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Perinatal and infant outcome of fetuses with prenatally diagnosed hyperechogenic kidneys

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KEYWORDS: enlarged kidneys; hyperechogenic kidneys; postnatal outcome; prenatal diagnosis; ultrasound

CONTRIBUTION

What are the novel findings of this work?
The renal outcome of infants with prenatally diagnosed isolated hyperechogenic kidneys is good, with over 70% of cases having normal renal function. Importantly, for prognostic counseling, all of the fetuses in our non-selected series with isolated hyperechogenic kidneys and normal amniotic fluid levels had normal renal outcome in infancy.

What are the clinical implications of this work?
Prenatal diagnosis of hyperechogenic kidneys allows early recognition and treatment of renal disease in addition to facilitating counseling on postnatal prognosis, helping parents to make decisions regarding pregnancy management and delivery.

ABSTRACT

Objective *Hyperechogenic kidneys are a relatively rare antenatal finding, which can generate significant parental anxiety due to uncertain prognosis. We report on the perinatal and infant outcomes of a large cohort of fetuses with antenatally diagnosed hyperechogenic kidneys.*

Methods *This was a retrospective analysis of all cases diagnosed prenatally with hyperechogenic kidneys between 2002 and 2017 in a large tertiary fetal medicine unit. Hyperechogenicity was defined as kidney parenchyma with greater echogenicity than that of the liver. Pregnancy, pathological and postnatal outcomes were collected from hospital and general practitioner records up to 1 year of age. Abnormal renal outcome was defined as elevated creatinine beyond 6 months of age, hypertension requiring medication or major kidney surgery, such as nephrectomy. Severe abnormal renal outcome was defined as the need for dialysis or kidney transplant at any stage.*

Results *Three-hundred and sixteen fetuses with hyperechogenic kidneys were identified at a mean gestational age of 21 (range, 13–37) weeks. The majority of cases (97%) had bilateral hyperechogenic kidneys. In the 265 cases with available follow-up data, other associated renal tract abnormalities were identified prenatally in 36%, concomitant extrarenal structural abnormalities in 39% and abnormal karyotype in 15% of cases. Of the 316 included cases, 139 did not survive, including 105 terminations of pregnancy, five intrauterine deaths and 29 early neonatal deaths. Only 4.3% (6/139) of these fetuses had isolated hyperechogenic kidneys while 28.1% (39/139) had associated multiple renal tract abnormalities alongside hyperechogenic kidneys and over two-thirds (67.6%; 94/139) had concomitant extrarenal abnormalities. Of the 177 cases that survived beyond 1 month of age, outcome data were available in 126. Of these, based on the antenatal findings, 60 (47.6%) cases had isolated hyperechogenic kidneys, 56 (44.4%) had associated renal structural abnormalities and 10 (7.9%) had additional extrarenal abnormalities. Considering renal outcome alone, kidney function was abnormal in 13 (21.7%), 10 (17.9%) and 0 (0%) infants in these three groups, respectively, although concurrent pathology clearly affected global outcome in the more complex cases. Neonatal mortality of 1.6% was observed in the isolated renal hyperechogenicity group. The presence of oligohydramnios or abnormal renal volume was not associated significantly with abnormal renal function*

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(odds ratio (OR), 2.32 (99% CI, 0.54–10.02) and OR, 0.74 (99% CI, 0.21–2.59), respectively) in this group.

Conclusions *Hyperechogenic kidneys are often complicated by associated renal tract and extrarenal abnormalities, aberrant karyotype and genetic disease, and these factors have a greater effect on overall outcome than does kidney echogenicity. The renal outcome of fetuses with isolated hyperechogenic kidneys is good generally, with over 70% of cases having normal renal function postpartum. Importantly, for prognostic counseling, all of the fetuses in this non-selected series with isolated hyperechogenic kidneys and normal amniotic fluid levels had normal renal outcome in infancy.* © *2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Routine evaluation of the fetal kidneys is an essential requirement of the second-trimester anomaly scan; by 20 weeks' gestation they should be readily visible with clear corticomedullary differentiation[1]. Kidneys are generally considered hyperechogenic if the renal parenchyma has a greater ultrasound echogenicity than that of the liver and this becomes more apparent with the associated loss of corticomedullary differentiation[2–5]. Hyperechogenic kidneys may be the first indicator of underlying renal disease and are detected in around 1.6 per 1000 scans[6].

