Prenatal Diagnosis and Prognosis of Fetal Hyperechogenic Kidney: A Study of 80 Cases

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Abstract

Background

Prenatal diagnosis of fetal hyperechogenic kidney poses a challenge. The aim of this study was to investigate the genetic reasons and prognosis of fetal hyperechogenic kidney diagnosed on prenatal ultrasonography.

Methods

We retrospectively reviewed the clinical data of 80 cases of prenatally diagnosed fetal hyperechogenic kidney by the obstetric ultrasound. The genetic characteristics and pregnancy outcomes were analyzed using chromosome karyotype analysis, chromosome microarray analysis, and whole-exome sequencing.

Results

Of the 80 cases, 48 (60%) were those of isolated fetal hyperechogenic kidney and 32 (40%) were those of non-isolated cases, including 4 cases (5%) of urinary system abnormalities, 7 (8.75%) of central nervous system abnormalities, 5 (6.25%) of cardiac abnormalities, and 16 (20%) of multiple abnormalities. Chromosome karyotype analysis and microarray analysis revealed 17 (21.25%) abnormalities, including isolated fetal hyperechogenic kidney (9, 11.25%) and chromosome microdeletion microduplication (17q12 microdeletion syndrome, Williams-Beuren syndrome, 4p16.3-p16.1 microduplication syndrome) (8, 10%). Moreover, 9 patients had single gene mutations, including those of BBS2, BBS7, HNF1B, ACE, CEP290, COL4A5, and PKHD1. Total 48 pregnancies were terminated (57.3%), and the remaining 32 fetuses survived and grew normally, the neonatal renal function tests were normal.

Conclusions

Fetal hyperechogenic kidney chromosome abnormalities are common, in particular, there is considerable prevalence of isolated fetal hyperechogenic kidney. Therefore, advances in prenatal diagnosis are crucial, if necessary, with the combined use of whole-exome sequencing and other comprehensive detection methods.

Introduction

Fetal kidneys are generally considered hyperechogenic if the renal cortex has greater echogenicity than the liver or spleen and this becomes more ascertained with associated absence of corticomedullary differentiation^[1]. In physiological conditions, fetal kidney echo also shows changes during the pregnancy. 40% normal cases were observed renal hyperechogenic during the early second trimester, but progressively were replaced by iso- and hypo-echogenicity thereafter^[2]. Hyperechogenic kidneys, may be the first indicator of underlying renal disease. Part of the fetal with hyperechogenic kidney is combined with chromosome aneuploidy, chromosome microdeletion syndrome (chromosome 17q12 deletion), autosomal dominant (ADPKD) and autosomal recessive polycystic kidney disease, single gene disorders (Bardet-biedl syndrome, Meckel-Gruber syndrome, Perlman syndrome), or even with obstructive uropathy, teratogenic exposure, other renal dysplasia^[3]. However, it is impossible to determine the renal function of the fetus during pregnancy. The clarification and prognosis establishment are challenging in the clinical treatment and prenatal consultation, because of a wide range of outcomes from completely normal renal function to early end-stage renal failure and/or pulmonary hypoplasia in the childhood.

As a significant development in next-generation sequencing, whole exome sequencing (WES) has proven to be a useful tool for evaluating the fetus with structural abnormalities as the chromosomal microarray analysis (CMA)^[4]. Genetic results could be a reference to provide the predicted information about the fetal health risks to pregnant women. Not only this, the need of designing prenatal counseling based on the results of studies on prenatal cohorts and a long-term postnatal follow-up are also important.

In the present study, we retrospectively analyzed the results of ultrasonography, karyotype analysis, chromosome microarray examination, whole-exome sequencing, pregnancy outcome, and follow-up results of 80 cases of fetal hyperechogenic kidney diagnosed on prenatal ultrasonography. We further explored the prenatal diagnosis and clinical significance of fetal hyperechogenic kidney.

