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SYSTEMATIC REVIEW

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Outcome of isolated fetal talipes: A systematic review and meta-analysis

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Abstract

Introduction: The aim of this systematic review was to explore the outcome of fetuses with a prenatal diagnosis of isolated talipes.

Material and methods: Medline, Embase, Cinahl, and Clinicaltrials.gov databases were searched. The outcomes explored were: associated anomalies detected at follow-up ultrasound examination; fetal magnetic resonance imaging (MRI) and birth; chromosomal abnormalities detected with standard and chromosomal microarray analysis, intrauterine, neonatal, and perinatal death, and termination of pregnancy; rate of surgical and nonsurgical treatment; neurodevelopmental outcome; and false-positive rate of prenatal diagnosis. Meta-analyses of proportions were used to combine data.

Results: Twenty-five studies (1567 fetuses) were included. Associated anomalies were detected in 7.8% (95% CI 0.1%-29.3%) of cases at follow-up ultrasound, and in 4.0% (95% CI 0.1%-13.2%) of cases, fetal MRI identified anomalies not detected at ultrasound assessment. Similarly, 7.0% (95% CI 3.4%-11.7%) of cases labeled as isolated talipes on prenatal imaging were found to have associated anomalies at birth. Abnormal karyotype was present in 3.6% (95% CI 1.7%-6.2%) of fetuses, whereas no anomaly was found at chromosomal microarray analysis, although this outcome was reported by only 1 study. Intrauterine death occurred in 0.99% (95% CI 0.4%-1.9%) of fetuses, whereas the corresponding figures for neonatal death and termination of pregnancy were 1.5% (95% CI 0.6%-2.6%) and 2.2% (95% CI 1.2%-3.4%), respectively. Surgical management of anomalies after birth was found in 41.7% (95% CI 27.0%-57.2%) of fetuses with isolated talipes, and 54.8% (95% CI 31.5%-77.0%) had nonsurgical management of the anomalies after birth. Abnormal neurodevelopmental outcome was reported in 7.6% (95% CI 1.0%-19.4%) of children, although this analysis was affected by the small number of included cases and short time of follow up.

Conclusions: Isolated talipes detected on prenatal ultrasound carries a generally good prognosis. The incidence of additional abnormalities detected on fetal MRI,

Abbreviations: CMA, chromosomal microarray analysis; CNS, central nervous system; MRI, magnetic resonance imaging.

aneuploidy, or neurodevelopmental disability is relatively low. However, longitudinal ultrasound assessment during pregnancy and a thorough postnatal evaluation are recommended to rule out associated anomalies that may significantly impact short- and long-term prognosis.

KEYWORDS
clubfoot, fetal MRI, karyotype, talipes equinovarus, ultrasound

1 | INTRODUCTION

Talipes (clubfoot) equinovarus is one of the most common congenital anomalies detected prenatally with a prevalence ranging from 1/1000 to 3/1000 live births.[1] It is a multiplanar deformity resulting in the fetal foot fixed in adduction, supination, varus or valgus position, and is characterized by a subluxation of the talo-calcaneo-navicular joint, with underdevelopment of the soft tissues on the medial side of the foot and, frequently, of the calf and peroneal muscles.[2]

Talipes may be unilateral or bilateral and can be classified as congenital, syndromic, or positional. Congenital talipes exclusively affects the bones, muscles, tendons, and blood vessels of one or both feet and commonly presents as an isolated condition in an otherwise structurally normal fetus. Conversely, syndromic or complex cases are associated with additional structural malformations and/or chromosomal or genetic anomalies. Finally, positional talipes results from a persistently adducted/abducted foot position in a restrictive uterine environment.

The precise etiology of isolated talipes has not been completely elucidated. Isolated talipes has been shown to be the result of a polygenetic inheritance, as confirmed by the elevated prevalence in some populations and the male-to-female ratio of 2:1.[3-5] Complex talipes is present in the setting of chromosomal or genetic syndromes, especially those involving the neuromuscular system.[6-11] Conversely, mechanical factors such as breech presentation, oligohydramnios, uterine anomalies, and amniotic bands are the most commonly reported factors responsible for positional talipes.[3,5] Talipes can be diagnosed on ultrasound from the early first trimester of pregnancy when the plantar surface of the fetal foot is persistently seen in the same sagittal plane as both lower extremity bones.[12-16]

Isolated talipes is commonly considered a benign condition with a low risk of adverse perinatal outcome. However, the small sample size of previously published studies and inclusion of cases associated with other anomalies do not allow extrapolation of the actual association between apparently isolated talipes and the risk of additional structural malformations, genetic syndromes, and aneuploidies. Furthermore, the type of prenatal follow up and role of prenatal magnetic resonance imaging (MRI) when isolated talipes is diagnosed on ultrasound remains to be ascertained.

