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Incidence and Risks of Congenital Anomalies of Kidney and Urinary Tract in Newborns

A Population-Based Case–Control Study in Taiwan

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Abstract: Congenital anomalies of the kidney and urinary tract (CAKUT) are 1 of the major factors in young adults needing renal replacement therapy, but there is little extensive assessment of their incidence and risk factors. This study aimed to evaluate trends in the incidence of and risk factors for CAKUT among all births in Taiwan.

This population-based case–control study design was conducted using the Taiwan national births registry, which contains detailed information about maternal health and characteristics of newborns, supplied by health professionals. Of 1,603,794 newborns registered between 2004 and 2014, 668 infants were reported to have CAKUT. Newborns without congenital anomalies were matched with CAKUT cases by birth year, month, and Apgar score in a ratio of 5:1. Odds ratio (OR) and 95% confidence interval (CI) for developing CAKUT were calculated using a conditional multivariate logistic regression model.

The incidence of CAKUT was approximately 4.2 per 10,000 births. The adjusted ORs for CAKUT in newborns associated with maternal age of 20 to 29 (OR, 2.18; 95% CI, 1.11–4.28), or 30 to 39 (OR, 2.29; 95% CI, 1.17–4.51), maternal gestational diabetes (OR, 2.22, 95% CI, 1.06–4.67), maternal thalassemia/hemochromatosis (OR, 2.67; 95% CI, 1.35–5.27), polyhydramnios or oligohydramnios (OR, 9.16; 95% CI, 5.46–15.37), birth parity >1 (OR, 0.27; 95% CI, 0.15–0.50), having a gestational age <37 weeks (OR, 1.48; 95% CI, 1.23–1.78), and being a boy (OR, 1.83; 95% CI, 1.53–2.19). Infants of mother with gestational diabetes were more likely to have congenital anomalies, small gestational age (<37 weeks) and low birth weight.

CAKUT are associated with several maternal health risk factors. As Taiwan has the highest prevalence and incidence rates of end-stage renal disease in the world, these findings strongly support the need to develop professional guidelines for prenatal counseling and management of women at risk of adverse birth outcomes, to prevent kidney disease progression and reduce complications.

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Abbreviations: AGA = appropriate gestational age (37–40 weeks), BCA = Birth Certificate Application, CAKUTc = ongenital anomalies of the kidney and urinary tract, CKD = chronic kidney disease, DM = diabetes mellitus, ESRD = end-stage renal disease, GDM = gestational diabetes mellitus, HBW = high birth weight (>4000 g), HPA = Health Promotion Administration, LBW = low birth weight (<2500 g), LGA = large gestational age (>40 weeks), NBW = normal birth weight (2500–4000 g), RRT = renal replacement therapy, SGA = small gestational age (<37 weeks), UPJ = ureteropelvic junction.

INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) are characterized by structural and functional abnormalities of kidney, collecting system, bladder, and urethra.[1] CAKUT have been identified in 20% to 50% of all fetal congenital anomalies in some populations,[2–4] but the causes remain unclear. Although children with CAKUT are often asymptomatic, CAKUT are estimated to be implicated in 30% to 60% of cases of childhood-onset chronic kidney disease (CKD) in different populations.[5] They are also 1 of the major causes of renal replacement therapy (RRT) and premature mortality in the young adult population.[6,7] Data from the European Renal Association-European Dialysis and Transplant Association Registry indicated that RRT for end-stage renal disease (ESRD) occurred earlier in patients with CAKUT (31 years old) than others (61 years old).[7] A Taiwanese population-based study indicated that the incidence rate of ESRD had substantially increased in adolescents (13–17 years) and young adults (18–30 years),[8] reflecting a high burden of both CKD and ESRD in Taiwanese young people.

An increase in women with diabetes mellitus (DM) at childbearing age has been reported in some populations.[9–11] Diabetes during pregnancy increases the risk of adverse outcomes, including congenital malformations.[12,13] Some studies have suggested that gestational DM accounts for 5% to 6.1% of malformations in newborns, compared with a general population risk of 1.3% to 2.8%, with a relative risk of 1.86 of congenital anomalies.[12–14] A recent study suggested that diabetes during the first 20 weeks of gestation is more crucial than late gestational diabetes, giving an additional 34% risk of having infants with CAKUT.[15] The possible causes of congenital kidney and urinary tract-specific malformations are multifactorial and involve

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maternal health,[12] genetics, and in utero environmental factors.[16,17] As the presence of CAKUT has implications for subsequent morbidity and mortality and provision of services, understanding of changes in epidemiological trends and relevant risk factors, particularly modifiable maternal factors, is imperative for early detection and prediction of prognosis during gestation.

