Prenatal Risk Factors for Congenital Anomalies of the Kidney and Urinary Tract

Doğumsal Böbrek ve Üriner Sistem Anomalilerinde Prenatal Risk Faktörleri

ABSTRACT

OBJECTIVE: Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of chronic renal disease in childhood. Abnormal intrauterine conditions as well as genetic disorders play role in CAKUT development. We evaluated antenatal factors in CAKUT.

MATERIAL and METHODS: The study and control groups included 140 CAKUT cases and 140 children without urinary malformation, respectively. Both groups were compared for antenatal (gestational period, prematurity, oligohydramios, preeclampsia, gestational diabetes, accompanying malformation, in vitro fertilization), maternal (age, body weight at pregnancy onset, weight gain during pregnancy, systemic disease, smoking, alcohol, medications) and familial (consanguinity, renal disease, urinary malformation) parameters.

RESULTS: The study group had a shorter gestational period (38.8±2.9 vs. 39.5±0.9 week, p=0.004), but higher prematurity (9.3% vs. 0.7%, p=0.001), parity (≥2 parity 57.9% vs. 41.4%, p=0.006), oligohydramnios (6.4% vs. 0%, p=0.002), accompanying malformation (15.7% vs. 5.7%, p=0007), weight gain in pregnancy (18.8±2.9 vs. 18.1±2.8 kg, p=0.047) and familial renal disease (7.9% vs. 2.1%, p=0.028) rates. In vitro fertilization was present in only two cases in the study group.

CONCLUSION: Weight gain in pregnancy and increased parity may be risk factors for CAKUT. Population-based studies are needed to determine the role of subfertility.

KEY WORDS: CAKUT, Maternal weight, Parity, Risk factors, Subfertility

ÖZ

AMAÇ: Doğumsal böbrek ve üriner sistem anomalileri (DBÜSA) çocuklarda kronik böbrek hastalığının önde gelen nedenidir. DBÜSA gelişiminde genetik bozukluklar yanında, uygunsuz intrauterin koşulların da rol oynadığı düşünülmektedir. Çalışmada, DBÜSA olgularında antenatal etkenlerin rolü incelenmiştir.

GEREÇ ve YÖNTEMLER: Çalışma grubuna DBÜSA tanılı 140 hasta, kontrol grubuna ise malformasyon olmaksızın üriner enfeksiyonu olan 140 olgu alındı. Gruplar antenatal (gestasyon süresi, prematürite, oligohidroamnioz, preeklampsi, gestasyonel diabetes mellitus, eşlik eden malformasyon, invitro fertilizasyon), maternal (gebelik yaşı, gebelik öncesi ağırlık, gebelikte ağırlık artışı, sistemik hastalık, sigara, alkol, ilaç) ve ailesel (akraba evliliği, böbrek hastalığı, üriner anomali) parametreler yönünden karşılaştırıldı.

BULGULAR: Çalışma grubunda gestasyon süresi daha kısa (38,8±2,9'a 39,5±0,9 hafta, p=0,004), prematürite oranı (%9,3'e %0,7, p=0,001), parite (≥2 gebelik oranı %57,9'a %41,4, p=0,006), oligohidramnioz (%6,4'e %0, p=0,002), eşlik eden malformasyon (%15,7'ye %5,7, p=0,007), gebelikte ağırlık artışı (18,8±2,9'e 18,1±2,8 kg, p=0,047) ve ailede böbrek hastalığı sıklığı (%7,9'a %2,1, p=0,028) daha yüksek idi. In vitro fertilizasyon uygulaması sadece çalışma grubundaki iki olguda mevcut idi.

SONUÇ: DBÜSA için gebelikte fazla ağırlık artışı ve artan gebelik sayısı risk faktörü olabilir. Ancak, subfertilitenin rolünü tespit etmek için geniş kapsamlı çalışmalara gereksinim vardır.