The aim of this systematic review was to explore the outcome of fetuses with apparently isolated talipes diagnosed on prenatal ultrasound.

Key message
Fetuses with prenatal diagnosis of isolated talipes are generally associated with a good prognosis and a low incidence of aneuploidies.

2 | MATERIAL AND METHODS

2.1 | Protocol, eligibility criteria, information sources, and search

This review was performed according to an a priori designed protocol recommended for systematic reviews and meta-analysis.[17-19] Medline, Embase, Cinahl, and Clinicaltrials.gov databases were searched electronically in October 2018, using combinations of the relevant medical subject heading (MeSH) terms, keywords, and word variants for "clubfoot" or "talipes equinovarous" and "outcome". The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were manually searched for additional reports. PRISMA and MOOSE guidelines were followed.[20-22] The study was registered with the PROSPERO database (registration number: CRD42018111329).

2.2 | Study selection, data collection, and data items

Inclusion criteria were fetuses with a prenatal diagnosis of isolated talipes, defined as talipes with no apparently associated anomalies at the time of diagnosis.

The outcomes explored were:

- Associated anomalies detected at follow-up ultrasound examination.
- Associated anomalies detected only at fetal MRI and not detected at ultrasound.
- Associated anomalies detected only at birth or at autopsy and not detected at prenatal imaging.
- Chromosomal abnormalities detected with standard karyotype analysis.
- Pathogenic copy number variants at chromosomal microarray analysis (CMA).

- Intrauterine, neonatal, and perinatal death, and termination of pregnancy.
- Rate of surgical and nonsurgical treatment.
- Neurodevelopmental outcome.
- False-positive rate of prenatal diagnosis.

Data from studies reporting the incidence of these outcomes in fetuses with a prenatal diagnosis of isolated talipes were considered eligible for analysis. Furthermore, we planned to perform a subgroup analysis considering cases with unilateral and bilateral anomalies separately.

For the assessment of the incidence of abnormal karyotype, only cases of isolated talipes, defined as having no additional central nervous system (CNS), and extra-CNS anomalies detected at the ultrasound scan were included in the analysis. Only cases that had their full karyotype tested either prenatally or postnatally were included. For the occurrence of genetic abnormalities detected only at CMA, only fetuses with isolated talipes and normal standard karyotype were considered suitable for analysis. The presence of additional anomalies detected only at prenatal and postnatal MRI or at birth was assessed only in fetuses with no additional anomalies on ultrasound. The neurodevelopmental outcome of infants with talipes was ascertained exclusively in cases of isolated anomaly with normal full standard karyotype and no other CNS or extra-CNS anomalies confirmed postnatally. Finally, the type of postnatal treatment (surgical vs nonsurgical) was explored only in fetuses with isolated anomaly confirmed at birth.

Studies reporting non-isolated cases of talipes were excluded. Autopsy-based studies were excluded on the basis that fetuses undergoing termination of pregnancy are more likely to show associated major structural and chromosomal anomalies. Likewise, studies including only cases treated postnatally were excluded because they report higher rates of adverse outcomes and do not reflect the natural history of the anomaly. Finally, studies published before 1998 were also excluded because we felt that advances in prenatal imaging techniques and improvements in the diagnosis and definition of fetal anomalies make them less relevant.

Only full text articles were considered eligible for inclusion; case reports, conference abstracts, and case series with <3 cases, irrespective of whether the anomaly was isolated or not, were also excluded to avoid publication bias.

Two authors (DDM, DB) reviewed all abstracts independently. Agreement regarding potential inconsistencies was reached by discussion with a third reviewer (FDA). Full text copies of those papers were obtained, and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. If >1 study was published on the same cohort with identical end points, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale for cohort studies. According to Newcastle-Ottawa Scale, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest.[23] Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and the demonstration that the outcome of interest was not present at the start of the study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length, and adequacy of follow up. According to the Newcastle-Ottawa Scale, a study can be awarded a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for Comparability.[23]

2.3 | Statistical analyses

We used meta-analyses of proportions to combine data and reported pooled proportion. Funnel plots (displaying the outcome rate from individual studies vs their precision—1 per SE) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was <10. In this case, the power of the tests is too low to distinguish chance from real asymmetry.

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values ≥50% indicate a substantial level of heterogeneity. A random effect model was used to compute the pooled data analysis. All proportion meta-analyses were carried out by using StatsDirect version 2.7.9 (StatsDirect, Ltd, Cambridge, UK).

