Ultrasound Obstet Gynecol 2023; **62**: 778–787
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.26283.

Prenatal diagnosis and postnatal outcome of fetal congenital knee dislocation: systematic review of literature

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KEYWORDS: congenital anomaly; congenital knee dislocation; early conservative treatment; genu recurvatum; pregnancy; prenatal diagnosis; ultrasound

CONTRIBUTION

What are the novel findings of this work?
The prognosis of congenital knee dislocation (CKD) is highly dependent on the presence of associated anomalies, being excellent in isolated cases and poor in complex cases, with the latter showing about 80% risk of a genetic syndrome. Early postnatal conservative treatment of CKD is effective when it is isolated, achieving resolution after manipulation, serial casting and physiotherapy. Surviving cases with associated anomalies may require surgery.

What are the clinical implications of this work?
The diagnosis of CKD is possible from the early second trimester. Prenatal management requires detailed ultrasound assessment and amniocentesis for genetic testing to exclude the possibility of associated anomalies, and subsequent early referral to a pediatric orthopedist.

ABSTRACT

Objectives *Congenital knee dislocation (CKD) is a rare condition, affecting 1 in 100 000 newborns. Its prenatal diagnosis is challenging and not well described in the literature, especially when it appears isolated and not as part of a complex malformation or syndromic pattern. The purpose of this study was to provide a comprehensive review of the available literature on the prenatal diagnosis and postnatal outcome of CKD and to summarize the current evidence on this topic.*

Methods *A systematic review of the literature on the prenatal diagnosis of CKD was performed in PubMed, Scopus and EMBASE. A predefined combination of specific keywords was used, focusing on intrauterine manifestations, diagnostic methods, prenatal behavior, postnatal treatment and neonatal outcome as well as long-term outcome in terms of ambulation, motion and joint stability. The quality of studies was assessed using the National Institutes of Health tool for quality assessment of case series. A summary of results was carried out providing proportions and rates of diagnostic and prognostic features associated with this rare condition.*

Results *In total, 20 cases were retrieved for analysis, of which 19 were obtained from the identified eligible studies (*n = *16) and one was an unpublished case from our center. The median gestational age at prenatal diagnosis, which was made using ultrasound in most cases, was 20 weeks (range, 14–38 weeks). Bilaterality was observed in 11/20 (55%) cases. The condition was isolated in 7/20 (35%) cases and associated with other anomalies in 13/20 (65%) cases. An association was observed with oligohydramnios (4/20 (20%)), and an invasive procedure was performed in 13/20 (65%) cases, including 11 cases with an invasive procedure performed for diagnostic purposes. Genetic testing was normal in all isolated cases for which information was available (4/7), while a genetic syndrome was present in 10/13 (77%) non-isolated cases (Larsen, Noonan, Grebe, Desbuquois or Escobar syndrome). There were seven terminations of pregnancy, of which six were performed in cases with associated anomalies and one in an isolated case, 11 cases of*

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Accepted: 24 May 2023

postnatal survival, one case of intrauterine death and one of neonatal death. The fetal and neonatal deaths occurred in cases with associated anomalies or abnormal genetic findings. Postnatal treatment was mostly conservative, with only two reports (18% of the 11 surviving neonates) of surgical intervention, both in cases with associated anomalies. Postnatal follow-up was up to 1 year in most cases, and motor outlook appeared normal in all isolated cases.

Conclusions *CKD is a rare fetal anomaly with a prenatal diagnosis achievable from the early second trimester, for which a favorable outcome can be expected when no associated anomalies are present. Prenatal diagnosis should include detailed ultrasound assessment and amniocentesis for extensive genetic studies, particularly in non-isolated cases. Early postnatal treatment achieves success in most cases without surgical intervention and leads to a normal motor outlook. © 2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Congenital knee dislocation (CKD), also known as genu recurvatum, is a rare condition, with an estimated incidence of about 1 in 100 000 live births[1]. The causes of CKD can be either intrinsic or extrinsic. Intrinsic causes include genetic syndromes and complex anomalies with no obvious underlying genetic anomaly. Among the extrinsic causes, breech presentation, oligohydramnios and compression may contribute to the etiology. The first description of the anomaly is believed to date back to 1820[2]. It can occur either as an isolated finding or in association with other skeletal malformations, as well as in the context of a congenital syndrome (such as Larsen syndrome or arthrogryposis multiplex congenita). Meningomyelocele and other neurological conditions may also be associated with this disorder[3]. The main clinical findings related to this defect include hyperextension of the knee joint, increased transverse skin folds over the anterior surface of the knee and protrusion of the femoral condyles into the popliteal fossa[4]. The postnatal spectrum of this condition comprises three different phenotypes, including simple hyperextension of the knee joint (Type 1), anterior subluxation (Type 2) and anterior luxation (Type 3) of the tibia relative to the femoral bone[5]. A more recent classification, based on 51 neonatal cases, introduced reduction and stability criteria, distinguishing three types of CKD: Type I (55%) is easily reducible, remaining stable in flexion; Type II (31%) is reducible but unstable; and Type III (14%) is irreducible with absence of anterior skin folds[6].

The prenatal diagnosis and development of this rare condition have not been described extensively. The first *in-utero* diagnosis was made using X-ray in 1986[7]. The few reports that are available in the literature describe contradictory findings and used different management strategies, ranging from a conservative approach to termination of pregnancy (TOP)[7–22]. Moreover, the risk of associated anomalies is uncertain for both structural and genetic conditions.

The aim of this systematic review was to describe the current available knowledge regarding the prenatal diagnosis and postnatal outcome of CKD and to provide a protocol for prenatal counseling and perinatal management.

METHODS

Search strategy, information sources and eligibility

PubMed, Scopus and EMBASE were searched with the following keywords alone or in combination: ('knee dislocation' OR 'genu recurvatum' OR 'knee hyperextension') AND ('congenital' OR 'prenatal' OR 'intrauterine' OR 'fetal' OR 'ultrasound' OR 'anomalies' OR 'abnormal' OR 'prenatal diagnosis' OR 'malformation'); ('knee dislocation' OR 'congenital genu recurvatum') AND ('intrauterine' OR 'fetal' OR 'ultrasound' OR 'prenatal diagnosis' OR 'genu recurvatum') AND 'prenatal diagnosis'. The exploded indexing terms and truncations functions were also used. The systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[23]. The review protocol was not registered, but methodology concerning inclusion/exclusion criteria, data extraction and quality assessment were defined *a priori*. Studies written in any language, published up to May 2023 and reporting on the prenatal diagnosis and postnatal outcome of CKD were considered, including 'gray literature'. Pediatric, postnatal and postmortem cases or series were excluded, as these are based on a different population and have a high risk of selection bias. The local electronic database of San Raffaele Hospital was explored from the year 2004 to May 2023 to find additional unpublished cases diagnosed and managed at our center.