ANAHTAR SÖZCÜKLER: Doğumsal böbrek ve üriner sistem anomalileri, Gebelikte ağırlık artışı, Parite, Risk faktörleri, Subfertilite

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Received : 04.02.2016
Accepted : 20.09.2016

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INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) are frequent malformations leading to deterioration of renal functions, morbidity and early mortality. CAKUT frequency has been reported as 0.5-1.0% in all gestations in prenatal screening studies (1). CAKUT is the leading cause of end stage renal disease in children under 5 years of age (2). Severe malformations like bilateral renal agenesis are not compatible with life. On the other hand, mild malformations like vesicoureteral reflux may not be detected in childhood and may appear as hypertension, proteinuria and renal dysfunction in adulthood (3).

The etiology of CAKUT has been the subject of detailed investigation in recent years. The determination of genes involved in renal development and the recognition of mutations in a considerable number of these genes have demonstrated the role of impaired genetic control (4). In parallel with this discovery, evolving experimental and clinical data support the influence of suboptimal intrauterine environment in renal development. Particularly, maternal protein malnutrition has been found to be associated with low nephron number and renal hypoplasia (5).

Determination of maternal risk factors associated with CAKUT may facilitate the development of targeted medical interventions during antenatal period in women of childbearing age in order to decrease the morbidity and mortality due to these anomalies. Attempts to define CAKUT-related maternal risk factors have been limited to diabetes mellitus (DM), gestational DM, smoking and alcohol consumption until now (6,7). In a recent population-based study pregestational DM, maternal renal disease, Caucasian race and increased parity have been found to be associated with CAKUT (8). In particular, DM and maternal renal disease were found to be correlated with isolated renal anomalies, and maternal age, race, parity, and renal disorder with isolated low urinary tract anomalies.

Though the correlation between maternal protein malnutrition and fetal kidney development is known well, little is known about the effect of maternal obesity on renal ontogenesis and postnatal renal functions. The fact that obesity and DM prevalence tend to increase globally has aroused suspicion that maternal over-nutrition and its metabolic results may cause the formation of a similar negative environment for *in utero* kidney development (9). It was suggested that risk for having a child with obstructive renal anomaly increased in over-weight/ obese and sub-fertile women (10).

While the correlation of pre-pregnancy maternal obesity with CAKUT was investigated, correlation of weight gain during pregnancy has not been evaluated. In this study, our aim was to examine the maternal factors (age, parity, obesity, weight gain during pregnancy, obstetric disorder, systemic disease, renal disease) in cases diagnosed with CAKUT as well as the effect of factors such as subfertility and in-vitro fertilization practices.

MATERIALS and METHODS

Children aged 0 to 18 years with a diagnosis of CAKUT in the prenatal or postnatal period formed the study group. CAKUT included unilateral renal agenesis, renal hypoplasia/dysplasia, ectopic kidney, renal fusion anomalies, ureteropelvic junction obstruction, ureterovesical junction obstruction, vesicoureteral reflux, posterior urethral valve and double collecting system. The control group included children having urinary tract infection (UTI) without CAKUT which was confirmed by normal ultrasonography, voiding cystourethrography and 99mTc-dimercaptosuccinic acid scintigraphy. Patients with renal anomalies due to single gene mutation (polycystic renal disease, nephronophthisis, etc) were excluded. Hospital files of all cases were retrospectively examined in terms of gender, age, CAKUT type, gestational age, oligohydramnios, extrarenal malformation, preeclampsia, maternal factors [subfertility and in vitro fertilization, gestational DM, prepregnancy maternal age, number of pregnancy, prepregnancy weight (W), prepregnancy body mass index (BMI), weight gain during pregnancy (WG), WG/W, hypertension, systemic disease, smoking, alcohol use, drug use (other than iron and vitamin preparations)] and familial factors (consanguinity, kidney disease in family, urinary system anomaly in family). Familial kidney disease was queried as the presence of chronic renal failure and/or renal stone disease, while familial urinary anomalies were defined as the anomalies present in the study group. All antenatal data were obtained by routine questionnaire during clinical visits except W and WG which were asked retrospectively to mothers by a phone call. These variables were compared between the study and control groups. The study was approved by the Dokuz Eylül University Ethics Committee (No: 2015/17-34, Date: 09.07.2015).