Materials And Methods

Study Participants and sample collection

This retrospective study on the prenatal diagnosis of fetal hyperechogenic kidney was performed in the Guangzhou Women and Children's Medical Center between January 2013 and May 2019. We included 80 women who underwent fetal ultrasonography at our center and were diagnosed with fetal hyperechogenic kidney. We divided the patients as those with normal-size or slightly enlarged isolated fetal hyperechogenic kidneys and those with non-isolated fetal hyperechogenic kidneys. All the examinations were performed using a Voluson Expert E8 (GE Healthcare, USA), using curvilinear 2.0 to 5.0-MHz transducers. The whole body and accessory structures of the fetus were examined systematically; routine biometric measurements were performed. Fetal kidney examination parameters included bilateral kidney size, renal echogenicity, amniotic fluid volume, corticomedullary differentiation (CMD), and cyst characteristics. The diagnostic marker of fetal hyperechogenic kidney is that the echo of the kidney is stronger than that of the liver in the normal fetus during

the second and third trimester [5]. The examinations were performed by experienced maternal fetal medicine specialists and ultrasonography technicians. (Fig. 1)

Karyotype Analysis

G-banded chromosome analysis was performed for the 80 cases as per the standard protocols. All fetuses with a hyperechogenic kidney were referred for chromosomal microarray analysis (CMA).

Chromosomal Microarray Analysis

The CMA was performed by using CytoScan HD Array (Affymetrix, Santa Clara, CA, USA) as per the manufacturer's instructions, and the reporting threshold of the copy number variations (CNVs) was set at 100 kb with a marker count of ≥ 50 . The results were analyzed using the Chromosome Analysis Suite software. The detected copy number losses or gains were aligned with the known CNVs listed in the publicly available databases, including the Database of Genomic Variants, UCSC, ClinGen, OMIM, the DECIPHER database, As per the guidelines [6, 7, 8], the CNVs were classified as benign, likely benign, likely pathogenic, pathogenic, variants of unknown significance (VOUS). Disease-associated analysis and biological analysis were also performed.

Whole exome sequencing

Considering the economic situation and the severity of the ultrasonography examination, the whole-exome sequencing was performed for 45 fetuses. All the trio genomic DNA samples were extracted, and DNA libraries were prepared using a NEXTflex™ Rapid DNA Sequencing kit (5144-02) (Bioo Scientific, Austin, TX, USA) as per the manufacturer's instructions. A HiSeq2500 sequencer (version 3, Illumina, Inc, San Diego, CA, USA) was used for sample sequencing. MES was performed with at least 200-fold average coverage. Sequencing reads were mapped to the reference human genome version hg19. Variants from the proband and parents were processed together, and the source of each variant was annotated. The MAFs (minor allele frequencies) of all known variants were also reported according to their presence in the dbSNP, 1000 Genomes Project, Exome Aggregation Consortium. Databases such as OMIM, ClinVar and All whole-exome variants were subjected to biological effects analysis, which included the use of databases such as Mutation Taster, SIFT, PolyPhen-2, REVEL, Human Splicing Finder and PROVEAN to predict whether an amino acid substitution or indel has an important biological effect. All of the above selected variants were then classified as pathogenic, likely pathogenic, variant of unknown significance, likely benign or benign according to the American College of Medical Genetics and Genomics guidelines (ACMG) [9, 10].

During the postnatal follow-up, we evaluated the renal function of neonates on the 42nd day after birth. All the parents received a written explanation of the study and signed a consent form before study participation. Ethical approval was not required because of the retrospective nature of the study.

