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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, intra-uterine, neonatal, perinatal death and termination of pregnancy; rate of surgical and non-surgical 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, while 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 labelled 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, while no anomaly was found at chromosomal microarray analysis, although this outcome was reported by only one study. Intra-uterine death occurred in 0.99% (95% CI 0.4-1.9) of fetuses, while 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, while 54.8% (95% CI 31.5-77.0) had non-surgical 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 very small number of included cases and short time at follow-up. **Conclusions:** Isolated talipes detected on prenatal ultrasound carries a generally good prognosis. The incidence of additional abnormalities detected on fetal MRI, aneuploidy, or neurodevelopmental disability is relatively low. However, longitudinal ultrasound assessment during pregnancy and a thorough postnatal evaluation is recommended to rule out associated anomalies which may significantly impact short- and long-term prognosis.

KEYWORDS

Clubfoot, fetal MRI, karyotype, talipes equinovarus ultrasound

ABBREVIATIONS

CMA: chromosomal microarray analysis

CNS: central nervous system

IUD: intra-uterine death

MRI: magnetic resonance imaging

KEY MESSAGE

Fetuses with prenatal diagnosis of isolated talipes generally have a good prognosis, but a longitudinal ultrasound assessment is recommended to rule out additional anomalies which may significantly affect the long-term outcomes of these fetuses.

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 yet. Isolated talipes have 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.

MATERIAL AND METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to 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, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, 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).

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).
- Intra-uterine (IUD), neonatal, perinatal death and termination of pregnancy.
- Rate of surgical and non-surgical 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 sub-group 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 which 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 were 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 post-natal treatment (surgical vs non-surgical) 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 more than one study

was published on the same cohort with identical endpoints, 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 start of 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 Newcastle-Ottawa Scale, 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.[23]

Statistical analyses

We used meta-analyses of proportions to combine data and reported pooled proportion (PP). Funnel plots (displaying the outcome rate from individual studies vs their precision (one 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 I2 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, Altrincham, Cheshire, United Kingdom).

RESULTS

General characteristics

778 articles were identified; 46 were assessed for eligibility for inclusion and 25 studies were included in the systematic review (Table 1, Figure 1, Table 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 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 lack of stratification according to the laterality of the defect for the majority of the included studies.

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, while in 4.0% (95% CI 0.1-13.2) of cases, fetal MRI detected anomalies which were not detected at ultrasound assessment. Similarly, 7.0% (95% CI 3.4-11.7) of cases, labelled as isolated talipes on prenatal imaging, were found to be associated anomalies at post-natal 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, while 2.5% (95% CI 0.8-5.0) were affected by minor anomalies at birth. Skeletal (PP: 2.2, 95% CI 0.7-4.2) and neuromuscular (PP: 3.3, 95% CI 1.6-5.6) anomalies were the most common associated conditions detected exclusively after birth (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, Trisomy 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, while sex chromosome anomalies occurred in 2.4% (95% CI 0.9-4.6) (Table S3, Figure 2). 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, I2: 0%; eight studies, 4/339 fetuses)[14,24,25,29-31,14,31,33,37]. It was not possible to explore the presence of pathogenic copy number variants, as there was only one study in which two fetuses were tested for these anomalies using CMA[24].

IUD occurred in 0.99% (95% CI 0.4-1.9) of cases, while 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 IUD among the included cases, one was due to placental abruption, while 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, while 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 sub-group analysis considering the laterality of the defect (unilateral vs bilateral talipes) could be computed for only two outcomes: abnormal karyotype and associated anomalies detected at birth (Table S4). Overall, there was no

difference in the risk of associated anomalies not detected at prenatal imaging and abnormal karyotype in unilateral compared to bilateral talipes.

DISCUSSION

The findings from this systematic review show that fetuses with prenatal diagnosis of apparently isolated talipes have a generally good prognosis. About 7% of cases labelled as isolated talipes on prenatal imaging were found to have associated anomalies, especially skeletal and neuromuscular, at post-natal examination, thus underlying the need for serial follow-ups during pregnancy. The incidence of abnormal karyotype is low, although there is lack of robust data on CMA. About 40% of fetuses with isolated talipes included in the present review undergoes surgical correction of the anomaly, while the incidence of abnormal neurodevelopmental outcome is about 7%. Finally, the risk of adverse outcome does 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 are diagnosed represent the major limitation of the present systematic review. Some anomalies may be evident only later on in gestation, thus 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 over-estimation of the actual incidence of chromosomal anomalies in fetuses with a prenatal diagnosis of talipes.

