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Review

Hereditary kidney diseases: New perspectives through next-generation sequencing analysis

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Abstract. *Background and aim*: Hereditary kidney diseases are characterized by a specific phenotypic homology while differing in prognosis and follow-up. The genetic analysis may not be conclusive, thereby limiting a better understanding of these types of kidney diseases. The next-generation sequencing (NGS) technique allows for the simultaneous analysis of multiple genes, which, although more time consuming, enables new pathogenetic mutations to be recognized, and encourages research and diagnosis of hereditary kidney diseases. The aim of the present article is to provide a comprehensive review of the literature regarding the isolated finding of fetal hyperechoic kidneys. *Methods:* A systematic review was conducted in MEDLINE including articles evaluating the genetic approach to fetal hyperechoic kidneys. The PRISMA-P recommendations were used to guide this review. *Results:* A genetic etiology was identified in 48% of cases. Of these, 38% were autosomal recessive polycystic kidney disease (ARPKD), 29% were autosomal dominant polycystic kidney disease (ADPKD), and 22% were HNF1B-related autosomal dominant tubulointerstitial kidney disease. Genetic analysis was performed using karyotype, chromosomal microarray, and specific sequencing for PKD1-PKD2 or PKHD1. Only 4 studies reported NGS analysis permitting complex diagnoses. *Conclusions:* The genetic approach using the NGS technique is still underused despite allowing a faster etiological classification without an increase in diagnostic costs. Since genetic etiology is responsible for 48% of fetal hyperechoic kidneys, the application of NGS techniques should be implemented in order to encourage research in this not-yet-widely-known field of study. (www.actabiomedica.it)

Key words: solitary fetal hyperechoic kidneys, inherited kidney disease, next-generation sequencing analysis, prenatal diagnosis, nephropathy

Introduction

Innovations in prenatal imaging techniques have enhanced the possibility of detecting fetal abnormalities which, however, may remain of uncertain significance (1-3). Among these, fetal hyperechoic kidneys (HKs) represent a heterogeneous clinical entity, attributable to different etiological contexts with very variable outcomes (4,5). Fetal HKs can indicate diseases characterized by progressive deterioration of renal function or transient renal distress (1,6). Despite the absence of studies with large case series, most of these images are considered attributable to monogenic diseases such as autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD) and HNF1B-related autosomal dominant tubulointerstitial kidney disease (1,7-9). The etiological classification often takes place after birth through a prolonged and expensive follow-up (10).

The genetic heterogeneity of these pathologies makes it difficult to choose the appropriate test, thus

requiring repeated, and often inconclusive, gene sequencing (11). Furthermore, the clinical phenotype can be modified by the presence of mutations other than the known pathogenic ones (11). Given the genetic and phenotypic complexity of HKs, Next-generation sequencing (NGS), with simultaneous analysis of multiple genes, represents an efficient strategy for the characterization of congenital HKs (12).

The primary aim of this systematic review is to evaluate the relevance of genetic pathology in the etiology of fetal HKs and how many of these remain of uncertain significance. Secondarily, the use of genetic diagnostic tests was evaluated, with the aim of defining the application of NGS in the research and diagnostics of fetal HKs.

Materials and methods

The Preferred Reporting Items for Systematic Reviews and MetaAnalyses protocols (PRISMA-P) recommendations were used to guide this review (http://www.prisma-statement.org/). The electronic databases Medline PubMed Advanced Search Builder, Scopus, Web of Science (from January 1991 to June 2021) were analyzed, using medical subject headings (MeSH) terms and text words (their combinations and truncated synonyms): (KIDNEY OR RENAL) AND (FOETAL OR CHILD OR CHILDREN OR INFANT) AND (HYPERECHOIC OR HYPERECHOGENICITY). The abstracts were reviewed after removal of duplicate articles. The full text of suitable papers was analyzed. This review is not limited to any geographical area, age, or gender.

The inclusion criteria were studies reporting the results of case reports, case series, case-control studies, cohort studies, with synthesized data. The search was limited to English language articles.

The exclusion criteria were: sonographically detected malformations and/or obstructive urinary tract diseases of the fetus, narrative and systematic reviews (with no synthesis of data), studies published only as abstracts, letters, or conference proceedings, discussion papers, animal studies, and editorials.

Initial screening of titles was carried out to identify potentially relevant studies, followed by the screening of abstracts and then by full paper review. All titles and abstracts were independently evaluated by two reviewers (SP and CT), not blinded to authors, journals, results, etc., for consistency of inclusion/exclusion and any disagreement was solved by consensus. If the two review authors did not reach an agreement, a third review author adjudication (MB) was adopted to solve disagreements. Quality assessments were conducted by two independent reviewers (SP and CT) and articles potentially fulfilling the inclusion criteria were retrieved in full text.