Results

Total 80 fetuses diagnosed with hyperechogenic kidney using fetal ultrasonography were included. The age of the pregnant women ranged 20–37 years, with a gestational age ranging 13–35 weeks. Among the 80 cases, 48 (60%) were diagnosed with isolated fetal hyperechogenic kidneys, and 32 (40%) comprised the non-isolated group. The primary associated malformation that accompanied non-isolated fetal hyperechogenic kidneys included urinary abnormality (4 cases, 5%), central nervous system abnormality (7 cases, 8.75%), cardiac abnormality (5 cases, 6.25%), and multiple congenital anomalies (16 cases, 20%) (Table 1). Amniotic volume as well as the size and number of affected kidneys are often used as indicators for prenatal ultrasonographic diagnosis. As shown in Table 2, in the patients with isolated fetal hyperechogenic kidneys, hydramnios, oligohydramnios, and normal amniotic fluid were seen in 8 (16.7%), 6 (12.5%), and 34 cases (70.8%), respectively. Unilateral 12 cases (25%), bilateral 36 cases (75%). The size of the kidney was increased in 14 cases (29.1%), reduced in 3 cases (6.25%), and normal in 31 cases (64.6%).

Table 1
Characteristics of cases with hyperechogenic kidney and outcome

	Case (n, %)	Abnormal case (n, %)	Outcome				
			Vaginal delivery (n)	Cesarean delivery (n)	TOP (n)	Sex (M/F, n)	Kindney function (N/Ab,n)
Isolated hyperechogenic kidney	48 (60%)	9 (11.25%)	16	10	22	16/10	26/0
Combined with other anomalies							
Urinary abnormality	4 (5%)	1 (1.25%)	1	1	2	0/1	2/0
Central nervous system abnormality	7 (8.75%)	0	2	1	4	2/1	3/0
Cardiac abnormality	5 (6.25%)	2 (2.5%)	0	0	5	0	0/0
Multiple anomalies	16 (20%)	5 (6.25%)	1	0	15	0/1	1/0
Total	80	17 (21.25%)	20	12	48	18/14	32/0
TOP, termination of pregnancy; N, normal; Ab, abnormal							

Table 2
Characteristics of cases with isolated hyperechogenic kidney

	Case (n, %)	Chromosomal abnormality (n, %)	Outcome (n, TOP/Birth)
Amniotic fluid volume			
Hydramnios	8 (16.7%)	4 (50%, 4/8)	5/3
Oligohydramnios	6 (12.5%)	1 (16.7%, 1/6)	6/0
Normal	34 (70.8%)	2 (5.9%, 2/34)	11/23
Numbers of affected kidney			
Unilateral	12 (25%)	2 (16.7%, 2/12)	9/3
Bilateral	36 (75%)	7 (19.4%, 7/36)	13/23
Kidney size			
Increased	14 (29.1%)	1 (7.14%, 1/14)	13/1
Reduced	3 (6.25%)	1 (33.3%, 1/3)	3/0
Normal	31 (64.6%)	7 (22.6%, 7/31)	6/25
TOP, termination of pregnancy			

Chromosomal abnormalities may be associated with hyperechogenic kidney. Total 80 fetuses diagnosed with hyperechogenic kidney were subjected to interventional prenatal diagnosis using fetal karyotyping, CMA, and WES. Seventeen fetuses (21.25%) were detected to have chromosomal abnormalities (details are shown in Table 3). Isolated fetal kidney hyperechoic in 9 cases (11.25%), urinary system malformation in 1 case (1.25%), and cardiac abnormality in 2 cases (2.5%), 5 (6.25%) cases with multiple malformations (Table 1). Further analysis showed chromosomal abnormalities in 9 cases (11.25%), including trisomy 21 syndrome, trisomy 13 syndrome, 46, XX, add (12) (p13), 46 XX, der (1), 45 X, and 46, XY, der (10), 21 pstk+. In addition, 8 cases (10%) of chromosomal microdeletion microduplication syndrome were detected, including 17q12 microdeletion syndrome (6 cases, 7.5%), Williams-Beuren syndrome, and 4p16.3-p16.1 duplication syndrome (Table 5). Further analysis of the chromosomal abnormalities in the isolated group revealed 4 cases of hydramnios (50%, 4/8), 1 case of oligohydramnios (16.7%, 1/6), 2 cases of normal amniotic fluid (5.9%, 2/34), 2 cases of unilateral affected (16.7%, 2/12), and 7 cases of bilateral affected (19.4%, 7/36). Among those with abnormal renal volume with chromosomal abnormalities, the kidney size was increased in 1 case (7.14%, 1/14), reduced in 1 case (33.3%, 1/3), and normal in 7 cases (22.6%, 7/31) (Table 2).

