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Prenatal diagnosis of fetal urinary system anomalies

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Abstract

Objective: The aim of this study is to determine concurrent structural and chromosomal anomalies in the cases found to have fetal urinary system anomaly.

Methods: The pregnant women established with the diagnosis of fetal urinary system anomaly in our clinic between 2010 and 2015 were included in the study. Age, week of gestation, gravida, parity, number of abortion, anomaly type, presence of concurrent anomaly, prenatal diagnosis method and fetal karyotype results of the pregnant women were recorded. Urinary system anomalies were categorized in sub-groups which were renal agenesis, pyelectasis, multicystic dysplastic kidney, polycystic kidney and megacystis.

Results: Pyelectasis was the most common fetal urinary system anomaly. In terms of other concurrent anomalies, the central nervous system anomaly was the most common anomaly seen in 17 (28.3%) pregnant women. The most common concurrent urinary system anomalies seen with additional anomalies were unilateral pyelectasis (91.7%), unilateral renal agenesis (75%), bilateral multicystic dysplastic kidney (66.7%), and bilateral pyelectasis (62.5%). Anhydramnios developed in 5 (8.3%) cases. When karyotype results were assessed, it was seen that one (1.7%) case had triploidy, and 16 (26.6%) cases had trisomy. Of the cases with trisomy as karyotype, 3 (17.6%) had isolated urinary system anomaly and other 14 (82.4%) had additional anomaly. The difference between the cases whose karyotype results were normal, and trisomy and the cases with additional anomaly was statistically significant (p=0.040).

Conclusion: The concurrent structural and chromosomal anomalies should be determined in the management of pregnancies with fetal urinary system anomaly diagnosed during prenatal period.

Keywords: Fetal urinary system anomaly, karyotype, pyelectasis, trisomy.

Özet: Fetal üriner sistem anomalilerinin prenatal tanısı

Amaç: Çalışmanın amacı fetal üriner sistem anomalisi saptanan olgulara eşlik eden yapısal ve kromozomal anomalileri belirlemektir.

Yöntem: 2010–2015 yılları arasında kliniğimizde fetal üriner sistem anomali tanısı alan gebeler çalışmaya dahil edildi. Gebeliklere ait yaş, gebelik haftası, gravida, parite, abortus sayısı, anomalinin tipi, eşlik eden anomali varlığı, prenatal tanı yöntemi ve fetal karyotip sonucu kayıt edildi. Üriner sistem anomalileri renal agenezi, piyelektazi, multikistik displastik böbrek, polikistik böbrek ve megasistis olarak alt gruplara ayrıldı.

Bulgular: En sık görülen fetal üriner sistem anomalisi piyelektazi idi. Eşlik eden diğer anomaliler incelendiğinde 17 (%28.3) gebe ile santral sinir sistemi anomalisi en fazla karşılaşılan anomaliydi. Ek anomalilerle ile en sık birliktelik gösteren üriner sistem anomalileri; ünilateral piyelektazi (%91.7), ünilateral renal agenezi (%75), bilateral multikistik displastik böbrek (%66.7) ve bilateral piyelektazi idi (%62.5). Beş (%8.3) olguda anhidramniyos gelişti. Karyotip sonuçları değerlendirildiğinde bir (%1.7) olguda triploidi ve 16 (%26.6) olguda trizomi mevcuttu. Karyotipi trizomi olan olguların 3'ü (%17.6) izole üriner sistem anomalisine sahipti ve diğer 14 (%82.4) hastada ek anomali mevcuttu. Karyotip sonucu normal ve trizomi olan olgular ile ek anomali arasındaki fark istatistiksel olarak anlamlıydı (p=0.040).

Sonuç: Prenatal dönemde tanı alan fetal üriner sistem anomalili gebeliklerin yönetiminde eşlik eden yapısal ve kromozomal anomalilerin belirlenmesi gereklidir.

Anahtar sözcükler: Fetal üriner sistem anomalisi, karyotip, piyelektazi, trizomi.