Statistical Analyses

Windows SPSS v16.0 was used to analyze the data. Chi-square test (percentages) and student-t test (measurable data) were used for comparison of the groups. $P < 0.05$ was accepted as statistically significant.

RESULTS

There were 140 patients in the study group. The same number of children with a history of UTI but without urinary system anomalies was elected into the control group. CAKUT included unilateral renal agenesis (17%), dysplasia (16%), ureteropelvic junction obstruction (16%), ectopic kidney (16%), double collecting system (10%), hypoplasia (9%), fusion anomalies (7%), vesicoureteral reflux of grades 2 to 4 (6%), ureterovesical junction obstruction (1%) and posterior urethral valve (1%).

Comparison of the study and control groups is seen in Table I. While a third of the cases in the study group were girls and two thirds were boys, girls were predominant in the control group that was composed of children being followed up for UTI. Gestational period was shorter in the study group and almost

Table I: Comparison of the study and the control group.

	Study Group (n=140)	Control Group (n=140)	*p*
Demographic variables			
Gender: Boy/Girl	91/49	24/116	**< 0.001**
Gestational week	38.8 ± 2.9	39.5 ± 0.9	**0.004**
Prematurity n (%)	13 (9.3%)	1 (0.7%)	**0.001**
Age (year)	6.9 ± 3.8	5.6 ± 4.3	**0.008**
Antenatal variables			
Maternal parity			
1/ > 1	59 / 81	82 / 58	**0,006**
≤ 2 / ≥ 3	124 / 16	133 / 7	**0.050**
Oligohydramnios	9 (6.4%)	0 (0%)	**0.002**
Preeclampsia	3 (2.1%)	0 (0%)	0.247
Gestational DM	14 (10.0%)	7 (5.0%)	0.112
Associated malformations	22[a] (15.7%)	8[b] (5.7 %)	**0.007**
In vitro fertilisation	2 (1.4%)	0 (0%)	0.498
Maternal variables			
Age at gestation	27.4±5.0	27.1±3.8	0.611
Prepregnancy weight (W) (kg)	71.7±9.7	72.4±6.7	0.514
BMI >25	96 (68.6%)	95 (67.9%)	0.898
Weight gain in pregnancy (WG) (kg)	18.8±2.9	18.1±2.8	**0.047**
WG/W	0.263±0.032	0.246±0.031	**<0.001**
Systemic disease	15 (10.0%)	14 (10.0%)	0.845
Hypertension	5 (3.6%)	2 (1.4%)	0.251
Smoking	4 (2.9%)	2 (1.4%)	0.409
Drug consumption	10 (7.1%)	7 (5.0%)	0.453
Familial variables			
Consanguinity	13 (9.3%)	6 (4.3%)	0.096
Renal disease	11 (7.9%)	3 (2.1%)	**0.028**
Urinary anomaly	26 (18.6%)	25 (17.9%)	0.877

(a) Anal atresia 3, hypospadias 5, testicular atrophy 2, cardiac malformation (ASD 2, VSD 2, PDA 3, tetralogy of Fallot 1), esophageal atresia 1, limb anomalies (phocomelia 1, syndactyly 1), microgenitalia 1 (b) cardiac malformation (ASD 1, VSD 3, PDA 2, bicuspid aortic valve 2)

10% were premature. Multiparity rate was significantly higher in the study group (58%) compared to control group (41%). While none of the control cases had oligohydramnios, 6.4% of cases in study group had a history of oligohydramnios. The study group also had a significantly higher rate of associated malformations (15.7% vs. 5.7%).

Even though not statistically significant, gestational DM was twice as common in the study group compared to the control group (10% vs. 5%). Maternal overweight/obesity frequency (67% and 69%, respectively) was quite high in both groups. However, weight gain during pregnancy (WG) and especially ratio of WG to prepregnancy weight was significantly higher in the study group compared to the control group (0.263±0.032 vs. 0.246±0.031, p<0.001). An *in vitro* fertilization method was applied to only two mothers in study group. The familial kidney disease rate was four times higher in the study group (7.9% vs. 2.1%, p=0.028) (Table I).