Table 3
Genetic characteristics of cases with fetal hyperechogenic kidney

Case	Type	Prenatal Ultrasound finding	GW	Cytoband	Chromosome regions	Size	Copy number	Karyotype	Gene Mutation	Outcome
1	Isolated	Hyperechogenic kidney	25	17q12	34822465~36243365	1.42Mb	Loss	Normal		TOP
2	Isolated	Hyperechogenic kidney	23	17q12	34822465~36404136	1.58Mb	Loss	Normal		TOP
3	Isolated	Hyperechogenic kidney	30	17q12	34822492~36404104	1.58Mb	Loss	Normal		TOP
4	Isolated	Hyperechogenic kidney	33	4p16.3- p16.1	1770533~9514461	7.74Mb	Gain	Normal		TOP
5	Isolated	Hyperechogenic kidney	24					47, XY, + 13		TOP
6	Isolated	Hyperechogenic kidney	30					47, XY, + 13		TOP
7	Isolated	Hyperechogenic kidney	28					46,XX,add(12)(p13)		TOP
8	Isolated	Hyperechogenic kidney	25					47,XY,+21,22pss		TOP
9	Isolated	Hyperechogenic kidney	19					45, X		TOP
10	Non- isolated	Hyperechogenic kidney; Double outlet right ventricle	24					46,XY,der(10),21pstk+		TOP
11	Non- isolated	Hyperechogenic kidney; Ventricular septal defect	32					47, XX, + 21		TOP
12	Non- isolated	Hyperechogenic kidney; Polycystic kidney;	23	7q11.23	72723370~74154209	1.43Mb	Loss	Normal		TOP
13	Non- isolated	Hyperechogenic kidney; Polycystic kidney; Ventricular septal defect	25	17q12	34822465~36307773	1.49Mb	Loss	Normal		TOP
14	Non- isolated	Hyperechogenic kidney; Ventriculomegaly; Polycystic kidney;	24	17q12	34822465~36244332	1.42Mb	Loss	Normal		TOP
15	Non- isolated	Hyperechogenic kidney; Hydramnios; Polydactyly	31	17q12	34477479~36404104	1.93Mb	Loss	Normal		TOP
16	Non- isolated	Hyperechogenic kidney; Omphalocele; Cerebellar dysplasia	24					47, XX, + 13		TOP
17	Non- isolated	Hyperechogenic kidney; Hydrocephalus; Echogenic bowel	19					46, XX, der(1)		TOP

GW, Gestational weeks; TOP, termination of pregnancy

Case	Type	Prenatal Ultrasound finding	GW	Cytoband	Chromosome regions	Size	Copy number	Karyotype	Gene Mutation	Outcome
18	Non- isolated	Hyperechogenic kidney; Polydactylia; Ventriculomegaly	29					Normal	BBS2	TOP
19	Non- isolated	Hyperechogenic kidney; Polydactylia; Polycystic kidney;	30					Normal	BBS7	TOP
20	Non- isolated	Hyperechogenic kidney; Polycystic kidney;	24					Normal	HNFI β	TOP
21	Isolated	Hyperechogenic kidney; Oligohydramnios	30					Normal	ACE	TOP
22	Isolated	Hyperechogenic kidney	29					Normal	BBS2	TOP
23	Non- isolated	Dandy-Walker syndrome; Polycystic kidney; Oligohydramnios	25					Normal	CEP290	TOP
24	Isolated	Oligohydramnios; Hyperechogenic kidney	27					Normal	COL4A5	TOP
25	Non- isolated	Polycystic kidney; Oligohydramnios; Cardiomegaly	24					Normal	PKHD1	TOP
26	Non- isolated	Hydrocephalus; Hyperechogenic kidney	30					Normal	CEP290	TOP
GW, Gestational weeks; TOP, termination of pregnancy										