3 | RESULTS

3.1 | General characteristics

In all, 778 articles were identified; 46 were assessed for eligibility for inclusion and 25 studies were included in the systematic review (Table 1, Figure 1, see Supplementary material, Table S1, Figure S1).[14,16,24-46] These 25 studies included 1567 fetuses affected by isolated talipes on ultrasound, defined as the presence of talipes with no associated anomalies at the time of diagnosis.

The results of the quality assessment of the included studies using the Newcastle-Ottawa Scale are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size, absence of robust information on the long-term outcome, different protocols for antenatal monitoring and management of fetuses affected by talipes, and

TABLE 1 General characteristics of the included studies

Author	Year	Country	Study design	Prenatal imaging	Gestational age at diagnosis
Sharon-Weiner[24]	2017	Israel	Retrospective	Ultrasound	II-III trimester
Viaris de le Segno[25]	2016	France	Retrospective	Ultrasound	II trimester
Seravalli[26]	2015	Italy	Retrospective	Ultrasound	II-III trimester
Gat[27]	2015	Israel	Retrospective	Ultrasound, MRI	II-III trimester
Toufaily[28]	2014	United States	Retrospective	Ultrasound	II-III trimester
Hartge[29]	2012	Germany	Retrospective	Ultrasound	I-II-III trimester
Nemec[30]	2012	Austria	Retrospective	Ultrasound, MRI	II-III trimester
Sharma[31]	2011	United Kingdom	Retrospective	Ultrasound	I-II-III trimester
Glotzbecker[32]	2010	United States	Retrospective	Ultrasound	NS
Lauson[14]	2010	Canada	Retrospective	Ultrasound	II-III trimester
Canto[33]	2008	Spain	Retrospective	Ultrasound	II trimester
Offerdal[34]	2007	Norway	Prospective	Ultrasound	I-II-III trimester
Cohen-Overbeek[35]	2006	The Netherlands	Retrospective	Ultrasound	II-III trimester
Bar-On[36]	2005	Israel	Retrospective	Ultrasound	II-III trimester
Mammen[16]	2004	United States	Retrospective	Ultrasound	I-II-III trimester
Bakalis[37]	2002	United Kingdom	Retrospective	Ultrasound	II trimester
Keret[38]	2002	Israel	Retrospective	Ultrasound	II-III trimester
Carroll[39]	2001	United Kingdom	Retrospective	Ultrasound	II-III trimester
Malone[40]	2000	United States	Retrospective	Ultrasound	II-III trimester
Tillet[41]	2000	United Kingdom	Retrospective	Ultrasound	II trimester
Rijhsinghani[42]	1998	United States	Retrospective	Ultrasound	II-III trimester
Katz[43]	1999	Israel	Retrospective	Ultrasound	II-III trimester
Treadwell[44]	1999	USA	Prospective	Ultrasound	II-III trimester
Woodrow[45]	1998	Australia	Retrospective	Ultrasound	II trimester
Shipp[46]	1998	United States	Retrospective	Ultrasound	II-III trimester

lack of stratification according to the laterality of the defect for the majority of the included studies.

3.2 | Synthesis of the results

Three studies[14,27,36] (118 fetuses) explored the occurrence of associated anomalies detected only at a follow-up examination in fetuses with a prenatal diagnosis of isolated talipes. Overall, associated anomalies not detected on ultrasound were detected in 7.8% (95% CI 0.1%-29.3%) of cases at follow-up ultrasound, whereas in 4.0% (95% CI 0.1%-13.2%) of cases, fetal MRI detected anomalies that were not detected at ultrasound assessment. Similarly, 7.0% (95% CI 3.4%-11.7%) of cases labeled as isolated talipes on prenatal imaging, were found to have associated anomalies at postnatal examination (Table 3, Figure 2). When assessing the severity of the associated anomalies, 4.9% (95% CI 2.3%-8.3%), of included cases were found to be affected by major anomalies at birth, whereas 2.5% (95% CI 0.8%-5.0%) were affected by minor anomalies at birth. Skeletal (pooled proportion 2.2, 95% CI 0.7-4.2) and neuromuscular (pooled proportion 3.3, 95% CI 1.6-5.6) anomalies were the most