All data, numerical calculations and graphic extrapolations were independently confirmed. For each study meeting the exclusion criteria, the data extracted and summarized in a table were: first author, year of publication, type of article, objective of the study, number of cases, number of isolated hyperechoic fetal kidneys cases, week of gestational age at the time of screening, amniotic fluid, genetic test performed, diagnosis, family renal history, follow up performed, renal outcomes. An initial search yielded 145 unique articles. An analysis based on the key questions and the inclusion and exclusion criteria using a PRISMA flow diagram, narrowed down the result to 64 papers which fitted the inclusion criteria (Figure 1). Further screening of the full-text articles led to the exclusion of 27 additional articles as a result of: full-text not available, no cases in the topic presented, HK forms not isolated (13-21) and studies not related to the subject. No ethics committee approval was required for this study. The Systematic review registration number is CRD42023400804.

Results

Table 1 and Table 2 show the data extracted from the 37 articles (1,3-8,12,22-50) and finally included in the present review.

Among them, 17 were case reports (Table 3) (1,12,36-50).

In total, 506 cases of isolated hyperechoic kidneys, which were identified in the second and third trimesters (1,4,5,7,8,12,22-24,27-32), were collected. In 79 cases, the time of diagnosis was not reported (3,6,25,26). In 271 cases the amount of amniotic fluid was normal

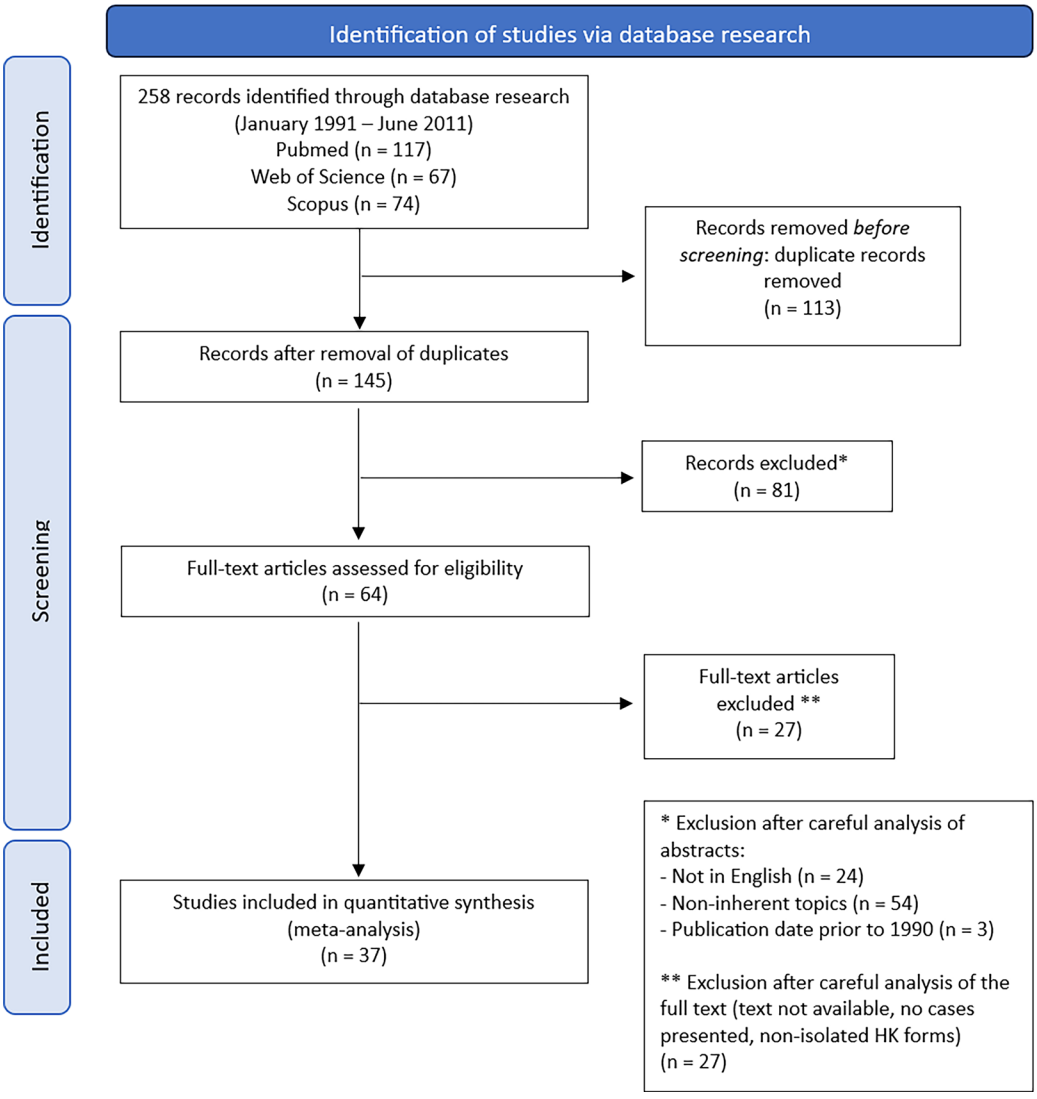

Figure 1. PRISMA flow diagram.

