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Maternal and Fetal Risk Factors for Congenital Abnormalities of the Kidney and Urinary Tract: A Hospital-based Case-control Study in Southern China

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Abstract

Background: The aetiology of congenital abnormalities of the kidney and urinary tract (CAKUT) remains incompletely understood, despite several risk factors having been reported in previous literature. Maternal and fetal-related clinical characteristics are hypothesised to contribute to CAKUT susceptibility, yet epidemiological evidence remains inconsistent. This study aimed to evaluate maternal and fetal risk factors for CAKUT among infants in southern China to improve understanding of this common congenital malformation.

Methods: A retrospective hospital-based case-control study was performed at a tertiary women-and-children hospital in Hainan, China, from January 2021 to October 2025. Newborns diagnosed with CAKUT served as cases, and newborns without CAKUT were selected as controls adopting a 1:5 individual-matching design based on neonatal sex and date of birth (±3 days). In total, 109 CAKUT cases and 545 matched controls were included. Maternal demographic and clinical information were obtained via telephone interviews and routine survey data; clinical perinatal information was validated against hospital medical records. We compared maternal and fetal characteristics between offspring with and without CAKUT. Multivariable conditional logistic regression was applied to identify independent risk factors for CAKUT.

Results: After adjusting for confounding variables, advanced maternal age (adjusted odds ratio [aOR] = 2.58, 95% confidence interval [CI] 1.33-5.01), gestational hypertension (aOR = 3.48, 95%CI 1.32-9.23), maternal hypothyroidism (aOR = 9.84,

95%CI 1.70-56.99), multiple pregnancies (aOR = 7.68, 95%CI 1.07-54.85), and preterm gestational age (aOR = 4.65, 95%CI 1.78-12.75) were independently associated with elevated CAKUT risk. Hydronephrosis was the most frequent CAKUT subtype observed in this cohort.

Conclusions: Advanced maternal age, gestational hypertension, hypothyroidism, multiple pregnancies, and preterm gestation were associated with increased CAKUT risk in this hospital-based sample. These findings may support early identification of high-risk pregnancies and provide evidence for clinical prevention and management of CAKUT in Hainan.

Keywords: Congenital Anomalies of the Kidney and Urinary Tract; Risk Factors; Case-control study

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) arise from disrupted spatial-temporal regulation during renal and urinary tract organogenesis[1,2]. This spectrum comprises multiple phenotypes including renal parenchymal anomalies, ectopic or fused kidneys, and malformations of the collecting system [3]. Hydronephrosis represents the most prevalent CAKUT subtype; other presentations include renal hypoplasia, horseshoe kidney, renal agenesis, vesicoureteral reflux (VUR), mega-ureter, ureteral displacement, cystic renal lesions, duplicated collecting systems, and posterior urethral valves (PUVs) [4] . CAKUT constitutes the leading cause of childhood kidney failure; its incidence has been rising year-by-year, imposing substantial disease burden and impairing children's quality of life [5,6]. Although CAKUT accounts for a notable proportion of paediatric end-stage renal disease cases (40–50%) [7,8], its aetiology remains elusive but likely involves various risk factors, including genetic, epigenetic, and environmental influences[9,10]. Nevertheless, existing epidemiological studies have reported inconsistent findings regarding risk factors associated with CAKUT. Accordingly, the present retrospective case-control study was conducted in a tertiary hospital in southern China to explore associations between maternal-fetal characteristics and CAKUT risk, providing further insights into disease pathogenesis.

Methods and procedures

Study design, participants, and data source

This retrospective hospital-based case-control study was carried out at Hainan Women and Children's Medical Center, a tertiary-level referral hospital for high-risk pregnancy and neonatal care. Study subjects were screened from preconception clinic and obstetric delivery electronic medical records collected between January 2021 and October 2025. Ethical approval (HNWCMC2025150) was granted for secondary data extraction and retrospective statistical analysis using archived clinical datasets, rather than for prospective participant recruitment. Participants satisfied the following eligibility criteria: (1) maternal age 18-45 years; (2) no prior history of severe chronic illnesses including uncontrolled hypertension, type 1 or type 2 diabetes mellitus, or autoimmune disease; (3) no history of congenital anomalies in previous gestations; (4) no long-term pre-pregnancy medication exposure known to directly alter thyroid function, blood pressure, glucose homeostasis or induce intrahepatic cholestasis; gestational complications spontaneously occurring during pregnancy were eligible as exposure variables and were not grounds for exclusion; (5) no pre-pregnancy or gestational history of tobacco smoking or alcohol consumption. Exclusion criteria included participants with incomplete prenatal, obstetric or neonatal record information.