Outcomes observed	Stratification according to laterality of the defect	Fetuses (n)	Isolated clubfoot (n)	Unilateral (n)	Bilateral (n)
Anomalies at birth, abnormal karyotype, CMA, mortality, surgical outcome, neurodevelopmental outcome, diagnostic accuracy	Performed	109	76	43	33
Anomalies at birth, abnormal karyotype, mortality, diagnostic accuracy	Performed	90	56	19	37
Diagnostic accuracy	Not performed	858	672	NR	NR
Anomalies at follow up, anomalies at MRI	Performed	28	14	NR	NR
Anomalies at birth, mortality	Not performed	208	83	NS	NS
Abnormal karyotype, mortality, surgical outcome	Not performed	106	41	16	25
Anomalies at MRI, anomalies at birth	Performed	44	19	4	15
Abnormal karyotype, mortality, diagnostic accuracy	Not performed	174	83	44	39
Mortality, diagnostic accuracy	Not performed	83	83	NS	NS
Anomalies at follow up, abnormal karyotype, mortality, surgical outcome, neurodevelopmental outcome, diagnostic accuracy	Performed	65	65	25	40
Anomalies at birth, abnormal karyotype	Not performed	42	28	13	29
Abnormal karyotype, mortality, diagnostic accuracy	Not performed	69	27	8	19
Mortality, surgical outcome, diagnostic accuracy	Performed	57	20	6	14
Anomalies at follow up, anomalies at birth, surgical outcome, diagnostic accuracy	Not performed	52	40	NR	NR
Abnormal karyotype	Not performed	87	27	16	11
Anomalies at birth, mortality, neurodevelopmental outcome, diagnostic accuracy	Not performed	107	55	25	26
Surgical outcome	Not performed	51	51	NS	NS
Mortality, surgical outcome, diagnostic accuracy	Not performed	76	35	NR	NR
Anomalies at birth, abnormal karyotype, diagnostic accuracy	Not performed	51	51	32	19
Anomalies at birth, surgical outcome, diagnostic accuracy	Not performed	14	14	NR	NR
Anomalies at birth, abnormal karyotype, mortality, diagnostic accuracy	Not performed	35	7	NR	NR
Abnormal karyotype, mortality, surgical outcome, diagnostic accuracy	Not performed	13	10	NR	NR
Mortality, diagnostic accuracy	Not performed	61	20	NR	NR
Anomalies at birth, abnormal karyotype, mortality, surgical outcome, diagnostic accuracy	Not performed	17	17	NR	NR
Anomalies at birth, abnormal karyotype, mortality, surgical outcome, neurodevelopmental outcome, diagnostic accuracy	Not performed	68	68	NR	NR

common associated conditions detected exclusively after birth (see Supplementary material, Table S2).

Eleven studies[14,24,25,29,31,33,40,42,43,45,46] (264 fetuses) explored the prevalence of chromosomal anomalies in fetuses with a prenatal diagnosis of apparently isolated talipes. Overall, abnormal karyotype was present in 3.6% (95% CI 1.7%-6.2%) of fetuses with isolated clubfeet on ultrasound. When looking at the prevalence of different chromosomal anomalies in fetuses with a prenatal diagnosis of isolated talipes, Trisomies 21 and 18 occurred in 1.3% (95% CI 0.3%-3.0%) and 1.4% (95% CI 0.3%-3.2%) of cases, respectively, and sex chromosome anomalies occurred in 2.4% (95% CI 0.9%-4.6%) (Figure 2, see Supplementary material, Table S3). However, when analyzing the incidence of abnormal karyotype following either genotypic or phenotypic assessment after birth, the rate of chromosomal anomalies was 2.3% (95% CI 1.2%-3.6%). More importantly, when only including studies published in the last decade, the incidence of abnormal karyotype was 1.5% (95% CI 0.5%-3.0%, I^2 0%; 8 studies, 4/339 fetuses).[14,24,25,29-31,33,37] It was not possible to explore the presence of pathogenic copy number variants, as there was only 1 study in which 2 fetuses were tested for these anomalies using CMA.[24]