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Introduction

Congenital urinary system anomalies include various levels of structural and functional malformations such as kidney, collecting ducts, bladder and urethra, and its incidence is approximately between 0.3 and 1.6 per 1000 births.[1] They consist of 15–20% of all anomalies during prenatal period.[2]

Many structures forming the fetal urinary system develop between 10 and 20 weeks of gestation, and most of these anomalies can be diagnosed by ultrasonography during this period. The most common urinary system anomalies are obstructive pathologies. However, they contain a wide spectrum between mild asymptomatic malformations and severe pathologies with high mortality.[3,4]

The common findings of urinary system anomalies during antenatal period are oligohydramnios, and the distinct changes in kidney, ureter or bladder morphology. While some of the forms are seen together with the syndromes accompanied by multi-organ anomalies, most of the cases are non-syndromic.[5] Although it has been shown in sporadic cases and some animal models that some genes play a role in the developmental defects of urinary system, it is still controversial for determining which has the main role. Multiple genes play a role in the development of urinary system pathologies as in many congenital anomalies. Environmental factors also affect the development of embryo and fetus.

Urinary system anomalies may affect not only the current system but also other fetal functions. For example, some anomalies in this group may lead to oligohydramnios and therefore fetal pulmonary hypoplasia and extremity contractures. While most of the urinary system anomalies are progressive, functional reversion can be possible by treatment methods carried out during intrauterine or postnatal period.[6] Therefore, the prenatal diagnosis of urinary system anomalies has a significant role on planning the timing, location and type of delivery.

In our study, we aimed to assess the frequency of chromosomal anomaly in cases found to have urinary system anomaly, its association with other system anomalies, and their impacts on karyotype results.

Methods

In this study, we retrospectively evaluated 60 cases which were found to have fetal urinary system anomaly during fetal anomaly screening and routine obstetric ultrasound examination and underwent karyotyping for prenatal diagnosis at the Gynecology and Obstetrics Clinic of Tepecik Training and Research Hospital, Health Sciences University between January 1, 2010 and December 31, 2015. For genetic diagnosis purpose, the cases underwent chorionic villus sampling (CVS), amniocentesis or cordocentesis. Approval of ethics committee required for the study was obtained from the Local Ethics Committee of Tepecik Training and Research Hospital with the number 30.09.2015/1.

Age, week of gestation, gravida, parity, number of abortion, anomaly type, presence of concurrent anomaly, prenatal diagnosis method and fetal karyotype results of the pregnant women found to have fetal urinary system anomaly were recorded. Urinary system anomalies were categorized in sub-groups which were renal agenesis, pyelectasis, multicystic dysplastic kidney, polycystic kidney and megacystis. For pyelectasis diagnosis, the threshold for renal anterior-posterior diameter was determined 4 mm for up to 32 weeks of gestation and 7 mm for 33 weeks of gestation and above.

For prenatal diagnosis, all families were provided genetic consultancy before the karyotyping procedure. Written and oral information about the technique of karyotyping procedure and possible complications were given and informed consents were obtained. The procedures were done together with ultrasonography. Local anesthesia was not applied during any procedure, and antibiotic prophylaxis was performed for all patients after the procedure. For CVS procedure, chorion frondosum was entered by using 18 gauge needle through double-need technique and then the stylet was removed. Afterwards, sampling needle was inserted. After it was fixed to the needle tip of 20 ml injector containing heparinized culture medium, aspiration was conducted by forward and backward movements. In the amniocentesis procedure, 22 gauge spinal needle was used to enter into amniotic cavity where there was no fetal structure and cord. Amniotic fluid was aspired by means of 10 ml injector by applying slight negative pressure, and 1 ml was collected per week of gestation. In order to prevent contamination, separate injectors were used and first 2–3 ml of fluid was discarded. In the cordocentesis procedure, 20 gauge spinal needle was used and umbilical vein was entered on 1–2 cm away from the entrance point of cord into placenta. About 1–5 ml blood sample was collected by heparinized injector. The pregnant women

who had normal karyotype results and no significant anomaly were followed up by ultrasonography until delivery. The fetuses who had fatal chromosomal or structural anomaly were evaluated by the perinatology council of our clinic and the family was offered the option for terminating the pregnancy.

All statistical analyses of the data were done by using SPSS software, version 17.0 (SPSS, Inc., Chicago, IL, USA). Conformity of the numerical variables to normal distribution was evaluated by Shapiro-Wilk test. The categorical variables were determined by frequency and percentage while numerical variables were determined by mean and standard deviation or median and minimum-maximum values. The correlation between two categorical variables was investigated by chi-square test. Two independent mean values were compared by Student's-t test while two independent median values were compared by Mann-Whitney U test. The study was evaluated within 95% confidence interval. The value $p<0.05$ was considered statistically significant.

Results

The study group consisted of 60 pregnant women who were found to have fetal urinary system anomaly and underwent karyotyping. The demographic characteristics of the cases are shown in **Table 1**.