It is important to distinguish isolated hyperechogenic kidneys from hyperechogenicity associated with other urinary tract disease or multiorgan syndromes. The differential diagnosis should be guided by kidney size, corticomedullary differentiation, visible cysts, any dilatation of the collecting system and the amount of amniotic fluid. Family history of renal conditions, particularly autosomal dominant or autosomal recessive polycystic kidney disease (ADPKD and ARPKD, respectively), should be taken into account, whilst the presence of anomalies in the brain, heart, limbs and other systems should raise suspicion of aneuploidies such as trisomy 13 or trisomy 18, infections such as cytomegalovirus and genetic conditions, including overgrowth disorders (Beckwith–Wiedemann and Perlman syndromes), or other syndromes such as Meckel–Gruber or Bardet–Biedl syndrome[2,4,5,7].

Prognosis of hyperechogenic kidneys in the midtrimester can be difficult to establish without serial scans to assess parameters of renal function, such as renal growth and amniotic fluid. Families often face the challenge of an immediate decision on whether to continue the pregnancy performing longitudinal assessment or to terminate the pregnancy[8]. Oligo/anhydramnios is a poor prognostic sign, whilst outcome in syndromic cases may be more dependent on extrarenal structural anomalies. In this observational study, we report on the perinatal and infant outcomes of fetuses diagnosed antenatally with hyperechogenic kidneys.

METHODS

This was a retrospective analysis of all pregnancies diagnosed with fetal hyperechogenic kidneys in the Fetal Medicine Unit of University College London Hospital, London, UK over a 16-year period. A free-text search of the imaging obstetric database (ViewPoint®, GE Healthcare, Zipf, Austria) was conducted to identify cases of fetal hyperechogenic kidneys between 2002 and 2017. Cases included local pregnancies and women referred to the Fetal Medicine Unit from across a catchment area of approximately 30 000 deliveries. The pregnancies were dated by measurement of crown–rump length in the first trimester. Women underwent routine first- and second-trimester screening for anomaly, according to the national guideline, between $11+0$ and $13+6$ and between $18+0$ and $23+6$ weeks of gestation, respectively[9–11]. In case of suspected hyperechogenic kidneys, women were referred for assessment by a multidisciplinary team consisting of fetal medicine, pediatric nephrology and urology specialists. This clinic has been running for over 20 years and women provided consent for their anonymized data to be used for internal audit and research purposes. Kidneys were considered as hyperechogenic if echogenicity of the entire kidney was greater than that of the liver (rather than just an isolated component of the kidney, i.e. the cortex, medulla or pyramids). As the primary ultrasound parameter that may affect significantly renal echogenicity is gain, the subjective assessment of renal echogenicity and comparison with echogenicity of the liver tissue were only performed once the ultrasound gain setting was appropriately adjusted and reduced. Ultrasound assessment included the identification of hyperechogenic kidneys and measurement of the transverse and anteroposterior diameters (in the axial plane after identifying the fetal spine and kidneys in cross-section; Figure 1a) and the longitudinal diameter (in the sagittal plane, used to identify the fetal spine in the dorsoanterior position; Figure 1b) of each kidney[1]. Amniotic fluid was evaluated by calculating the amniotic fluid index (AFI) and the deepest vertical pool (DVP)[12,13]. Renal volume of $< 5^{th}$ or $> 95^{th}$ centile per gestational age was considered abnormal[14]. Oligohydramnios was defined as AFI of < 5 cm or DVP of < 2 cm[12,13].