The reported rate of IUD 0.99% may look surprisingly high. However, of the four deaths reported, one was due to placental abruption. A specific cause was not provided in the other three cases that were diagnosed at 18 weeks, and whether these were isolated cases of talipes remains questionable. Therefore, the actual incidence of IUD in fetuses with isolated talipes

may be lower than that we have reported, and the findings of this review do not suggest any association between isolated talipes and IUD.

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 to unilateral anomaly.

Assessment of neurodevelopmental outcome represents another peculiar issue. The very 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 the risk of additional anomalies impacting the neurodevelopmental performance of the children has been reported to occur 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 are 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) while 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 central nervous system 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 joints contractures, lack of fetal movements and polyhydramnios.[48] Therefore, serial, longitudinal ultrasound assessments throughout pregnancy are needed in order to rule out that talipes are the first sign of a general neuromuscular disorder.

Fetal MRI has been shown to add additional information compared to ultrasound in fetuses affected by central nervous system 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 one case consisting of delayed sulcation. On this basis, there is no evidence to support the routine use of fetal 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 very small number of cases included in this analysis.

Talipes associated with other structural anomalies are commonly associated with a high risk of aneuploidy, mainly Trisomy 18, while 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, thus 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, while 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 having genotypic or phenotypic assessment at birth, the incidence of abnormal karyotype was 2.3% and was even lower when considering only studies form 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.

CMA 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 analysis. 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 (ACOG) and the Society of Maternal-Fetal Medicine (SMFM) recommended that CMA analysis 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 one 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 two fetuses were tested. However, pediatric studies on genetic assessment of children with isolated talipes has 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 in order 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 since the majority 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 as 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 very 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.

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 large majority of 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, fetal MRI and to elucidate the actual burden of short and long-term neurodevelopmental disabilities in fetuses with a prenatal diagnosis of isolated talipes.

REFERENCES

1. Lochmiller C, Johnston D, Scott A, Risman M, Hecht JT. Genetic epidemiology study of idiopathic talipes equinovarus. Am J Med Genet 1998; 79:90–96.
2. Drvaric DM, Kuivila TE, Roberts JM. Congenital clubfoot. Etiology, pathoanatomy, pathogenesis, and the changing spectrum of early management. Orthop Clin North Am 1989; 20:641–647.
3. Alderman BW, Takahashi ER, LeMier MK. Risk indicators for talipes equinovarus in Washington State, 1987–1989. Epidemiology 1991; 2:289–292.
4. Cardy AH, Sharp L, Torrance N, Hennekam RC, Miedzybrodzka Z. Is there evidence for aetiologically distinct subgroups of idiopathic congenital talipes equinovarus? A case-only study and pedigree analysis. PLoS One 2011; 6:e17895.
5. Skelly AC, Holt VL, Mosca VS, Alderman BW. Talipes equinovarus and maternal smoking: a population-based case-control study in Washington state. Teratology 2002; 66 :91–100.
6. McGahan JP, Pilu G, Nyberg DA. Neural tube defects and the spine. In: Nyberg DA, McGahan JP, Pretorius DH, Pilu G. Diagnostic Imaging of fetal anomalies. Williams & Wilkins, Lippincott, pp 291–334.
7. Bronshtein M, Liberson A, Lieberson S, Blumenfeld Z. Clubfeet associated with hydrocephalus: new evidence of gradual dynamic development in utero. Obstet Gynecol 1992;79:864-867.
8. Plotkin S, Cann RP, Valmassy RL. In utero fetal lower extremity examination by diagnostic ultrasound. J Am Podiatr Med Assoc 1988;78:287-291.
9. Bar-Hava I, Bronshtein M, Orvieto R, Shalev Y, Stal S, Ben-Rafael Z. Caution: prenatal clubfoot can be both a transient and a late-onset phenomenon. Prenat Diagn 1997;17:457-460.
10. Cho SY, Lim G, Kim SY, et al. A case of pseudoisodicentric chromosome 18q detected at prenatal diagnosis. Korean J Lab Med 2010; 30:440–443.
11. Lesniewicz R, Posmyk R, Lesniewicz I, Wołczynski S. Prenatal evaluation of a fetus with trisomy 18 and additional balanced de novo Rob(13;14). Folia Histochem Cytobiol 2009; 47:S137–S140.
12. Bronshtein M, Zimmer EZ. Transvaginal ultrasound diagnosis of fetal clubfeet at 13 weeks' menstrual age. Clin Ultrasound 1989; 17:518–520.

