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Risk of congenital malformation in newborns from mothers with kidney diseases in a nationwide cohort study

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Abstract

Background Maternal chronic kidney disease (CKD) is associated with an increased risk of adverse pregnancy outcomes. However, the overall risk of congenital malformations (CMs) in offspring of mothers with kidney disease, including CKD and end-stage kidney disease (ESKD), remains unclear.

Methods In this nationwide cohort study, we analyzed National Health Insurance Service (NHIS) data from 2,680,092 women who gave birth between 2008 and 2017. Major CMs were identified using the International Classification of Diseases-10 (ICD-10) codes during the first 12 months after birth. A multivariable generalized estimating equation model was used to compare the risk of CMs between women with CKD or ESKD, including those on dialysis and post-kidney transplantation (KT), and healthy controls.

Results Major CMs prevalence is 4.79% in offspring of healthy mothers, 5.29% in CKD mothers, and 9.65% in ESKD mothers, with congenital heart defects being the most common anomaly across all groups. After adjustment, mothers with kidney diseases show a higher risk of major CMs than healthy controls (adjusted odds ratio [aOR], 1.07; 95% confidence interval [CI], 1.03–1.11 in CKD; aOR, 1.71; 95% CI, 1.16–2.52 in ESKD, respectively). Among ESKD patients, KT recipients show an increased risk (aOR, 1.65; 95% CI, 1.06–2.59), but dialysis patients do not reach statistical significance (aOR, 2.02; 95% CI, 0.92–4.41).

Conclusions Our findings suggest that neonates born to mothers with kidney diseases have an increased risk of CMs compared to those born to healthy mothers.

Plain language summary

Chronic kidney disease (CKD) in women can increase health problems during pregnancy, but its impact on birth defects in babies is not well understood. In this study, we used South Korea's National Health Insurance Service data from 2008 to 2017 to investigate whether babies born to mothers with kidney disease have a higher chance of birth defects. We compared mothers with CKD, those receiving dialysis, and those who had a kidney transplant with mothers without kidney disease. We found that babies of mothers with kidney disease had a higher risk of birth defects involving several major organs. These findings show the importance of early counseling, close monitoring, and careful prenatal care for women with kidney disease.

Chronic kidney disease (CKD) is a global health challenge with an increasing prevalence among women of childbearing age, affecting an estimated 3% of pregnancies in high-income countries[1]. Pregnancy in women with CKD is associated with increased risks of adverse maternal and fetal outcomes, including hypertension, preeclampsia, preterm delivery, intrauterine growth restriction, and neonatal intensive care unit (NICU)

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admission, despite advancements in medical management[1–5]. Even mild to moderate kidney impairment increases the likelihood of adverse pregnancy outcomes compared to women with normal kidney function[6]. However, although the severity of maternal CKD or pharmacologic interventions is known to influence child outcomes[7], evidence remains limited regarding complications with potential life-long consequences, such as congenital malformations (CMs).

CMs are a critical concern for pregnant women, particularly as the average maternal age and the prevalence of maternal chronic diseases have risen in recent generations[8,9]. According to the World Health Organization, while neonatal and under-five mortality rates are declining globally, congenital disorders account for a growing proportion of neonatal deaths[10]. Maternal chronic diseases, such as systemic lupus erythematous, hypertension, and thyroid diseases, as well as their medical treatments, have been linked to an increased risk of CMs in prior studies[11–14]. Furthermore, maternal obesity has been identified as a significant risk factor for congenital anomalies[15].

However, the impact of maternal kidney disease on the risk of CMs in offspring remains poorly understood. A recent Japanese cohort study reported an 80% higher risk of isolated congenital anomalies of the kidney and urinary tract (CAKUT) in children born to mothers with kidney diseases[11]. Similarly, a Denmark study found that children born to mothers receiving a kidney transplant (KT) had an increased risk of hospitalization due to infections and malformations during the first year of life[16]. However, these studies are limited by small sizes, single-center settings, or a narrow focus on specific CMs. Moreover, comprehensive data comparing outcomes across different groups of kidney disease, such as those managed with dialysis or transplantation, are lacking.