Fetal and neonatal data collected included gestational age at antenatal diagnosis, coexisting anomalies (renal and extrarenal structural anomalies), karyotype if assessed, outcome of pregnancy and infant outcome. We divided the cases with known postnatal outcome into three groups, according to the antenatal findings: cases with isolated hyperechogenic kidneys with no other detectable abnormalities; those with additional associated renal tract abnormalities, such as cystic dysplasia, multicystic dysplastic kidneys or hydroureter, but normal ultrasound findings of the other organs/systems; and those with concomitant extrarenal abnormalities.

In the event of termination of pregnancy (TOP), fetal or neonatal loss, data were collected from postmortem reports. For surviving babies, detailed postnatal renal outcome was obtained when the babies were referred

to our associated pediatric nephrology and urology centers and additional information was collected from the general practitioners, contacted by telephone and/or secure email up to 1 year of age. The following parameters were recorded: creatinine level, development of hypertension and the need for nephrectomy, dialysis or renal transplant. Adverse perinatal outcome was defined as the occurrence of TOP, intrauterine fetal demise (IUD) or neonatal death within 1 month after delivery (NND). Abnormal renal outcome was defined as a composite of abnormal creatinine level at 6 months of age (> 67 µmol/L), hypertension requiring medication or nephrectomy. Severe abnormal renal outcome was defined as the requirement for dialysis or renal transplant.

Within the isolated-hyperechogenic-kidneys group, the AFI and the renal volume were compared between cases with normal and those with abnormal outcome. All data were tested initially for normality using the Kolmogorov–Smirnov test. Normally distributed data were analyzed using the parametric Student's *t*-test. Data that were not normally distributed were analyzed using the Mann–Whitney *U*-test for unpaired data. $P < 0.05$ was considered statistically significant. We also analyzed whether the presence or absence of risk factors for poor prognosis was predictive of outcome in the group with isolated hyperechogenic kidneys by calculating the odds ratios (OR).

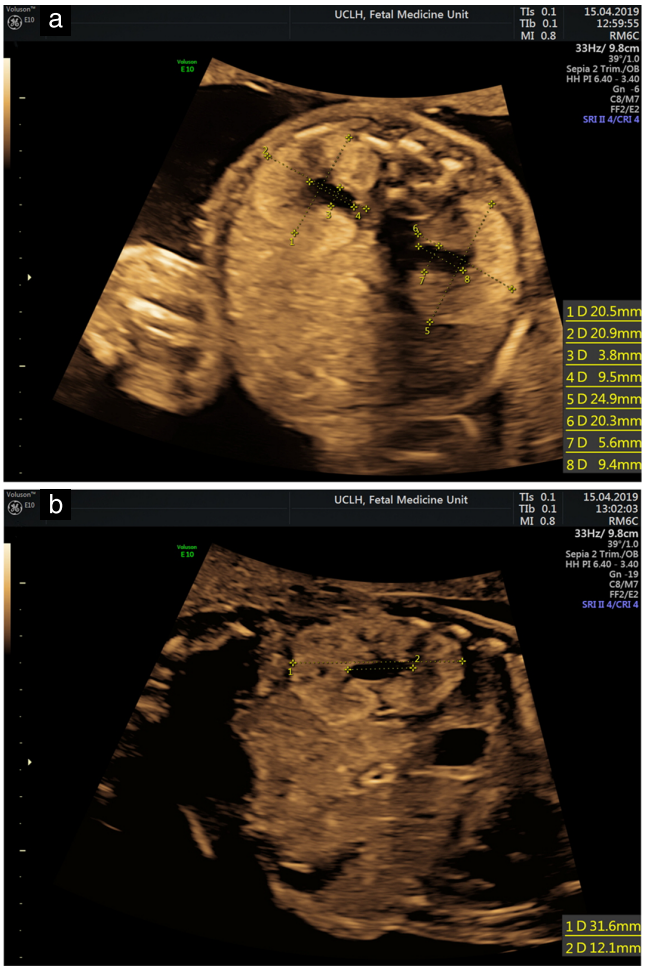

Figure 1 Axial plane (a) and sagittal plane (b) of hyperechogenic kidneys, showing measurement of their anteroposterior, transverse and longitudinal diameters, respectively.