13. Hashimoto BE, Filly RA, Callen PW. Sonographic diagnosis of clubfoot in utero. J Ultrasound Med 1986; 5:81–83.
14. Lauson S, Alvarez C, Patel MS, Langlois S. Outcome of prenatally diagnosed isolated clubfoot. Ultrasound Obstet Gynecol 2010; 35:708–714.
15. Yamamoto H. A clinical, genetic and epidemiologic study of congenital clubfoot. Jinrui Idengaku Zasshi 1979; 24:37–44.
16. Mammen L, Benson CB. Outcome of fetuses with clubfeet diagnosed by prenatal sonography. J Ultrasound Med 2004; 23:497–500.
17. Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. Nephrology (Carlton) 2010; 15: 617-624.
18. NHS Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. University of York: York (UK), 2009. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Retrieved December 3, 2016.
19. Welch V, Petticrew M, Petkovic J, et al. Extending the PRISMA statement to equity-focused systematic reviews (PRISMA-E 2012): explanation and elaboration. J Clin Epidemiol 2016; 70: 68-89.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, and the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Intern Med 2009; 151: 264–269.
21. Zorzela L, Loke YK, Ioannidis JP, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016; 352: i157.
22. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–2012.
23. Newcastle-Ottawa Scale for assessing the quality of non randomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
24. Sharon-Weiner M, Sukenik-Halevy R, Tepper R, Fishman A, Biron-Shental T, Markovitch O. Diagnostic accuracy, work-up, and outcomes of pregnancies with clubfoot detected by prenatal sonography. Prenat Diagn. 2017; 37:754-763.
25. Viaris de le Segno B, Gruchy N, Bronfen C, et al. Prenatal diagnosis of clubfoot: Chromosomal abnormalities associated with fetal defects and outcome in a tertiary center. J Clin Ultrasound. 2016; 44:100-105.

26. Seravalli V, Pierini A, Bianchi F, Giglio S, Vellucci FL, Cariati E. Prevalence and prenatal ultrasound detection of clubfoot in a non-selected population: an analysis of 549, 931 births in Tuscany. J Matern Fetal Neonatal Med 2015; 28:2066-2069.
27. Gat I, Bar Yosef O, Hoffmann C, et al. Prenatal Brain Imaging in Isolated vs. Complicated Club Foot: A Cohort Study. Ultraschall Med 2016; 37:591-597.
28. Toufaily MH, Westgate MN, Holmes LB. Congenital talipes equinovarus: frequency of associated malformations not identified by prenatal ultrasound. Prenat Diagn 2015; 35:254-257.
29. Hartge DR, Gaertner S, Weichert J. Prenatal detection and postnatal outcome of congenital talipes equinovarus in 106 fetuses. Arch Gynecol Obstet 2012; 286:831-842.
30. Nemec U, Nemec SF, Kasprian G, et al. Clubfeet and associated abnormalities on fetal magnetic resonance imaging. Prenat Diagn 2012; 32:822-828.
31. Sharma R, Stone S, Alzouebi A, Hamoda H, Kumar S. Perinatal outcome of prenatallydiagnosedcongenital talipes equinovarus. Prenat Diagn 2011; 31:142–145.
32. Glotzbecker MP, Estroff JA, Curtis TA, et al. Prospective evaluation of a prenatal sonographic clubfoot classification system. Fetal Diagn Ther 2013; 34:236-240.
33. Canto MJ, Cano S, Palau J, Ojeda F. Prenatal diagnoses of clubfoot in low-risk population: associated anomalies and longterm outcome. Prenat Diagn 2008; 28:343–346.
34. Offerdal K, Jebens N, Blaas HG, Eiknes SH. Prenatal ultrasound detection of talipesequinovarus in a non-selected population of 49 314 deliveries in Norwa. Ultrasound Obstet Gynecol 2007; 30:838–844.
35. Cohen-Overbeek TE, Grijseels EW, Lammerink EA, Hop WC, Wladimiroff JW, Diepstraten AF. Congenital talipesequinovarus: comparison of outcome between a prenatal diagnosis and a diagnosis after delivery. Prenat Diagn 2006; 26:1248–1253.
36. Bar-On E, Mashiach R, Inbar O, Weigl D, Katz K, Meizner I. Prenatal ultrasound diagnoses of club foot: outcome and recommendations for counselling and follow-up. J Bone Joint Surg Br 2005; 87:990–993.
37. Bakalis S, Sairam S, Homfray T, Harrington K, Nicolaides K, Thilaganathan B. Outcome of antenatally diagnosed talipesequinovarus in an unselected obstetric population. Ultrasound Obstet Gynecol 2002; 20:226–229.
38. Keret D, Ezra E, Lokiec F, Hayek S, Segev E, Wientroub S. Efficacy of prenatal ultrasonography in confirmed clubfoot. J Bone Joint Surg Br 2002; 84:1015–1019.