From January 2021 to October 2025, 130 newborns diagnosed with CAKUT were initially identified as potential cases. We adopted a 1:5 individual matching design. Matching variables included neonatal sex and date of birth (±3 days). For each potential case, five controls without CAKUT were randomly sampled from eligible newborns satisfying the matching criteria, prior to any exclusions for missing-data reasons, generating 130 original independent matched strata. No rematching was performed at any stage of the study. Offspring with CAKUT were initially identified using relevant International Classification of Diseases diagnostic codes. All enrolled cases were diagnosed and confirmed by professional pediatric urologists. Controls were confirmed to be free of CAKUT at birth via postnatal physical examination performed by pediatric urologists and verified through medical records.

Under our available-case rule, a matched stratum was retained for analysis only

when at least one case and one control within the stratum had complete non-missing values for model covariates. 21 original matched strata were completely discarded because the corresponding case within each stratum had missing values for model covariates; these 21 cases and their originally matched 105 controls were removed together, and these controls were not reused for other strata. The final analytical dataset included 109 informative matched strata, consisting of 109 cases and 545 controls. No further individual-level covariate missingness was observed within these retained 109 strata.

Only one infant per pregnancy was included in the study; multiple fetuses from the same pregnancy were not enrolled simultaneously to avoid non-independent observations.

Consent to Participate

This retrospective study performed secondary analyses using de-identified archived clinical data. Written informed consent from guardians was formally waived by the institutional ethics committee because all personal identifiers were removed prior to dataset extraction and statistical analysis.

Ethical approval

The study was conducted with approval from the Ethics Committee of Hainan Women and Children's Medical Centre under protocol number HNWCMC2025150, and was performed in accordance with the principles of the Declaration of Helsinki. Clinical trial number: not applicable.

Covariates assessment

We abstracted maternal variables including maternal age at delivery, maternal ethnicity, maternal educational attainment, parity, mode of delivery (vaginal delivery / caesarean section), plurality (singleton, twin, triplet or higher-order multiple gestation), and fertility treatment status. Obstetric complications were retrieved from perinatal medical records, including gestational hypertension, gestational diabetes mellitus, hypothyroidism, hyperthyroidism, intrahepatic cholestasis of pregnancy (ICP), thalassemia, hepatitis B virus (HBV) infection, and syphilis infection. Pre-pregnancy weight and pre-delivery weight were recorded; pre-pregnancy BMI and

BMI at delivery were calculated. Gestational weight gain was computed as pre-delivery weight minus pre-pregnancy weight. Pre-pregnancy BMI was categorised according to Chinese clinical criteria: underweight (<18.5 kg/m²), normal weight (18.5-23.9 kg/m²), overweight (24.0-27.9 kg/m²), obesity (⩾28.0 kg/m²). Maternal educational attainment was grouped for statistical analysis.

Diagnosis of hypertensive disorders of pregnancy followed the Guidelines for the Diagnosis and Treatment of Hypertensive Disorders in Pregnancy (2020). All pregnant women underwent oral glucose tolerance test (OGTT) between gestational week 24-28. Gestational diabetes mellitus (GDM) was diagnosed when any one threshold was satisfied: fasting glucose ⩾5.1 mmol/L; 1-hour post-load glucose ⩾ 10.0 mmol/L; 2-hour post-load glucose ⩾8.5 mmol/L. Intrahepatic cholestasis of pregnancy was diagnosed according to the Clinical Diagnosis, Treatment and Management Guidelines for Intrahepatic Cholestasis of Pregnancy (2024). Maternal thyroid dysfunction (hypothyroidism and hyperthyroidism) was defined following the Guidelines for the Diagnosis and Treatment of Thyroid Disorders During Pregnancy and Postpartum.

Neonatal variables extracted included infant sex, gestational age in weeks, and birth weight. Gestational age was dichotomised as preterm birth (<37 weeks gestation) versus term birth (⩾37 weeks gestation). Low birth weight was defined as birth weight <2500 g.