Therefore, we conducted a nationwide population-based cohort study to evaluate the risk of both general and specific CMs in offspring born to women with kidney diseases, including those who have undergone a kidney transplant or are receiving dialysis, compared to offspring of women without kidney diseases. We find that maternal kidney disease is associated with an increased risk of CMs in offspring. The elevated risks are observed across all groups, suggesting that maternal kidney dysfunction is an important contributor to CM risk.

Methods

Study Design

This nationwide population-based cohort study used the database from the Korean National Health Insurance Service (NHIS), National Health Screening Program for Infants and Children (NHSP-IC), and National Health Screening Examination (NHSE). The NHIS Korea, established in 2000, covers approximately 97% of the Korean population, providing extensive information on demographics, diagnostic codes based on ICD-10, and treatment records, including all prescribed surgeries, procedures, and drugs. To evaluate maternal and child health outcomes, we integrated the NHIS data with the NHSP-IC, which tracks child health and development, enabling linkage between maternal health records and their children's health outcomes. Detailed descriptions of the NHIS dataset and its study design have been described previously[17]. From January 2008 to December 2017, we retrieved information on all mothers who delivered live births recorded in the Korean NHIS database. Then, we excluded mothers with multiple pregnancies, as their malformation outcomes vary from those observed in singleton births[18]. Mothers were also excluded if they had incomplete information on pregnancy or neonatal outcomes, or if they lacked prenatal health checkup records required for diagnosing maternal pre-pregnancy kidney disease.

Definitions

Maternal kidney conditions were identified through ICD-10 codes and corresponding laboratory data. First, we categorized women with ESKD group as those with documented records of receiving kidney replacement therapy (KRT), including maintenance dialysis or undergoing a KT within 1 year before delivery. Maintenance dialysis was defined as undergoing hemodialysis or peritoneal dialysis for a minimum of one month. KT was identified by the presence of either the ICD-10 code Z94.0 or procedural codes related to kidney transplant surgery. Second, we defined pre-dialysis CKD as meeting at least one of the following within the five years prior to childbirth: (1) two or more measurements of estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, (2) dipstick albuminuria ≥1+ on at least two separate dates, or (3) a recorded ICD-10 diagnosis code for CKD (N18.x). The healthy control group comprised women who neither met the criteria for the kidney disease group nor showed evidence of eGFR <60 mL/min/1.73 m^2, or dipstick albuminuria of 1+ or higher on two consecutive tests within five years prior to delivery.

Outcomes

The primary outcome was the occurrence of 67 major CMs in liveborn neonates, identified using ICD-10 codes during the first 12 months after birth. Each of the major CMs was classified according to the European Surveillance of Congenital Anomalies classification (EUROCAT) 2014 definition criteria, which are structural changes that carry significant medical, surgical, or social consequences for the individuals and typically require intervention (Supplementary Table S1)[19]. The malformations were broadly grouped into 12 major subgroups: nervous system, eye/ear/face/neck, congenital heart defects, respiratory system, orofacial clefts, digestive system, abdominal wall defects, genital and urinary system, limb anomalies, chromosomal anomalies, and others. The secondary outcomes included the incidence of all CMs identified by ICD codes, encompassing both major and minor malformations. The specific ICD-10 codes used to define each subgroup of CMs, including nervous system (Q00–Q07), circulatory system (Q20–28), and urinary system (Q60–64), are listed in Supplementary Table S2.

Covariates

Maternal factors that might be associated with major CMs were collected as co-variates. Maternal age at the time of delivery, parity[20], and pre-pregnancy comorbidities such as hypertension[12], diabetes mellitus[21] were obtained. Parity was categorized as first versus second or higher births, as nearly 90% of pregnancies were first or second births. Neonatal sex was also included in the analysis, as it is known to influence CM risks[22]. Additionally, the socioeconomic variables such as family income level and urbanization of the residence were also included as covariates in the study. Comorbidities prior to pregnancy were identified using ICD-10 codes.

