (F), <i>n</i> (%)	38 (48.1)	68 (45.6) ^g	45 (54.9)	33 (44.0) ^h
Baby percentile, median (Q1–Q3)	23.0 (6.0–59.5)	22.0 (6.0–45.5)	41.5 (17.5–65.2)	46.5 (29.3–72.7)
Baby percentile (<5), <i>n</i> (%)	18 (22.8)	33 (20.2)	4 (4.9)	6 (3.7)
Baby percentile (<10), <i>n</i> (%)	23 (29.1)	51 (31.3)	4 (4.9)	11 (6.7)
Discordance of baby's weight ≥20%, <i>n</i> (%)	9 (24.3)	11 (13.6)		
Need for NICU, <i>n</i> (%)	28 (50.9) ⁱ	39 (25.2) ^j	7 (11.5) ^k	3 (1.8)
Perinatal death, <i>n</i> (%)	1 (1.3)	2 (1.6) ^l	0 (0.0)	0 (0.0)

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; DKD, diabetic kidney disease; GDM, gestational diabetes mellitus; GW, gestational week; HELLP, hemolysis-elevated liver enzyme low platelet; NICU, neonatal intensive care unit; PE, preeclampsia; PIH, pregnancy-induced hypertension; PTU, proteinuria.

^aThree missing data.

^bNephrolithiasis-pyelonephritis.

^cFive missing data.

^dFive missing data.

^e11 missing data.

^fThree missing data.

^g14 missing data.

^h89 missing data.

ⁱ23 missing data.

^jEight missing data.

^k21 missing data.

^l39 missing data.

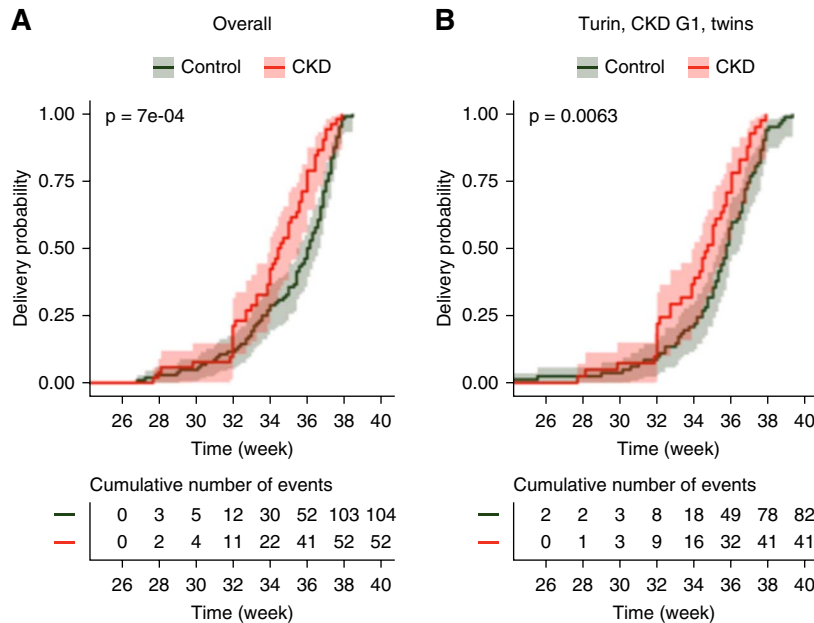


Figure 2. Kaplan–Meier curves. (A) Multifetal pregnancies CKD all cases versus matched controls. (B) Multifetal CKD G1 pregnancies from Turin versus matched controls.