Study selection, data collection and outcomes

Data were gathered and recorded in a dedicated database by three different authors (M.C., G.C., A.F.). Data on the features of fetuses prenatally diagnosed with CKD were collected along with their neonatal outcome. Frequencies and proportions of each relevant feature and outcome collected were calculated and presented. A prenatal diagnosis of CKD by ultrasound was generally established when the knee presented an overextension over the zero-degree plane without movements of flexion. All other diagnostic imaging techniques were considered. The outcomes analyzed were associated structural abnormality, genetic anomaly, TOP, gestational age (GA) at prenatal diagnosis and pregnancy outcome. Three authors (M.C., G.C., A.F.) reviewed the papers independently, and consensus was reached about their relevance. Any uncertainty or inconsistency was resolved by consulting the senior author (P.I.C.). The study did

not require ethical approval. Information regarding an unpublished CKD case from our center was collected retrospectively from the electronic hospital database in which patient data were anonymized and stored, and complied with the ethical standards of human research established by the Declaration of Helsinki. The patient provided written informed consent for publication of the anonymized case report.

Assessment of study quality

Quality assessment of the included studies was performed using the National Institutes of Health (NIH) tool for quality assessment of case series (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools; accessed on 10 December 2022). This method is recommended by the National Institute for Health and Care Excellence (NICE). The score was assigned based on principal factors (questions 1, 6 and 7) as 'good' if all three were present; 'fair' if two were present; or 'poor' if only one was present. A comprehensive assessment according to the NICE and NIH standards was performed for each study.

RESULTS

Systematic review of the literature

The systematic search of the literature identified 742 studies, of which 726 were excluded and 16 were included in the analysis (Figure 1)[7–22]. Nineteen cases with a prenatal diagnosis of CKD were retrieved from the identified studies and an additional case was found in the database of our center. Table 1 and Figure 2 summarize the results.

The 20 cases included in the analysis had a median GA of 20 (range, 14–38) weeks at prenatal diagnosis, which was made using ultrasound in most cases. Bilaterality was observed in 11/20 (55%) and unilaterality in 9/20 (45%) cases. The condition was isolated in 7/20 (35%) cases and associated with other anomalies in 13/20 (65%) cases, of which 10/13 (77%) were confirmed to have a genetic basis and 3/13 (23%) were not found to be part of a genetic syndrome, despite the association with other structural abnormalities. Genetic testing was normal in all isolated cases for which information was available (4/7). Oligohydramnios was observed in 4/20 (20%) cases, and an invasive procedure was performed in 13/20 (65%) cases, with some evidence of early amniotic fluid loss after amniocentesis. First-trimester screening results were reported for 8/20 cases and were abnormal in four non-isolated cases, but no sign of knee dislocation at this GA was described.

In two cases, multiple anomalies were found without a specific diagnosis, including prenatal findings of CKD, fragile bones, clubfoot and abnormal growth of other skeletal components, in particular of the long bones, thorax and mandible[13]. A similar phenotype is associated with gracile bone dysplasia; however, this diagnosis was excluded, given the absence in these cases of other major characteristics, such as osteocraniostenosis with cloverleaf skull deformity, microphthalmia, small thorax and bowed or short long bones. In another case, prenatal ultrasound performed at 17 weeks' gestation revealed bilateral clubfoot, which raised the suspicion of fetal arthrogryposis[21]. Amniocentesis was performed at 18 weeks; comparative genomic hybridization (CGH) was normal, no aneuploidy was detected, and the skeletal dysplasia genetic panel was negative. Subsequent

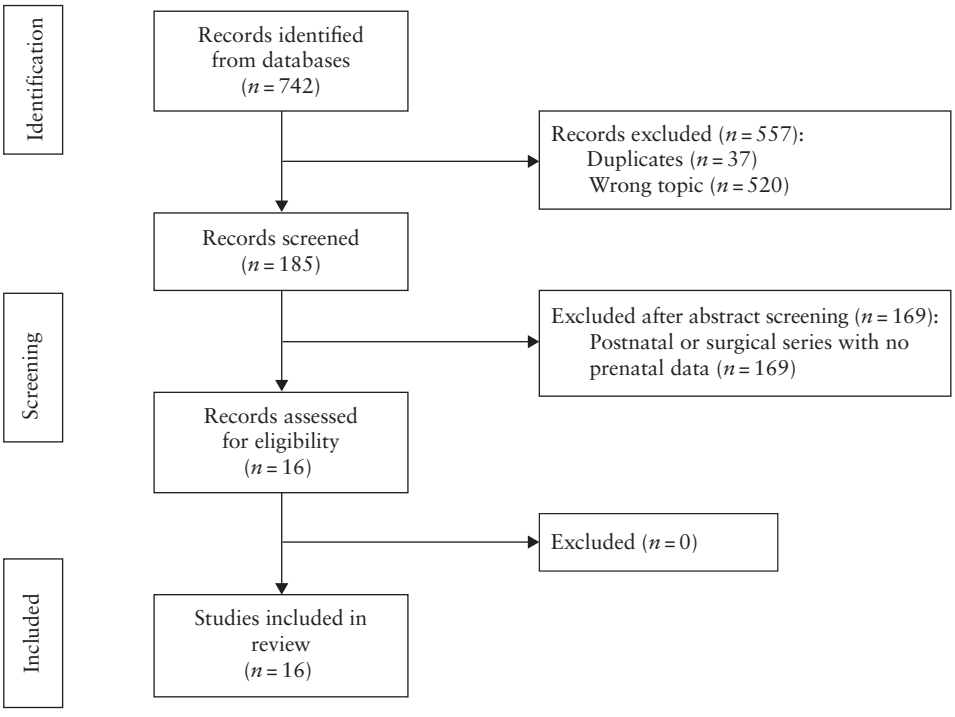

Figure 1 PRISMA flowchart summarizing study selection and inclusion in systematic review.