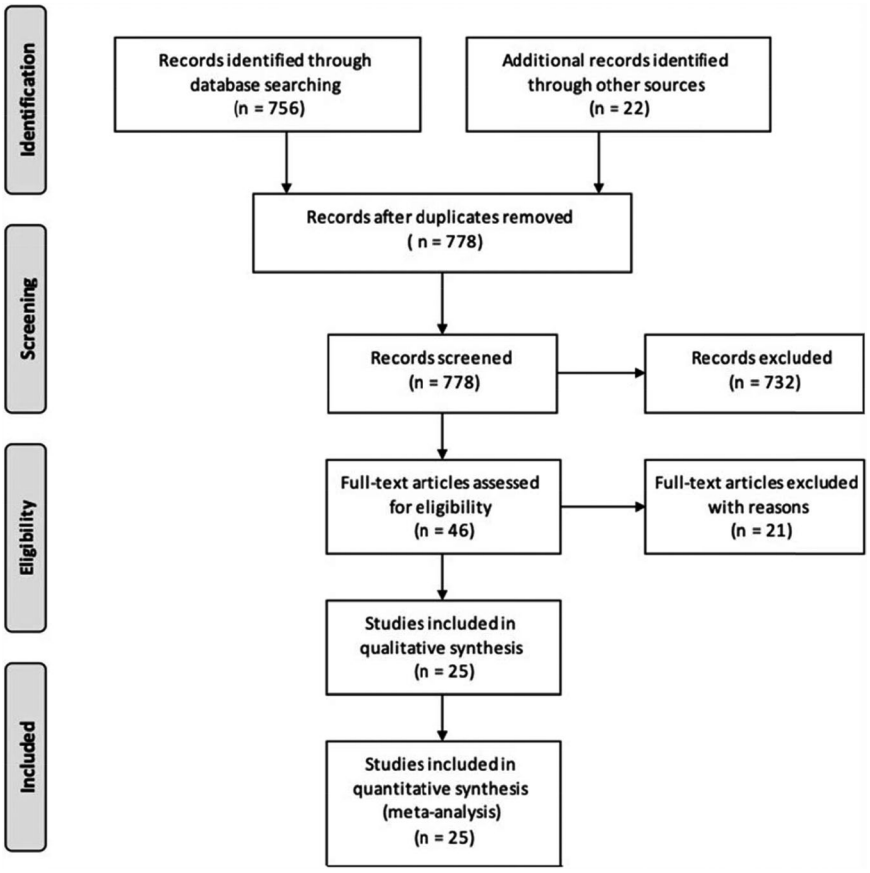

FIGURE 1 Pooled odd ratios (95% confidence intervals) for the risk of composite morbidity in twins affected compared to those not affected by different degree of birthweight (BW) discordance [Color figure can be viewed at wileyonlinelibrary.com]

Intrauterine death occurred in 0.99% (95% CI 0.4%-1.9%) of cases; the corresponding figures for neonatal death and termination of pregnancy were 1.5% (95% CI 0.6%-2.6%) and 2.2% (95% CI 1.2%-3.4%), respectively. When assessing the cause of the intrauterine death among the included cases, one was due to placental abruption, and for three a precise cause of death was not reported, although two of them occurred at 18 weeks of gestation.

Surgical management of anomalies after birth was found in 41.7% (95% CI 27.0%-57.2%) of fetuses with isolated talipes, and 54.8% (95% CI 31.5%-77.0%) had non-surgical management, although the analysis was affected by the large heterogeneity in time of follow up among the included studies. However, it was not specified which kind of surgical approach (whether minimal or more invasive) was performed in these fetuses as the majority of the studies did not report such information.

Assessment of neurodevelopmental outcome was affected by the very small number of included cases and even smaller number of events, relatively short time of follow up, and heterogeneity in neurodevelopmental tool adopted. Therefore, the results from this analysis should be interpreted with caution as they may not reflect the actual incidence of developmental delay in fetuses affected by talipes. Overall, an abnormal neurodevelopmental outcome was reported in 7.6% (95% CI 1.0%-19.4%) of children.

A comprehensive, pooled subgroup analysis considering the laterality of the defect (unilateral vs bilateral talipes) could be computed for only 2 outcomes: abnormal karyotype and associated anomalies detected at birth (see Supplementary material, Table S4). Overall, there was no difference in the risk of associated anomalies not detected at prenatal imaging and abnormal karyotype in unilateral compared with bilateral talipes.

4 | DISCUSSION

The findings from this systematic review show that fetuses with a prenatal diagnosis of apparently isolated talipes have a generally good prognosis. About 7% of cases labeled as isolated talipes on prenatal imaging were found to have associated anomalies, especially skeletal and neuromuscular, at postnatal examination, indicating the need for serial follow ups during pregnancy. The incidence of abnormal karyotype was low, although there is a lack of robust data on CMA. About 40% of fetuses with isolated talipes included in the present review underwent surgical correction of the anomaly, whereas the incidence of abnormal neurodevelopmental outcome was about 7%. Finally, the risk of adverse outcome did not seem to be related to the laterality of the defect.

A small number of included studies, their retrospective non-randomized design, differences among the included populations in gestational age at diagnosis, prenatal management, and time at follow up of fetuses with an ultrasound diagnosis of talipes are the main limitations of the present systematic review. Differences in ultrasound follow up once talipes is diagnosed represent the major limitation