(1,4-8,12,22,23,26,29,30,32-34,39,42,44,48), in 121 cases oligohydramnios was described (1,4,5,7,8,12,22-24,27-32), polyhydramnios was reported in 24 cases (1,4,5,7,8,12,22-24,27,32) and in 90 cases the amount of amniotic fluid was not specified (1,4,5,7,8, 12,22-24,27-32).

A genetic etiology was specified in 246 cases (48%) (1,4,5,7,8,12,22-24,27-32). Of these, 38% were ARPKD, 29% were ADPKD, and 22% were HNF1B nephropathy, 11% other genetic disorders. Family history of renal disease was identified in only 50 cases (1,4,5,7,8,12,22,24,27-32). The reported genetic diagnosis mostly referred to prenatal investigations (1,4,5,7,8,12,22-24,27-32). The proposed tests included karyotype, chromosomal microarray and specific sequencing for PKD1-PKD2 or PKHD1. The NGS technique, which allows for the diagnosis of many complex diseases through the association with specific mutated genes, including nephrocalcinosis, Ivemark syndrome II, propionic acidemia and PKD, was applied only in four of the studies examined (12,37,40,42). An alternative diagnosis such as renal dysplasia, multicystic dysplastic kidney or correlation with congenital anomalies of the kidney and urinary

Table 1. Data extracted from the 37 articles. Part 1.

Ref. (yr)	Country	Objective	Cases (n.)	Isolated HK cases (n.)	GA at diagnosis	AF (n.)	Genetic study (n.)	Diagnosis (n.)	Family history (n.)	Follow up	Renal outcomes (reasons) (n.)
Carr (1995) (26)	USA	Postnatal outcome in prenatally diagnosed bilateral hyperechoic kidneys with normal amniotic fluid	(n. 8)	Solitary HK (n. 8)	-	Normal (n.8)	NA	NA	NA	3 years	LB (n. 8) with normal renal function • HK (n. 4) resolved • HK (n. 1) diminished • HK (n. 3) remained
Suranyi (2000) (28)	Hungary	Correlation between abnormal renal arterial blood flow and clinical outcome in fetuses with hyperechogenic renal medullae to early detection of chronically hypoxic fetal life	Pregnancies complicated by chronic hypoxia in the 3rd trimester (n.207)	HK (n. 37)	3rd trimester	NA	NA	NA	NA	14 days after delivery	36 LB (n.36), of which post-natal HK (n.6) and NND (n.1)
Suranyi (2001) (22)	Hungary	Correlation between fetal renal medullary hyperechogenicity and postnatal clinical outcome in IUGR	IUGR (n.90)	Fetal medullary hyperecho-genicity (n. 25)	18-37 GA (mean 32.7 GA)	Normal (n.24); Oligohydramnios (n.1)	NA	Multicystic kidney (n.1)	NA	pregnancy since 14 dys after delivery	NND (n. 1) IUD (n. 1) Resolution of HK in 73% of cases in 14 dys
Tsatsaris (2002) (23)	France	Perinatal and long-term outcome following prenatal diagnosis of HK	fetuses with isolated HK (n.45)	HK (n. 45)	18-36 GA	Oligohydramnios (n.22) Normal (n.19) Polihydramnios (n.2)	Karyotype	ARPKD (n. 20) ADPKD (n. 8) Other(n. 9) SFSWAD (n.6)	ARPKD **(n. 5)** ADPKD **(n. 8)**	34-132 months	TOP • ARPKD (n. 10) • ADPKD (n. 3) • Other (n. 6) NND • ARPKD (n. 4) • Other (n. 1) LB: • normal renal function (n. 14); • mild renal failure (n. 3); • ESRD (n. 2)