RESULTS

During the study period, 316 cases with hyperechogenic kidneys were identified prenatally. The mean gestational age at diagnosis was 21 (range, 13–37) weeks, and the majority (97%) of cases had bilateral hyperechogenic kidneys. Perinatal death occurred in 139 (44.0%) cases, comprising 105 cases of TOP, five of IUD and 29 that resulted in NND (Figure 2). In this adverse-perinatal-outcome group, only six (4.3%) cases had isolated hyperechogenic kidneys, 39 (28.1%) had associated renal tract abnormalities but were otherwise normal on ultrasound and 94 (67.6%) cases had extrarenal structural abnormalities (Figure 2). Of the six fetuses with isolated hyperechogenic kidneys who did not survive, five underwent TOP and one case resulted in NND. The latter case had ARPKD and oligohydramnios from 20 weeks' gestation. Antenatal findings were confirmed, with no additional diagnoses generated, in the small proportion of cases (23/139) in which postmortem examination was performed.

Of the 316 cases with prenatally diagnosed hyperechogenic kidneys, 177 survived beyond 1 month of age. Follow-up data were available in 126 of these cases, of which 60 had isolated hyperechogenic kidneys (47.6%), 56 had associated renal abnormalities (44.4%) and 10 had associated extrarenal structural abnormalities (7.9%) prenatally (Figure 2).

AFI and DVP values and renal volume were available in all 66 cases with isolated hyperechogenic kidneys. Forty-two cases resulted in live birth without long-term infant complications, whereas 24 had either adverse perinatal outcome (TOP, IUD, NND) or abnormal renal postnatal outcome. Mean and range values of AFI and

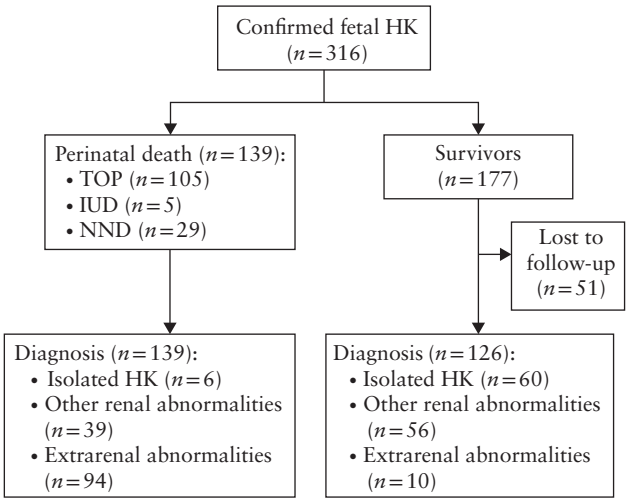

Figure 2 Flowchart summarizing antenatal findings and perinatal outcome of 316 fetuses with prenatally diagnosed hyperechogenic kidneys (HK). IUD, intrauterine demise; NND, neonatal death; TOP, termination of pregnancy.

Table 1 Renal outcome of 126 surviving infants with prenatal diagnosis of hyperechogenic kidneys (HK), for which follow-up data were available, according to antenatal findings

Outcome	*Isolated HK (n = 60)*	*HK plus other renal/ urinary tract abnormalities (n = 56)*	*HK plus extrarenal structural abnormalities (n = 10)*
Hypertension requiring medication	6 (10.0)	3 (5.4)	0 (0)
Nephrectomy needed	2 (3.3)	2 (3.6)	0 (0)
Dialysis needed	2 (3.3)	2 (3.6)	0 (0)
Renal transplant needed	3 (5.0)	3 (5.4)	0 (0)

Data are given as *n* (%).