Pyelectasis was the most common one among urinary system anomalies (**Table 2**). While fetal pyelectasis was observed in 28 (46.7%) pregnant women, 12 (20%) of them was unilateral and 16 (26.7%) of them were bilateral. Of the other pregnant women, 8 (13.3%) had unilateral multicystic dysplastic kidney, 6 (10%) had bilateral multicystic dysplastic kidney, 4 (6.7%) had unilateral renal agenesis, 2 (3.3%) had bilateral renal agenesis, 2 (3.3%) had polycystic kidney and 6 (18.3%) had megacystis. In terms of other anomalies accompanying urinary system anomalies, the central nervous system was the most common anomaly seen in 17 (28.3%) pregnant women (**Table 2**). Thirteen (21.7%) pregnant women had fetal hyperechogenic intestine, 12 (20%) cases had cardiovascular system anomaly, 4 (6.7%) cases had facial anomaly, 5 (8.3%) cases had extremity anomalies, 4 (6.7%) cases had single umbilical artery, 2 (3.3%) cases had anterior abdominal wall defect, one (1.7%) case had diaphragmatic hernia, and one (1.7%) case hydrops. In addition, the most common concurrent urinary system anomalies seen with additional anomalies were unilater-

Table 1. The demographic data of the pregnant women who participated in the study.

Age (Mean, SD)	28.4	5.7
Age (n, %)		
<35	51	85
≥35	9	15
Week of gestation (Mean, SD)	22.1	6.1
Week of gestation (n, %)		
≤22 weeks	23	38.3
>22 weeks	37	61.7
Gravida (Median, min-max)	2	1–5
Gravida (n, %)		
1	20	33.3
2	19	31.7
3	12	20
4	6	10
5	3	5
Parity (Median, min-max)	1	0–3
Parity (n, %)		
0	25	41.7
1	23	38.3
2	9	15
3	3	5
Abortion (Median, min-max)	0	0–3
Abortion (n, %)		
0	43	71.7
1	12	20
2	3	5
3	2	3.3

SD: Standard deviation

Table 2. Urinary system anomalies and concurrent anomaly types.

Urinary system anomalies	n	%	Additional anomaly (%)
Unilateral renal agenesis	4	6.7	75
Bilateral renal agenesis	2	3.3	50
Unilateral pyelectasis	12	20	91.7
Bilateral pyelectasis	16	26.7	62.5
Unilateral MCDK	8	13.3	37.5
Bilateral MCDK	6	10	66.7
PKD	2	3.3	0
Megacystis	6	10	27.3
Additional anomalies	37	61.7	
CNS	17	28.3	
CVS	12	20	
Facial	4	6.7	
Anterior abdominal wall defect	2	3.3	
Extremity	5	8.3	
Diaphragmatic hernia	1	1.7	
Hyperechogenic intestine	13	21.7	
Single umbilical artery	4	6.7	

CNS: central nervous system; **CVS:** cardiovascular system; **MCDK:** multicystic dysplastic kidney; **PKD:** polycystic kidney disease

al pyelectasis (91.7%), unilateral renal agenesis (75%), bilateral multicystic dysplastic kidney (66.7%), and bilateral pyelectasis (62.5%) (**Table 2**). Anhydramnios developed in 5 (8.3%) cases in addition to other organ anomalies.

Amniocentesis procedure was carried out on 47 cases between 16 and 20 weeks of gestation, cordocentesis procedure was carried out on 6 cases between 20 and 28 weeks of gestation, and CVS procedure was carried out on 5 cases between 11 and 14 weeks of gestation. In two cases which were decided for termination by the perinatology council due to the fetal conditions which were found to have fatal urinary system anomaly, karyotype was determined through abortion material after the termination procedure. Karyotype results were evaluated to be normal in 41 (70.7%) cases. In one patient, karyotype result was reported as maternal contamination. Triploidy was found in one case, and all other karyotype anomalies were trisomies, and 16 (26.6%) cases had trisomy (**Table 3**).

The maternal age was <35 years in 92.7% of the cases with normal karyotype results. The karyotype result was trisomy in 6 (66.7%) out of 9 patients who were 35 years old and older. The correlation between age and normal and trisomy groups was statistically significant (p=0.014) (**Table 4**). No significant correlation was found between karyotype results and all urinary system anomalies. In the majority of the cases found to have trisomy by karyotype results, multiple anomalies were observed. Of the cases with trisomy as karyotype, 3 (17.6%) had isolated urinary system anomaly and other 14 (82.4%) had additional anomaly. The difference between the cases whose karyotype results were normal and trisomy and the cases with additional anomaly was statistically significant (p=0.040) (**Table 4**).