Suranyi (2003) (25)	Hungary	to investigate the fetal biparietal diameter/ kidney length ratio in normal and HK during the 3rd trimester of gestation	IUGR (n.90)	HK (n.28)	NA	NA	NA	NA	NA	14 days after	LB with Normal renal function (n. 28)
Cassart (2004) (27)	Belgium	The objectives of our study were to evaluate the contribution of adding MRI findings to inconclusive sonographic data when assessing fetal urinary tract anomalies and to determine how this addition may affect the management of pregnancy.	pregnancies with prenatal MRI because of bilateral urinary tract anomalies suspected in the fetus as a result of sonographic findings (n = 14) or equivocal urinary tract findings due to poor sonographic conditions related to oligohydramnios (n = 2)	Fetuses with enlarged HK (n. 4)	30 GA	NA	NA	bilateral renal vein thrombosis (n.1)	family history of Jeune's syndrome (n. 1)		NA (n. 1) LB (n. 3) with normal renal function at the birth. 2 babies developed renal cystics lesions
Gilboa (2016) (24)	Israel	To present prenatal diagnosis of normal-sized fetal hyperechogenic kidneys leading to the diagnosis of 17q12 deletion syndrome and autism spectrum disorder	Fetuses with HK (n.7)	(n. 6)	23-33 GA	Normal (n.6)	Karyotype CMA PKD1 sequencing	17q12/ HNF1B delection (n.6)	ARPKD	4 years	TOP (n. 1) (17q12/HNF1B delection) LB with normal renal function (n. 5) • 17q12/ HNF1B delection developed renal cystis (n. 3) • spontaneous resolution of HK (n. 2)

Abbreviations: HKs: hyperechogenic kidneys; GA: gestational age; AF: amniotic fluid; NA: not available; LB: Live Born; NND: neonatal death; IUD: intrauterine death; IUGR: intrauterine growth restriction; ARPKD: autosomal recessive polycystic kidney; ADPKD: autosomal dominant polycystic kidney; ESRD: end stage renal disease; SFSWAD: symptom-free survivors wothour aetiological diagnosis; MRI: magnetic resonance imaging; CMA: chromosomal microarray analysis; PKD: polycystic kidney disease; TOP: termination of pregnancy; HNF1B: hepatic nuclear factor 1B.

Table 2. Data extracted from the 37 articles. Part 2.

Ref. (yr)	Country	Objective	Cases (n.)	Isolated HK cases (n.)	GA at diagnosis	AF (n.)	Genetic study (n.)	Diagnosis (n.)	Family history (n.)	Follow up	Renal outcames (reasons) (n.)
Dillon (1998) (3)	UK	Audit	Fetus with antenatal suspect renal anomaly (n.125)	HK (n.9)	NA	NA	NA	Trisomy 21 (n.1) trisomy 13 (n.1) ADPKD (n.2)	NA	At 1 year of age	TOP (Trisomy 13) (n. 1) LB (n. 8)
Estroff (1991) (5)	USA	To determine the prevalence of TOP, NDD and LB	Fetus with solitary HK (n. 19)	Pregnancies with solitary HK (n.19): enlarged (n.12) normal (n.7); unilateral (n.5) bilateral (n.14)	16-40 GA	Hydramnios (n.4) normal (n.7); oligohydramnios (n.8)	NA	Unilateral dysplasia and contralateral MCDK (n.2); renal dysplasia (n.4); 2 hydronephrosis (n.2); ARPKD (n.4); renal cystic dysplasia of UE (n.3)	Family history of ARPKD (n.4)	-	TOP (Bilateral MCDK with severe oligohydramnios) (n. 1) NDD with ARPKD and oligohydramnios) (n. 4) LB (n. 15)
Brun (2004) (33)	France and Belgium (multi-center study)	To determine whether a specific prenatal sonographic pattern can be identified for ADPKD	ADPKD diagnosis (n. 27)	HK (n.25) • Renal size ≤ +1SD (n.14) • Renale size > +1SD (n.13)	28 GA (mean)	Normal (n.22); Polihydramnios (n.1); oligohydramnios (n.2)	NA	ADPKD (n. 25)	ADPKD (n. 5)	2 months-10 years (mean 32 months)	LB (n. 25), in 3 cases chronic renal dysfunction developed
Muller (2004) (6)	France	Fetal serum ß2-microglobulin and cystatin C to predict post-natal renal function in newborns with combined bilateral hypoplasia and hyperechogenic enlarged kidneys	Bilateral nephropathy (n.54)	HK (n. 34)	NA	Severe oligohydramnios (n.14); oligohydramnios (n.9) normal AF (n.11)	Chromosomal analysis (n.54) ADPKD/ ARPKD analysis	ADPKD (n.8); ARPKD (n.19)	NA	1-7 years	TOP: cystic dysplasia with oligohydramnios (n. 1); ARPKD with oligohydramnios (n. 12); ADPKD with oligohydramnios (n. 3) IUD: oligohydramnios with SFSWAD (n. 1) NND ARPKD and oligohydramnios (n. 1) LB: ADPKD (n. 5) ARPKD (n. 6) SFSWAD (n. 5)