Statistical analysis

The demographic data for groups were presented as mean ± standard deviation (SD) for continuous variables and as number (percentage) for categorical variables. The risk of major CM in offspring born to women with or without kidney diseases was analyzed using a multivariable generalized estimating equations (GEE) model to account for clustering of repeated pregnancies within the same mothers. Variables were selected for the multivariable model based on clinical relevance and statistical significance in univariate logistic analysis. This criterion ensured that only variables demonstrating a meaningful association with the outcome were included in the final model. The odds ratio (OR) and 95% confidence interval (CI) for the risk of major CM were adjusted for the following covariates: Maternal age, neonatal sex, and parity for Model 1; All variables in Model 1, history of maternal comorbidities, urbanity, and family income level for Model 2. Comorbidities were defined as the presence of hypertension or diabetes diagnosed before pregnancy. The OR and 95% CI of the Crude, Model 1, and Model 2 are all presented. Sensitivity analyses were performed to examine the robustness of the results by expanding the primary outcome from major CMs to total CMs (major + minor), thereby assessing whether the associations were consistent across anomaly definitions. Additionally, an analysis according to CKD stage was conducted, categorizing eGFR as <60 vs ≥ 60 mL/min/1.73 m^2. Separate subgroup analyses were also conducted to assess differences in associations according to maternal comorbidities and parity. A two-tailed p-value < 0.05 was considered statistically significant. All

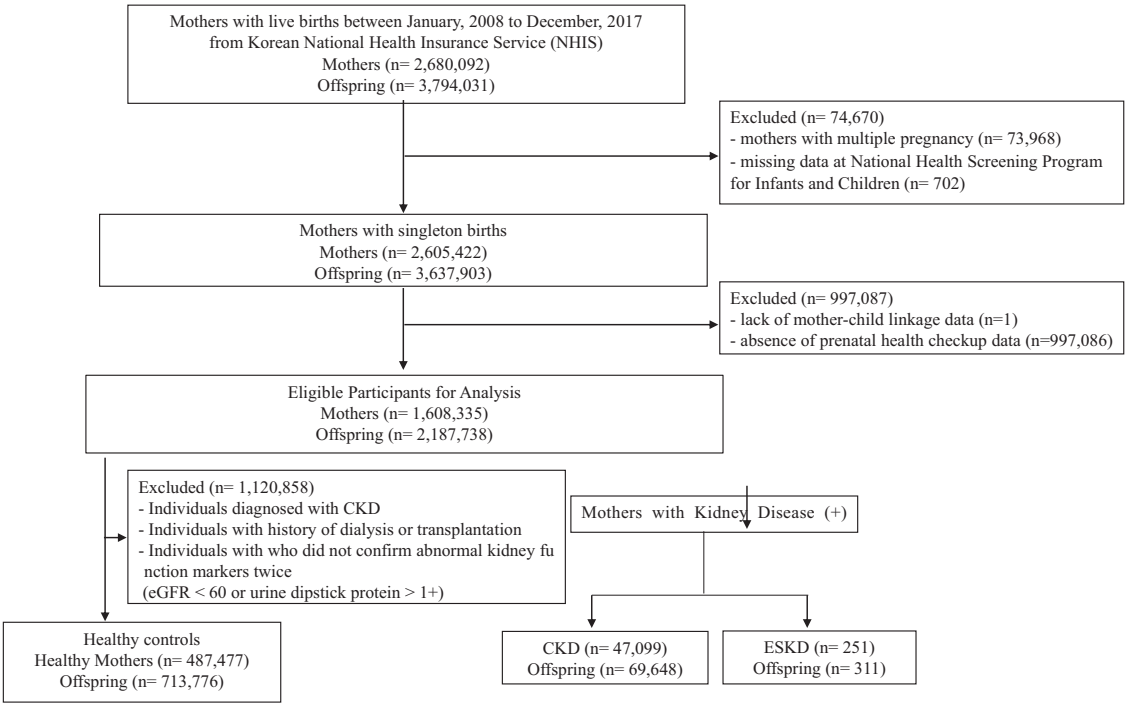

Fig. 1 | Study flow chart of the study population. CKD chronic kidney disease, ESKD end-stage kidney disease

statistical analyses were conducted using SAS Enterprise Guide software version 9.4 (SAS Institute Inc, Cary, North Carolina, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

This retrospective study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. 2102-127-1198). The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was waived due to the study's design, as it utilized anonymized and publicly available data.

Results

Baseline characteristics

During the study period, a total of 2,680,092 mothers and 3,794,031 offspring are registered from the Korean NHIS database (Fig. 1). After excluding women with multiple pregnancies and women with incomplete clinical data, the final study population included 534,827 mothers who gave birth to 783,735 children. These were categorized into three groups: 487,477 healthy women with 713,776 children, 47,099 women with CKD with 69,648 children, and 251 women with ESKD with 311 children.