Outcomes

The primary outcome was CAKUT, ascertained via systematic imaging assessment according to pre-specified study protocol and documented within the hospital electronic medical-record information system.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0. Continuous variables with normal distribution were described as mean ± standard deviation; categorical variables were summarised as counts and proportions. Normality for continuous variables was examined. For descriptive inter-group comparison, the t-test

was used for normally-distributed continuous variables and χ^2 test for categorical variables. These univariate descriptive tests are presented for illustrative purposes only; all formal inferential analyses accounting for the matched study design were implemented using conditional logistic regression.

Given that SPSS 26.0 lacks dedicated conditional-logistic-regression procedure for 1:5 matched case-control datasets, stratified Cox proportional-hazards regression was utilised to approximate conditional logistic regression: a constant dummy time variable was generated for all subjects; matched-set ID was designated as the stratum variable; case-control status served as the event indicator. Exponentiated regression coefficients were interpreted as odds ratios consistent with conditional-logistic-regression outputs.

Covariates entered into multivariable models were predefined before statistical analysis on the basis of clinical plausibility, biological mechanisms and previously published epidemiological evidence. No post-hoc data-driven variable screening was conducted to guarantee model robustness. Matching variables (neonatal sex, date of birth $\pm$3 days) were inherently controlled via stratification and were not entered as additional covariates to avoid over-adjustment.

Missing data were handled using available-case analysis. A matched stratum remained eligible for analysis if at least one case and one control within that stratum possessed complete covariate values for multivariable modelling. Multiple imputation was not performed in this study. Conventional regression diagnostics including multicollinearity testing, outlier detection, goodness-of-fit assessment and residual analysis are statistically inappropriate for matched conditional-logistic-regression setting in SPSS and were therefore not implemented.

Results

Basic characteristics of the study participants

A total of 654 participants (109 CAKUT cases and 545 controls) were included in the final analytical dataset from January 1 2021 to October 31 2025. Among CAKUT cases, 80 (73.39%) were male, yielding a male-to-female ratio of approximately 2.76:1. The proportion of mothers of advanced maternal age (≥35 years) was 10.55%.

Most participants belonged to Han ethnicity (94.65%). The majority of women had normal pre-pregnancy BMI (79.82%), and 52.60% were nulliparous. The prevalence of GDM and gestational hypertension during pregnancy was 18.04% and 3.98%, respectively. Most newborns were term infants (93.43%) with normal birth weight (89.45%). Hydronephrosis was the most commonly observed CAKUT phenotype. Baseline demographic and clinical characteristics are summarised in Table 1.

Comparison of sample characteristics between the CAKUT and non-CAKUT group

Table 1 shows the comparison of maternal and neonatal characteristics between mothers of infants with CAKUT and mothers of unaffected infants. Differences were observed between the two groups for maternal age, maternal education, pre-gestational BMI, gestational hypertension, hypothyroidism, intrahepatic cholestasis of pregnancy, HBV infection, multiple pregnancies, mode of delivery, gestational age, and birth weight. Compared with the control group, mothers in the CAKUT group had a higher proportion of advanced maternal age (21.10% vs. 8.44%), lower educational attainment (70.64% vs. 59.45%), higher proportions of low pre-pregnancy BMI (16.51% vs. 7.80%), gestational diabetes mellitus (29.36% vs. 15.78%), gestational hypertension (12.84% vs. 2.20%), HBV infection (9.17% vs. 3.85%), intrahepatic cholestasis of pregnancy (5.50% vs. 1.28%), and multiple pregnancies (7.34% vs. 0.37%). In addition, neonates in the CAKUT group exhibited higher proportions of preterm birth (25.69% vs. 2.75%) and low birth weight (24.77% vs. 3.30%). All formal statistical inferences regarding risk-factor associations are derived from the conditional logistic regression analyses presented in Table 2, which properly account for the 1:5 matched study design.

Association between maternal and fetal risk factors and the risk of CAKUT

Exposure variables showing statistical significance in univariable analyses were incorporated into the multivariable conditional logistic-regression framework (Table 2). After adjustment for confounders, maternal age ≥35 years (aOR = 2.58, 95%CI 1.33-5.01), gestational hypertension (aOR = 3.48, 95%CI 1.32-9.23), hypothyroidism (aOR = 9.84, 95%CI 1.70-56.99), multiple pregnancies (aOR = 7.68,

95%CI 1.07-54.85), and preterm gestational age (aOR = 4.65, 95%CI 1.78-12.75) were independently associated with increased CAKUT risk. No statistically-significant independent association was observed for fertility treatment or birth weight in fully-adjusted multivariable models.