Chaumoitre (2006) (7)	France Belgium	Factors involved in differential diagnosis of renal cysts associated HK	Fetus with HK with confirmed nephrophaties after birth (n.93)	HK (n.12)	13-32 GA	Oligo/ anhydramnios (n.7) normal (n.5)	-	ADPKD (n.3), ARPKD (n.9)	PKD (n.9)	3-7 years	TOP (ARPKD) (n. 4) NND (ARPKD) (n. 2) LB (n. 6) • 2 with normal renal function (ADPKD) Chronic renal failure (n. 4): • renal transplant needed (n. 1); • died (n. 1)
Decramer (2007) (30)	France	Implication of *TCF2* gene anomalies in 62 newborns or fetuses with antenatal hyperechogenic bilateral kidneys	Fetus HK (n. 62)	HK (n.58)	18-35 GA	Oligo-hydramnios (n.21) Polihydramnios (n.2) Normal (n.35)	Fetal karyotype CMA	ARPKD with oligohydramnios (n. 12) ADPKD (n. 8): 2 with olygohydramnios Autosomal recessive tubular dysgenesis (n. 1) Beckwith-Wiedemann syndrome (n. 1) bilateral dysplasia (n. 1) Ivemark Syndrome (n. 1) familial nephroblastoma (n. 1) transient HE (n. 1) HNF1B/TCF2 mutation (n. 1) kidney displasia (n. 10)	autosomal recessive disease tubular dysgenesis (n. 1) ADPKD (n. 3) dominant glomerulocystic kidney disease with diabetes (n. 1) familial hypoplastic cystic kidney disease (n. 1)	NA	TOP: • ARPKD (n. 10) • ADPKD (n. 2) • renal dysplasia (n. 3) • autosomal recessive tubular dysgenesis (n. 1) • Ivemark Syndrome (n. 3) NND: • ARPKD (n. 1) LB (n. 37)
Chaumoitre (2007) (35)	France	To assess the use of diffusion-weighted magnetic resonance imaging in the evaluation of the fetal kidney and to estimate age-dependent changes in the apparent diffusion coefficient of normal and pathological fetal kidneys	pregnant women (n. 51) in whom the fetal kidneys were normal and in 10 whose fetuses had renal pathology	HK (n.3)	26-33 GA	Normal (n.1); oligohydramnios (n.1); NA (n.1)	NA	ADPKD (n. 1) ARPKD (n. 2)	ADPKD	NA	TOP (ARPKD with oligohydramnios) (n. 1) LB (n. 2) • ADPKD (n. 1) • ARPKD (n. 1)

Table 2 (*Continued*)

Ref. (yr)	Country	Objective	Cases (n.)	Isolated HK cases (n.)	GA at diagnosis	AF (n.)	Genetic study (n.)	Diagnosis (n.)	Family history (n.)	Follow up	Renal outcames (reasons) (n.)
Jones (2015) (32)	UK	to report the prenatal ultrasound scan findings in four fetuses from two families postnatally diagnosed with 17q12 microdeletion syndrome	HK (n. 4)	HK (n.4) • enlarged and with fetal cysts (n. 1)	20 GA	Oligohydramnios (n.1) Polyhydramnios (n.2) Normal (n.1)	Karyotype CMA	Delection 17q12 (n.4)	Mothers with renal cystis	NA	TOP with oligohydramnios (n. 1) LB normal renal function (n. 3); in 2 cases renal cystis developed
Jing (2019) (31)	China	to present the experience on prenatal diagnosis of 17q12 deletion to further define the prenatal phenotypes of this syndrome	pregnancies with foetal 17q12 deletion (n. 12)	HK (n. 10)	22-32 GA	Polihydramnios (n.3) NA (n.7)	CMA	17q12 deletion (n. 10)	NA	NA	TOP (n. 4) LB (n. 7)
Shuster (2019) (4)	Canada	To delineate the etiology and outcome of prenatally diagnosed isolated bilateral HK	pregnancy with bilateral HK (n. 260)	HK (n. 52) • enlarged (n. 34) • small (n. 2) • normal size (n. 16)	As early as 13 GA	Normal (n. 27) Oligohydramnios (n. 25)	analysis for ARPKD/ ADPK (n. 22) CMA (n. 34) chromosomal analysis (n. 18)	ADPKD (n. 7) ARPKD (n. 15) HNFB1/TCF2 (n. 1) duplication 3p26.1 (n. 1)	one of the parents was affected (n. 4)	NA	TOP: duplication 3p26.1 (n. 1) ARPKD (n. 6) bilateral MCDK (n. 2) SFSWAD (n. 3) lost in follow up (n. 7) NND: • ARPKD (n. 8) • ADPKD (n. 1) • bilateral MCDK (n. 1) • SFSWAD (n. 1) Born Alive: • Spontaneous resolution (n. 1) • ADPKD (n. 6) • ARPKD (n. 1) • Unilateral renal agenesis (n. 1) • HNF1B/TCF2 (n. 1) • SFSWAD (n. 12)