We conducted a population-based study using data from the nationwide birth registry to identify possible risk factors and temporal trends in the incidence of CAKUT in the population of Taiwan from 2004 to 2011. We also examined the prevalence of maternal diabetes and compared the differences in birth characteristics between the children of women with and without diabetes.

MATERIALS AND METHODS

Data Source

The Birth Certificate Application (BCA) is maintained by the Health Promotion Administration (HPA) of the Ministry of Health and Welfare in Taiwan, and contains information about birth defects in newborns, reported from the medical perspective. According to the Protection of Children and Youth Welfare and Rights Act, medical facilities or midwives have to inform the Household Registration Office and HPA in Taiwan of relevant birth information within 7 days of a birth.[18] Congenital anomalies in newborns are recorded by the birth delivery doctor in a birth defects form, which classifies defects into 9 types: nervous system; eye and face; heart and circulatory system; digestive system; genitourinary system; musculoskeletal system; respiratory system; chromosomal abnormalities; and others. Births classified as ''with birth malformations'' could have any of these, and births ''without birth malformations'' have none.

Design and Study Subjects

A population-based, case–control study was designed to evaluate trends in the incidence of CAKUT and associated risk factors in a birth cohort using the BCA dataset for the period between 2004 and 2011 in Taiwan. A newborn with renal hypoplasia, polycystic kidney disease, ureteropelvic junction (UPJ) obstruction, and other kidney disorders were classified as having CAKUT. Genital anomalies, including hypospadias, indeterminate sex, and cryptorchidism were excluded. In this population-based study, the number of cases is relative small and a large number of potential controls to select from the national registry. In order to ensure the necessary statistical power to detect an effect of important risk factor, a control group of newborns was randomly selected from births without any congenital malformation and matched by birth year and Apgar score at 5 min (<7, ≥ 7, missing) to cases in a 5:1 ratio with most pair-match cases to maximize the statistical power for significance testing.[19] The Institutional Review Board of Medical Research Ethics in Chang Gung Medical Foundation approved the study.

Risk Factors and Covariate Assessment

The BCA dataset includes information on maternal characteristics, including maternal age, original nationality, mode of delivery (vaginal delivery, caesarean section), birth order (1 or >1), maternal health conditions (21 categories since 2004), and complications during labor (16 categories). The variables used in this study included age, nationality, medical conditions (eg, cardiovascular disease, hypertension, diabetes, renal disease) existing before and during pregnancy, lifestyle habits during pregnancy (any alcohol and tobacco use), and illicit drug use. Maternal age was categorized into age groups (<20, 20–29, 30–39, and 40 or more years). Nationality was initially evaluated using multiple categories. However, no differences were seen among those of non-Taiwanese nationality, and race was therefore categorized as Taiwanese or non-Taiwanese. Complications during labor and delivery were dichotomized into with or without complications.

Birth outcomes were obtained from the BCA dataset, including congenital anomalies (9 categories), gender, gestational age in weeks, and birth weight in grams. Gestational age at birth was classified as <37 weeks (small gestational age, SGA), 37 to 40 weeks (appropriate gestational age, AGA), and >40 weeks (large gestational age, LGA). Birth weight was categorized as <2500 g (low birth weight, LBW), 2500 to 4000 g (normal birth weight, NBW), and >4000 g (high birth weight, HBW).

Statistical Analysis

The incidence of CAKUT and any anomalies were reported by year as number of births per fiscal year as the denominator. Data were summarized as counts and proportions or as means with standard errors for the characteristics of mothers and newborns. Chi-squared tests were used to calculate the significance of distribution between groups.

Associations between prenatal risk factors for the development of CAKUT were investigated among maternal and birth characteristics reported in the birth registry dataset. In order to avoid potential informative missing gender information, ''missing'' was also included as a category for gender and adjusted in the model and to prevent loss of data because of missing covariates. The candidate predictors associated with the outcome were selected according to the adjusted odds ratio (OR) with $P < 0.05$ of individual factors using conditional multivariate logistic regression including 20 individual factors with 25 degrees of freedom. The selected variables that can explain significant variability in the likelihood of CAKUT were assessed by adding into the multivariate logistic regression separately, and the final adjusted predicted model was determined based on the smallest value of Akaike Information Criterion. The Hosmer–Lemeshow test was employed to confirm goodness of fit of the model.