Discussion

Our study shows that CKD carries an increased risk to developing HDP in multifetal pregnancies, it is associated with a shorter duration of gestation and an increased risk of having a baby small for gestational age with a higher need for NICU admission compared with non-CKD multifetal ones and that multifetal pregnancies are a risk factor for HDP compared with singleton gestations in patients living with CKD. None of the large studies, systematic

reviews, and meta-analyses, which have investigated the risk of APOs for women with CKD, have addressed the issue of multifetal pregnancies; hence, high-quality evidence is lacking.^{3,24,25} As highlighted in a recent review, over the past 7 years, only 8% of trials on fetal growth restriction, 17% of those on preeclampsia and 2% of those on diabetes, included multifetal pregnancies.²⁶

This knowledge gap is of particular importance in the case of CKD. Both CKD and multifetal pregnancies are

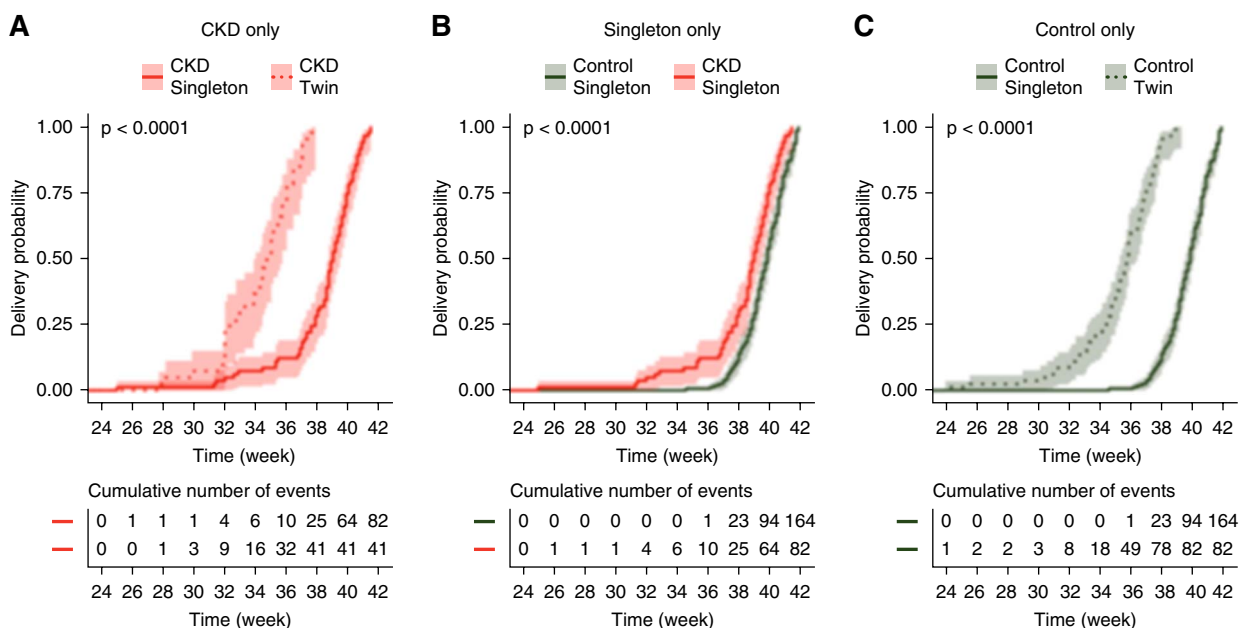


Figure 3. Kaplan–Meier curves. (A) CKD singletons versus CKD multifetal pregnancies. (B) CKD singletons versus singleton controls. (C) Non-CKD multifetal controls versus non-CKD singleton controls.

Table 3. Logistic regression: multifetal pregnancies in mothers with CKD G1 versus mothers without CKD