Yulia (2020) (29)	UK	To report perinatal and infant outcomes in a large cohort of fetuses with antenatal HK	HK (n. 316)	HK (n. 66)	18-37 GA (Mean 21)	Normal (n. 65) Oligohydrmanios (n.1)	NA	bladder outflow obstruction (n. 14) ARPKD (n. 7) ADPKD (n. 2) Cystic dysplasia (n. 16) MCDK (n. 7) HNFB 1 mutation (n. 1) Aneuploidy (n. 3)	NA	1 year of age	TOP (n. 5) NND (ARPKD with oligohydramnios from 20 GA) (n. 1) LB (n. 13) hypertension requiring medication (n. 6) nephrectomy needed (n. 2) dialysis needed (n. 2) Renal transplant needed (n. 3)
Digby (2021)(8)	Canada	To determine etiologies and outcomes of fetal hyperechogenic kidneys	solitary HK (n. 20)	HK (n. 20): • enlarged size (n.7) • normal size (n.13)	18-38 GA	Normal (n. 18) Polihydramnios (n.1) Oligohydramnios (n.1)	CMA Prenatal PKHD1 sequencinq	clinical diagnosis ADPKD (n. 5) 17q12/HNF1B delection (n. 1) clinical diagnosis BBS (n. 1) ARPKD (n. 1) Prenatal resolved (n. 1) postnatal resolved (n. 3) persistent HK at 2 months of FU (n. 1)	NA	3-75 months	TOP (ARPKD) (n. 1) NA (n. 2) LB, most with normal renal function (n. 17)
Zhou (2021) (34)	China	To present the experience on prenatal features of 17q12 microdeletion and microduplication syndromes	fetus with 17q12 microdeletion or microduplication syndromes were retrospectively collected and prenatal findings were reviewed (n. 10)	solitary HK (n. 7)	Second-third trimester	Polyhydramnios (n.1) Normal (n.6)	CMA	17q12 microdeletion and microduplication syndromes (n. 7)	NA	NA	TOP (n. 5) NND (n. 2) LB with normal renal function (n. 1)

Abbreviations: HKs: hyperechogenic kidneys; GA: gestational age; AF: amniotic fluid; NA: not available; MCDK: multicystic dysplastic kidney; LB: Live Born; NND: neonatal death; IUD: intrauterine death; IUGR: intrauterine growth restriction; ARPKD: autosomal recessive polycystic kidney; ADPKD: autosomal dominant polycystic kidney; ESRD: end stage renal disease; SFSWAD: symptom-free survivors wothour aetiological diagnosis; CMA: chromosomal microarray analysis; PKD: polycystic kidney disease; TOP: termination of pregnancy; HNF1B: hepatic nuclear factor 1B; TCF2: transcription factor 2; BBS: Bardet-Biedl syndrome; FU: follow-up.

Table 3. Data extracted from case reports. Part 3.

Ref. (yr)	Country	Isolated HK cases (n.)	GA at diagnosis	AF (n.)	Genetic study (n.)	Diagnosis (n.)	Family history (n.)	Follow up	Renal outcames (reasons) (n.)
Nishi (1991) (46)	Japan	enlarged HK without CMD and with cystics lesion (n.1)	22 GA	oligohydramnios	Karyotype	ARPKD	NA	NA	NND (unknown)
Hofstaetter (1996) (47)	Germany	fetus with enlarged HK (n.1)	14 GA	Polihydramnios	NA	Diffuse mesangial glomerulosclerosis	Yes	NA	NND (renal failure) (n.1)
Withfield (1996) (50)	USA	fetus with enlarged HK (n.1)	32 GA	NA	Karyotype	Glutaric aciduria type 2	None	NA	NDD (metabolic acidosis) (n.1)
Jeffery (1998) (44)	UK	enlarged HK (n.1)	21 GA	normal	PKD1 sequencing	ADPKD	Yes	1 yrs	LB (transitory perinatal resolution of HK)
Kjaergaard (1998) (48)	Denmark	fetuses with enlarged HK (n.2)	20-21 GA	Normal LA	Karyotype	Glutaric aciduria type 2	none	NA	TOP (n.2)
Mashiach (2005) (1)	Israel	HK with enlarged kidneys (n.7)	19-31 GA	Normal (n. 7)	NA	ADPKD (n. 3) ARPKD (n.1) multifocal renal dysplasia (n.2)	1 yes (n.1)	Variable	TOP • Normal (n.1) • Multifocal dysplasia (n.2) NND (ARPKD) (n.1) ADPKD LB (n.3)
Guerriero (2006) (39)	Italy	Fetus with bilateral HK (n.1)	30 GA	Normal AF	NA	NA	NA	6 months	LB with a spontaneous resolution at 6 months old (n.1)
Okumura (2006) (41)	Brazil	fetus with enlarged kidneys with pyramidal hyper echogenicity (n.1)	34 GA	Oligohydramnios	NA	ARPKD (n.1)	NA	NA	NND (unknown) (n.1)
Rajanna (2013) (43)	India	Fetus with enlarged HK and loss of CMD (n.1)	25 GA	Severe oligohydramnios	NA	ARPKD	None	NA	TOP
Thakur (2014) (49)	USA	fetus with enlarged HK (n.1)	19 GA	Oligohydramnios since 29 GA	Karyotyper PKHD1 sequencing	ARPKD	None	NA	NND (respiratory failure) (n.1)