Tests for trends were performed for incidence of both congenital anomalies more generally, and CAKUT specifically, and prevalence of maternal health risk factors, based on the number of cases per year among births and the number of births per year. Changes over time were tested using the Cochran–Armitage test (Z statistic, P value)[20] to identify increasing or decreasing prevalence (P value for 1-sided test) of major maternal health risk factors. This is useful to flag potential changes in patterns of prevalence of specific anomalies.[21] All statistical tests were 2-tailed and the level of significance was $P \leq 0.05$. Data processing and analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the Study Population

During the study period (2004–2011), there were 1,603,794 births reported, and 12,611 newborns with at least 1 congenital anomaly, an average incidence of 7.83 ($\pm$0.88) per 1000 births. There were 668 cases of CAKUT, an average incidence of 0.42 ($\pm$0.02) per 1000 births. The most common genital-urinary system malformations were polycystic kidney (10.63%), UPJ obstruction (10.22%), cryptorchidism (9.81%),

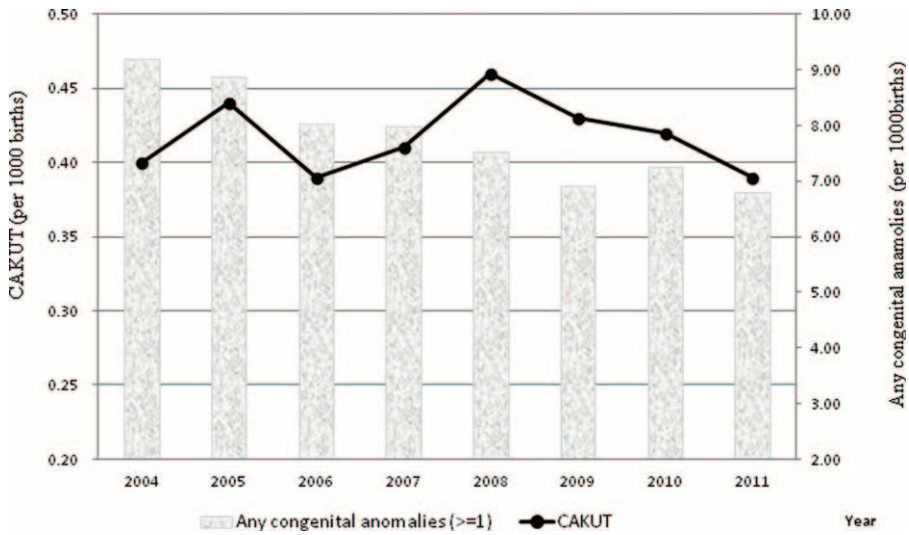

FIGURE 1. Incidence of CAKUT and overall congenital anomalies by year, 2004 to 2011. Mean incidence was 0.42 (±0.02) per 1000 births for CAKUT and 7.83 (±0.88) per 1000 births for any congenital anomalies. There was a significant downward trend in the incidence of any congenital anomalies ($Z = -11.42$, $P < 0.001$), but not in CAKUT ($Z = -0.05$, $P = 0.48$).

and renal hypoplasia (9.73%). Figure 1 shows the trend in the incidence of any congenital anomalies and CAKUT over time. The trend declined significantly for overall congenital malformation ($Z = -11.42$, $P < 0.001$), but not for CAKUT ($Z = -0.05$, $P = 0.48$).

Table 1 shows the characteristics of newborns with CAKUT and without any congenital anomalies in the study cohort. There was no difference in maternal age, nationality, and mode of delivery, but there were more mothers in the CAKUT group than in the control group with at least 1 comorbid condition, such as gestational diabetes, polyhydramnios or oligohydramnios, and histories of abnormal weight babies, thalassemia/hemochromatosis, and smoking or substance misuse. Overall, 22.75% of mothers in the CAKUT group and 19.88% in the control group had at least 1 type of complication during labor ($P = 0.09$). Malposition and fetal distress were more likely to occur in the CAKUT group (8.53%) than control group (6.14%) ($P = 0.02$). There were more boys in the CAKUT group (66.17%) than in the control group (53.05%), more infants born at <37 weeks of gestational age (40.42% vs 31.17%), and more with birth weight <2500 g (37.72% vs 30.90%) (Table 1).

Risk Factors Associated With CAKUT

Eight predictive factors for CAKUT in newborns were identified by full model of multivariate regression (Table 2). Significant maternal factors associated with CAKUT in the multivariate model were: maternal age (20–29 years: OR, 2.18, 95% confidence interval [CI], 1.10–4.28; 30–39 years: OR, 2.29, 95% CI, 1.17–4.50), gestational diabetes (OR, 2.22; 95% CI, 1.06–4.67), polyhydramnios or oligohydramnios (OR, 9.16; 95% CI, 5.46–15.37), thalassemia or hemochromatosis (OR, 5.69; 95% CI, 1.68–19.34), and other illness (OR, 2.43; 95% CI, 1.38–4.28). Also, infants with CAKUT were more likely to be boys (OR, 1.83; 95% CI, 1.53–2.19), and born at SGA (OR, 1.48; 95% CI, 1.23–1.78).