Discussion

CAKUT represents a major category of congenital malformation among Chinese children [3]. It comprises a heterogeneous spectrum of urinary-tract phenotypes ranging from mild lesions requiring no intervention to life-threatening conditions [11]. In the present hospital-based cohort, hydronephrosis constituted the most frequent CAKUT subtype (53.21%). This case-control study identified that advanced maternal age, gestational hypertension, hypothyroidism, multiple pregnancies, and preterm gestational age were independent risk factors for CAKUT.

Consistent with several meta-analyses, advanced maternal age was associated with elevated CAKUT risk in our study. One investigation conducted by Tain et al.[12] indicated that mothers over 40 years increased the chances of CAKUT as compared to mothers under 20 years (OR: 2.32, $P = 0.05$). On the other hand, Fang et al.[13] did not find a significant difference in the incidence of CAKUT compared to mothers who were under 20 years and over 40 years. In this study, we found a positive association between advanced maternal age and CAKUT. The link between maternal age and CAKUT is likely influenced by genetic, environmental, and socioeconomic factors, which may explain these inconsistencies. Future research should adequately account for these potential confounders to clarify the magnitude of maternal-age-related risk.

Prior studies reported that maternal pre-pregnancy obesity may increase CAKUT susceptibility [14,15]. Hsu et al.'s case-control study identified pregnancy-related risk factors with chronic kidney disease children [16]. In their investigation, CAKUT offspring were more prone to having mothers whose BMI >25 kg/m^2. However, in our multivariable model, pre-pregnancy BMI was not an independent predictor for CAKUT after adjustment. Further mechanistic research is warranted to interpret this observation.

Gestational diabetes mellitus has been linked to overall congenital malformations

including urinary-system defects in existing literature[17-19]. Dart et al. [20] indicated that the effect of gestational diabetes on newborn CAKUT is slight but that it is more significant if the gestational diabetes occurs during the first 20 weeks. However, our study found no association between GDM and CAKUT. In our adjusted model, GDM did not achieve statistical significance for CAKUT risk. One plausible explanation is the relatively high baseline prevalence of GDM within this local cohort.

Gestational hypertension was an independent risk factor for CAKUT in our dataset. This finding is not universally replicated across previous investigations. In a research undertaken by Chou et al. [21], no links were detected between hypertension and any kind of kidney abnormalities, nor cystic kidney disease. On the contrary, a Dutch study discovered that preeclampsia was linked with posterior hypospadias, another congenital genitourinary malformation, regardless of pharmacological treatment [22]. This further supports the hypothesis that early placental dysfunction may disturb fetal genitourinary developmental programming.

Preterm birth emerged as an important independent risk factor for CAKUT. Hays et al. [11] detected that the rate of CAKUT among infants born preterm with a gestational age of 23–33 weeks, classified as moderate to extreme preterm, was 20 per 1000 births, which is higher than in the general population. Thus, we were able to observe the same correlation between prematurity and CAKUT. Nephron formation largely completes by approximately gestational week 36; accordingly, preterm delivery may disturb renal organogenesis, providing a potential biological explanation for higher CAKUT burden among preterm neonates [23].

Multiple pregnancies were confirmed as an independent risk factor for CAKUT in this study. The findings of multiple pregnancies associated with CAKUT may involve placental dysfunction and fetal growth restriction [24]. Multiple pregnancies potentially cause placental ischemia and hypoxia [25]. This impairs fetal renin-angiotensin system development, increasing risks of posterior urethral valves and vesicoureteral reflux. Significantly elevated maternal estrogen and progesterone levels may disrupt differentiation of the fetal urogenital sinus, which has been hypothesised to slightly increase the incidence of CAKUT in female fetuses compared

with singletons. Multiple pregnancies lead to multiple pregnancy complications, such as preterm births [26] and alterations in maternal thyroid function [27]; these pregnancy-related disturbances may contribute to elevated CAKUT risk.

Maternal hypothyroidism was strongly associated with CAKUT risk in this cohort. A cohort from another city in China documented the associations between maternal hypothyroidism and postnatal CAKUT in either preterm infants or term infants [28]. Moreover, the likelihood of isolated UTD or KA was raised among fetuses of mothers presenting thyroid dysfunction [29].Nevertheless, other studies have reported contrary outcomes. ZhH Hao et al. [3] found no relationship between thyroid disorders and CAKUT. The relationships between hypothyroidism and CAKUT are unclear, primarily through thyroid hormone (TH)-mediated regulation of embryonic development, with particularly significant effects during early pregnancy (the critical period of organogenesis). Further studies are needed to achieve a clearer understanding of CAKUT.