Samples from 63 fetuses with normal chromosomal array and karyotyping results were subjected to whole exon sequencing (WES). Data from fetus-father-mother trios were analyzed. The characteristics of structural malformations by WES are summarized in Tables 3 and 4. The mean depth of coverage for the coding regions targeted with the WES was $10^2 \times$ A mean of 99.56% of bases in the targeted coding regions were covered by at least 10 reads. Moreover, total 9 gene mutations were found in the whole exon sequencing. As shown in table, we detected pathogenic variants of five genes (including BBS2, BBS7, HNF1B, ACE and PKHD1), likely pathogenic variants of three genes (including BBS2, CEP200) and one mutation gene (COL4A5) with variants of unknown significance (*VOUS*). In isolated fetal hyperechogenic kidneys, three pathogenic heterozygous mutation genes (HNF1B, ACE and BBS2) were detected and one hemizygous mutation gene (COL4A5) with *VOUS*, which was X-linked dominant inheritance. However, in non-isolated cases, three pathogenic mutations (BBS7, HNF1B and PKHD1) and three likely pathogenic mutations (BBS2, CEP290) were found.

Table 4
Characteristics of likely pathogenic variants revealed on whole exome sequencing of structurally abnormal cases with normal karyotyping and chromosomal microarray results

Case	Type	Mutation Gene	Transcript	Genetic change	Zygosity	Inheritance model	Clinical classification	Ultrasound finding	Associated disease
18	Non-isolated	BBS2	NM_031885	c.814C > T c.943C > T	Het Het	AR	LP LP	Hyperechogenic kidney; Polydactylia; Ventriculomegaly	Bardet-Biedl syndrome 2
19	Non-isolated	BBS7	NM_176824	c.1002delT c.1611delA	Het Het	AR	P P	Hyperechogenic kidney; Polydactylia; Polycystic kidney;	Bardet-Biedl syndrome 7
20	Non-isolated	HNF1B	NM_000458	c.192_191:ins GTAT	Het	AD	P	Hyperechogenic kidney; Polycystic kidney;	Renal cysts and diabetes syndrome
21	Isolated	ACE	NM_000789	c.418-2A > G c.1028G > A	Het Het	AR	P P	Hyperechogenic kidney; Oligohydramnios	Renal tubular dysgenesis
22	Isolated	BBS2	NM_031885	c.823G > A c.1015G > A	Het Het	AR	P P	Hyperechogenic kidney	Bardet-Biedl syndrome 2
23	Non-isolated	CEP290	NM_025114	c.4156delA c.5011C > T	Het Het	AR	LP LP	Dandy-Walker syndrome; Polycystic kidney; Oligohydramnios	Bardet-Biedl syndrome 14
24	Isolated	COL4A5	NM_000495	c.2915C > A	Hemi	XLD	VOUS	Oligohydramnios; Hyperechogenic kidney	Alport syndrome 1
25	Non-isolated	PKHD1	NM_138694	c.852dupT c.9037T > C	Het Het	AR	P LP	Polycystic kidney; Oligohydramnios; Cardiomegaly	Polycystic kidney disease 4, with or without hepatic disease
26	Non-isolated	CEP290	NM_025114	c.2340_2341delGA c.4220G > A	Het Het	AR	LP	Hydrocephalus; Hyperechogenic kidney	Bardet-Biedl syndrome 14
AD, autosomal dominant; AR, autosomal recessive; Hemi, hemizygous; Het, heterozygous; VOUS, variants of unknown significance; LP, likely pathogenic; P, pathogenic; XLD, X-linked dominant; Clinical classification was according to American College of Medical Genetics and Genomics guidelines.									