Although more CAKUT infants were born to mothers with anemia (OR, 1.64; 95% CI, 0.69–3.92), pregestational diabetes (OR, 1.63; 95% CI, 0.38–7.09), pre-existing renal disease (OR, 1.68; 95% CI, 0.33–8.58), and cigarette/substance misuse (OR, 1.68; 95% CI, 0.42–6.76), no statistically significant associations were found after adjustment for other factors. The risk of delivery complications was not significant (OR, 1.07; 95% CI, 0.85–1.33) on CAKUT after adjustment for other maternal and newborn characteristics.

Maternal Health and Birth Outcomes

The rate of mothers with at least 1 illness consistently increased over time in the study population (Supplemental Figure 1A, http://links.lww.com/MD/A661). Significant upward trends over time were identified in subgroups of any maternal risk factor ($Z = 28.33$, $P < 0.001$). The most common disease was GDM. The overall maternal diabetes exposure (pregestational and gestational) was 7.87 per 1000 births. The prevalence increased for both GDM (5.41 per 1000 births in 2010, and 8.47 per 1000 births in 2011, Cochran–Armitage test for trend with $Z = 16.42$, $P < 0.001$) and pre-existing DM (1.18 and 1.5 per 1000 births in 2010 and 2011, respectively; Cochran–Armitage test for trend with $Z = 3.49$, $P < 0.001$) in Supplemental Figure 1B, http://links.lww.com/MD/A661. Hypertension was also prevalent and showed an upward trend over the study period in both before (0.09 and 0.14 per 1000 births in 2010 and 2011, respectively; Cochran–Armitage test for trend with $Z = 6.44$, $P < 0.001$) and during pregnancy (0.57 and 0.71 per 1000 births in 2010 and 2011, respectively; Cochran–Armitage test for trend with $Z = 9.01$, $P < 0.001$) (Supplemental Figure 1C, http://links.lww.com/MD/A661).

The distributions of birth outcomes by maternal diabetes status are shown in Table 3. GDM mothers were slightly more likely to have infants with at least 1 anomaly (1.25% compared with 0.78% in mothers without diabetes, $P < 0.001$). Mothers with GDM also had a higher proportion of LBW babies (11.88% vs 9.33%), babies born at <37 weeks of gestational age (20.04% vs 9.64%), and boys (54.42% vs 52.19%). There was an increasing number over time of both newborns with LBW (9.15 per 1000 births in 2010, and 9.80 per 1000 births in