Table 1 Characteristics of 20 cases included in systematic review

Study	*GA at diagnosis (weeks)*	*Isolated vs non-isolated*	*Laterality*	*AF*	*Diagnostic method*	*Genetics*	*First-trimester screening*	*Invasive procedure*	*Fetal presentation*	*Pregnancy outcome*	*Treatment*	*Postnatal outcome*	*Follow-up (months)*
Lage (1986)[7]	32	Isolated	Bilateral	NA	X-ray	NA	No	No	Breech	LB, CS	Conservative	Normal	NA
Mostello (1991)[8]	20	Non-isolated	Unilateral	Reduced	2D-US	Larsen syndrome	NA	Amnio†	NA	LB, CS	—	Neonatal death (day 8)	—
Elchalal (1993)[9]	38	Isolated	Unilateral	Reduced	X-ray	NA	No	No	Breech	LB, VD	Conservative	Normal	3
Gorincour (2003)[10]	24	Isolated	Unilateral	Normal*	2D-US	Normal karyotype	Normal	Amnio	NA	LB, VD	Conservative	Normal§	10
Shih (2004)[11]	18	Non-isolated	Bilateral	Increased	3D-US	Larsen syndrome	NA	Amnio	NA	LB, CS	Conservative	Abnormal, Larsen syndrome	12
Monteagudo (2006)[12]	21	Isolated	Unilateral	Normal*	2D-US	NA	Normal	ST	NA	LB, CS	Conservative	Normal¶	18
Shalev (2007)[13]	16	Non-isolated	Unilateral	NA	2D-US	Normal karyotype	NA	No	NA	TOP	—	TOP, multiple anomalies	—
Shalev (2007)[13]	14	Non-isolated	Unilateral	NA	2D-US	Normal karyotype	NT, 4.8 mm	CVS	NA	TOP	—	TOP, multiple anomalies	—
Barber (2009)[14]	20	Non-isolated	Bilateral	NA	2D-US	Larsen syndrome	NA	No	NA	TOP	—	TOP, Larsen syndrome	—
Barber (2009)[14]	22	Isolated	Bilateral	Reduced	2D-US	Normal karyotype	NA	Amnio	NA	TOP	—	TOP, isolated	—
Jain Ghai (2011)[15]	16	Non-isolated	Unilateral	Reduced	2D-US	Noonan syndrome	Hydrops	CVS	NA	TOP‡	—	TOP, multiple anomalies	—
Ghazle (2012)[16]	26	Non-isolated	Bilateral	Normal	2D-US	Larsen syndrome	NA	Amnio	NA	LB, CS	NA	Abnormal, Larsen syndrome	NA
Bildner (2014)[17]	19	Non-isolated	Unilateral	Increased	2D-US	Escobar syndrome	NA	Amnio	Breech	LB, CS	Conservative	Abnormal, Escobar syndrome	NA
Al Kaissi (2014)[18]	35	Non-isolated	Bilateral	Increased	2D-US	Grebe syndrome	NA	Amniodrainage	NA	IUD, VD	—	IUD, Grebe syndrome	—
Matar (2017)[19]	20	Non-isolated	Bilateral	NA	2D-US	Larsen syndrome	NA	No	NA	LB, CS	Conservative + surgical	Abnormal, Larsen syndrome	84
Forster (2019)[20]	16	Non-isolated	Bilateral	NA	2D-US	Type-1 Desbuquois dysplasia	NT, 6.9 mm	No	NA	TOP	—	TOP, Type-1 Desbuquois dysplasia	—
Forster (2019)[20]	17	Non-isolated	Bilateral	NA	2D-US	Type-1 Desbuquois dysplasia	Increased NT	Amnio	NA	TOP	—	TOP, Type-1 Desbuquois dysplasia	—
Barreto Mota (2022)[21]	22	Non-isolated	Bilateral	Normal	2D-US	Normal karyotype, array CGH, skeletal dysplasia panel	NA	Amnio	NA	LB, CS	Conservative + surgical	Normal	7
Morales-Roselló (2022)[22]	20	Isolated	Bilateral	Normal	2D-US, MRI	Low risk on NIPT	Normal	No	NA	LB, VD	Conservative	Normal (congenital hip dysplasia)	3
Cavoretto (2023) (current case)	16	Isolated	Unilateral	Normal	2D-US	Normal karyotype, array CGH and custom gene panel	Normal	CVS	Cephalic	LB, CS	Conservative	Normal	24

Only first author is given for each study. Normal postnatal outcome was defined as no residual anatomical or functional abnormality described following treatment (normal ambulation observed or expected in cases with insufficient follow-up). *Transient oligohydramnios was observed in second trimester after invasive procedure. †Amniocentesis (Amnio) performed at 37 weeks (no prenatal genetic testing). ‡Maternal mirror syndrome. §Reduced knee mobility on one side (0–110°) and normal on other side (0–150°). ¶Patient walked independently, but there was hypoplastic patella that may require surgical correction in future. 2D, two-dimensional; 3D, three-dimensional; AF, amniotic fluid; CGH, comparative genomic hybridization; CS, Cesarean section; CVS, chorionic villus sampling; GA, gestational age; IUD, intrauterine fetal demise; LB, live birth; MRI, magnetic resonance imaging; NA, not available; NIPT, non-invasive prenatal testing; NT, nuchal translucency; ST, selective fetal termination; TOP, termination of pregnancy; US, ultrasound; VD, vaginal delivery.

