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IS DIABETES MELLITUS A RISK FACTOR FOR CONGENITAL ANOMALIES OF THE KIDNEY AND URINARY TRACT (CAKUT)?

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Abstract

Background: Congenital anomalies of kidney and urinary tract (CAKUT) are characterized by structural and functional abnormalities of kidney, collecting system, bladder, and urethra [1]. In Egypt, CAKUT comprised 46% of the underlying etiology in Egyptian CKD pediatric patients [2]. Evolving studies postulating CAKUT and related risk factors addressed diabetes mellitus (DM) as one of preventable risk factors. However more is needed to address the pattern of DM exposure during pregnancy in relation to CAKUT occurrence.
Study Design: Retrospective case-control study from April 2018 –November 2020.
Setting & Participants: Children aged (0-5) diagnosed with CAKUT attending Minia University Hospitals and their controls

Methodology: Questionnaire data were collected from mothers of 150 children with CAKUT and 150 healthy controls. Maternal risk factors investigated included maternal age, residence, history of obesity during pregnancy and diabetes mellitus. Logistic regression analyses were performed to assess associations between these potential risk factors and CAKUT occurrence.

Results: 150 case patients with CAKUT and 150 controls aged from 0 to 5 years were interviewed. Maternal DM occurred in 33 (22%) of CAKUT cases and in 16 (10.7%) of controls (P=0.01) .Maternal pre gestational DM (diagnosed before pregnancy type 1 or type 2 DM occurred in 7 cases (4.7%) of the CAKUT group versus 5 cases (3.4%) controls (P=0.5), whereas gestational DM (diagnosed during pregnancy) occurred in 26 (17.3%) of the CAKUT group and 11 (7.3%) controls (P=0.01). In multivariable logistic regression model, gestational DM was associated with CAKUT (OR =2.8; 95% CI, 1.3-59), whereas pre gestational DM was not (OR =1.6; 95% CI, 0.4-5.4).
Conclusions: This study suggests that gestational DM is associated with CAKUT in exposed infants. Screening and intervention studies in women of childbearing age with DM are warranted to determine whether the risk of chronic kidney disease in children can be modified.

Key Words: Congenital anomalies of the kidney and urinary tract (CAKUT); diabetes mellitus (DM); pregnancy; maternal health.

Manuscript

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) are the most frequent form of malformation at birth have been identified in 20% to 50% of all fetal congenital anomalies and affecting 3–7 out of 1000 live births in some populations [3] .Only the most severe forms are diagnosed during the first year after birth and less severe cases of CAKUT can be identified later on during development. CAKUT has severe implications for the health system, as they can be responsible for up to 50% of pediatric chronic kidney disease cases.[4] Also, CAKUT is one of the major underlying diseases in the young adult population on renal replacement therapy. Many of them, even if they are undiagnosed and remain healthy in adolescence, have an increased risk of end stage renal disease during adulthood.[5] The underlying cause of CAKUT generally is not known. The diverse phenotypes of CAKUT are thought to result from disturbances at any point in renal morphogenesis. Most importantly, imbalances in the communication between the

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metanephric mesenchyme (MM) and the ureteric bud (UB), secondary to environmental or genetic causes [6].On the other hand, Diabetes is one of the potential clinical factors in pregnancy that can affect kidney development, in addition to other teratogens such as alcohol, illicit drugs such as cocaine[7]. Therefore, effective interventions to prevent or modify diabetes effect may have the potential to prevent substantive CAKUT. Diabetes is accepted as one of major risk factors for congenital anomalies generally, but evidence of diabetes as a risk factor specifically for CAKUT is sparse.[8] Worldwide, there has been a reported increase in women with diabetes mellitus in the childbearing age either early or (pre gestational) or late (gestational DM). Diabetes does not only affect high-income countries, but its burden is spread across low- and middle-income countries as well[9]. An increase of diabetic pregnancies can increase the incidence of adverse pregnancy outcomes, both for mother and infant. It is therefore important to understand if diabetes in pregnancy is associated specifically with CAKUT[10]. Unfortunately, the pathobiological mechanisms underlying diabetic embryopathy are not well understood. It has been demonstrated that exposure to maternal diabetes during pregnancy changes gene expression thereby disrupting essential cellular activities which is essential for organogenesis. Thus, hyperglycemia during pregnancy could have a teratogenic effect by altering the embryonic epigenome, leading to defects like CAKUT in the fetus[11]. Although preconception and antenatal care in developed countries is focused mainly on effective self-management, recommendations for women with diabetes are fragmented and inconsistent among countries and need further evidence-based standardized guidelines which is worse in developing country. Thus the rate of birth defects in diabetic pregnancies remains higher than that in the general population.[12] So in this study we evaluated the potential effect of maternal diabetes and relation of pattern of exposure to the cumulative effect on development of CAKUT.

Methodology:

Our study was designed as a case-control study involving children with CAKUT attending Minia University Hospitals in the period between June 2019 and August 2020. We involved 150 Inpatients or outpatient children in either Pediatric or Urology departments up to five years of age who was suffering from CAKUT. Another 150 children attending hospital for different reasons were included to serve as age matched controls after exclusion of presence of CAKUT by routine examination and ultrasound investigation. Cases and control was interviewed after approval of the study and obtaining well-informed consent from the child mother. Data was collected from the mother of the children with special emphasis on maternal diabetes.

Statistical analysis

Statistical analyses were performed using the SPSS statistics version 21. Differences in the mean of continuous variables were analyzed using parametric test (independent sample Test. And differences between categorical variables were analyzed using Chi Square test. For all tests .Only significantly associated risk factors in uni-variable analyses were included in the multivariable logistic regression model, the values $P<0.05$ were regarded statistically significant.