TABLE 1. Characteristics of Newborns With and Without CAKUT, 2004 to 2011

Characteristics	CAKUT (n = 668)		Controls (n = 3340)		*P* Value
Mother					
Maternal age, y					0.15
<20	10	1.50%	99	2.96%	
20–29	312	46.71%	1592	47.66%	
30–39	329	49.25%	1576	47.19%	
40 or more	17	2.54%	73	2.19%	
Original nationality					0.77
Taiwanese	604	90.42%	3032	90.78%	
Other nationality	64	9.58%	308	9.22%	
Mode of delivery					0.65
Vaginal delivery	450	67.37%	2280	68.26%	
Caesarean section	218	32.63%	1060	31.74%	
Birth order					<0.001
1	655	98.05%	3167	94.82%	
>1	13	1.95%	173	5.18%	
Number of maternal illness					<0.001
0	565	84.58%	3091	92.54%	
1	87	13.02%	216	6.47%	
2	16	2.40%	33	0.99%	
Anemia (HCT < 30 or Hb < 10)	8	1.20%	26	0.78%	0.28
Pregestational diabetes	3	0.45%	7	0.21%	0.26
Gestational diabetes	11	1.65%	24	0.72%	0.02
Polyhydramnios/oligohydramnios	48	7.19%	24	0.72%	<0.001
Pregestational hypertension	4	0.60%	23	0.69%	0.80
Gestational hypertension	8	1.20%	33	0.99%	0.62
Pre-eclampsia	4	0.60%	27	0.81%	0.57
Previous low/very low or over-birth weight births	0	0%	23	0.69%	0.03
Pregestational renal disease	3	0.45%	5	0.15%	0.11
Thalassemia/hemochromatosis	7	1.05%	5	0.15%	<0.001
Pregestational heart disease or hypertension	4	0.60%	23	0.69%	0.80
Cigarette/alcohol/substance use	3	0.45%	14	0.42%	>0.05
Others	20	2.99%	41	1.23%	<0.001
Delivery complications					0.09
0	516	77.25%	2676	80.12%	
≥1	152	22.75%	664	19.88%	
Meconium aspiration syndrome, middle to severe	13	1.95%	76	2.28%	0.60
Premature rupture of membranes	21	3.14%	116	3.47%	0.67
Abruptio placenta	6	0.90%	56	1.68%	0.14
Placenta previa	7	1.05%	25	1.05%	0.43
Bleeding (vaginal delivery > 500 mL or CS > 1000 mL)	3	0.45%	22	0.66%	0.53
Precipitous labor (<3 h)	8	1.20%	58	1.74%	0.32
Prolonged labor (regular uterine contraction > 20 h)	9	1.35%	37	1.11%	0.60
Failure to progress	13	1.95%	43	1.29%	0.19
Malposition	57	8.53%	205	6.14%	0.02
Cephalopelvic disproportion	9	0.35%	19	0.57%	0.03
Fetal distress	17	2.54%	74	2.22%	0.60
Others	10	1.50%	55	1.65%	>0.05
Newborns					
Gender					<0.001
Boy	442	66.17%	1772	53.05%	
Girl	213	31.89%	1542	46.17%	
Unknown	13	1.95%	26	0.78%	
Gestational age, wk					<0.001
SGA	270	40.42%	1041	31.17%	
AGA	380	56.89%	2224	66.59%	
LGA	18	2.69%	75	2.25%	
Birth weight					<0.01
LBW	252	37.72%	1032	30.90%	
NBW	409	61.23%	2261	67.69%	
HBW	7	1.05%	47	1.41%	

AGA = appropriate gestational age (37–40 wk), CAKUT = congenital anomalies of the kidney and urinary tract, CS = caesarean section, Hb = hemoglobin, HBW = high birth weight (>4000 g), HCT = hematocrit, LBW = low birth weight (≤2500 g), LGA = large gestational age (>40 wk), NBW = normal birth weight (2501–4000 g), SGA = small gestational age (<37 wk).

TABLE 2. Associations Between Maternal and Birth Characteristics and Development of CAKUT

Characteristics	OR	(95% CI)	*P* Value
Maternal age, y			
<20	Reference		
20–29	2.18	(1.11, 4.28)	0.03
30–39	2.29	(1.17, 4.51)	0.02
40 or more	2.32	(0.98, 5.48)	0.054
Birth order			
1	Reference		
>1	0.27	(0.15, 0.50)	<0.001
Gestational diabetes	2.22	(1.06, 4.67)	0.03
Polyhydramnios/ oligohydramnios	9.16	(5.46, 15.37)	<0.001
Thalassemia/ hemochromatosis	2.67	(1.35, 5.27)	<0.01
Others	2.26	(1.27, 4.02)	<0.01
Gender			
Girl	Reference		
Boy	1.83	(1.53, 2.19)	<0.001
Unknown 1	2.91	(1.4, 6.05)	0.004
Gestational age, wk			
SGA	1.48	(1.23, 1.78)	<0.01
AGA	Reference		
LGA	1.49	(0.88, 2.53)	0.14

Results of final multivariate logistic regression model, including 8 candidate predictive factors associated CAKUT in children, with $P = 0.16$ for Hosmer–Lemeshow test.

AGA = appropriate gestational age (37–40 wk), CAKUT = congenital anomalies of the kidney and urinary tract, CI = confidence interval, LGA = large gestational age (>40 wk), OR = odds ratio, SGA = small gestational age (<37 wk).

2011) and gestational age <37 weeks (9.74 per 1000 births in 2010, and 10.09 per 1000 births in 2011). The upward trend was significant in the incidence of LBW ($Z = 10.81$, $P < 0.001$) and gestational age <37 weeks ($Z = 8.87$, $P < 0.001$) (see Supplemental Figure 1D and E, http://links.lww.com/MD/A661). Mother's behavior risk ($P = 0.08$) showed an increased trend over time but not statistical significant (Supplemental Figure 1F, http://links.lww.com/MD/A661).