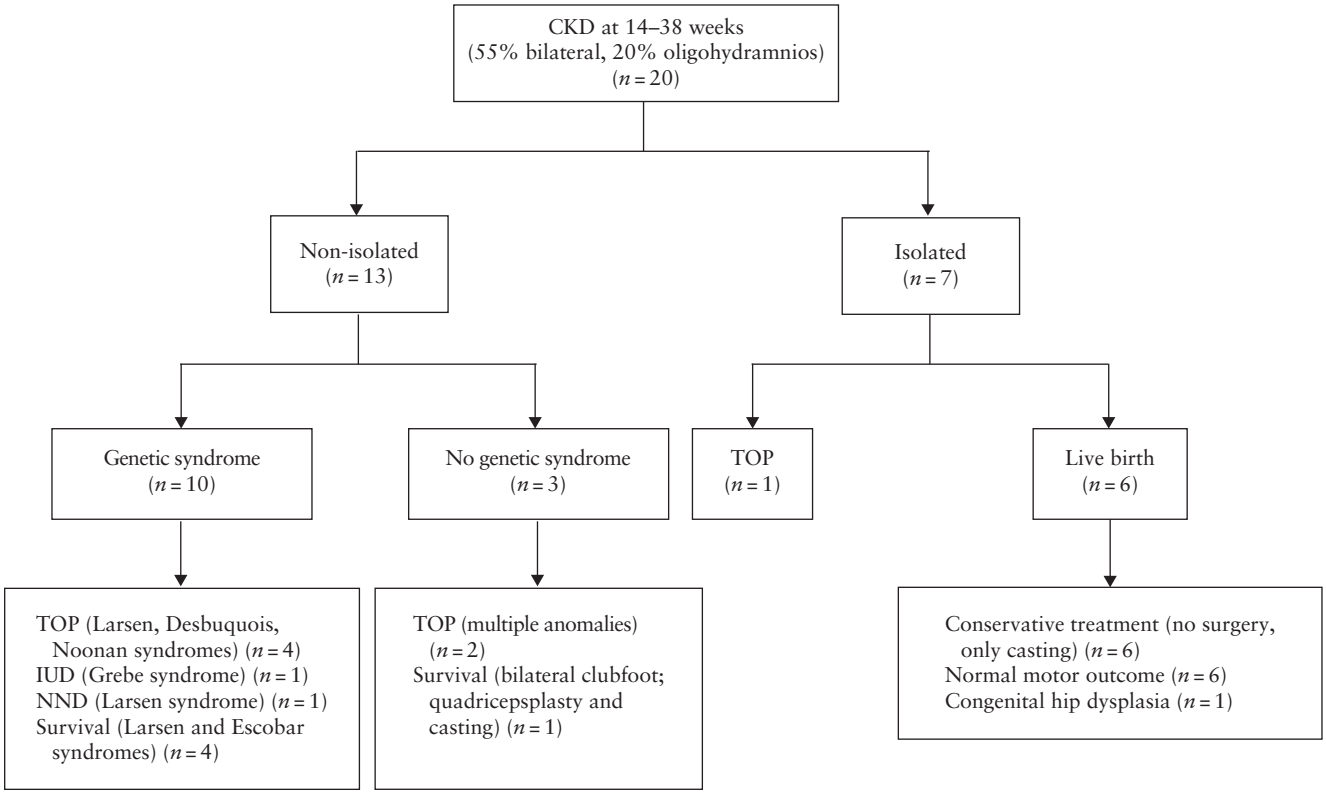

Figure 2 Flowchart summarizing outcome of cases with prenatal diagnosis of congenital knee dislocation (CKD). IUD, intrauterine death; NND, neonatal death; TOP, termination of pregnancy.

ultrasound performed at 22 weeks showed persistence of bilateral clubfoot, in association with hyperextension of the lower limbs, internal rotation of the knee and the size of the cerebellum to be at the lower limit of the normal range. Investigations carried out at birth (physical examination and ultrasound of the brain and hip) confirmed the presence of bilateral clubfoot and CKD and excluded the presence of arthrogryposis or other abnormalities. In one of the isolated cases, ultrasound at 20 weeks revealed hyperextension of the knees, and magnetic resonance imaging (MRI) at 26 weeks confirmed malalignment of the legs with anterior translation of both tibial axes[22]. Cell-free fetal DNA testing was normal, and no invasive testing was performed. Ultrasound and radiographic examinations performed at birth were normal, but the neonate was diagnosed with congenital hip dysplasia and was treated with a Pavlik harness.

The malformations most frequently found in association with CKD among the non-isolated cases are shown in Table 2. Among the three non-isolated cases without a clear underlying syndrome, one had clubfoot only and the other two had complex malformation patterns. Our review did not show an association with conditions previously reported as co-occurring with CKD in postnatal series, such as open spina bifida and fetal akinesia deformation sequence (arthrogryposis). This is probably owing to the fact that prenatal diagnosis of these conditions is relatively well established, and interest in these cases is related to the primary anomaly, whereas CKD is easily interpreted as a secondary manifestation of the primary diagnosis, resulting in a lack of scientific publications on this topic.

Five (50%) of the 10 cases with a genetic disorder had Larsen syndrome. Cases with Larsen syndrome presented with a flat facial profile (60%), micrognathia (100%), hypertelorism (60%), bilateral or unilateral hip dislocation (60%), short nasal bridge (40%) and low-set ears (40%). Prenatal diagnosis of Larsen syndrome was suspected following ultrasound detection of fetal abnormalities, with three cases confirmed postnatally based on clinical assessment alone by a geneticist[8,11,16] and two confirmed with the adjunct of *LAR1* mutation genetic testing[14,19]. The diagnosis of Noonan syndrome was made after TOP at 17 weeks for mirror syndrome in a fetus with multiple anomalies with DNA analysis showing *PTPN11* mutation[15]. In the remaining four cases with abnormal genetic testing, the antenatal suspicion of a genetic syndrome based on structural anomalies was confirmed postnatally with a clinical diagnosis of Escobar syndrome, Grebe syndrome and Desbuquois dysplasia[17,18,20].

There were seven TOPs, which were performed in six (86%) cases with multiple malformations and one (14%) isolated case, 11 cases of postnatal survival, one intrauterine death and one neonatal death. The fetal and neonatal deaths occurred in cases with associated anomalies and abnormal genetic findings. The neonatal death occurred in a fetus with Larsen syndrome and multiple anomalies, in which severe hypoxia developed as a consequence of pulmonary insufficiency by day 2 postpartum[8]. The intrauterine death occurred in a fetus with Grebe syndrome and

Table 2 Clinical findings of cases of congenital knee dislocation with documented associated anomalies (with prenatal or postnatal diagnosis)

Clinical feature	*Cases* (n *(%)*)	*Genetic syndrome* (n)*
Micrognathia	5 (25)	Larsen (5)
Clubfoot	5 (25)	Escobar (1)
Short, broad or depressed nasal bridge	4 (20)	Larsen (2), Escobar (1), Grebe (1)
Hypertelorism	4 (20)	Larsen (3), Grebe (1)
Low-set ears	4 (20)	Larsen (2)
Oligohydramnios	4 (20)	—
Skin edema	3 (15)	Noonan (1), Escobar (limited to feet) (1)
Polyhydramnios	3 (15)	Grebe (1)
Flat face	3 (15)	Larsen (3)
Bilateral or unilateral hip dysplasia	3 (15)†	Larsen (3)
Absent or hypoplastic patella	2 (10)†	—
Short or gracile long bones	2 (10)	—
Micromelia	2 (10)	Desbuquois (2)
Polysyndactyly	2 (10)	Desbuquois (2)
Maternal mirror syndrome	1 (5)	Noonan (1)
Skeletal dysplasia	1 (5)	Grebe (1)
Oligodactyly	1 (5)	Grebe (1)
Frontal bossing	1 (5)	Grebe (1)
Clenched hands	1 (5)	Escobar (1)
Agenesis of corpus callosum	1 (5)	Larsen (1)
Pachygyria	1 (5)	Larsen (1)
Unilateral kidney hypoplasia	1 (5)	Larsen (1)
Extra ribs	1 (5)	Larsen (1)
Ureterocele and hydronephrosis	1 (5)	Larsen (1)
AVSD	1 (5)	—
Hypospadias	1 (5)	—
Absent thymus	1 (5)	—
Pulmonary hypoplasia	1 (5)†	—

*Number of cases with genetic syndrome and clinical feature is indicated, whereas remaining clinical features were found in non-isolated cases without genetic syndrome. †Undetectable prenatally. AVSD, atrioventricular septal defect.

multiple severe associated anomalies, which was delivered stillborn at 35 weeks after amniodrainage because of severe polyhydramnios[18]. Postnatal treatment was conservative in most cases, with only 2/11 (18%) reports of surgical intervention. All isolated cases in which the pregnancy continued had a favorable outcome with no need for surgery, whereas two of the complex cases required surgery. Postnatal follow-up was up to 1 year in most cases, with favorable motor outcome in all isolated cases.

Study quality

The quality of the studies is reported in Table 3. All studies were case reports or small case series with sufficient quality in most cases.