Discussion

Congenital urinary system anomalies are the malformations which have a broad spectrum and can be seen in 0.3–1.6 cases per 1000 deliveries.[1] Although most of them are sporadic and isolated, they also can be seen the part of a syndrome. Urinary system anomalies are genetically heterogeneous complex developmental anomalies which may display various phenotypic characteristics. However, single gene diseases also may lead to congenital anomaly in kidney and urinary system; similar conditions can also be observed in family history. Congenital

Table 3. Karyotype results of fetal urinary system anomalies.

	n	%
Karyotyping technique		
AC	47	78.3
CC	6	10
CVS	5	8.3
Abortion material	2	3.3
Karyotype material		
Normal	41	69.5
69XXX	1	1.7
Trisomy 13	2	3.4
Trisomy 16	1	1.7
Trisomy 18	4	6.8
Trisomy 21	10	17

AC: amniocentesis; **CC:** cordocentesis; **CVS:** chorionic villus sampling

Table 4. Distribution of fetal urinary system anomalies according to karyotype results.

	Normal (n, %)	Trisomy (n, %)	p-value
Age			0.014
<35	38 (92.7)	11 (64.7)	
≥35	3 (7.3)	6 (35.3)	
Week of gestation			0.268
≤22	13 (31.7)	8 (47.1)	
>22	28 (68.3)	9 (52.9)	
Gravida			0.114
Primigravida	16 (39)	3 (17.6)	
Multigravida	25 (61)	14 (82.4)	
Abortion			0.067
Not available	32 (78)	9 (52.9)	
Available	9 (22)	8 (47.1)	
Unilateral renal agenesis	3 (7.3)	1 (5.9)	>0.999
Bilateral renal agenesis	0 (0)	2 (11.8)	0.082
Unilateral pyelectasis	6 (14.6)	5 (29.4)	0.270
Bilateral pyelectasis	12 (29.3)	4 (23.5)	0.755
Unilateral MCDK	8 (19.5)	0 (0)	0.090
Bilateral MCDK	6 (14.6)	0 (0)	0.166
PKD	1 (2.4)	0 (0)	>0.999
Megacystis	9 (22)	2 (11.8)	0.480
Additional anomaly			0.040
Not available	19 (46.3)	3 (17.6)	
Available	22 (53.7)	14 (82.4)	
CNS	10 (24.4)	6 (35.3)	0.520
CVS	3 (7.3)	9 (52.9)	<0.001
Facial	3 (7.3)	1 (5.9)	>0.999
Anterior abdominal wall defect	1 (2.4)	1 (5.9)	0.504
Extremity	3 (7.3)	2 (11.8)	0.624
Diaphragmatic hernia	1 (2.4)	0 (0)	>0.999
Diaphragmatic hernia	6 (14.6)	7 (41.2)	0.040
Single umbilical artery	3 (7.3)	1 (5.9)	>0.999

CNS: central nervous system; **CVS:** cardiovascular system; **MCDK:** multicystic dysplastic kidney; **PKD:** polycystic kidney disease

anomalies of renal and urinary systems may cause hypertension and renal failure, and it is accounted for 30–50% of end-stage renal failure in children.[5,7] Therefore, the early diagnosis of urinary system malformations are very important in terms of fetal prognosis and postnatal problems. While the diagnosis of urinary system anomalies is easy (89% success rate for diagnosis), we could establish diagnosis at over 20 weeks of gestation in 61.7% of the cases in our study.[8] The patients in this group referred to the hospital at a late period and did not undergo regular follow-up previously.