DISCUSSION

Maternal health and intrauterine environment are determinants of infant's future health including the kidneys (11). The frequency of obesity and diabetes mellitus has been tending to increase all over the world since 1980 (12,13). The current pandemic of obesity and diabetes mellitus may affect the health of future generations.

Some congenital kidney anomalies like renal dysplasia have been correlated to maternal DM (14). Correlation of the congenital kidney malformation risk with maternal obesity and overweight is still controversial. Two studies regarding this subject were published recently. Maternal risk factors of congenital urinary anomalies were investigated in one of these studies. Gestational DM (OR 1.4) and pre-gestational DM (OR 3.4) were determined to increase the risk of a kidney anomaly (15). In the other study investigating the causes of chronic kidney disease in childhood, it was found that maternal pre-gestational

DM increased the renal aplasia and dysplasia risk and maternal overweight/obesity increased the obstructive uropathy risk (11). In the latter study, 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. Gestational DM frequency in our CAKUT group (10%) was twice the rate in the control group (5%), but the difference was not significant. Moreover, gestational DM frequency in our CAKUT cases was quite above the level reported in the literature (11,15). The statistical insignificance of the gestational DM rate despite this high level in our study was probably due to limited number of cases.

Pre-pregnancy maternal obesity is known to be correlated with multiple fetal anomalies (16,17). Mothers of children with chronic kidney disease (mostly associated with CAKUT) are likely to be overweight and obese (11). In our study, a difference was not found between mothers of cases with and without CAKUT in terms of pre-gestational weight and BMI. Similarly, pre-gestational weight and BMI of mothers were not different also in cases with upper and lower urinary tract anomalies. However, maternal overweight/obesity frequency (BMI >25) was 68.6% in the study group and 67.9% in the control group and these values were quite higher than those reported in the literature (26% and 21%, respectively) (11). In fact, the obesity frequency (BMI >30) of adult women in Turkey has been reported as 41% (18). When all cases in our study were considered, the obesity frequency was 17.1% and the frequency of overweight and obesity was 68.2%. A comprehensive study investigating the prevalence of CAKUT is not present in Turkey. In the light of the current obesity data, the prevalence of CAKUT in Turkey can be expected to be above the global average.

Association of gestational weight gain with CAKUT has not been investigated previously. In our study population, weight gain during pregnancy and the gestational weight gain/pre-pregnancy weight ratio were significantly higher in CAKUT cases than the control group. Thus, not only the prepregnancy weight, but also gestational weight gain may have a role in the development of CAKUT. On the other hand, there are numerous factors affecting gestational weight gain such as the educational level, socioeconomic status, pre-gestational BMI, maternal age, parity, smoking, gestational period, and fetal gender (9). Maternal age and pre-gestational BMI were not different in the study and control groups. However, male fetus and multiparity rate (both associated with increased weight gain during pregnancy) were significantly higher in the study group. Thus, it should not be ignored that fetal gender and parity could have played role in increased gestational weight gain in CAKUT group. Absence of regression analyses is a limitation of the present study.

It has been reported that the risk of having an infant with obstructive renal anomaly increased in overweight/obese and sub-fertile women (10). Therefore, application of assisted reproduction techniques due to subfertility was also evaluated in our study. There were only two cases with an IVF history, both in the CAKUT group. One of these two mothers was overweight (BMI 25.7) and the other was normal (BMI 23.9). However, both mothers gained weight above the average during pregnancy (WG/W was 0.29 and 0.32). Due to the limited number of cases, we cannot comment on the role of IVF in CAKUT development.

In conclusion, the results of this preliminary study indicate that increased gestational weight gain and multiparity might increase the risk of CAKUT. However, our study population is too small to derive strict conclusions. Thus, further studies with larger series of patients would be needed to complement the results of this study.

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