Case presentation

A 38-year-old woman was referred to our department for first-trimester screening. Ultrasound scan documented 1.1-mm nuchal translucency, 68-mm crown–rump

Table 3 Quality assessment of case series according to National Institutes of Health (NIH) questions (1–9)

Study	*1. Was study question or objective clearly stated?*	*2. Was study population clearly and fully described, including case definition?*	*3. Were cases consecutive?*	*4. Were subjects comparable?*	*5. Was intervention clearly described?*	*6. Were outcome measures clearly defined, valid, reliable and implemented consistently across all study participants?*	*7. Was length of follow-up described?*	*8. Were statistical methods well described?*	*9. Were results well described?*	*AHRQ grade*
Lage (1986)[7]	Yes	No	NA	NA	No	No	No	NA	No	Poor
Mostello (1991)[8]	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Good
Elchalal (1993)[9]	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Good
Gorincour (2003)[10]	Yes	Yes	NA	NA	No	No	Yes	NA	Yes	Fair
Shih (2004)[11]	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Good
Monteagudo (2006)[12]	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Good
Shalev (2007)[13]	Yes	Yes	NA	NA	No	Yes	No	NA	Yes	Fair
Barber (2009)[14]	Yes	No	NA	NA	No	No	No	NA	Yes	Poor
Jain Ghai (2011)[15]	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Good
Ghazle (2012)[16]	Yes	No	NA	NA	Yes	No	No	NA	No	Poor
Bildner (2014)[17]	Yes	Yes	NA	NA	Yes	Yes	No	NA	Yes	Fair
Al Kaissi (2014)[18]	Yes	Yes	NA	NA	Yes	Yes	No	NA	Yes	Fair
Matar (2017)[19]	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Good
Forster (2019)[20]	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Good
Barreto Mota (2022)[21]	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Good
Morales-Roselló (2022)[22]	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Good

Only first author is given for each study. AHRQ, Agency for Healthcare Research and Quality; NA, not applicable.

length and normal limbs and fetal anatomy. Placental biomarkers were also normal, with a low risk for major aneuploidies and preterm pre-eclampsia on combined testing. After genetic counseling, and despite the low-risk results with normal nuchal translucency, the woman requested chorionic villus sampling owing to her personal anxiety in relation to her past obstetric history, in which her previous child had a postnatal diagnosis of Prader–Willi syndrome. Chorionic villus sampling was performed without complications at a GA of 12 + 5 weeks, showing a normal female karyotype (46 XX) and normal array CGH. During a routine ultrasound assessment performed at 16 + 0 weeks using a Voluson E8 scanner with a 5–7-MHz convex transducer (GE Healthcare, Zipf, Austria), CKD was diagnosed with about 45° of knee dislocation (overextension). Altered orientation of the left knee was observed, causing a minimal range of motion of the knee joint with an inverted-convex popliteal fossa (Figure 3). The position and motility of all other limbs and joints appeared completely normal, and no additional structural abnormality was detected. Because of this finding, further genetic analysis was carried out on preserved chorionic tissue using a custom gene panel to exclude single-gene mutations. The results were normal for 1000 genes associated with known diseases, including all those related to CKD. A pediatric orthopedic consultation was conducted in which we explained to the parents all possible postnatal orthopedic treatment options and expected outcomes. Subsequent serial ultrasound examinations were performed every 4 weeks, confirming in all cases an isolated anomaly and normal growth and placental function. Elective Cesarean section was performed at 38 + 5 weeks at our center, delivering a newborn with a birth weight of 2910 g and 1-min and 5-min Apgar scores of 8 and 10, respectively. The neonate underwent pediatric orthopedic evaluation at birth, showing severe clinical findings (Type II CKD according to Mehrafshan *et al.*[6]) (Figure 4a,b). Hip dysplasia was excluded based on ultrasound examination. Further diagnostic testing was performed in the following days, including abdominal ultrasound scan, brain MRI and echocardiography, all showing normal results. Subsequent pediatric orthopedic treatment involved weekly changing of serial plaster casts with progressive correction of the deformity (Figure 4c,d). After removal of the last cast, the child underwent physiotherapy. An anterior knee brace was applied to maintain position overnight (Figure 4e). After 6 weeks, 130° knee flexion had been achieved (Figure 4f). Ultrasound scan of the knee demonstrated normal alignment and development of the patella. Physiotherapy was then performed for 6 more weeks. The infant was 24 months old at the time of writing, walked normally and did not require surgery.

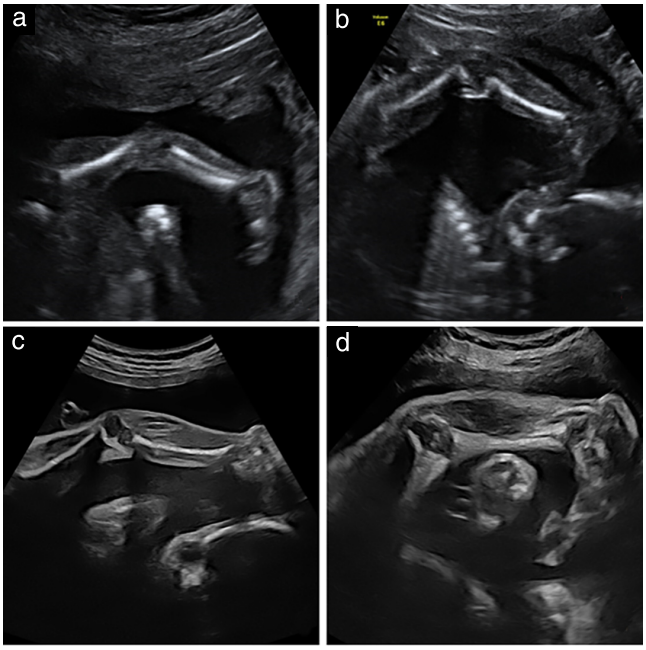

Figure 3 Longitudinal prenatal ultrasound in a case with isolated congenital knee dislocation (CKD). At 12 weeks, both legs and knees were normal (not shown). (a) At 16 weeks, diagnosis of CKD with 30–45° hyperextension was made. (b) At 20 weeks, diagnosis was confirmed with 45° hyperextension. (c,d) At 26 weeks (c), 32 weeks (d) and 36 weeks (not shown), persistence of anomaly with stable degree of hyperextension was observed. Extensive anatomy survey was carried out during each prenatal assessment, demonstrating normal anatomy and normal range of movements in all joints, with exception of affected knee, which was immobile at all assessments.

DISCUSSION

Principal findings

Our systematic review has several main findings. First, it confirms that the prenatal diagnosis of CKD is rare. Second, the outcome of CKD is heterogeneous, being excellent in isolated cases with appropriate orthopedic treatment and poor in complex cases. Third, referral for extensive ultrasound assessment, amniocentesis, detailed genetic testing (including cytogenetics, CGH array and gene panel to exclude associated syndromes) and subsequent management is mandatory, with reassurance for isolated cases regarding favorable outcome to avoid TOP and careful discussion and genetic consultation for complex cases, which have a poor outcome. Fourth, surgery is generally not required, particularly in isolated cases, and effective treatment is mostly by early postnatal intervention with serial casting and physiotherapy. Based on our findings, we present a comprehensive protocol for prenatal counseling and perinatal management (Figure 5). Finally, we also hypothesize a distinct developmental step of anatomical maturation of the fetal knee in the second trimester owing to the absence of first-trimester CKD diagnoses in the limited data available (eight reports).