Gondra (2016) (38)	France	HNF1B mutation and polyhydramnios 2nd or 3rd trimester gestation) (n.7); Solitary HK (n.6)	Second-third trimester	Polyhydramnios (n. 6)	NA	Heterozygous HNF1B deletion	NA	From 6 months To 14 yrs	IUD (n.1) LB (normal renal function after birth) (n. 5); 1 developed mild renal failure at 14 years old).
Bernheim (2017) (40)	France	HK with nephromegaly (n.1)	24 GA	oligohydramnios	Karyotype Genetic test NGS	Propioni acidemia	None	1 yrs old	LB with normal renal function
Hureaux (2018) (12)	France	HK (n.3)	II trimester	Normal (n. 3)	NGS	infantile hypercalcemia - mutation in SLC34A1 gene	NA	2 months old	Nephrocalcinosis (n.3)
Belin (2019) (36)	Switzerland	Fetus with HK enlarged fetal kidneys without CMD (n.1)	31 GA	severe oligohydramnios	ARPKD analysis	ARPKD	None	1 yrs	LB with Renal failure
Jordan (2020) (37)	France	Enlarged microcystic HK	23 GA	anhydramnios	CGH array analysis NGS Sanger sequencing	Homozygous variation in DNAJB11 with Ivemark II syndrome	3 pregnancy lost because renal disease	NA	TOP
Dorval (2021) (42)	France	PMM2 variant associated in a cystic kidney disease (n.6); enlarged HK (n.4)	22-32 GA	normal (n.2) anhydramnios (n.1) polhydramsnios (n. 1)	NGS	PMM2 variant in a polycystics kidney disease (n. 4)	None	NA	TOP (n. 3) LB who developed progressive kidney dis- ease with an eGFR of 72 mL/min/1.73 m2 at 15 years old (n. 1)
Lopes (2021) (45)	Portugal	HK (n.1)	20 GA	NA	NA	HNF1B associated disease	None	19 yrs	LB (progressive ESRD and renal transplantation)

Abbreviations: HKs: hyperechogenic kidneys; GA: gestational age; AF: amniotic fluid; NA: not available; CMD: cortico-medullary differentiation; MCDK: multicystic dysplastic kidney; LB: Live Born; NND: neonatal death; IUD: intrauterine death; IUGR: intrauterine growth restriction; ARPKD: autosomal recessive polycystic kidney; ADPKD: autosomal dominant polycystic kidney; ESRD: end stage renal disease; CMA: chromosomal microarray analysis; CGH: Comparative Genomic Hybridization; NGS: next-generation sequencing; PKD: polycystic kidney disease; TOP: termination of pregnancy; HNF1B: hepatic nuclear factor 1B; PMM2: phosphomannomutase 2.

tract was provided in 14% of cases (1,4,5,7,8,12,22-24,27-32). In 33% of cases the diagnosis was not available (1,4,5,7,8,12,22-24,27-32). The outcome was identified as termination of pregnancy (TOP), intrauterine death (IUD), neonatal death (NND) or as Live Born (LB), of which renal function is described when available (1,4,5,7,8,12,22-24,27-32). Out of the 506 cases, 19,6% underwent TOP while IUD occurred in 1% of cases and NND occurred in 6.4%, 11.9% of outcomes were not available o were lost in follow up while 61% of cases were LB. Renal function was specified only in 33% of cases (1,4,5,7,8,12,22-24,27-32), even within a variable temporal follow-up. Specifically, 24% maintained adequate renal function while 8.6% developed renal failure, hypertension, kidney transplantation or required nephrectomy. However, the overall available data were often partial because of limited follow-up or undetermined diagnoses and therefore it was not possible to provide further characterization of these patients.

Discussion

Renal echogenicity was described in relation to the ultrasound appearance of the liver and/or spleen (12). The fetal kidneys appear physiologically hyperechogenic with respect to the later periods of life (32). Specifically, in the first and in the initial part of the second trimester, the cortex appears hyperechoic, and then attenuates and becomes hypoechoic starting from the 32nd gestational week (12,30). Perinatal expression of PKD frequently occurred with enlarged and/or hyperechoic kidneys (23). A monogenic disease was identified in 50-70% of children with at least two renal cysts and/or an HK (23,25). The literature shows that most of the HKs isolated belong to hereditary kidney diseases such as ADPKD, ARPKD or HNF1B Nephropathy (7, 12). These conclusions are confirmed in the present review, in which 246/506 cases of HKs are attributed to genetic diseases such as ADPKD (29%) ARPKD (38%) and HNF1B Nephropathy (22%), other genetic diagnoses (11%).