Pyelectasis was the most commonly diagnosed urinary system anomaly in our study (46.7%). Twelve (20%) patients had unilateral pyelectasis and 16 (26.7%) patients had bilateral pyelectasis. In many studies, pyelectasis is the most common anomaly among urinary system anomalies.[2,5,9] In the cases found to have urinary system anomaly, the risk of chromosome anomaly increases especially in the presence of additional anomalies. Although isolated pyelectasis is "soft marker" for Down syndrome, it is not an indication alone for chromosomal analysis. On the other hand, it should be remembered that it increases the risk of age-related anomaly for 1.5 times, and prenatal consultancy of pregnant women should be carried out accordingly. In cases where additional anomaly is not observed in the ultrasonography, it is usually a common view that chromosome analysis is not required. In their study, Bornstein et al. reviewed 671 cases which were found to have pyelectasis between 1995 and 2004, and they found major trisomies in 35 (5.22%) cases.[10] In the same study, the ages of 133 (19.8%) cases were above 35 years. In this study, they did not observe isolated pyelectasis as a major marker for trisomies; however, they found that trisomy risk increased in fetuses which had additional sonographic findings together with pyelectasis or had abnormalities in their maternal serum markers. Observing another sonographic marker in addition to pyelectasis increases trisomy risk for 8 times. With more than one concurrent anomaly, the risk increases for 62 times.[10] The authors highlighted that evaluating chromosomal anomaly risk together with maternal age and/or maternal serum markers in cases with pyelectasis would yield more accurate results.[10]

In our study, unilateral pyelectasis was the group in which additional anomalies were the most concurrent, and the prevalence of additional anomaly was 91.6% in this patient group. Also, pyelectasis was the most common urinary system anomaly among the fetuses with chromosomal anomaly. Although isolated pyelectasis cases were rare in our study group and therefore it was not a significant data in terms of chromosomal analysis in this group, observing high rates of concurrent structural and chromosomal anomalies is concordant with the literature when we evaluated all cases with pyelectasis.[11,12]

In the literature, chromosomal defect rate has been reported 21% in cases with rare fetal megacystis.[13] While trisomy 13 is the most common among concurrent chromosomal anomalies, triploidy is quite rare.[14] Sebire et al. carried out chromosomal analysis on the cases with fetal megacystis and found chromosomal anomaly in 3 out of 15 cases.[13] In their prospective study where Favre et al. reviewed 5240 cases in France between 1992 and 1998 and found megacystis in 16 cases between 11 and 15 weeks of gestation, the authors showed the correlation between megacystis and chromosomal anomalies. While chromosomal anomaly is not found in cases with isolated megacystis, it was found in four cases with concurrent additional anomaly.[15] Two of them had trisomy 13, one had trisomy 21, and one had trisomy 18. In this study, it was shown that aneuploidy (25%) was accompanying megacystis at a high rate as well as other structural anomalies, particularly intestinal malformations (33%).[15] In our study, we found chromosomal anomaly only in 2 (18.1%) out of 11 cases who had megacystis.

Of 14 (23.3%) patients established with the diagnosis of multicystic dysplastic kidney, 8 (13.3%) were unilateral and 6 (10%) were bilateral. De La Vega and Torres reviewed 117 cases with congenital renal anomaly between 2001 and 2004, and found that the rate of multicystic dysplastic kidney was 17.9%.[16] In a recent study, the rate of multicystic dysplastic kidney has been reported 23.8%.[12] Also, bilateral renal agenesis was 12.8% in the study of De La Vega and Torres while it was 3.3% in our patient group.[16]

In our study, there were 37 (61.7%) fetuses which had other structural anomalies together with urinary system anomalies. In the study of Batukan et al., 23.6% of 165 fetuses with urinary system anomaly had also other structural anomalies.[17] In our study group, the high rate of concurrent anomalies can be due to the fact that our institution is a reference unit for prenatal diagnosis. On the other hand, some urinary system anomalies can be unnoticed during ultrasonography when

oligohydramnios is not present and therefore the patients are not referred to our clinic.

The prevalence of cardiac anomaly is usually high in fetuses with chromosomal anomaly, and while aneuploidy prevalence is 16% in the presence of isolated cardiac anomaly, it increases to 66% when there are other anomalies accompanying to cardiac anomaly.[2,5] Therefore, chromosomal anomaly should be recommended due to the high aneuploidy risk for pregnant women who are found to have cardiac anomaly. In our study, we found trisomies in 75% of the cases with cardiac anomalies accompanying to urinary system anomalies.

Conclusion

In conclusion, urinary system anomalies are approximately one fourth of all congenital anomalies. Congenital urinary system malformations with a broad spectrum differ greatly in terms of etiological reasons. Additional structural anomalies may accompany urinary system anomalies at a high rate; and while they negatively affect the prognosis on one hand, they cause the incidence of chromosomal anomaly to increase on the other hand. As a result, fatal and severe malformation can be observed. Urinary system anomalies which are isolated or have a good fetal prognosis may cause urinary infection, hypertension and various levels of renal failure during childhood. Prenatal diagnosis is very important to identify these anomalies which may cause poor outcomes during fetal period or childhood.

Conflicts of Interest: No conflicts declared.

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