Interpretation

Various treatments for CKD have been described, including closed reduction, physiotherapy, serial casting, minimally invasive or open quadricepsplasty and femoral

Figure 4 Postnatal images of isolated congenital knee dislocation. (a,b) Clinical findings after birth with severe deformity of knee with 70° hyperextension. (c) Gentle manipulation and application of first plaster cast for progressive correction of deformity at 2 days of age. (d) Subsequent weekly changing of plaster cast resulted in progressive correction of deformity, achieving 90° flexion with seventh cast. (e) Following removal of last cast, patient underwent physiotherapy and anterior knee brace treatment overnight. (f) Functional outcome after 6 weeks, with 130° flexion and normal motor function.

shortening[6,24–32]. The success rate of manipulation is 77%, and the outcome improves further after treatment with serial casting[25]. However, with late presentation (> 5 weeks after birth), manipulation and serial casting have been shown to be successful in only 27% of cases, with other cases requiring surgery[26,27]. Overall, this evidence from postnatal studies suggests that: (1) early therapy achieves better outcome compared with delayed therapy; (2) surgery is rarely required when conservative treatment is initiated early but is more frequently required when management is delayed; and (3) treatment generally requires early manipulation, serial casting and physiotherapy, with surgery limited to cases in which the conservative approach is unsuccessful. Since early orthopedic care improves the outcome, all affected neonates should be referred early (before 48 h postpartum) for expert pediatric orthopedic treatment. Finally, given that prenatal diagnosis favors timely referral to pediatric orthopedic therapy, it becomes an important determinant of improvement in outcome.

Clinical implications

Our systematic review found Larsen syndrome to be the commonest genetic condition related to CKD. Besides postnatal clinical evaluation, prenatal genetic diagnosis of the condition has become possible (mutation in the *B3GAT3* gene on chromosome 11q12). Other genetic syndromes associated with CKD in our study were Escobar syndrome (heterozygous mutation in the *CHRNG* gene on chromosome 2q37), Grebe syndrome (homozygous or compound heterozygous mutation in the *CDMP1* gene on chromosome 20q11), Desbuquois dysplasia (Type 1 mutation in *CANT1*; type 2 mutation in *XYLT1*) and Noonan syndrome (heterozygous pathogenic variant in *BRAF*, *KRAS*, *MAP2K1*, *MRAS*, *NRAS*, *PTPN11*, *RAF1*, *RASA2*, *RIT1*, *RRAS2*, *SOS1* or *SOS2*, or a heterozygous variant or biallelic pathogenic variants in *LZTR1* identified by molecular genetic testing). Other genetic syndromes characterized by joint hypermobility include Ehlers–Danlos syndrome (heterozygous mutation in the

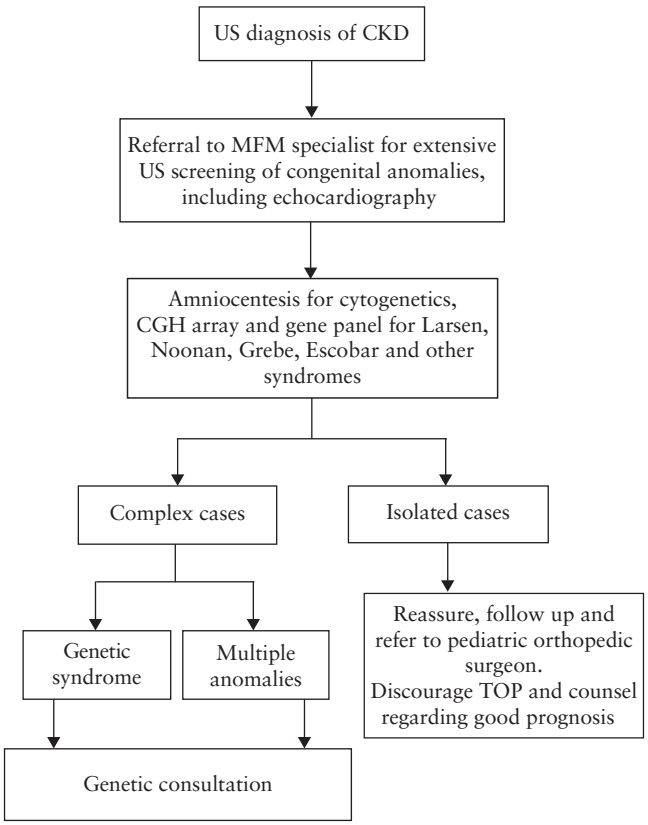

Figure 5 Suggested algorithm for prenatal management of congenital knee dislocation (CKD), including ultrasound (US) assessment, genetic testing and classification into isolated *vs* complex cases with specific indications. CGH, comparative genomic hybridization; MFM, maternal–fetal medicine; TOP, termination of pregnancy.

collagen alpha-1(V) gene on chromosome 9q34), Marfan syndrome (heterozygous mutation in the fibrillin-1 gene on chromosome 15q21), spondyloepiphyseal dysplasia (homozygous or compound heterozygous mutation in the gene encoding carbohydrate sulfotransferase-3 on chromosome 10q22) and osteogenesis imperfecta (a heterogeneous condition caused by a variable genetic basis and wide clinical spectrum). Non-genetic conditions predisposing to joint hypermobility in the differential diagnosis encompass arthrogryposis multiplex, spastic cerebral palsy, myelomeningocele and cervical myopathy.

We were not able to find data in the literature on the challenging issue of prenatal classification as well as on performance of the prenatal diagnosis. A false-negative diagnosis of severe forms is unlikely with up-to-date prenatal ultrasound, whereas breech fetuses with milder forms may be missed; however, they rarely present with overextension over 0° and generally undergo spontaneous resolution. We propose an evidence-based algorithm for the prenatal management of CKD based on the available evidence (Figure 5). Our presented case achieved a good outcome within 3 months and maintained it at follow-up, despite the severe clinical findings at birth. This was possible owing to multidisciplinary engagement, starting with prenatal orthopedic consultation, immediate reduction and casting after birth and subsequently an appropriate physiotherapy program after removal of the cast.

Strength and limitations

One of the limitations of this study is the paucity of the literature available owing to the rarity of CKD. Moreover, some cases of CKD may not be reported when it is associated with a well-known diagnosis, such as open spina bifida or arthrogryposis, in which CKD is clearly secondary. Performing systematic reviews on rare conditions based on single case reports may lead to bias, and results should be generalized with caution. However, it is particularly important to emphasize that isolated cases of CKD have a good outcome, as shown by this review. The major strength of this study is that it is the first to present all the available evidence on the topic of prenatally diagnosed CKD, providing a comprehensive guide with a standardized protocol for prenatal counseling and perinatal management in cases with this rare condition (Figure 5).