DVP were significantly higher in the normal-outcome group compared with the abnormal-outcome group: 15.3 (range, 9.7–25.0) *vs* 7.8 (range, 1.0–11.2) cm for AFI ($P < 0.05$) and 5.0 (range, 3.4–7.8) *vs* 2.5 (range, 0.0–4.0) cm for DVP ($P < 0.05$). Ranges in the normal-outcome group were comparable to normal reference values for the AFI[12,13]. It should be noted, however, that poor outcome was observed in the non-isolated cases with AFI or DVP values within the normal range. Mean renal volume was lower in the normal outcome group compared with the abnormal outcome group (3.1 mL *vs* 14.9 mL ($P < 0.05$)).

Focusing on the renal outcome of the 126 surviving infants with available follow-up data, abnormal renal outcome was noted in 13 of the 60 (21.7%) babies with isolated hyperechogenic kidneys, 10 of the 56

Table 2 Perinatal characteristics and outcome of 265 fetuses with prenatally diagnosed hyperechogenic kidneys (HK), for which follow-up data were available, according to antenatal findings

Perinatal characteristic	*Isolated HK (n = 66)*	*HK plus other renal/ urinary tract abnormalities (n = 95)*	*HK plus extrarenal structural abnormalities (n = 104)*
Survivor with known postnatal outcome	60 (90.9)	56 (58.9)	10 (9.6)
First-trimester diagnosis	0 (0)	19 (20.0)	32 (30.8)
Second-trimester diagnosis	66 (100)	76 (80.0)	72 (69.2)
Termination of pregnancy	5 (7.6)	36 (37.9)	64 (61.5)
Intrauterine demise	0 (0)	0 (0)	5 (4.8)
Neonatal death	1 (1.5)	2 (2.1)	26 (25.0)
Chromosomal anomaly	3 (4.5)	1 (1.1)	37 (35.6)
Gestational age at delivery			
≤ 37 weeks	3 (4.5)	3 (3.2)	0 (0)
> 37 weeks	57 (86.4)	53 (55.8)	10 (9.6)
Oligohydramnios	0 (0)	28 (29.5)	62 (59.6)
Changed group after delivery	4 (6.1)	6 (6.3)	0 (0)

Data are given as *n* (%).

Table 3 Histopathological diagnoses of study group of 316 fetuses with prenatally diagnosed hyperechogenic kidneys (HK), according to antenatal findings

Diagnosis	*Total*	*Isolated HK*	*HK plus other renal/ urinary tract abnormalities*	*HK plus extrarenal structural abnormalities*	*Recurrence risk (%)*
Bladder outflow obstruction	36	14	22		Low
ARPKD	10	7	3		25
ADPKD	12	9	2	1	50
Bilateral CD	13	7	6		5
Unilateral CD	22	9	11	2	Low
MCDK	18	7	10	1	Low
Duplex kidneys	8		8		Low
Mucopolysaccharidosis type I	1		1		Low
WTX mutation	1			1	Low
HNF-1β mutation	1	1			Low
Bardet–Biedl syndrome	2		1	1	Low
Beckwith–Wiedemann syndrome	1			1	Low
Roberts syndrome	1			1	25
Aneuploidy	41	3	1	37	Low
Euploid multiple congenital anomalies	10			10	Low
Other*	8		3	5	Varies

Data are given as *n* unless specified otherwise. *Preterm prelabor rupture of the membranes, small kidneys, neonatal alloimmune thrombocytopenia, fetal akinesia deformation sequence, congenital pulmonary airway malformation, VACTERL (association of vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, and renal and limb abnormalities), pentalogy of Cantrell.
ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CD, cystic dysplasia; HNF, hepatocyte nuclear factor; MCDK, multicystic dysplastic kidney; WTX, Wilms tumor gene on X chromosome.

(17.9%) babies with additional renal tract abnormalities and none of the 10 babies with concomitant extrarenal abnormalities (Table 1). It may seem paradoxical that there was a greater chance of renal dysfunction in fetuses with isolated hyperechogenic kidneys, but we speculate that this may reflect labeling of kidneys with milder changes as hyperechogenic when more detailed scanning was performed because of concurrent abnormalities in the non-isolated cases. Excluding renal status, however, overall outcome was contingent on the associated extrarenal structural abnormalities or underlying syndrome.