DISCUSSION

In this population-based birth cohort study, we found that the rate of overall congenital malformations steadily declined over the study period, which is in line with data from EUROCAT (1999–2008),[21] the UK (1980–1997),[22] and other registry data.[15] The prevalence of both CAKUT (4.2 per 10,000 births) and all genitourinary tract and kidney anomalies (10% of all anomalies) present at birth was much lower than the figures of 20 per 10,000 live births and 23% to 30% of all identified birth defects in registrations,[21,22] and 30 to 60 per 10,000 live births previously reported.[23] The discrepancy in reported incidence is likely to be related to the size of the study population, the method of diagnosis, the way in which the birth defect information used was recorded, and ethnic differences. Genitourinary tract and kidney anomalies were among the top 5 anomalies in the study population. The top 4 (musculoskeletal system, eye and face, chromosomal abnormalities, and heart and circulatory system) were found in similar roles in other populations.[4,21,22]

One of strengths of this study is that the BCA birth record includes comprehensive maternal health information, which enabled us to carry out this large study to examine their effect on the outcomes for children. Being male, having a gestational age of <37 weeks and various maternal factors, including GDM, anemia or thalassemia, polyhydramnios or oligohydramnios, and maternal age, were contributors to the occurrence of CAKUT. Maternal health conditions are known to be independent risk factors for CAKUT. Our study found that thalassemia/anemia in mothers increased the odds of having a baby with CAKUT. Although thalassemia has been reported to increase risk of congenital anomalies (eg, spina bifida) and maternal complications (eg, shorter gestational age, gestational hypertension, and severe pre-eclampsia),[24,25] the role of a genetic disorder such as thalassemia in congenital malformation in the urinary tract and kidney needs further investigation.

Although pre-GDM did not show statistically significant increased risk of CAKUT (OR = 1.63; 95% CI, 0.38–7.09, $P = 0.51$), an association could still exist because of recall bias or limited self-reported cases in the registry, which could make it difficult to detect any significant association. The number of mothers with pre-existing hypertension, cardiovascular disease, and renal disease was small in the study cohort. Data sources linking birth registry data with information about pregnant women and infants from the healthcare system would help increase the certainty of correct reporting of medical conditions.

This study suggested that polyhydramnios, oligohydramnios, and gestational age <37 weeks are strong risk factors for CAKUT, which is consistent with previous studies.[4,26] Alternations in amniotic fluid volume have been reported as contributing to poorer perinatal outcomes.[27,28] For example, oligohydramnios is highly associated with being SGA and increased mortality, and polyhydramnios with birth weight >90th centile.[28] The association between oligohydramnios and congenital anomalies in the urinary tract and kidney was also found in newborns with renal agenesis.[26] A shorter gestational age and CAKUT shared the same risk factors, so it is not surprising to see gestational age <37 weeks associated with occurrence of CAKUT in newborns.

Over the study period, the rate of congenital anomalies showed a downward trend, but the rate of maternal illness increased by 1.31 per 1000 births (from 3.66 to 4.97 per 1000 births). For mothers with diabetes, the adjusted OR (2.22; 95% CI, 1.06–4.67) confirmed the well-known association between GDM and CAKUT and other major malformations. The upward trends in reported diabetes[11,12] and hypertension[29] in pregnant women were consistent with those previously reported in some populations. Infants of diabetic mothers had approximately twice the incidence of congenital malformations than those of mothers without DM in the study population. Previous studies have suggested that LBW, a surrogate for low nephron number,[30] is a risk factor for postnatal CKD in both childhood and adulthood.[31] Our study results showed that LBW may not be an independent risk for the presence of CAKUT at birth, however, because after adjustment for other maternal illnesses and prematurity, the positive association was no longer statistically significant. Despite this, the significant increasing trend of LBW suggested that careful monitoring and efforts to prevent LBW long-term sequelae of kidney injury are required.

Our study had some registry database-related limitations. The analysis was based on BCA data (reported within 7 days of

TABLE 3. Frequency of Congenital Anomalies by Maternal Diabetes Status (2004–2011)