Conclusions

This hospital-based case-control study indicated that advanced maternal age, gestational hypertension, hypothyroidism, multiple pregnancies, and preterm gestational age were associated with higher CAKUT risk. These results facilitate identification of high-risk pregnancies for CAKUT in Hainan and provide epidemiological evidence supporting prenatal prevention and clinical management strategies for CAKUT.

Limitations

This study has several important limitations. One concern is that information on exposures and some covariates such as history of severe chronic diseases and maternal weight before pregnancy were obtained by self-report, which increases the risk of recall bias and misclassification. Selection bias may have been introduced as participants were primarily recruited from urban tertiary hospitals, potentially excluding rural or underserved populations and thus limiting the generalizability of our findings to broader communities. Referral-center bias is another concern: since our study was conducted at a specialized pediatric urology center, the cases included

may represent more complex or severe forms of CAKUT than those seen in primary care settings, which could overestimate the association between certain risk factors and the condition. In addition, some clinical information was collected via face-to-face or telephone communication during routine antenatal clinical care. Although information was obtained at the time of clinical encounters, self-reported historical exposures may still be subject to recall bias, which could compromise data accuracy. Furthermore, this study does not contain data on the severity of CAKUT cases. The relatively small sample size of different CAKUT subtypes limits the ability to conduct in-depth analysis of pregnancy-related risk factors of CAKUT with different severity. In the future, large-scale multi-center cohort research is needed to address these limitations.

As an observational study, our design does not allow for the inference of causal relationships between identified factors and CAKUT; further experimental or interventional studies would be needed to establish causality. Potential sparse-data bias also represents an important limitation. Several exposure categories contained a relatively small number of events, which may introduce sparse-data bias and lead to large odds ratios with wide confidence intervals. Sensitivity analyses and Firth regression were not performed in this study. Therefore, the stability of effect estimates cannot be fully guaranteed. Our findings should be interpreted strictly as associative relationships rather than causal conclusions. Accordingly, these observed associations should be interpreted with caution and need to be replicated in larger cohorts. Due to the functional limitations of SPSS, formal model diagnostics and Firth-type penalized regression were not performed. Moreover, covariate missing data was processed via available-case analysis without multiple imputation, and unquantifiable variable-specific missing rates may bring potential selection bias if data were not missing completely at random. Conventional regression diagnostics are also inapplicable to the matched case-control conditional logistic regression model, limiting the assessment of model fitness and stability. Overall, these limitations suggest that the current findings need cautious interpretation and further validation in large-scale, multicenter prospective cohorts.

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Ethical approval and consent to participate

This study was approved by the full Ethics Committee of Hainan Women and Children's Medical Center (HNWCMC2025150). The requirement for written informed consent to participate was formally waived by the full ethics committee, since this retrospective study performed secondary analysis using de-identified archived clinical data. The study was performed in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable

Data availability

The datasets for this article are not publicly available. Requests to access the datasets should be directed to the corresponding author.

Competing Interests

The authors declare that they have no competing interests.

Authors' contributions

Zhenli Zhao conceived and designed the study. Weizhen Bu, Shaohua Hu, Songqiang Chen and Zhisheng Wan were responsible for participant recruitment and data collection. Xiaohua Li performed the statistical analysis. Weizhen Bu drafted the original manuscript. Zhenli Zhao, Shaohua Hu, Songqiang Chen and Zhisheng Wan revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript to be submitted, and agreed to be

accountable for all aspects of the work.

Abbreviations

aOR adjusted odds ratio

BMI body mass index

CI confidence interval

CAKUT congenital anomalies of the kidney and urinary tract

GDM gestational diabetes mellitus

HBV hepatitis B virus

ICP intrahepatic cholestasis of pregnancy

OGTT oral glucose tolerance test

OR odds ratio

SPSS Statistical Package for the Social Sciences

References

[1] Arantes RR, Aguiar MB, Cunha KCCMS, et al. Risk factors for perinatal and neonatal mortality in cases with congenital anomalies of the kidney and urinary tract: a nested cohort study. Pediatr Nephrol. 2025;40(12):3697-3705.