Conclusions

This systematic review found that isolated CKD is an anomaly with a favorable prognosis in isolated cases and excellent outlook for the motor function of the lower limbs and ambulation. In contrast, complex cases with a genetic syndrome or multiple anomalies without an identifiable genetic cause generally have a poor prognosis. Further research should explore if prenatal treatment could improve the outcome (e.g. early external cephalic version in breech fetuses and amnioinfusion in cases of oligohydramnios). A combination of prenatal diagnosis, early referral to expert pediatric orthopedic management and early conservative treatment minimizes the need for surgery and improves outcome.

ACKNOWLEDGMENT

Open access funding provided by BIBLIOSAN.

REFERENCES

1. Jacobsen K, Vopalecky F. Congenital dislocation of the knee. *Acta Orthop Scand* 1985; **56**: 1–7.
2. Potel G. Etude sur Les Malformations Congenitales du Genu. *These de Lille*; 1897. Accessed the 15th May 2023 at: https://iiif.wellcomecollection.org/pdf/b21072838
3. Johnson E, Audell R, Oppenheim WL. Congenital dislocation of the knee. *J Pediatr Orthop* 1987; **7**:194–200.
4. Laurence M. Genu recurvatum congenitum. *J Bone Joint Surg Br* 1967; **49**: 121–134.
5. Curtis BH, Fisher RL. Congenital hyperextension with anterior subluxation of the knee. *J Bone Joint Surg Am* 1969; **51**: 255–269.
6. Mehrafshan M, Wicart P, Ramanoudjame M, Seringe R, Glorion C, Rampal V. Congenital dislocation of the knee at birth – Part I: Clinical signs and classification. *Orthop Traumatol Surg Res* 2016; **102**: 631–633.
7. Lage J de A, Guarniero R, de Barros Filho TE, de Camargo OP. Intrauterine diagnosis of congenital dislocation of the knee. *J Pediatr Orthop* 1986; **6**: 110–111.
8. Mostello D, Hoechstetter L, Bendon RW, Dignan PS, Oestreich AE, Siddiqi TA. Prenatal diagnosis of recurrent Larsen syndrome: further definition of a lethal variant. *Prenat Diagn* 1991; **11**: 215–225.
9. Elchalal U, Ben Itzhak I, Ben-Meir G, Zalel Y. Antenatal diagnosis of congenital dislocation of the knee: a case report. *Am J Perinatol* 1993; **10**: 194–196.
10. Gorincour G, Chotel F, Rudigoz RC, Guibal-Baggio AL, Berard J, Pracros JP, Guibaud L. Prenatal diagnosis of congenital genu recurvatum following amniocentesis complicated by leakage. *Ultrasound Obstet Gynecol* 2003; **22**: 643–645.
11. Shih JC, Peng SS, Hsiao SM, Wang JH, Shyu MK, Lee CN, Hsieh FJ. Three-dimensional US diagnosis of Larsen syndrome with further characterization of neurological sequelae. *Ultrasound Obstet Gynecol* 2004; **24**: 89–93.

12. Monteagudo A, Kudla MM, Essig M, Santos R, Timor-Tritsch IE. Real-time and 3-dimensional sonographic diagnosis of postural congenital genu recurvatum. *J Ultrasound Med* 2006; **25**: 1079–1083.
13. Shalev SA. A syndrome characterized by intra-uterine lower limb dislocation, gracile bones, clubfeet, and other skeletal features. *Am J Med Genet A* 2007; **143**: 395–398.
14. Barber MA, Equiluz I, Plasencia W, Cortes E, Garcia JA. Prenatal features of genu recurvatum and genu flexum. *Int J Gynaecol Obstet* 2009; **105**: 267–268.
15. Jain Ghai S, Keating S, Chitayat D. PTPN11 gene mutation associated with abnormal gonadal determination. *Am J Med Genet* 2011; **155**: 1136–1139.
16. Ghazle HH. Larsen Syndrome: sonographic findings. *J Diagn Med Sonogr* 2012; **28**: 240–244.
17. Bildner A. Prenatal sonographic detection of skeletal dysplasias: a case of Multiple Pterygium syndrome, or Escobar syndrome. *J Diagn Med Sonogr* 2014; **30**: 205–210.
18. Al Kaissi A, Chehida FB, Ganger R, Grill F. Neonatal death dwarfism in a girl with distinctive bone dysplasia compatible with Grebe chondrodysplasia: analysis by CT scan-based phenotype. *J Clin Imaging Sci* 2014; **4**: 53.
19. Matar HE, Garg NK. Management of joint dislocations of the lower limb in Larsen syndrome: practical approach. *Ann R Coll Surg Engl* 2017; **99**: e8–e10.
20. Forster KR, Hooper JE, Blakemore KJ, Baschat AA, Hoover-Fong J. Prenatal diagnosis of Desbuquois dysplasia Type 1: Utilization of high-density SNP array to map homozygosity and identify the gene. *Am J Med Genet A* 2019; **179**: 2490–2493.
21. Barreto Mota R, Rodrigues Santos N, Martins R, Soares H. Congenital Dislocation of the Knee: Idiopathic or Arthrogryposis? *Cureus* 2022; **14**: e21684.
22. Morales-Roselló J, Loscalzo G, Hueso-Villanueva M, Buongiorno S, Jakaitė V, Perales-Marín A. Congenital knee dislocation, case report and review of the literature. *J Matern Fetal Neonatal Med* 2022; **35**: 809–811.
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71.
24. Rampal V, Mehrafshan M, Ramanoudjame M, Seringe R, Glorion C, Wicart P. Congenital dislocation of the knee at birth – Part 2: Impact of a new classification on treatment strategies, results and prognostic factors. *Orthop Traumatol Surg Res* 2016; **102**: 635–638.
25. Yeoh M, Athalye-Jape G. Congenital knee dislocation: a rare and unexpected finding. *BMJ Case Rep* 2021; **14**: e234881.
26. Biswas D, Akter FA, Roy A, Aolad FR, Khan SA. Congenital hyper-extension with subluxation of the knees – report of 2 cases. *Mymensingh Med J* 2014; **23**: 811–813.
27. Youssef AO. Limited open quadriceps release for treatment of congenital dislocation of the knee. *J Pediatr Orthop* 2017; **37**: 192–198.
28. Salguero-Sánchez JA, Sánchez-Duque SA, Lozada-Martínez ID, Liscano Y, Díaz-Vallejo JA. Bilateral congenital knee dislocation in Colombia: case report and literature review. *Children (Basel)* 2022; **10**: 20.
29. Salvador Marín J, Miranda Gorozarri C, Egea-Gámez RM, Alonso Hernández J, Martínez Álvarez S, Palazón Quevedo Á. Congenital knee dislocation. Therapeutic protocol and long-term functional results. *Rev Esp Cir Ortop Traumatol (Engl Ed)* 2021; **65**: 172–179.
30. Patwardhan S, Shah K, Shyam A, Sancheti P. Assessment of clinical outcome of percutaneous needle quadriceps tenotomy in the treatment of congenital knee dislocation. *Int Orthop* 2015; **39**: 1587–1592.
31. Çıraklı S, Çıraklı A. Neglected intrauterine bilateral congenital knee dislocation. *Jt Dis Relat Surg* 2021; **32**: 542–545.
32. Amrath Raj BK, Singh KA, Shah H. Surgical management of the congenital dislocation of the knee and hip in children presented after six months of age. *Int Orthop* 2020; **44**: 2635–2644.