TABLE 2 Quality assessment of the included studies according to Newcastle-Ottawa Scale for cohort studies; a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Author	Year	Selection	Comparability	Outcome
Sharon Weiner[24]	2017	**	*	***
Viaris de le Segno[25]	2016	**	*	**
Seravalli[26]	2015	**	*	**
Gat[27]	2015	**	*	**
Toufaily[28]	2014	**	*	**
Hartge[29]	2012	**	*	**
Nemec[30]	2012	**	*	*
Sharma[31]	2011	**	**	**
Glotzbecker[32]	2010	**	*	**
Lauson[14]	2010	**	*	**
Canto[33]	2008	**	*	*
Offerdal[34]	2007	**	*	*
Cohen-Overbeek[35]	2006	**	*	***
Bar-On[36]	2005	**	*	**
Mammen[16]	2004	**	*	**
Bakalis[37]	2002	**	*	**
Keret[38]	2002	**	*	*
Carroll[39]	2001	**	**	**
Malone[40]	2000	**	*	**
Tillet[41]	2000	**	*	**
Rijhsinghani[42]	1998	**	*	**
Katz[43]	1999	**	*	**
Treadwell[44]	1999	**	*	*
Woodrow[45]	1998	**	*	*
Shipp[46]	1998	*	*	*

of the present systematic review. Some anomalies may be evident only later in gestation, so affecting the rate of associated malformations detected prenatally. In some centers, karyotype assessment in fetuses with isolated talipes is not performed unless there is suspicion of potential associated anomalies. Furthermore, the large majority of fetuses from the present review which were not tested for karyotype did not show any phenotypic anomaly after birth. In this scenario, the figures reported in the present systematic review may represent an overestimation of the actual incidence of chromosomal anomalies in fetuses with a prenatal diagnosis of talipes.

The reported rate of intrauterine death, 0.99%, may look surprisingly high. However, of the 4 deaths reported, 1 was due to placental abruption. A specific cause was not provided in the other 3 cases, which were diagnosed at 18 weeks, and whether these were isolated cases of talipes remains questionable. Therefore, the actual incidence of intrauterine death in fetuses with isolated talipes may be lower than we have reported, and the findings of this review do not suggest any association between isolated talipes and intrauterine death.

In the present review, we did not find any difference between unilateral and bilateral talipes for the outcomes explored although the small number of studies, and the even smaller number of cases included in each analysis, did not allow a comprehensive assessment of the strength of association between the laterality of the defect and adverse perinatal outcome. Therefore, it is yet to be ascertained whether bilateral defect carries a worse prognosis compared with unilateral anomaly.

Assessment of neurodevelopmental outcome represents another peculiar issue. The small number of included cases, short period of follow up, and heterogeneity in neurodevelopmental assessment tool used did not allow for a comprehensive assessment of the incidence of developmental delay in fetuses with isolated talipes. This highlights the need for a long-term assessment of these fetuses as there are reports of a risk of additional anomalies impacting the neurodevelopmental performance of the children in a significant proportion of fetuses with talipes in some recent series.[47]

Despite these limitations, the present study represents the most comprehensive up-to-date meta-analysis of the outcome of fetuses with a prenatal diagnosis of isolated talipes.

Isolated talipes is among the most common anomalies diagnosed on ultrasound. The first issue in the prenatal management of talipes is to rule out associated structural anomalies, which can significantly impact short- and long-term prognosis. In the present review, about 8% of fetuses with a prenatal diagnosis of isolated talipes showed associated anomalies at follow-up scan (mainly neuromuscular syndromes), whereas about 7% did so at birth. However, these figures may not represent the actual prevalence of undiagnosed anomalies both at follow-up ultrasound and at birth in view of the heterogeneity in the type and frequency of prenatal assessment of fetuses affected by talipes among the included studies. Nevertheless, this highlights the need for close ultrasound surveillance throughout pregnancy.

The most common neuromuscular condition found at birth and not detected at prenatal ultrasound was arthrogryposis. Arthrogryposis encompasses a heterogeneous group of conditions characterized by multiple joint contractures due to CNS disorders.[48] Prenatal diagnosis of arthrogryposis is commonly accomplished during the second and third trimester of pregnancy and is based upon the visualization of multiple joint contractures, lack of fetal movements, and polyhydramnios.[48] Therefore, serial, longitudinal ultrasound assessments throughout pregnancy are needed to rule out that talipes are the first sign of a general neuromuscular disorder.

Fetal MRI has been shown to add additional information compared with ultrasound in fetuses affected by CNS anomalies.[49,50] However, its role in fetal anomalies not involving the brain is less clear. In the present systematic review, associated anomalies were detected at MRI only in 1 case, consisting of delayed sulcation. On this basis, there is no evidence to support the routine use of fetal

TABLE 3 Pooled proportion for the outcomes explored in this systematic review in fetuses with a prenatal diagnosis of isolated talipes