Table 2 describes the perinatal characteristics and outcomes of fetuses with prenatal diagnosis of hyperechogenic kidneys. Table 3 summarizes the known underlying histopathology of all 316 fetuses included in this series.

Focusing on the outcome of the infants with prenatally diagnosed isolated renal hyperechogenicity, we observed a neonatal mortality of 1.6% (1/61 cases). In this group, presence of oligohydramnios or abnormal renal volume was not associated significantly with abnormal renal function (OR, 2.32 (99% CI, 0.54–10.02) and OR, 0.74 (99% CI, 0.21–2.59), respectively). Of the 60 infants with prenatal diagnosis of isolated hyperechogenic kidneys, 78.3% had intact survival, and in all of those cases amniotic fluid and renal volume were normal.

DISCUSSION

This is the largest study to date evaluating the outcome of fetuses diagnosed prenatally with hyperechogenic kidneys, with a total of 316 cases, including 265 babies with known outcome. Prenatal diagnosis of hyperechogenic kidneys may be useful by allowing more accurate counseling of the family about the postnatal outcome, helping them to make decisions regarding pregnancy care and delivery.

In this study, we used a qualitative definition to diagnose hyperechogenic kidneys, i.e. the renal parenchyma with a greater ultrasound echogenicity than that of the liver[2–5]. There are also quantitative methods to compare echogenicity, such as using the gray-level histogram width values. However quantitative echogenicity has not been validated in the evaluation of fetal kidney tissue and in view of the retrospective nature of this study it was not considered[15].

Fetal renal hyperechogenicity is a potential indicator of underlying disease due to the association with numerous pathologies, including chromosomal abnormality, ARPKD, ADPKD and Beckwith–Wiedemann syndrome. However, the cause of the increased echogenicity of the kidney is uncertain in many cases[2,4,5,7]. The mechanisms that have been proposed to explain similar findings include an increased degree of interstitial infiltration, glomerular disease, vascular infiltration and sclerosis[8]. Comparison of our findings with outcomes in the literature is potentially biased because several previous studies included centers with a high rate of polycystic kidney disease referrals and few cases of truly isolated hyperechogenic kidneys. This series included only 16 cases of ARPKD and ADPKD in the truly isolated hyperechogenic kidneys group, so it is not surprising that we reported better renal outcomes compared to previous studies. Our findings suggest that the risk of ARPKD/ADPKD is around 25%, which is much lower than previously cited.

Table 4 summarizes the previous literature regarding outcome of fetuses with prenatally diagnosed hyperechogenic kidneys. All studies utilized the same diagnostic criteria for hyperechogenicity, defined as the renal parenchyma with greater echogenicity than that of the liver. Estroff *et al.*[3] reported the outcome in 19 fetuses with isolated hyperechogenic kidneys. In their study, only four infants (21%) were healthy at birth with normal postnatal scans. Another 10 infants (53%) survived, but extrarenal abnormalities were found postnatally[3]. In our study, there were no babies at birth with undiagnosed extrarenal structural anomalies. In Estroff's series, oligohydramnios was predictive of poor prognosis and was present in all five cases which resulted in TOP/NND. None of the other babies with normal or moderately reduced amniotic fluid had severe abnormal renal outcome. This was confirmed in this study as all babies with isolated hyperechogenic kidneys and normal amniotic fluid had normal outcome.