Outcome	OR	CI Lower	CI Higher	P Value	VIF
Term <34 wk					
Group (multifetal CKD versus non-CKD multifetal control)	2.179	0.894	5.357	0.086	1.067
Dichorionic-diamniotic versus monochorionic-diamniotic	0.232 ^a	0.050 ^a	0.774 ^a	0.031 ^a	1.060 ^a
Not nulliparous versus nulliparous)	0.711	0.225	2.060	0.541	1.216
BMI ≥ 25 kg/m ²	1.410	0.438	4.315	0.551	1.136
Age ≥ 35 yr	0.591	0.209	1.586	0.306	1.214
Year of delivery (2013–2023 versus 2000–2012)	0.879	0.344	2.223	0.785	1.180
Mode of conception (assisted versus spontaneous)	1.232	0.435	3.424	0.689	1.217
Centile <10					
Group (multifetal CKD versus non-CKD multifetal control)	1.058	0.451	2.501	0.896	1.073
Dichorionic-diamniotic versus monochorionic-diamniotic	1.584	0.623	4.097	0.335	1.121
Not nulliparous versus nulliparous)	0.410	0.145	1.081	0.079	1.177
BMI ≥ 25 kg/m ²	0.972	0.322	2.854	0.959	1.134
Age ≥ 35 yr	0.869	0.350	2.164	0.762	1.196
Year of delivery (2013–2023 versus 2000–2012)	0.308 ^a	0.132 ^a	0.692 ^a	0.005 ^a	1.099 ^a
Mode of conception (assisted versus spontaneous)	0.495	0.176	1.329	0.170	1.238
Admission to an NICU					
Group (multifetal CKD versus non-CKD multifetal control)	1.103	0.472	2.531	0.818	1.059
Dichorionic-diamniotic versus monochorionic-diamniotic	0.721	0.270	1.837	0.501	1.115
Not nulliparous versus nulliparous)	0.499	0.174	1.314	0.174	1.243
BMI ≥ 25 kg/m ²	3.694 ^a	1.322 ^a	11.058 ^a	0.015 ^a	1.171 ^a
Age ≥ 35 yr	0.622	0.241	1.544	0.312	1.206
Year of delivery (2013–2023 versus 2000–2012)	1.043	0.456	2.382	0.920	1.122
Mode of conception (assisted versus spontaneous)	0.801	0.289	2.148	0.661	1.228

BMI, body mass index; CI, confidence interval; NICU, neonatal intensive care unit; OR, odds ratio; VIF, variance inflation factor.
^aStatistical significance.

common, estimated as present in 1%–3% and 3%–6% of pregnancies, respectively, and with the rise of multifetal pregnancies and the ongoing epidemics of CKD, this combination will presumably be increasingly encountered in the future.

Our study found a significant additional risk of APOs in the context of multifetal pregnancies in patients with CKD, allowing to quantify these risks more precisely than was previously possible. The comparison with propensity score-matched singleton pregnancies with and without CKD may support counseling and shared decision-making in medically assisted fertilization, increasingly common in women with CKD (Figure 1).

In detail, as compared with a low-risk cohort of women with multifetal pregnancies, women with CKD have a median pregnancy duration of 2 weeks less (34 versus 36 GW), particularly relevant considering that 34 GW corresponds to the early preterm period, associated with low birth weight and long-term health risk in the offspring (Tables 1 and 2).^{27,28}

The difference between the GW at delivery of multifetal gestations and singletons is higher (5 weeks, 34–39 GW) than the difference observed in low-risk pregnancies (3–4 weeks, 35 or 36–39 GW, in the two propensity-matched cohorts analyzed), indicating that multifetal pregnancies represent an additive risk factor for APOs in women with CKD (Figures 2 and 3 and Table 2). Although the incidence of small for gestational age babies is not significantly higher in women with CKD, the fragility of these pregnancies is underlined by the higher need for NICU admission (50.9% versus 25.2%, $P = 0.0014$), mainly linked to early preterm delivery (Table 2).

Only one perinatal death was observed in the CKD cohort (associated with severe cardiac malformations, in a diabetic patient). However, in multifetal pregnancies, one of the most feared APOs, *i.e.*, intrauterine fetal death of at least one twin, was significantly higher in women with CKD than in controls (12.96% versus 3.60%, $P = 0.0012$), and the difference persisted even after omitting seven cases of selective pregnancy termination (one in the CKD group

Table 4. Logistic regression: stage 1 CKD multifetal versus stage 1 CKD singleton pregnancies