Table 5
Analysis of chromosomal abnormalities

Abnormal	Case (n, %)
Chromosomal abnormality	9 (11.25%)
Trisomy 21 syndrome	3
Trisomy 13 syndrome	2
Other anomalies	
46,XX,add(12)(p13)	1
46,XX,der(1)	1
45,X	1
46,XY,der(10),21pstk+	1
Chromosomal microdeletion microduplication syndrome	8 (10%)
17q12 microdeletion syndrome	6
Williams-Beuren syndrome	1
4p16.3-p16.1 microduplication syndrome	1
Total	17 (21.25%)

Majority of the pregnant women decided to terminate their pregnancy owing to the presence of abnormalities; total 48 women (60%) chose to terminate their pregnancy, of which, 26 (32.5%) chose termination despite no genetic aberrations, 20 in vaginal delivery, 12 in cesarean section. There are 18 males and 14 females in the live birth fetuses (Table 1). After birth, the subjects were followed up for 42 days; no abnormalities were found during the monitoring of renal function.

Discussion

With the development of prenatal ultrasonography, hyperechogenic kidneys are occasionally observed during routine ultrasonography examinations. Obstetricians are increasingly facing the challenge of counseling pregnant women with fetal hyperechogenic kidneys. Fetal hyperechogenic kidney is diagnosed after 17 weeks of gestation when the kidneys appear more echogenic than the spleen and/or the liver. A recent research has shown that such hyperechogenic kidney can be a result of autosomal recessive polycystic kidney diseases, autosomal dominant polycystic kidney diseases, and cystic dysplasia. The remaining causes include tubulopathies, tubular dysgenesis, transient hyperechogenicity, tuberous sclerosis, and miscellaneous diseases^[11, 12]. The differential diagnosis should consider the family history and the presence of associated anomalies. Recent studies have shown that some fetal abnormalities are associated with hyperechogenic kidneys, including Meckel-Gruber syndrome, Joubert syndrome, Bardet-Biedl syndrome, and VACTERL syndrome^[13]. Our study also showed abnormalities, such as cystic renal dysplasia, enlarged lateral ventricles, choroid plexus cyst, congenital heart disease, polydactyly, and talipes varus. (Tables 1 and 3).

Prenatal ultrasonography examination plays an important role in the detection of fetal renal dysplasia. In the case of a fetus with renal cysts associated with hyperechogenic kidneys, detailed ultrasonography examination is useful, with careful attention to the brain, heart, hands, feet, spine, posterior fossa, etc. Fetal kidneys must be measured for renal echogenicity, CMD, cyst characteristics (size, location, and number), and amniotic fluid volume. In the subjects with isolated fetal hyperechogenic kidneys, amniotic fluid abnormalities were present in about 29.2% of the fetuses (8 cases of hydramnios and 6 cases of oligohydramnios) and about 35.4% had kidney size changes; the bilateral and unilateral ratio was 3:1 (Table 2). However, ultrasonography examination does not provide 100% sensitivity, especially for severe oligohydramnios; therefore, in such cases, fetal magnetic resonance imaging can be used^[14, 15].

Studies have shown that about 10% of fetal urinary system abnormalities associated with other systemic malformations is associated with chromosomal abnormalities, including trisomy 21 syndrome, trisomy 18 syndrome, trisomy 13 syndrome, and chromosomal microdeletions^[16]. Our retrospective analysis found that 9 fetuses had chromosomal abnormalities, accounting for about 11.25% of all cases. Trisomy 21 syndrome was present in 3 subjects, and trisomy 13 syndrome was present in 2 subjects. In isolated fetal hyperechogenic kidneys, we also detected fetuses with chromosomal abnormalities, including trisomy 21 syndrome and trisomy 13 syndrome, similar to previous reports. Moreover, eight cases of chromosomal microdeletion microduplication syndrome were also detected, including 17q12 microdeletion syndrome (6 cases), Williams-Beuren syndrome, and 4p16.3-p16.1 duplication syndrome.