	Mother With GDM (n = 10,543)	Mother With Any DM (n = 12,615)	Mother Without DM (n = 1,591,179)	*P* Value
Congenital anomalies				
Musculoskeletal system	34 (0.32%)	46 (0.36%)	2753 (0.17%)	<0.001
Eye and face	29 (0.28%)	42 (0.33%)	2626 (0.17%)	<0.001
Heart and circulatory system	28 (0.27%)	42 (0.33%)	1623 (0.10%)	<0.001
Genitourinary system	20 (0.19%)	25 (0.20%)	1188 (0.07%)	<0.001
Nervous system	4 (0.04%)	16 (0.13%)	1043 (0.07%)	0.01
Digestive system	7 (0.07%)	10 (0.08%)	1068 (0.07%)	0.60
Respiratory system, chromosomal abnormalities, or others	20 (0.20%)	25 (0.20%)	3248 (0.20%)	0.88
No anomalies	10,411 (98.75%)	12,431 (98.54%)	1,578,752 (99.22%)	<0.001
Gender				<0.001
Girl	4806 (45.58%)	5780 (45.82%)	760,086 (47.77%)	
Boy	5737 (54.42%)	6828 (54.13%)	830,502 (52.19%)	
Unknown	NA	7 (0.06%)	591 (0.04%)	
Gestational age, wk				<0.001
SGA	2113 (20.04%)	2831 (22.44%)	153,384 (9.64%)	
AGA	8237 (78.13%)	9569 (75.85%)	1,380,846 (86.78%)	
LGA	193 (1.83%)	215 (1.70%)	56,949 (3.58%)	
Birth weight				<0.001
LBW	1252 (11.88%)	1655 (13.12%)	148,502 (9.33%)	
NBW	8345 (79.15%)	9744 (77.24%)	1,417,002 (89.05%)	
HBW	946 (8.97%)	1216 (9.64%)	25,675 (1.61%)	

Number of births = 1,603,794 (2004–2011).

AGA = appropriate gestational age (37–40 wk), DM = diabetes mellitus, GDM = gestational diabetes mellitus, HBW = high birth weight (>4000 g), LBW = low birth weight (≤2500 g), LGA = large gestational age (>40 wk), NA = not available, NBW = normal birth weight (2501–4000 g), SGA = small gestational age (<37 wk).

birth), so the incidence of CAKUT may be under-estimated, as diagnosis of CAKUT may have been after this time. Second, there is potential for incomplete or inaccurate maternal health information, including diseases before and during pregnancy, and complications of labor and delivery. Similarly, not all potentially important risk factors are recorded on birth certificates. The HPA in Taiwan did not make any substantial changes to the reporting template, case ascertainment, or diagnostic methods for birth defects over the study period, so the quality of the dataset used was good. Finally, our study was unable to measure outcomes beyond the BCA itself, such as fetus and neonatal mortality and long-term morbidity.

The current knowledge of CKD epidemiology in children is mainly based on advanced stage CKD or ESRD from registry studies.[6,32] Evidence about congenital anomalies, and the earlier stages of childhood-onset CKD remains scanty. Taiwan has high prevalence and incidence of ESRD[33] and CKD.[34] This warrants an epidemiological study to evaluate trends in CAKUT and its risk factors. Our study used the nationwide birth cohort from 2004 to 2011, allowing us to assess trends and differences in rare events and providing generalizable study results. The BCA dataset enabled us to demonstrate a strong association between CAKUT and modifiable risk factors linked to adverse birth outcomes, including the increasing rate of diabetes and hypertension among women of childbearing age, and treatable or manageable risk factors, such as anemia, thalassemia, polyhydramnios, and oligohydramnios. These results could support service planning, monitoring trends, and assessing the disease burden because children with CKD are at increased risk for progression to ESRD and premature mortality. Further efforts are needed to study the potential causes and long-term outcomes of these trends linking clinical and administrative databases.

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REFERENCES

1. Song R, Yosypiv IV. Genetics of congenital anomalies of the kidney and urinary tract. *Pediatr Nephrol.* 2011;26:353–364.
2. Melo BF, Aguiar MB, Bouzada MC, et al. Early risk factors for neonatal mortality in CAKUT: analysis of 524 affected newborns. *Pediatr Nephrol.* 2012;27:965–972.
3. Mizuno R. Increase in male fetal deaths in Japan and congenital anomalies of the kidney and urinary tract. *Reprod Toxicol.* 2010;30:405–408.
4. Queisser-Luft A, Stolz G, Wiesel A, et al. Malformations in newborn: results based on 30,940 infants and fetuses from the Mainz congenital birth defect monitoring system (1990–1998). *Arch Gynecol Obstet.* 2002;266:163–167.
5. Harambat J, van Stralen KJ, Kim JJ, et al. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol.* 2012;27:363–373.
6. Saran R, Li Y, Robinson B, et al. US renal data system 2014 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2015;65 (6 suppl 1):A7.