It should be emphasized that the studies evaluated contain limited case histories and date back to an era characterized by a high heterogeneity of imaging and genetic diagnostic resources. In the last twenty years, broad progress has been observed in both ultrasound equipment and genetic analysis. For example, HNF1B nephropathy represents a rather recent clinical entity. Therefore, the real incidence of genetic pathologies and the relative etiology of fetal HKs could be grossly underestimated. In addition, in some of the studies identified the diagnosis was based on clinical and instrumental criteria rather than on genetic confirmation, therefore limiting knowledge of the real incidence of the disease. PKDs comprise a group of monogenic diseases characterized by a high genetic complexity and a significant phenotypic overlap that often leads to chronic kidney disease with evolution up to End-Stage Renal Disesase (ESRD) (3,8,38,39). The isolated presence of a fetal HK therefore constitutes a prognostic challenge in the prenatal period and a postnatal diagnostic odyssey, also in consideration of the lack of controlled studies which could be a means to guide counselling and subsequent management (23,40).

Although ultrasound is not sufficient alone for diagnostic purposes, some findings could suggest an underlying genetic condition or syndrome, these findings include CMD, kidney size, the presence of cysts and the association with other extra-renal anomalies (26,30,33). In addition, cases of ADPKD with transient perinatal resolution are described (1). In our series, cases with transient resolution of ultrasound anomalies are described in 2 patients with HNF1B nephropathy, 1 with ADPKD and 2 with unknown etiology.

Oligohydramnios is considered the main prognostic determinant regardless of the etiology (4,26). In fact, it is a predictor of both renal failure, especially in the presence of very large kidneys, and serious perinatal respiratory complications that aggravate the mortality and morbidity of these patients (4). The isolated presence of an HK of normal size and with regular amniotic fluid is associated with a favorable perinatal outcome even if the late development of chronic kidney disease cannot be excluded. (25) More than half of the patients examined had a favorable perinatal outcome. Although renal function is not specified in a considerable percentage of cases, chronic kidney disease is reported in only 8.6% of cases. Additional information

that can guide the diagnosis is the family history and ultrasound characteristics of the parents, while knowing that *de novo*, hypomorphic or recessive mutations can lead to erroneous conclusions (7,43,51,52).

Traditionally, laboratoristic methods offer direct, gene-specific sequencing but given the genetic complexity of renal cystic pathologies and the important phenotypic overlap, this should not be the first analysis proposed (53). NGS technology represents a powerful alternative (10,11,54). It includes the application of genetic panels that allow the simultaneous sequencing of multiple genes associated with a particular phenotype, the whole exome sequencing (WES) or the whole genome (whole genome sequencing-WGS) (55,56). NGS genetic panels in the context of PKD should include the analysis of PKD1, PKD2, PKHD1, DAZIP1L, HNF1B and other genes involved in ciliopathies with nephronophthisis and Bardet Biedle Syndrome (54). The reduction in the costs through the use of NGS panels has allowed this technology to spread as a first-level test, accelerating the diagnostic process and the correct classification of the clinical phenotype on the basis of which to optimize family assistance and counseling (4,49,57). Furthermore, WES/WGS techniques allow the identification of new pathogenetic mutations or mutations that may affect the clinical phenotype, encouraging knowledge in an area that is not yet fully understood (55).

Limitations

The review covers a very long period of time in order to increase the variability of the case series. It should therefore be emphasized how diagnostic possibilities have evolved over time, thanks to progress in terms of ultrasound sensitivity and genetic identification capacity. The simplicity of the results presented derives from an attempt to standardize the data collected from studies with very different objectives.

Conclusions

In the prenatal period, the management of HKs is based on the presence of oligohydramnios and kidney dimensions. Postnatally, the rapid determination of a diagnostic definition allows for the application of targeted follow-up and proper support for the family. The genetic approach using the NGS technique is still underused despite allowing a faster classification of the etiological context and patient classification in the absence of an increase in diagnostic costs. Furthermore, the application of NGS technology allows a more detailed analysis of the underlying genetic anomalies that may justify the variability of the clinical phenotype. Furthermore, a greater understanding of pediatric cystic pathology could facilitate research in an area where therapeutic possibilities are only supportive. Since the genetic pathology is so relevant in the diagnosis of fetal HK, the use of NGS technology seems mandatory.

Ethic Committee: Not applicable. This systematic review is registered on PROSPERO.

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