Chromosomal 17q12 microdeletions and microduplications syndrome have been associated with a wide range of clinical phenotypes. In the prenatal setting, deletion of 17q12 is associated with renal cysts and echogenicity^[17], developmental delay^[18, 19], autism, and schizophrenia^[20]. 17q12 microdeletions encompassing the hepatocyte nuclear factor 1-beta (HNF1B) gene, also referred to as transcription factor 2 (TCF 2). HNF1B plays a crucial role in early development, including causing renal pathology as a result of haploinsufficiency within the commonly deleted region^[21]. In humans, mutations in HNF1B cause congenital anomalies of the kidney and the urinary tract, maturity-onset diabetes of the young type 5, and genital malformations^[22]. Gondra L, et al. reported that HNF1B mutation is the leading cause of isolated hyperechogenic fetal kidneys with normal or moderately large size and that HNF1B can be associated with polyhydramnios in the absence of maternal diabetes^[23]. In their study, Loirat C, found that 3 out of the 53 children had cystic or

hyperechogenic kidneys and heterozygous 17q12 deletion encompassing HNF1B mutation [24]. In our study, we found 6 fetuses with hyperechogenic kidneys, including isolated cases with 17q12 deletion and detected HNF1B mutation (which cause Renal cysts and diabetes syndrome, OMIM:137920, autosomal dominance inheritance); 17q12 microdeletion syndrome has a variety of phenotypes. Even if the fetus only has kidney dysplasia without diabetes mellitus or neurocognitive impairment, future occurrence cannot be ruled out. Therefore, phenotypic prediction and consulting after birth are challenging in cases with prenatal diagnosis of fetal 17q12 microdeletion syndrome.

Furthermore, we detected Williams-Beuren syndrome through chromosome microarray analysis. Williams-Beuren syndrome is a common chromosome microdeletion syndrome characterized by a specific dysmorphic face and habitus, postnatal growth deceleration, mild to moderate psychomotor retardation, and multiple organ dysfunction [25, 26]. Sammour et al. have reported a prevalence of 75% for urinary tract abnormalities [27]. We also detected a fetus with multicystic dysplastic kidney and Williams-Beuren syndrome (chromosome 7q11.23 with a 1.43 Mb deletion). Moreover, with the development of whole-exome sequencing techniques, we have identified BBS2 (OMIM:606151), BBS7 (OMIM:607590), HNF1B (OMIM:189907), ACE (OMIM:106180), CEP290 (OMIM:610142), COL4A5 (OMIM:303630), and PKHD1 (OMIM:606702) gene mutations in 9 fetuses with hyperechogenic kidneys. The karyotype analysis and microarray analysis of these nine fetuses did not show any abnormalities.

Mutations in PKHD1 could cause Polycystic kidney disease 4, with or without hepatic disease syndrome (OMIM: 263200). The main clinical manifestations include renal enlargement, cystic kidney, renal failure, enhanced echogenicity of the parenchyma, loss of cortical medulla differentiation, interstitial fibrosis; prenatal ultrasound showed oligohydramnios. Mutations in BBS7 could cause Bardet-Biedl syndrome 7 (OMIM: 615984). Bhowmik A, et al [28] reported that ACE gene mutation could cause Renal tubular dysgenesis (OMIM:267430). Moreover, BBS2 gene mutation also could cause Bardet-Biedl syndrome 2 (OMIM:615981), which is manifested as severe retinitis pigmentosa, obesity, polydactyly, renal malformation and mental retardation. All these variants were considered to be pathogenic according to the ACMG criteria and these diseases are inherited in autosomal recessive patterns.