Tsatsaris *et al.*[4] studied the perinatal and long-term outcomes of 43 fetuses with prenatal diagnosis of isolated hyperechogenic kidneys. There were 19 TOP, five NND and 19 survivors. Twenty-eight of the 43 fetuses (65%) with hyperechogenic kidneys had ARPKD, ADPKD, genetic syndrome or extrarenal structural abnormalities diagnosed at birth. In our study, only 16 of 66 babies

Table 4 Summary of previous studies reporting on outcome of fetuses with prenatally diagnosed hyperechogenic kidneys (HK)

Study	*Total cases* (n)	*Isolated HK* (n)	*Kidney volume*	*Amniotic fluid*	*Normal postnatal renal outcome* (n (%))*	*TOP/IUD/NND* (n)
Estroff (1991)[3]	19	19	Normal	Normal/reduced	4 (21)	5 (ARPKD)
Carr (1995)[2]	8	8	Normal	Normal	8 (100)	0
Tsatsaris (2002)[4]	43	43	Variable	Normal/reduced	11 (26)	24†
Mashiach (2005)[17]	7	7	—	Normal	3 (43)	4
Current study	316	66	—	Normal/reduced	47 (71)	6
Total (*n*)	393	143	—	—	73 (51)	39

Only first author given for each study. *Percentages calculated against number of cases with isolated HK. †Nineteen terminations of pregnancy (TOP), of which 10 had autosomal recessive polycystic kidney disease (ARPKD), and five neonatal deaths (NND), of which four had ARPKD. IUD, intrauterine demise.

(24%) with isolated hyperechogenic kidneys had ARPKD or ADPKD, which may reflect the difference in the referral group and diagnostic performance.

Platt *et al.*[15] studied 153 cases of adult hyperechogenic kidneys, and the prevalence of renal disease was 26% (40/153). They concluded that prenatal hyperechogenicity was neither sensitive nor specific for detection of adult renal disease, with a positive predictive value of 35%[15]. Based on our findings, if hyperechogenic kidneys are diagnosed prenatally on ultrasound, the outcome is not necessarily abnormal. The majority of cases did not have polycystic kidney disease and the cause of hyperechogenicity was unknown. Normal AFI throughout gestation and normal kidney growth are good prognostic factors; however, renal insufficiency cannot be excluded later beyond infancy. Assessment of true functional renal mass remains difficult. The added value of this study was that it reported the renal volume, which was normal in all cases of isolated hyperechogenic kidneys with normal outcome.

We would therefore recommend serial scans to evaluate the AFI and measure the size of the kidneys. In some cases, discrepancies between antenatal findings and findings at birth could be due to the natural evolution of the sonographic appearance of some diseases such as ADPKD. ADPKD babies can have normal corticomedullary appearance postnatally and develop cysts later in life[16].

Limitations of this study are related to its retrospective design, which resulted in a significant number of babies being lost to follow-up and a lack of information on fetuses who underwent TOP. Nevertheless, this is still the largest study to date reporting on the perinatal and infant outcomes of fetuses with isolated hyperechogenic kidneys. Another limitation is the subjective qualitative assessment of hyperechogenicity used in the study and the lack of assessment of quantitative reproducibility of the ultrasound parameters. However, we have introduced diagnostic criteria within our fetal medicine unit by standardization of plane acquisition (Figure 1) and had a limited number of operators performing the scan after standardization. The level of experience of the operator might have influenced the results as they were all expert fetal medicine consultants. The use of the different ultrasound machines might have also influenced the diagnosis; however, we aimed to minimize the impact by standardizing the technique and adjusting the gain setting. This approach led to an appropriate diagnosis in almost all cases in the three groups. Only four of 66 cases were diagnosed with isolated hyperechogenic kidneys prenatally and were found to have other renal abnormalities after birth. No other renal or extrarenal abnormalities were found at follow-up scans after the initial diagnosis.

In conclusion, hyperechogenic kidneys are associated with other renal tract abnormalities in 36%, extrarenal structural abnormalities in 39% and abnormal karyotype in 15% of cases. We therefore recommend referring patients to a dedicated clinic and offering karyotype testing, including microarray evaluation through invasive testing. In cases with isolated hyperechogenic kidneys, the renal outcome was normal in 71% of cases, only 8% had severe abnormal renal function and the remaining children had mild renal impairment. Normal amniotic fluid and normal renal volume were present in all 71% of cases with normal outcome and therefore are reliable prognostic factors of favorable outcome.

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