Baseline characteristics and pregnancy outcomes of the study population are summarized in Table 1 and details on missing data are in Supplementary Table S3. Mothers with CKD and ESKD were older and exhibited higher prevalence rates of comorbidities, such as hypertension, diabetes mellitus, and dyslipidemia, compared to healthy mothers. Adverse fetal outcomes were more frequent in mothers with CKD and ESKD. These groups were more likely to give birth to low-birth-weight infants and to require NICU care to support their premature or medically complicated newborns, with these outcomes being more pronounced in ESKD mothers compared to those with CKD. Overall baseline characteristics and pregnancy outcomes showed statistical differences across groups, whereas neonatal sex did not.

Incidence of major congenital malformations according to maternal kidney function

The overall incidence of major CMs was higher in infants born to mothers with kidney diseases compared to those born to healthy mothers (Fig. 2, Supplementary Table S4), especially among those from ESKD mothers. The rates of major CMs were 5.29% in the CKD group and 9.65% in the ESKD group, compared to 4.79% in the healthy mother group. Congenital heart defects were the most common anomaly across all groups, with the highest prevalence in infants born to ESKD mothers (8.36%). Offspring of CKD mothers showed a relative increase in nervous system, digestive, and oro-facial clefts, while limb anomalies, despite being frequent, were slightly lower. Among infants of mothers with ESKD, chromosomal and digestive anomalies were the next most frequent, with a decreased proportion of limb anomalies compared to other groups.

Impact of maternal chronic kidney disease on major congenital malformations

Univariate and multivariate logistic regression analyses identified maternal kidney disease as an independent risk factor for major CMs (Table 2). The crude model revealed that both maternal CKD and ESKD were significantly associated with an increased risk of major CMs compared to healthy controls, with ORs of 1.11 (95% CI, 1.07–1.15) and 2.13 (95% CI, 1.44–3.14), respectively. In addition, fetal male sex, maternal comorbidities, low family income, and urban living revealed significant associations with an elevated risk of major CMs. When we adjusted these co-variables, both maternal CKD (aOR, 1.07; 95% CI, 1.03–1.11) and ESKD (aOR, 1.71; 95% CI, 1.16–2.52) remained significant risk factors. In analyses stratified by CKD stage, both strata showed higher odds of major CMs versus controls, with greater risk at lower eGFR in the unadjusted model (Supplementary Table S5). In the fully adjusted model, ORs were 1.12 (95% CI 1.08–1.17) for stage 1–2 and 1.24 (95% CI 0.90–1.70) for stage 3–5, showing an attenuated but consistent trend.

The adjusted ORs were 1.12 (95% CI 1.08–1.17) for stage 1–2 CKD and 1.43 (95% CI 1.05–1.90) for stage 3–5 CKD, though the fully adjusted model was not available for the latter due to small numbers.

Organ-specific analysis showed higher odds ratios for urinary system defects, followed by digestive system anomalies, oro-facial clefts, and congenital heart defects in offspring of CKD mothers in the crude model (Table 3). After fully adjustment, significant associations remained for urinary system (aOR, 1.40; 95% CI, 1.26–1.54), digestive system (aOR, 1.26; 95% CI, 1.06–1.49), and oro-facial clefts (aOR, 1.23; 95% CI, 1.01–1.50),

Table 1 | Baseline characteristics and pregnancy outcomes of the study population