Results:

Our study involved 300 child halved into two groups**,**

150 children diagnosed with CAKUT were included in the present study, 102 (68%) were males and 48 (32%) were females with no significant difference between cases and controls.

Maternal age in both groups did not significantly differ where more than half of mothers aged from 30 to 39. By asking mothers about their weight gain during pregnancy no significant difference was found

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Table 1: Different criteria of the two study groups

Variables		Cases (n=150)	Controls (n=150)	p-value
Child Sex	**Male**	102 (68%)	95 (63.3%)	0.1
	Female	48 (32%)	55 (36.7%)	
Residence	**Rural**	101 (67.3%)	98 (65.3%)	0.7
	Urban	49 (32.7%0	52 (34.7%)	
Maternal age at pregnancy (years)	**< 20**	9 (6%)	6 (4%)	0.8
	20-29	48 (32%)	52 (34.7%)	
	30-39	82 (54.7%)	79 (52.7%)	
	> 40	11 (7.3%)	13 (8.7%)	
Obesity	**Yes** **No**	49 (32.7%) 101 (67.3%)	55 (36.7%) 95 (63.3%)	0.4
DM	**Total DM**	33 (22%)	16 (10.7%)	0.01*
	Gestational DM	26 (17.3%)	11 (7.3%)	0.01*
	Pre-gestational DM	7 (4.7%)	5 (3.4%)	0.5

***significant**

There were more cases of diabetes among CAKUT than controls (22% versus 10.7%) respectively. P=0.01 and by further analysis by binary logistic regression diabetic mother has about 2 fold risk of occurrence of CAKUT.

Table 2: Logistic regression analysis of the effect of different factors on the occurrence of CAKUT

Variables	OR	95% CI		Sig.
		Lower	upper	
Total DM	2.3	1.211	4.455	0.01*
Residence	1	0.645	1.706	0.8
Mother age	0.9	0.706	1.365	0.9
Child Sex	0.6	0.417	1.117	0.1

***significant**

Discussion

Because all types of DM are increasing worldwide (affecting low-, middle-, and high-income countries) in young women of childbearing age, understanding the teratogenic potential of DM in pregnancy is increasingly important and intrauterine environment are determinants of infant's future health including the kidneys and urinary tract. We tried to evaluate the relative association between DM and CAKUT emphasizes how crucial the exposure is, and the importance of thorough monitoring and counseling of diabetic women before and during the first trimester of pregnancy.

We studied the effect of diabetes during pregnancy on development of CAKUT by interviewing mothers of 150 child with CAKUT and 150 controls aged from 0 to 5 years where we found that maternal DM of any type occurred in 33 (22%) of the CAKUT group and 16 (10.7%) controls (P =(0.01).),(OR= 2.3 ; 95% CI, 1.12-4.5)

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Similar to our work, one population-based case-control study in Texas on 89 cases of renal agenesis/dysgenesis and 356 controls, it was reported that there were a significant difference between maternal diabetes among cases =6 (6.7%) and= 8 (2.3%) among controls. (OR= 3.1 ; 95% CI, 1.1-9.3)[13]

Another prospective case control survey assessed the role of gestational diabetes in the development of ureteric malformations after adjustment (an OR= 5.1; 95% confidence interval: 1.1-24.5) and found that gestational diabetes is a risk factor for urinary tract malformations.[14]. Also, prenatal risk factors for urinary malformations development was investigated and founded that Diabetes mellitus or gestational diabetes increases risk of CAKUT by 4- folds ([OR]=4.77; 95% CI, 1.16–19.65). [15]

On further analysis of DM in our study, we found that gestational DM (DM diagnosed during pregnancy) was significant associated with CAKUT occurrence (OR= 2.5 ; 95% CI, 1.2-5.3), whereas pre gestational DM (DM before pregnancy was not (OR=1.5; 95% CI, 0.4-5.1).

Similarly, Hsu et al studied prenatal risk factors of CAKUT in a large population-based cohort in Washington, the rate of gestational DM was 6.4% and 4.8% in the CAKUT and control groups, respectively, and the difference between them was significant, (OR, 1.97; 95% CI, 1.15-3.37). [16]

Also Shnorhavorian et al. reported a significant difference between congenital urinary tract anomalies cases with gestational DM (4.1%) and their control (OR =1.42, 95% CI 1.09-1.85). However, significant odds of preexisting DM for the risk of occurrence of CAKUT was reported (OR 3.46, 95% CI 2.17-5.54).[17]

On a close view, gestational DM frequency in our CAKUT cases (17.3%) was quite above the level reported by Hsu et al and Shnorhavorian et al. we attributed that to the increasing prevalence of gestational DM in low and middle income countries. [18]

On the opposite side, another study by Dart et al discussing the same issue showed that pre gestational diabetes significantly associates with CAKUT (odds ratio, 1.67; 95% confidence interval, 1.14-2.46), which implies a 67% increased chance of CAKUT in the offspring of mothers with pre gestational diabetes compared to the general population.[19]

We found that differences in strength of association between pre gestational versus gestational DM in our study may be due to diagnostic difficulties as many mothers did not seek medical advice unless during pregnancy. So, in many cases pre gestational diabetes misdiagnosed as gestational diabetes. Negligence may reach to the extent that mothers ignore being diabetic after delivery and neglect taking anti-diabetic medication till the upcoming pregnancy and so on.

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