7. Wuhl E, van Stralen KJ, Verrina E, et al. Timing and outcome of renal replacement therapy in patients with congenital malformations of the kidney and urinary tract. *Clin J Am Soc Nephrol.* 2013;8: 67–74.
8. Tsai TC, Chen YC, Lo CW, et al. Incidence and renal survival of ESRD in the young Taiwanese population. *Clin J Am Soc Nephrol.* 2014;9:302–309.
9. Patterson CC, Dahlquist GG, Gyurus E, et al. Incidence trends for childhood type 1 diabetes in Europe during 1998–2003 and predicted new cases 2005–20: a multicentre prospective registration study. *Lancet.* 2009;373:2027–2033.
10. Lawrence JM, Contreras R, Chen W, et al. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women. *Diabetes Care.* 2008;31:899–904.
11. Dabelea D, Bell RA, D'Agostino RB Jr et al. Incidence of diabetes in youth in the United States. *JAMA.* 2007;297:2716–2724.
12. Feig DS, Hwee J, Shah BR, et al. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada. *Diabetes Care.* 2014;37:1590–1596.
13. Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care.* 2004;27:2819–2823.
14. Moore LL, Singer MR, Bradlee ML, et al. A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. *Epidemiology.* 2000;11:689–694.
15. Dart AB, Ruth CA, Sellers EA, et al. Maternal diabetes mellitus and congenital anomalies of the kidney and urinary tract (CAKUT) in the child. *Am J Kidney Dis.* 2015;65:684–691.
16. Franke D, Volker S, Haase S, et al. Prematurity, small for gestational age and perinatal parameters in children with congenital, hereditary and acquired chronic kidney disease. *Nephrol Dial Transplant.* 2010;25:3918–3924.
17. Bartram MP, Hohne M, Dafinger C, et al. Conditional loss of kidney microRNAs results in congenital anomalies of the kidney and urinary tract (CAKUT). *J Mol Med (Berl).* 2013;91:739–748.
18. Health Promotion Administration, Ministry of Health and Welfare in Taiwan. Birth Reporting. http://www.hpa.gov.tw/English/ClassPrint.aspx?No=201502020008. Accessed August 29, 2015.
19. Hennessy S, Bilker WB, Berlin JA, et al. Factors influencing the optimal control-to-case ratio in matched case–control studies. *Am J Epidemiol.* 1999;149:195–197.
20. Agresti A. Categorical Data Analysis. New York: John Wiley & Sons; 2002.
21. Loane M, Dolk H, Kelly A, et al. Paper 4: EUROCAT statistical monitoring: identification and investigation of ten year trends of congenital anomalies in Europe. *Birth Defects Res A Clin Mol Teratol.* 2011;91 (suppl 1):S31–S43.
22. Dastgiri S, Stone DH, Le-Ha C, et al. Prevalence and secular trend of congenital anomalies in Glasgow, UK. *Arch Dis Child.* 2002;86:257–263.
23. Yosypiv IV. Congenital anomalies of the kidney and urinary tract: a genetic disorder? *Int J Nephrol.* 2012;2012:909083.
24. Liang ST, Wong VC, So WW, et al. Homozygous alpha-thalassaemia: clinical presentation, diagnosis and management. A review of 46 cases. *Br J Obstet Gynaecol.* 1985;92:680–684.
25. Jans SM, de Jonge A, Lagro-Janssen AL. Maternal and perinatal outcomes amongst haemoglobinopathy carriers: a systematic review. *Int J Clin Pract.* 2010;64:1688–1698.
26. Parikh CR, McCall D, Engelman C, et al. Congenital renal agenesis: case–control analysis of birth characteristics. *Am J Kidney Dis.* 2002;39:689–694.
27. Ott WJ. Reevaluation of the relationship between amniotic fluid volume and perinatal outcome. *Am J Obstet Gynecol.* 2005;192:1803–1809discussion 1809.
28. Morris RK, Meller CH, Tamblyn J, et al. Association and prediction of amniotic fluid measurements for adverse pregnancy outcome: systematic review and meta-analysis. *BJOG Int J Obstet Gynaecol.* 2014;121:686–699.
29. Roberts CL, Ford JB, Algert CS, et al. Population-based trends in pregnancy hypertension and pre-eclampsia: an international comparative study. *BMJ Open.* 2011;1:e000101.
30. Bertram JF, Douglas-Denton RN, Diouf B, et al. Human nephron number: implications for health and disease. *Pediatr Nephrol.* 2011;26:1529–1533.
31. Greenbaum LA, Munoz A, Schneider MF, et al. The association between abnormal birth history and growth in children with CKD. *Clin J Am Soc Nephrol.* 2011;6:14–21.
32. Wuhl E, van Stralen KJ, Wanner C, et al. Renal replacement therapy for rare diseases affecting the kidney: an analysis of the ERA-EDTA Registry. *Nephrol Dial Transplant.* 2014;29 (suppl 4):iv1–iv8.
33. U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013.
34. Wen CP, Cheng TY, Tsai MK, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet.* 2008;371:2173–2182.