Characteristic	Healthy (*n* = 713,776)	CKD (*n* = 69,648)	ESKD (*n* = 311)
Maternal factors			
Age, y	31.9 ± 3.53	32.3 ± 3.99	33.5 ± 4.22
<25	10,007 (1.3%)	1596 (2.3%)	7 (2.3%)
25–29	166,213 (21.2%)	15,082 (21.7%)	30 (9.7%)
30–34	388,112 (49.5%)	33,606 (48.3)	154 (49.5%)
35–39	131,685 (16.8%)	16,444 (23.6%)	97 (31.2%)
≥40	17,759 (2.3%)	2920 (4.2%)	23 (7.4%)
Maternal comorbidity			
Hypertension	11,426 (1.6%)	3468 (4.9%)	175 (56.3%)
Diabetes mellitus	19,229 (2.7%)	6794 (9.8%)	117 (37.6%)
Dyslipidemia	64,348 (9.0%)	18,569 (26.66%)	201 (64.6%)
Serum creatinine (mg/dL)	0.79 ± 0.88	0.80 ± 0.95	1.45 ± 1.59
Urine albuminuria (≥1+)	5472 (0.8%)	2448 (4.6%)	18 (16.5%)
Parity (Number of births), *n* (%)			
1	487,477 (68.3)	47,098 (67.62)	249 (80.06)
≥2	226,299 (31.7)	22,550 (32.38)	62 (19.94)
Family Income level, *n* (%)			
5th Quintile (Highest)	59,371 (8.3%)	8511 (12.2%)	69 (22.2%)
4th Quintile	110,040 (15.4%)	11,488 (16.5%)	49 (15.8%)
3rd Quintile	201,621 (28.3%)	17,912 (25.7%)	71 (22.8%)
2nd Quintile	216,601 (30.4%)	19,079 (27.4%)	56 (18.0%)
1st Quintile (Lowest)	84,936 (11.9%)	9412 (13.5%)	45 (14.5%)
Urbanity, *n* (%)			
Urban	499,557 (69.9%)	50,193 (72.1%)	213 (68.5%)
Rural	214,219 (30.0%)	19,455 (27.9%)	98 (31.5%)
Neonatal outcomes			
Neonatal sex, male	366,610 (51.4%)	35,609 (51.1%)	151 (48.6%)
Mean birth weight (kg)	3.21 ± 0.46	3.20 ± 0.48	2.60 ± 0.69
Low birth weight, *n* (%)	22,707 (3.3%)	2924 (4.3%)	102 (34.6%)
NICU admission	31,613 (4.4%)	3710 (5.3%)	80 (25.7%)

Data are presented as numbers (%) or mean ± Standard deviation (SD).
BMI body mass index, *NICU* neonatal intensive care unit, *CKD* chronic kidney disease, *ESKD* end-stage kidney disease.

while congenital heart defects (aOR, 1.01; 95% CI, 0.96–1.37) were no longer significant. However, in the ESKD group, the small number of cases limited the assessment of the incidence of all organ-specific malformations. Nevertheless, chromosomal anomalies and congenital heart defects demonstrated a significantly higher risk (aOR, 8.24; 95% CI, 2.05–33.15; aOR, 2.64; 95% CI, 1.41–3.91, respectively) (Supplementary Table S6).

Sensitivity analysis

Sensitivity analyses were conducted to assess the robustness of the findings by examining the risk of total CMs (Supplementary Table S7) and specific organ malformation sites (Supplementary Table S8). The results remained consistent, showing an elevated risk of total CMs in both CKD and ESKD groups compared to healthy controls, even after adjusting for multiple confounders (CKD: aOR, 1.07, 95% CI, 1.05–1.09; ESKD: aOR 1.46, 95% CI, 1.13–1.87).

Organ-specific analyses indicated that maternal CKD was associated with increased odds of malformations in the nervous system, eye, ear, face, and neck, circulatory system, respiratory system, and urinary system. Consistent with the analysis of major CMs, urinary system defects demonstrated the highest risk among neonates of mothers with CKD (aOR,1.46; 95% CI, 1.35–1.57). In contrast, ESKD groups showed no significant association for urinary system defects, while associations were predominantly in the circulatory and respiratory systems. Since comorbidities such as hypertension and diabetes, as well as obstetric factors like parity, are well-established independent risk factors for adverse pregnancy outcomes, we conducted a subgroup analysis to explore whether these conditions influence the association between maternal kidney disease and major CMs (Fig. 3). In mothers with CKD, the risks of major CMs were consistently elevated across all subgroups. Notably, hypertension significantly amplified the risk, with hypertensive mothers showing a higher risk (OR, 1.23; 95% CI, 1.05–1.43, interaction $p = 0.005$) compared to non-hypertensive mothers (OR 1.06; 95% CI, 1.02–1.10). For diabetes and parity, while the risks remained elevated, no statistically significant interaction was observed. Similarly, in the ESKD mother group, the risk of major CMs appeared consistently higher across all subgroups, without significant variation.