Outcome	OR	CI Lower	CI Higher	P Value	VIF
Term <37 wk					
Group (multifetal versus singletons) CKD	63.087 ^a	18.759 ^a	284.269 ^a	0.000 ^a	1.359 ^a
Not nulliparous versus nulliparous	0.707	0.207	2.228	0.561	1.058
BMI ≥ 25 kg/m ²	2.030	0.529	7.870	0.298	1.031
Age ≥ 35 yr	1.431	0.441	4.731	0.549	1.086
Year of delivery (2013–2023 versus 2000–2012)	0.182 ^a	0.045 ^a	0.589 ^a	0.008 ^a	1.436 ^a
Term <34 wk					
Group (multifetal versus singletons) CKD	9.733 ^a	3.260 ^a	33.567 ^a	0.000 ^a	1.112 ^a
Not nulliparous versus nulliparous	1.422	0.396	4.898	0.577	1.171
BMI ≥ 25 kg/m ²	0.482	0.083	2.076	0.364	1.149
Age ≥ 35 yr	0.496	0.120	1.712	0.291	1.031
Year of delivery (2013–2023 versus 2000–2012)	0.244 ^a	0.072 ^a	0.738 ^a	0.016 ^a	1.121 ^a
Centile <10					
Group (multifetal versus singletons) CKD	5.155	2.048	13.683	0.001	1.038
Not nulliparous versus nulliparous	0.958	0.314	2.743	0.938	1.107
BMI ≥ 25 kg/m ²	0.403	0.081	1.488	0.210	1.093
Age ≥ 35 yr	0.793	0.264	2.212	0.666	1.049
Year of delivery (2013–2023 versus 2000–2012)	0.693	0.262	1.823	0.455	1.078
Admission to an NICU					
Group (multifetal versus singletons) CKD	8.033	2.798	25.989	0.000	1.091
Not nulliparous versus nulliparous	0.824	0.221	2.741	0.760	1.117
BMI ≥ 25 kg/m ²	1.975	0.508	7.270	0.309	1.134
Age ≥ 35 yr	0.273	0.056	0.987	0.069	1.015
Year of delivery (2013–2023 versus 2000–2012)	0.260 ^a	0.080 ^a	0.764 ^a	0.018 ^a	1.114 ^a

BMI, body mass index; CI, confidence interval; NICU, neonatal intensive care unit; OR, odds ratio; VIF, variance inflation factor.

^aStatistical significance.

and six in the control group). These data are also in line with a higher, albeit nonsignificantly, prevalence in weight discordance between twins of mothers with CKD (24.3% versus 13.6%), suggestive of placental impairment. To contextualize these findings, the incidence of intrauterine fetal death in singleton pregnancies was in line with the data reported in the general population in the setting of study.²⁹

The additive risks of APOs in multifetal pregnancies in women living with CKD should be highlighted in counseling, especially in the case of assisted fertilization, and suggest a very cautious attitude toward multiple egg transfers in women affected by even early and mild CKD.

Since women with CKD often have fertility problems, due to hormonal imbalances, chronic inflammation, and reduced ovarian reserve, especially in advanced stages or following kidney transplantation,^{30,31} they are more likely to seek MART. A recent systematic review reported that pregnancy can be successfully achieved with MART in women with CKD, although with increased maternal and fetal risks compared with the general population.³² Accordingly, the Kidney and Pregnancy Group of the Italian Society of Nephrology recommends individualized evaluation before MART, considering CKD stage, PTU, hypertension, and the presence of comorbidities.³³

While this case series of 54 multifetal pregnancies in women with CKD is the largest one so far available and our study has the strength of using several control groups, the study has relevant limitations. Numbers are still small;

data come from only one country, whose population is mainly White; and the results discussed were obtained in settings with experience in the care of high-risk pregnancies.^{1,34} Data on single and multifetal low-risk pregnancies compare favorably with the recent literature, and the results discussed in this report might not be replicated in settings with different expertise.³⁵ Furthermore, there were very few patients in advanced CKD stages, where the risks are expected to be higher, and we could not stratify patients for assisted fertilization techniques, due to the low number of cases.⁴ Finally, the design of our study may carry the inherent biases of all retrospective studies, and some confounding factors may have been overlooked.