[2] Bajt P, Racetin A, Kelam N, et al. Expression of FGF23 and α-KLOTHO in Normal Human Kidney Development and Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). Biomolecules. 2025;15(6):811.

[3] Hao ZH, Jiang YP, Xu H, et al. Epidemiology and disease burden of pediatric congenital anomalies of the kidney and urinary tract: a national cross-sectional study of hospitalized children in China. World J Pediatr. 2025;21(3):306-321.

[4] Pavlović N, Kelam N, Racetin A, Filipović N, Pogorelić Z, Prusac IK, et al. Expression profiles of ITGA8 and VANGL2 are altered in congenital anomalies of the kidney and urinary tract (CAKUT). Molecules. 2024;29:3294.

[5] Walawender L, Becknell B, Matsell DG. Congenital anomalies of the kidney and urinary tract: defining risk factors of disease progression and determinants of outcomes. Pediatr Nephrol.2023;38(12):3963-3973.

[6] Barakat AJ, Butler MG. Genetics of anomalies of the kidney and urinary tract with congenital heart disease: A review. Clin Genet. 2024;106(6):667-678.

[7] Sanna-Cherchi S,Westland R, Ghiggeri GM,et al. Genetic Basis of Human Congenital Anomalies of the Kidney and Urinary Tract. J. Clin. Investig. 2018, 128, 4–15.
[8] Kelam N, Racetin A, Polovi´c M, et al. Aberrations in FGFR1, FGFR2, and RIP5 Expression in Human Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). Int. J. Mol. Sci. 2022, 23, 5537.
[9] Jain S, Chen F. Developmental pathology of congenital kidney and urinary tract anomalies. Clin Kidney J. 2018;12(3):382-399.
[10] Nicolaou N, Renkema KY, Bongers EM, Giles RH, Knoers NV. Genetic, environmental, and epigenetic factors involved in CAKUT. Nat Rev Nephrol. 2015;11(12):720-731.
[11] Hays T, Thompson MV, Bateman DA, et al. The Prevalence and Clinical Significance of Congenital Anomalies of the Kidney and Urinary Tract in Preterm Infants. JAMA Netw Open. 2022;5(9):e2231626.
[12] Tain YL, Luh H, Lin CY, et al. Incidence and Risks of Congenital Anomalies of Kidney and Urinary Tract in Newborns: A Population-Based Case-Control Study in Taiwan. Medicine (Baltimore). 2016;95(5):e2659.
[13] Fang NW, Huang YS, Yin CH, et al. Maternal risk factors in offspring with congenital anomalies of the kidney and urinary tract in Asian women. Pediatr Nephrol. 2023;38(9):3065-3070.
[14] Jadresić L, Au H, Woodhouse C, et al. Pre-pregnancy obesity and risk of congenital abnormalities of the kidney and urinary tract (CAKUT)-systematic review, meta-analysis and ecological study. Pediatr Nephrol. 2021;36(1):119-132. doi:10.1007/s00467-020-04679-0.
[15] Macumber I, Schwartz S, Leca N. Maternal obesity is associated with congenital anomalies of the kidney and urinary tract in offspring. Pediatr Nephrol. 2017;32(4):635-642.
[16] Hsu CW, Yamamoto KT, Henry RK, De Roos AJ, Flynn JT. Prenatal risk factors for childhood CKD. J Am Soc Nephrol. 2014;25(9):2105-2111.
[17] Parimi M, Nitsch D. A systematic review and meta-analysis of diabetes during