Different impact of kidney replacement therapy on major congenital malformation

Given the substantial heterogeneity within the ESKD group, subgroup analyses were performed to separately evaluate the impact of dialysis and kidney transplant recipients on major CM risk (Table 4). Interestingly, while the risk of major CMs was elevated in both the KT and dialysis groups, statistical significance was observed only in mothers who underwent KT (aOR, 1.65; 95% CI, 1.06–2.59). In contrast, the dialysis group demonstrated an increased risk that did not reach statistical significance (aOR, 2.02; 95% CI, 0.92–4.41).

Discussion

This nationwide population-based study provides comprehensive insights into the relationship between maternal kidney disease and the risk of major CMs. Our findings demonstrate that both CKD and ESKD are independent risk factors for major CMs in offspring, with ESKD presenting the highest risk. Maternal CKD was associated with increased odds of malformations across multiple organ systems, particularly the urinary system, while ESKD showed a stronger link to congenital heart defects and chromosomal anomalies. Notably, among ESKD mothers, KT was associated with increased CM risk, whereas dialysis showed a non-significant trend. These findings underscore the need for risk stratification and the intergenerational impact of maternal kidney disease.

Our findings align with previous studies showing that chronic maternal conditions, such as diabetes, hypertension and autoimmune disease, are significant risk factors for congenital anomalies in their offspring[23–25]. A recent U.S. study reported 2.4-fold increased risk in mothers with pre-pregnancy diabetes, and 1.3-fold increasing for those with gestational diabetes[23]. Similarly, maternal hypertension has been linked to fetal growth restriction, preterm delivery, and birth defects, including congenital heart defects[24]. These metabolic or inflammatory disturbances may contribute to oxidative stress and uteroplacental dysfunction, resulting in organ agenesis or fetal underdevelopment[26,27]. Because diabetes and hypertension are major causes of CKD, it is plausible that maternal kidney disease shares similar pathogenic pathways contributing to neonatal outcomes. Notably, we observed that neonates from CKD mothers with hypertension exhibited an even greater risk of anomalies compared to those without hypertension, highlighting the additive effect of maternal comorbidities on congenital anomalies risk.

The mechanism contributing to the increased risk of CMs in maternal kidney disease remains unclear but likely involves a combination of genetic predisposition, systemic metabolic changes, and placental dysfunctions. Familial clustering of congenital anomalies, particularly

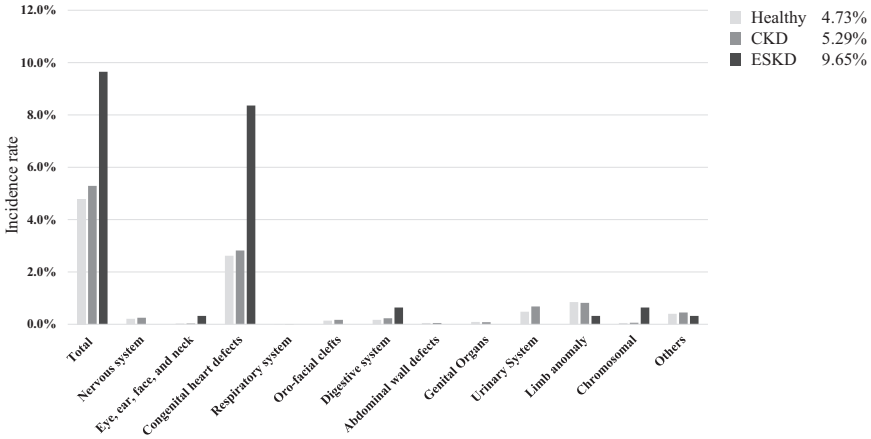

Fig. 2 | Prevalence of major congenital malformations by maternal kidney function. Shown are the prevalence rates (%) of major congenital malformations in offspring born to Healthy mothers, CKD mothers, and ESKD mothers. *CKD* chronic kidney disease, *ESKD* end-stage kidney disease.

Table 2 | Risk of major congenital malformation outcomes associated with maternal kidney disease

	Healthy OR (95% CI)	CKD	ESKD
Crude	Ref	1.11 (1.07–1.15)**	2.13 (1.44–3.14)**
Model 1	Ref	1.10 (1.06–1.14)**	2.01 (1.36–2.96)**
Model 2	Ref	1.07 (1.03–1.11)**	1.71 (1.16–2.52)*

Data are presented as OR (95% CI).
Crude: unadjusted
Model 1: adjusted for age, neonatal sex, and parity
Model 2: Model 1 + comorbidities, urbanity, family income level
OR, odds ratio; CI, confidential interval; CKD, chronic kidney disease; ESKD, end-stage kidney disease
*$p < 0.05$, **$p < 0.01$.