Prenatal diagnosis of hyperechogenic kidneys could benefit fetuses or neonates if the renal disorder is detected and treated early. However, prenatal diagnosis of a fetal renal abnormality may be extremely stressful for the parents, can make prenatal counseling challenging, and could even make the parents decide to terminate the pregnancy, especially when the long-term outcome is uncertain. Estroff et al. reported that the survival rate of non-isolated fetuses with hyperechoic kidneys was significantly lower than that of isolated fetuses, and oligohydramnios predicted a poor prognosis [29]. Kumar et al. suggested that the factors associated with poor prognosis included bilateral disease, absence of amniotic fluid, and presence of associated other malformation [30]. Our study also showed that the pregnancy outcome depends on whether other structural abnormalities are present. Among fetuses with isolated hyperechogenic kidneys, 11.25% had chromosomal abnormalities and 45.8% (22/48) terminated the pregnancy; some parents of fetuses with normal karyotype analysis also chose to terminate the pregnancy. In addition, among fetuses with other structural abnormalities, 25% had chromosomal abnormalities, and 81.25% (26/32) chose to terminate the pregnancy. Further study of fetuses with isolated hyperechogenic kidneys revealed that amniotic fluid volume, the size of the kidney, and the number of kidneys involved were important factors that affected the choice of pregnancy outcomes. Parents of fetuses with oligohydramnios and enlarged kidney volume were more likely to terminate the pregnancy. Moreover, no abnormal growth and development were observed in the follow-up of live births, and we found no abnormalities in the renal function of the newborns; this may be associated with an insufficient follow-up duration; additional regular follow-up may be required at a later stage. We also suggested that kidney size and amniotic fluid volume were the best prenatal predictors of outcome and found that patients with large kidneys and oligohydramnios are likely to have poor outcomes.

Conclusions

In summary, fetal hyperechogenic kidney is an important ultrasonographic manifestation of congenital kidney dysplasia. When combined with other system abnormalities, the survival rate is poor, and the incidence of chromosomal abnormalities with isolated hyperechogenic fetal kidneys is low. For fetuses with other systemic abnormalities, it is crucial to improve the prenatal gene detection rate by combining multiple monitoring techniques, such as chromosome karyotype analysis, chromosome microarray, and/or whole-exome sequencing, to obtain more reliable evidence for guiding prenatal counseling and providing preventive treatment. In addition, whole-exome sequencing has potential value as a first-line prenatal diagnostic tool for the diagnosis of disease population, especially in the identification of incidental discoveries unrelated to phenotypic presentation. Therefore, it is also very important to improve the accuracy of interpretation of variant types.

Abbreviations

CAKUT= Congenital anomalies of the kidney and the urinary tract, CMA= chromosomal microarray analysis, CNVs= copy number variants, VUS= variants of unknown significance, CMD= corticomedullary differentiation, WES= whole exome sequencing

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Guangzhou Women and children's medical center. Signed informed consent was obtained from all participants. all methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

Consent for publication

Written informed consent was obtained from the patient for publication of this paper.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Authors' contributions

JH and YJ H performed the literature searching, data collection and was a major contributor in writing the manuscript. ZQ and BJ analyzed the patient data. LZ performed the data of ultrasound, RL and SZ X do the genetic test. CL revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Figures

Figure 1

Transverse scan shows bilateral hyperechogenic kidneys with normal size. B. Coronal scan of fetus shows bilateral enlarged and hyperechogenic kidneys. C. Coronal US image shows bilateral renal enlargement. Both kidneys show the multiple tiny cysts within the medulla giving the appearance of dilated tubules with relative preservation of the columns. D. Fetal US image shows an enlarged kidney with multiple tubular, cystic structures. E and F. Section from the kidneys using hematoxylin and eosin stain (H and E) shows sub-capsular nephrogenic zone with glomeruli. Lower cortex and medulla show some cysts of waring sizes lined by cuboidal epithelium.