Outcome	Studies (n)	Fetuses (n/N)	Pooled proportion (95% CI)	I^2 (%)
Associated anomalies not detected at initial ultrasound assessment				
Anomalies at follow-up ultrasound	3	9/118	7.76 (0.1-29.3)	88.6
Anomalies at fetal MRI	2	1/32	4.00 (0.1-13.2)	33
Anomalies at birth	15	52/581	6.98 (3.4-11.7)	71.7
Karyotype				
Abnormal karyotype	11	9/267	3.6% (1.7-6.2)	7
Abnormal CMA	1	0/2	0 (0-84.2)	–
Mortality				
Intrauterine death	14	4/586	0.99 (0.4-1.9)	0
Neonatal death	14	7/586	1.45 (0.6-2.6)	0
Termination of pregnancy	14	12/562	2.16 (1.2-3.4)	0
Surgical outcome				
Surgery	11	148/331	41.73 (27.0-57.2)	87.6
Nonsurgical management	11	171/331	54.78 (31.5-77.0)	94.7
Neurodevelopmental outcome				
Abnormal neurodevelopmental outcome	4	20/207	7.59 (1.0-19.4)	85.1

Abbreviations: CMA, chromosomal microarray analysis; MRI, magnetic resonance imaging.

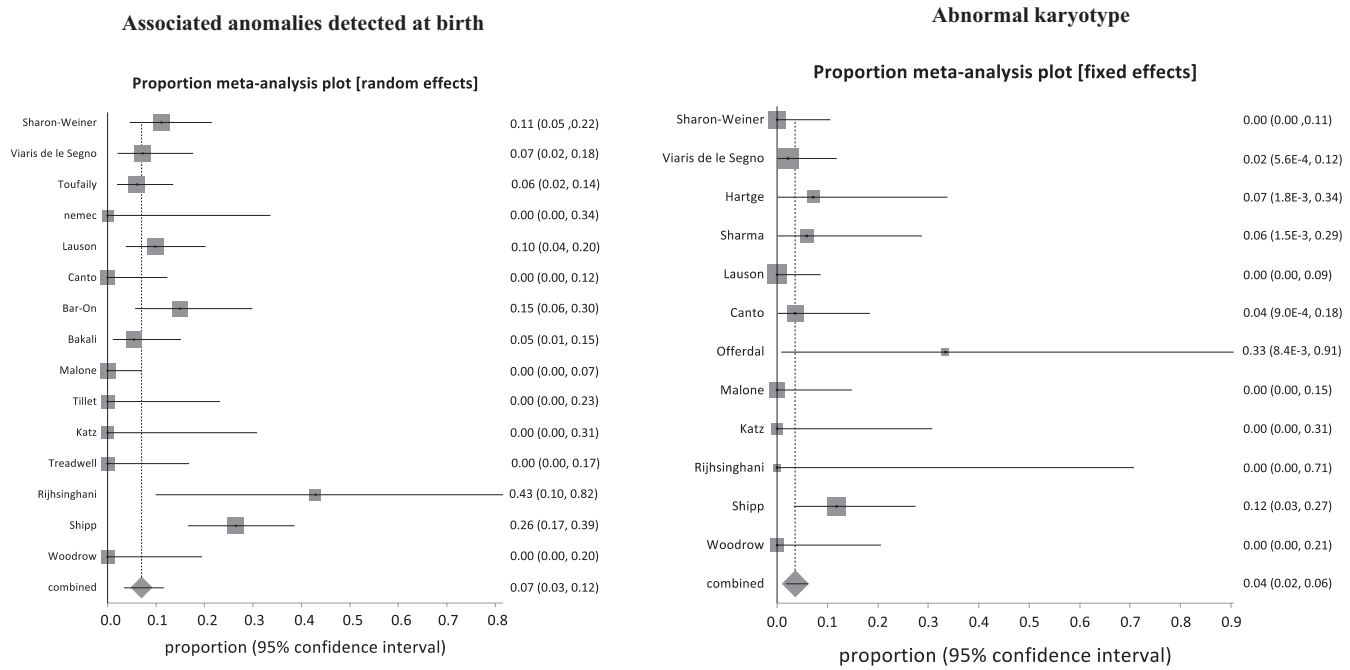

FIGURE 2 Pooled proportion showing the incidence of associated anomalies detected exclusively at birth and chromosomal anomalies in fetuses with a prenatal diagnosis of isolated talipes on ultrasound

MRI in fetuses with isolated talipes, unless there is suspicion of associated cerebral anomaly on ultrasound, although larger studies are needed in light of the small number of cases included in this analysis.