Table 3 | Multivariate analysis of mothers with CKD and specific major congenital malformation

	Crude OR (95% CI)	Adjusted OR# (95% CI)
CKD (*n* = **69,648**)		
Nervous system	1.17 (1.00–1.37)	1.14 (0.97–1.34)
Eye, ear, face, and neck	0.86 (0.54–1.37)	0.85 (0.53–1.37)
Congenital heart defects	1.05 (1.01–1.10)**	1.01 (0.96–1.05)
Respiratory system	1.26 (0.63–2.52)	NA
Oro-facial clefts	1.29 (1.06–1.56)*	1.23 (1.01–1.50)*
Digestive system	1.32 (1.12–1.56)**	1.26 (1.06–1.49)**
Abdominal wall defects	0.97 (0.69–1.37)	0.94 (0.67–1.33)
Genital Organs	0.93 (0.71–1.22)	0.90 (0.69–1.19)
Urinary System	1.43 (1.29–1.57)**	1.40 (1.26–1.54)**
Limb anomaly	0.96 (0.88–1.05)	0.96 (0.88–1.05)
Chromosomal	1.17 (0.84–1.62)	1.02 (0.73–1.42)
Others	1.11 (0.99–1.25)	1.08 (0.96–1.21)

Data are presented as OR (95% CI). OR is calculated with healthy mothers as the reference group.
#Adjusted for age, neonatal sex, parity, comorbidities, urbanity, and family income level
OR odds ratio, *CI* confidential interval, *CKD* chronic kidney disease
*$p < 0.05$, **$p < 0.01$.

congenital anomalies of the kidney and urinary tract (CAKUT), supported a genetic component, as up to 50% of affected families have a history of kidney or urinary tract disease[28]. A Japanese cohort also reported an increased risk of isolated CAKUT in offspring of mothers with kidney disease[29]. Consistent with these studies, urinary tract anomalies showed a higher prevalence among neonates of CKD mothers. Maternal CKD also introduces systemic metabolic and hemodynamic alterations that might impair placental and fetal development. Uremic toxin, such as indoxyl sulfate, causes endothelial dysfunction, contributing to placental insufficiency and preeclampsia[30]. CKD-related anemia could further exacerbate uteroplacental insufficiency, potentially leading to fetal underdevelopment[31]. Consistent with these pathophysiologic mechanisms, CM risk increased as renal function declined, rising with lower eGFR in CKD and peaking in ESKD in the present study.

In our data, the distribution of CMs appears to shift according to maternal kidney disease status. First, neonates born to ESKD mothers had a higher risk of congenital heart defects and chromosomal anomalies rather than urinary tract anomalies. This difference in CM distributions according to CKD severity suggests that as CKD progresses, the systemic effects of uremia or other metabolic conditions associated with ESKD become more direct and pronounced than genetic predisposition, exerting a more substantial impact during pregnancy on offspring outcomes[32–34]. This pattern is further supported by the higher proportion of congenital heart defects in the ESKD group, which may be linked to progressive placental maladaptation and maternal metabolic or vascular disturbances. Second, our subgroup analysis of the ESKD group revealed varying CM risks depending on KRT type. Both dialysis and KT showed increased risks, but statistical significance was observed only in KT recipients. In KT recipients, immunosuppressive medications such as mycophenolic acid and mammalian target of rapamycin (mTOR) inhibitors are essential to maintain allograft function but have known teratogenic potential[34–36]. Conversely, dialysis patients may experience a significant uremic burden; however, intensified dialysis regimens aimed at optimizing pregnancy outcomes could mitigate these risks[5]. Although our study lacked detailed information on immunosuppressive agents, previous evidence indicates that pregnancy-related complications are more frequent among transplant recipients, implying a role of maternal kidney condition itself[37]. Further studies are needed to clarify the related factors of fetal outcomes in this high-risk population.