pregnancy and congenital genitourinary abnormalities. Kidney Int Rep 2020;5:678–93.
[18] Nishiyama K, Sanefuji M, Kurokawa M, et al. Maternal Chronic Disease and Congenital Anomalies of the Kidney and Urinary Tract in Offspring: A Japanese Cohort Study. Am J Kidney Dis. 2022;80(5):619-628.e1.
[19] Zhang TN, Huang XM, Zhao XY et al. Risks of specific congenital anomalies in offspring of women with diabetes:a systematic review and meta-analysis of population based studies including over 80 million births. PLoS Med 2022;19:e1003900.
[20] 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(5):684-691.
[21] Chou HH, Chen CC, Tsai CF, et al. Associations between maternal chronic diseases and congenital anomalies of the kidney and urinary tract in offspring: a population-based cohort study. Clin Kidney J. 2023;16(12):2652-2660.
[22] Jamaladin H, van Rooij IALM, van der Zanden LFM, et al. Maternal hypertensive disorders and subtypes of hypospadias: A Dutch case-control study. Paediatr Perinat Epidemiol. 2020;34(6):687-695.
[23] Isert S, Müller D, Thumfart J. Factors Associated With the Development of Chronic Kidney Disease in Children With Congenital Anomalies of the Kidney and Urinary Tract. Front Pediatr. 2020;8:298.
[24] Filipecka-Tyczka D, Jakiel G, Kajdy A, Rabijewski M. Is growth restriction in twin pregnancies a double challenge? - A narrative review. J Mother Child.2021;24(4):24-30.
[25] Tang W, Zou L. Trends and characteristics of multiple births in Baoan Shenzhen: A retrospective study over a decade. Front Public Health. 2022;10:1025867.
[26] Stock S, Norman J. Preterm and term labour in multiple pregnancies. Semin Fetal Neonatal Med. 2010;15(6):336-341.
[27] Zgliczynska M, Ostrowska M, Szymusik I, et al. Maternal thyroid function in multiple pregnancies - a systematic review. Front Endocrinol (Lausanne).

2023;13:1044655.
[28] Liu Y, Shi H, Yu X, Xiang T, Fang Y, Xie X, et al. Risk factors associated with renal and urinary tract anomalies delineated by an ultrasound screening program in infants. Front Pediatr. 2021;9:728548.
[29] Ma Q, Li YQ, Meng QT, et al. Maternal diseases and congenital anomalies of the kidney and urinary tract in offspring: a cohort study. World J Pediatr. 2024;20(11):1168-1178.

Table 1 Basic characteristics of the study participants

Variables	Total (n = 654) No. (%)	Offspring without CAKUT (n = 545) No. (%)	Offspring with CAKUT (n = 109) No. (%)	*p*
Age, years				< 0.001
< 35	585(89.45)	499（91.56）	86（78.90）	
≥ 35	69（10.55）	46（8.44）	23（21.10）	
Maternal education				0.049
junior college level and below	401（61.31）	322（59.45）	77（70.64）	
Bachelor	230（35.17）	199（36.51）	31（28.44）	
Master and above	23（3.52）	22（4.04）	1（0.92）	
Race/ethnicity				0.105
Han	619（94.65）	516（94.68）	103（94.50）	
Li	22（3.36）	16（2.94）	6（5.50）	
others	13（1.99）	13（2.39）	0（0.00）	
Pre-pregnancy BMI				< 0.001
<18.5	51（7.80）	33（7.80）	18（16.51）	
18.5 - 23.9	522（79.82）	449（79.82）	73（66.97）	

24.0 - 27.9	73（11.16）	59（11.16）	14（12.84）	
≥ 28.0	8（1.22）	4（1.23）	4（3.67）	
BMI at delivery				0.906
< 18.5	2（0.31）	2（0.37）	0（0.00）	
18.5 - 23.9	129（19.72）	108（19.82）	21（19.27）	
24.0 - 27.9	352（53.82）	295（54.13）	57（52.29）	
≥ 28.0	171（26.15）	140（25.69）	31（28.44）	
BW gain during pregnancy	14.30 ± 4.60	14.30 ± 4.60	13.18 ± 4.38	0.653
Gestational diabetes				< 0.001
No	536 (81.96)	459(84.22)	77 (70.64)	
Yes	118 (18.04)	86 (15.78)	32 (29.36)	
Gestational hypertension				< 0.001
No	628 (96.02)	533 (97.80)	95 (87.16)	
Yes	26 (3.98)	12 (2.20)	14 (12.84)	
Hypothyroidism				< 0.001
No	644 (98.47)	542 (99.45)	102 (93.58)	
Yes	10 (1.53)	3 (0.55)	7 (6.42)	
Hyperthyroidism				0.422
No	651(99.54)	543 (99.63)	108 (99.08)	

	Yes	3(0.46)	2 (0.37)	1 (0.92)	
Intrahepatic cholestasis of pregnancy					0.012
	No	641 (98.01)	538 (98.72)	103 (94.50)	
	Yes	13 (1.99)	7 (1.28)	6 (5.50)	
Thalassemia					0.708
	No	603 (92.20)	498 (91.38)	105 (96.33)	
	Yes	51(7.80)	47 (8.62)	4 (3.67)	
HBV infection					0.017
	No	623 (95.26)	524 (96.15)	99 (90.83)	
	Yes	31 (4.74)	21 (3.85)	10 (9.17)	
Syphilis					1.000
	No	653 (99.85)	544 (99.82)	109 (100.00)	
	Yes	1 (0.15)	1 (0.18)	0 (0.00)	
Parity					0.405
	1	344 (52.60)	286 (52.48)	58 (53.21)	
	2	230 (35.17)	196 (35.96)	34 (31.19)	
	≥ 3	80 (12.23)	63 (11.56)	17 (15.60)	