Talipes associated with other structural anomalies is commonly associated with a high risk of aneuploidy, mainly Trisomy 18, whereas the risk of aneuploidy has been reported to be lower in isolated cases. Despite this, there is no consensus yet on whether invasive tests

should be offered in case of isolated talipes, as the incidence of karyotype abnormalities varied in published studies.[14] More importantly, the most commonly reported aneuploidy in fetuses with talipes is Trisomy 18, which usually presents with other associated anomalies, including abnormal head shape, growth restriction, and abdominal wall defects, all of which are potentially detectable on ultrasound, so questioning the need to routinely offer invasive testing when there are no ultrasound signs suggestive of such anomalies.[51,52]

In the present review, the prevalence of chromosomal anomalies was 3.4% and the majority of them were sex chromosomal anomalies, such as Klinefelter syndrome, whereas the incidence of Trisomy 18 was negligible. This poses the question of whether fetuses with isolated talipes should have an invasive prenatal diagnosis. The figure for abnormal karyotype reported in the present review may represent an overestimation of the actual incidence of aneuploidy in fetuses with isolated talipes, because the majority of fetuses from the original population with talipes did not undergo invasive testing. Furthermore, when considering cases undergoing genotypic or phenotypic assessment at birth, the incidence of abnormal karyotype was 2.3% and was even lower when considering only studies from the last decade, when advances in prenatal imaging were likely to have improved our ability to identify even subtle signs of anomalies. On this basis, parents should be informed that the risk of aneuploidy is small, but that ultrasound cannot completely rule this out. Conversely, prenatal invasive testing should be recommended when other associated risk factors for aneuploidy, such as advanced maternal age or abnormal first-trimester screening test results, co-exist with talipes.

Chromosomal microarray analysis has recently been introduced in routine genetic analysis, and it can identify clinically significant chromosome abnormalities (gain and losses of DNA) that are below the resolution of conventional chromosome analysis, known as copy number variations. Fetuses with CNS anomalies and normal karyotype have been shown to have a significantly higher risk of genetic anomalies at CMA. Furthermore, a higher incidence of CMA anomalies has been reported in children presenting with neuropsychological disabilities. On this basis, a recent joint committee opinion of the American College of Obstetricians and Gynecologists and the Society of Maternal-Fetal Medicine recommended that CMA should be performed in fetuses undergoing invasive procedures for major structural anomalies detected on ultrasound.[53]

In the present review, it was not possible to extrapolate robust evidence on the role of CMA analysis in fetuses presenting with isolated talipes on ultrasound. The majority of previously published studies includes only very few cases of fetuses affected by talipes and does not specify whether the anomaly was isolated. We found only 1 study evaluating the role of CMA in the case of prenatal diagnosis of isolated talipes, and no case of pathogenic copy number variants was reported, although only 2 fetuses were tested. However, pediatric studies on genetic assessment of children with isolated talipes have suggested a potential role of a gene or genes operating in high-risk families resulting in such an anomaly.[1,54,55] Therefore, further large studies are needed to elucidate whether CMA genetic assessment should be performed in fetuses with a prenatal diagnosis of isolated talipes.

Postnatal management of talipes has changed in the past 10 years. Evidence from long-term follow-up studies on children treated with minimally invasive procedures,[56] such as Ponseti's or Kite's methods, significantly decreased the rate of a more extensive surgical treatment. Ponseti's technique consists of sequential, manipulative castings and prolonged bracing, followed by eventual minor surgery, and is currently considered the best approach for children with isolated talipes.[56,57] In the present review, about 60% of fetuses with isolated talipes did not require surgery although it was not specified which kind of surgical approach (whether minimal or more invasive) was performed in these fetuses as most of the studies did not report such information. Therefore, the figures for surgery reported in the present review are likely to represent an overestimation of the actual need for surgery because most of the included cases were likely to have minor intervention related to Ponseti's technique, such as tenotomy.

Assessment of neurodevelopmental outcome was affected by the small number of included cases, lack of standardized tools for assessment, and heterogeneity in times at follow up among the included studies. Furthermore, formal neurodevelopmental assessment is not generally undertaken in fetuses with talipes and it is entirely possible that the children evaluated for neurodevelopmental performance might have presented additional risk factors for disabilities. In this scenario, the rate of abnormal developmental outcome reported by this review may represent an overestimation of the actual burden of neurodisabilities in fetuses with a prenatal diagnosis of isolated talipes.

5 | CONCLUSION

Fetuses with prenatal diagnosis of isolated talipes generally have a good prognosis. Longitudinal ultrasound assessment is recommended to rule out additional anomalies, especially neuromuscular anomalies, which may significantly affect the long-term outcomes of these fetuses. The neurodevelopmental outcome of fetuses with isolated talipes is normal in the most cases. Finally, the incidence of aneuploidy in isolated cases is low. However, large, prospective studies are needed in future to ascertain the role of CMA and fetal MRI, and to elucidate the actual burden of short- and long-term neurodevelopmental disabilities in fetuses with a prenatal diagnosis of isolated talipes.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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