Notwithstanding these limitations, we hope that our analysis will be the basis for further multicenter studies, needed to more clearly define APOs and better understand the risks inherent in these particularly difficult pregnancies. The availability of long-term follow-up of the children is likewise needed to allow us to offer comprehensive counseling to women with CKD, particularly with regard to assisted reproductive technologies, balancing the higher odds for success with multiple implantations, and the risks linked to multifetal pregnancies. Moreover, the rapidly expanding use of MART demands specific interventions, such as limiting the embryo transfer in at-risk patients, to reduce the risk of APOs in women living with CKD. In the wait for more evidence, a careful surveillance of multifetal

pregnancy in women living with CKD of any stage is mandatory, and ideally, these women should be followed up by a multidisciplinary team, including at least a nephrologist and a gynecologist, with a shared strategy agreed also with the expecting woman (for instance, alternate consultations). Acknowledging that specific expertise and dedicated resources are not universally available, each setting should try to identify referents who could collaborate for the benefit of these women and assure the highest standard of care to maximize favorable pregnancy maternal and fetal outcomes.

This study, to date the largest one assessing the risk of APOs in multifetal pregnancies in women with CKD, shows that multifetal gestation poses a 63-fold increased risk of preterm delivery, a nine-fold risk of very early preterm delivery, and a five-fold risk of giving birth to a SGA baby with an eight-fold risk of NICU admission with respect to singleton gestations in women living with CKD. These results underline the need for more in-depth investigations. Furthermore, our data may inform women during the preconception counseling phase about the risks of multifetal gestation following MART and, in general, in CKD. This study warrants careful attention to the CKD-multifetal pregnancy association and should inform national/international recommendations and serve as a benchmark for future research, including long-term offspring follow-up.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/KN9/B525>.

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Writing – review & editing: Giorgia Barbara Piccoli, Massimo Torreggiani.

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Declarative Statements

This study includes clinical experimentation and received Institutional Review Board or Ethics Committee approval. The need to obtain informed patient consent was waived.

Data Availability Statements

Original data generated for the study will be made available upon reasonable request to the corresponding author. Data Type:

Published Material. Reason for Restricted Access: We will make data available upon reasonable request without restrictions.

Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/KN9/B526>.

Supplemental Methods. Definitions employed.

Supplemental Table 1.1. Baseline data on multifetal pregnancies and CKD, excluded cases (not Torino or not twins or not CKD G1).

Supplemental Table 1.2. Delivery data on multifetal pregnancies and CKD, excluded cases (not Torino or not twins or not CKD G1).

Supplemental Table 2. Cox proportional hazard ratio, in women with CKD G1 multifetal pregnancies (Torino, multifetal, CKD G1) versus women without CKD and multifetal pregnancies (matched controls).

Supplemental Table 3. Cox proportional hazard ratio, multifetal pregnancies in women with CKD (all stages and settings) versus propensity-matched controls without CKD.

Supplemental Table 4. Cox proportional hazard ratio in CKD G1 multifetal versus CKD G1 singleton pregnancies.

Supplemental Table 5. Cox proportional hazard ratio, singleton pregnancies in women with CKD versus non-CKD controls.

Supplemental Table 6. Cox proportional hazard ratio, multifetal versus singleton non-CKD low-risk pregnancies.

Supplemental Table 7. Logistic regression, multifetal pregnancies in women with CKD (all cases) versus propensity matched controls without CKD.

Supplemental Table 8. Logistic regression, singleton pregnancies in women with CKD versus non-CKD singleton controls.

Supplemental Table 9. Logistic regression, multifetal versus singleton pregnancies in controls.

Supplemental Table 10. Pregnancies with at least one intrauterine death in women with CKD.

Supplemental Figure 1. Selection of case hierarchy charts.

Supplemental Figure 2. Standardized mean differences between groups for each variable of each matching.

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