The present study has several strengths. To our knowledge, this is the first to comprehensively evaluate the association between maternal kidney diseases–including dialysis and kidney transplantation–and neonatal CMs in a large, nationwide cohort. The use of stringent diagnostic criteria allowed for precise patient classification according to their kidney diseases and minimized potential misclassification. This methodological rigor is reinforced by the fact that the incidence of major CMs in the healthy controls (4.79%) aligns with the previous reported rate of 434/10,000 livebirths in Korean mothers[38]. In addition, by restricting the analysis to live births, we provided robust estimates of CM risks, as CMs are a leading cause of miscarriage and stillbirths.

However, the study also has several limitations. First, as a cross-sectional study, causal relationships cannot be established. Second, although selection bias is possible due to inclusion of only mothers with health screening data, similarities to prior nationwide NHIS cohorts suggest that potential bias is likely minimal. Third, the small sample size in the ESKD

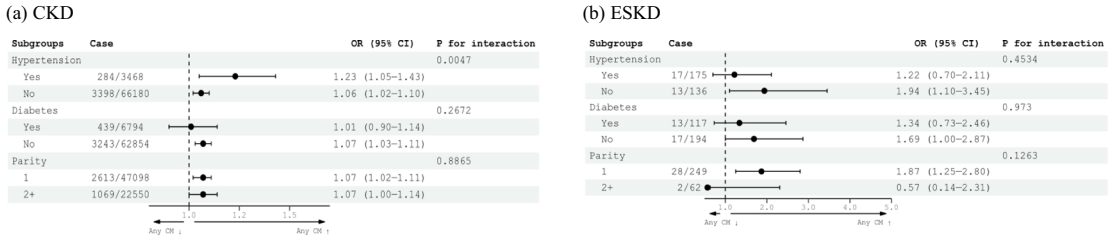

Fig. 3 | Subgroup analyses of major congenital malformations by maternal kidney disease. Forest plots show subgroup results by maternal hypertension, diabetes, and parity in (**a**) CKD and (**b**) ESKD mothers. The model was adjusted for age, neonatal sex, parity, comorbidities, urbanity, and family income level. CKD chronic kidney disease, ESKD end-stage kidney disease.

Table 4 | Risk analysis of major congenital malformations based on dialysis and kidney transplantation status

	Healthy OR (95% CI)	KT ($n = 242$)	Dialysis ($n = 69$)
Crude	Ref	2.09 (1.34–3.26)**	2.27 (1.03–5.03)*
Model 1	Ref	1.94 (1.24–3.03)**	2.23 (1.02–4.89)*
Model 2	Ref	1.65 (1.06–2.59)*	2.02 (0.92–4.41)

Data are presented as OR (95% CI) and p-value.
Crude: unadjusted
Model 1: adjusted for age, neonatal sex, and parity
Model 2: Model 1 + comorbidities, urbanity, and family income level
OR odds ratio, *CI* confidential interval, *KT* kidney transplant
*$p < 0.05$, **$p < 0.01$.

subgroup, particularly for dialysis participants, limited the analysis of organ-specific malformations and may have introduced bias. Fourth, residual confounders, such as medication use, lifestyle, and genetic predispositions, may have influenced the results. In particular, exposure to medications commonly used in patients with kidney disease, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and immunosuppressants in transplant recipients, could contribute to drug-induced malformations. Further studies are needed to evaluate their impact on this population. Lastly, CM were identified using ICD-10 codes, which may not capture all cases during postpartum assessments. However, major CMs are reliably recorded due to their clinical significance, mitigating this limitation.

Conclusion

This nationwide cohort study identified an increased risk of CMs in neonates born to mothers with CKD and ESKD. These findings underscore the importance of preconception counseling and careful prenatal care to optimize pregnancy outcomes and neonatal health. Further research is essential to clarify these associations and develop effective interventions.

Data availability

This study used data from the National Health Insurance Service of the Republic of Korea (NHIS), including data from the National Health Screening Program for Infants and Children (NHSP-IC), and the National Health Screening Examination (NHSE). The NHIS data are not publicly available due to privacy restrictions, but are available for research purposes through the Korean National Health Insurance Data Sharing Service upon institutional approval and request. Researchers who wish to access the data may apply at https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do. The numerical source data underlying the main figures are provided as Supplementary Data files. The source data for Fig. 2 is in Supplementary Data 1, and for Fig. 3 are in Supplementary Data 2.

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Competing interests

The authors declare no competing interests.

Additional information

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