Ultrasound Obstet Gynecol 2023; **62**: 778–787
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.26283.

Diagnóstico prenatal y resultado postnatal de la luxación congénita fetal de rodilla: revisión sistemática de la bibliografía

RESUMEN

Objetivos. La luxación congénita de rodilla (LCR) es una enfermedad poco frecuente, que afecta a 1 de cada 100 000 recién nacidos. Su diagnóstico prenatal es un reto y no está bien descrito en la bibliografía, especialmente cuando aparece de forma aislada y no como parte de una malformación compleja o un patrón sindrómico. El objetivo de este estudio fue proporcionar una revisión exhaustiva de la bibliografía disponible sobre el diagnóstico prenatal y el resultado postnatal de la LRC y resumir la evidencia actual sobre este tema.

Métodos. Se realizó una revisión sistemática de la bibliografía sobre el diagnóstico prenatal de la LRC en PubMed, Scopus y EMBASE. Se utilizó una combinación predefinida de palabras clave específicas, centrada en las manifestaciones intrauterinas, los métodos de diagnóstico, el comportamiento prenatal, el tratamiento postnatal y el resultado neonatal, así como el resultado a largo plazo en términos de deambulación, movimiento y estabilidad articular. La calidad de los estudios se evaluó mediante la herramienta de los Institutos Nacionales de Salud para la evaluación de la calidad de series de casos. Se realizó un resumen de los resultados que incluía proporciones y tasas de características de diagnóstico y de pronóstico asociadas a esta enfermedad infrecuente.

Resultados. En total, se recuperaron 20 casos para el análisis, de los cuales 19 se obtuvieron de los estudios elegibles identificados (n=16) y uno fue un caso no publicado de nuestro centro. La mediana de edad gestacional en el momento del diagnóstico prenatal, que se realizó mediante ecografía en la mayoría de los casos, fue de 20 semanas (rango, 14–38 semanas). Se observó bilateralidad en 11/20 (55%) casos. La enfermedad estaba aislada en 7/20 (35%) casos y asociada a otras anomalías en 13/20 (65%) casos. Se observó una asociación con oligohidramnios (4/20 (20%)), y se realizó una intervención traumática en 13/20 (65%) casos, incluidos 11 casos con una intervención traumática realizada con fines diagnósticos. Las pruebas genéticas fueron normales en todos los casos aislados de los que se disponía de información (4/7), mientras que en 10/13 (77%) casos no aislados (síndrome de Larsen, Noonan, Grebe, Desbuquois o Escobar) existía un síndrome genético. Hubo siete interrupciones del embarazo, de las cuales seis se realizaron en casos con anomalías asociadas y una en un caso aislado, 11 casos de supervivencia postnatal, un caso de muerte intrauterina y uno de muerte neonatal. Las muertes fetales y neonatales se produjeron en casos con anomalías asociadas o hallazgos genéticos anómalos. El tratamiento postnatal fue mayoritariamente conservador, con sólo dos informes (18% de los 11 neonatos supervivientes) de intervención quirúrgica, ambos en casos con anomalías asociadas. El seguimiento postnatal fue de hasta 1 año en la mayoría de los casos, y el pronóstico motor parecía normal en todos los casos aislados.

Conclusiones. La LRC es una anomalía fetal rara con un diagnóstico prenatal posible desde principios del segundo trimestre, para la que cabe esperar un resultado favorable cuando no existen anomalías asociadas. El diagnóstico prenatal debería incluir una evaluación ecográfica detallada y una amniocentesis para realizar estudios genéticos exhaustivos, sobre todo en los casos no aislados. El tratamiento postnatal precoz tiene éxito en la mayoría de los casos sin intervención quirúrgica y conduce a un pronóstico motor normal.

胎儿先天性膝关节脱位的产前诊断和产后结局：文献系统综述

摘要

目标先天性膝关节脱位（CKD）是一种罕见病，新生儿患病率为1/100000。其产前诊断难度较大，文献中的描述并不详尽，尤其是在该病孤立出现而不属于某一复杂畸形或综合征时。本研究的目的是全面综述有关 CKD 产前诊断和产后结局的现有文献，并总结有关该主题的现有证据。

方法 在 PubMed、Scopus 和 EMBASE 上对有关 CKD 产前诊断的文献进行了系统综述。采用预先确定的特定关键词组合，重点关注宫内表现、诊断方法、产前行为、产后治疗、新生儿结局以及在行走、运动和关节稳定性方面的长期结局。研究质量采用国立卫生研究院的系列病例质量评估工具进行评估。对结果进行了总结，呈现了与这种罕见病症相关的诊断和预后特征的比例和比率。

结果 共检索到 20 个分析病例，其中 19 个来自已确定的合格研究（n=16），剩余 1 个是本中心未发表的病例。大多数病例的产前诊断通过超声检查进行，中位胎龄为 20 周（范围为 14-38 周）。11/20例（55%）胎儿的膝关节脱位呈双侧性。7/20例（35%）胎儿为单发，13/20例（65%）伴有其他异常。观察到与羊水过少的相关性（4/20（20%））；13/20例（65%）进行了侵入性手术，其中 11 例为诊断目的进行了侵入性手术。有资料可查的所有孤立病例（4/7）的基因检测结果均正常，而 10/13 例（77%）非孤立病例存在遗传综合征（Larsen、Noonan、Grebe、Desbuquois 或 Escobar综合征）。共有 7 例终止妊娠，其中 6 例伴有畸形，1 例孤立病例；11 例产后存活，1 例宫内死亡，1 例新生儿死亡。胎儿和新生儿死亡发生在伴有畸形或遗传检测结果异常的病例中。产后治疗多为保守治疗，仅有 2 例（占 11 例存活新生儿的 18%）报告进行了手术干预，均为伴有异常的病例。大多数病例的产后随访时间长达 1 年，所有孤立病例的运动功能无明显异常。

结论 CKD 是一种罕见的胎儿畸形，可在孕中期第一个月通过产前检查实现诊断，如果没有相关的畸形，可望获得良好的预后。产前诊断应包括详细的超声评估和羊膜穿刺，以进行广泛的遗传学研究，尤其是对于非孤立病例。大多数病例的产后早期治疗都取得成功，无需手术干预，并可获得正常的运动功能。