Multiple pregnancies				< 0.001
No	644 (98.47)	543 (99.63)	101 (92.66)	
Yes	10 (1.53)	2 (0.37)	8 (7.34)	
Cesarean section				0.016
No	314 (54.51)	342 (62.75)	55 (50.46)	
Yes	262 (45.49)	203 (37.25)	54 (49.54)	
Fertility treatment				0.002
No	630 (96.33)	531 (97.43)	99 (90.83)	
Yes	24 (3.67)	14 (2.57)	10 (9.17)	
Gestational age, weeks				< 0.001
Preterm (< 37)	43 (6.57)	15 (2.75)	28 (25.69)	
Full term (≥ 37)	611 (93.43)	530 (97.25)	81 (74.31)	
Birth weight, g				< 0.001
< 2500	45 (6.88)	18 (3.30)	27 (24.77)	
2500-4000	585 (89.45)	506 (92.84)	79 (72.48)	
> 4000	24 (3.67)	21(3.85)	3 (2.75)	

Table Footnote. Table 1 presents descriptive baseline characteristics for case and control groups. No inferential statistical tests are reported here. All formal association analyses accounting for the 1:5 matched-study design were performed via conditional logistic regression, as reported in Table 2. The descriptive sample (109 cases, 545 controls, total N = 654) in this table is identical to the analytical dataset used for the multivariable conditional logistic regression shown in Table 2.

Table 2. Univariate and multivariable conditional logistic regression analyses of risk factors for CAKUT

Variables	Unadjusted OR (95% CI)	Adjusted OR （95%CI）	*P*
Age, years			
< 35	1.00 (Reference)	1.00 (Reference)	
≥ 35	2.90 (1.67 - 5.03)	2.58 (1.33 - 5.01)	0.005
Maternal education			
junior college level and below	1.00 (Reference)	1.00 (Reference)	
Bachelor	0.66 (0.42 - 1.03)	0.82 (0.49 - 1.36)	0.444
Master and above	0.19 (0.03 - 1.44)	0.23 (0.03 - 1.85)	0.165
Pre-pregnancy BMI			
<18.5	1.00 (Reference)	1.00 (Reference)	
18.5 - 23.9	3.35 (1.80 - 6.27)	3.06 (1.47 - 6.34)	0.003
24.0 - 27.9	1.46 (0.77 - 2.75)	1.08 (0.51 - 2.26)	0.843
≥ 28.0	6.15 (1.50 - 25.14)	4.16 (0.74 - 23.40)	0.105
Gestational hypertension	6.55 (2.94 - 14.59)	3.48 (1.32 - 9.23)	0.012

Gestational diabetes	2.22 (1.38 - 3.56)	1.75 (0.99 - 3.10)	0.055
Intrahepatic cholestasis of pregnancy	4.48 (1.47 - 13.59)	1.99 (0.43 - 9.13)	0.375
Hypothyroidism	12.40 (3.15 - 48.74)	9.84 (1.70 - 56.99)	0.011
HBV infection	2.52 (1.15 - 5.52)	2.26 (0.88 - 5.78)	0.089
Cesarean section	1.65 (1.09 - 2.50)	0.89 (0.54 - 1.47)	0.658
Fertility treatment	3.83 (1.66 - 8.87)	1.47 (0.48 - 4.45)	0.499
Multiple pregnancies	21.50 (4.50 - 102.67)	7.68 (1.07 - 54.85)	0.042
Gestational age	12.21 (6.25 - 23.85)	4.65 (1.78 - 12.15)	0.002

Table Footnote. Univariate and multivariable conditional logistic regression analyses of factors associated with CAKUT. Each unadjusted model contained a single predictor. The fully-adjusted model was conditioned on matched strata (neonatal sex and date of birth ± 3 days) and fitted on the final analytical dataset comprising 109 informative matched strata (109 cases and 545 controls; total N = 654). OR, odds ratio; CI, confidence interval.