39. Carroll SG.M, Lockyer H, Andrews H, Abdel-Fattah S, McMillan D, Kyle PM, Soothill PW. Outcome of fetal talipes following in utero sonographic diagnoses. Ultrasound Obstet Gynecol 2001; 18:437–440.
40. Malone FD, Marino T, Bianchi DW, Johnston K, D'Alton ME. Isolated clubfoot diagnosed prenatally: is karyotyping indicated? Obstet Gynecol 2000; 95:437–440.
41. Tillett RL, Fisk NM, Murphy D, Hunt DM. Clinical outcome of congenital talipesequinovarus diagnosed antenatally by ultrasound. J Bone Joint Surg 2000; 82:876–880.
42. Rijhsinghani A, Yankowitz J, Kanis AB, Mueller GM, Yankowitz DK, Williamson RA. Antenatal sonographic diagnosis of club foot with particular attention to the implications and outcomes of isolated club foot. Ultrasound Obstet Gynecol 1998; 12:103-106.
43. Katz K, Meizner I, Mashiach R, Soudry M. The contribution of prenatal sonographic diagnoses of clubfoot to preventive medicine. J Pediatr Orthoped 1999; 19:5–7.
44. Treadwell MC, Stanitski CL, King M. Prenatal sonographic diagnoses of clubfoot: implications for patient counseling. J Pediatr Orthop 1999; l9:8–10.
45. Woodrow N, Tran T, Umstad M, Graham HK, Robinson H, de Crespigny L. Mid-trimester ultrasound diagnosis of isolated talipes equinovarus: accuracy and outcome for infants. Aust N Z J Obstet Gynaecol 1998; 38:301–305.
46. Shipp TD, Benacerraf BR. The significance of prenatally identified isolated clubfoot: is amniocentesis indicated? Am J Obstet Gynecol 1998; 178:600–602.
47. Stone P, Martis W, Crawford H. Idiopathic congenital talipes equinovarus; not always an isolated anomaly. A review of long-term outcomes. J Matern Fetal Neonatal Med. 2018; 31: 2693-2698.
48. Dimitraki M, Tsikouras P, Bouchlariotou S, Dafopoulos A, Konstantou E, Liberis V. Prenatal assessment of arthrogryposis. A review of the literature. J Matern Fetal Neonatal Med 2011; 24:32–36.
49. Rossi AC, Prefumo F. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system anomalies: a systematic review of the literature. Ultrasound Obstet Gynecol 2014; 44:388–393.
50. Di Mascio D, Sileo FG, Khalil A, et al. Systematic review and meta-analysis on the role of prenatal magnetic resonance imaging in the era of fetal neurosonography: mild and moderate ventriculomegaly. Ultrasound Obstet Gynecol. 2018 Dec 14. doi: 10.1002/uog.20197. [Epub ahead of print]
51. Pont SJ, Robbins JM, Bird TM, et al. Congenital malformation among liveborn infants with trisomy 18 and 13. Am J Med Genet A 2006; 140:1749–1756.

52. Watson WJ, Miller RC, Wax JR, Hansen WF, Yamamura Y, Polzin WJ. Sonographic findings of trisomy 18 in the second trimester of pregnancy. J Ultrasound Med 2008; 27:1033–1088.
53. American College of Obstetricians and Gynecologists. Microarrays and next-generation sequencing technologies: the use of advanced genetic diagnostic tools in obstetrics and gynecology. Committee Opinion No. 682. Obstet Gynecol 2016; 128:e262-e268.
54. Hecht JT, Ester A, Scott A, et al. NAT2 variation and idiopathic talipes equinovarus (clubfoot). Am J Med Genet A 2007;143A:2285-91.
55. Heck AL, Bray MS, Scott A, Blanton SH, Hecht JT. Variation in CASP10 gene is associated with idiopathic talipes equinovarus. J Pediatr Orthop 2005;25:598-602.
56. Bridgens SJ, Kiely N. Current management of clubfoot (congenital talipes equinovarus). BMJ 2010; 2:340–345.
57. Matos MA, de Oliveira LA. Comparison between Ponseti's and Kite's clubfoot treatment methods: a meta-analysis. J Foot Ankle Surg 2010; 49:395–397.

Supporting information legends

Table S1: Excluded studies and reason for the exclusion.

Table S2: Pooled proportion for the incidence of different types of associated anomalies detected at birth in fetuses with a prenatal diagnosis of isolated clubfeet.

Table S3: Pooled proportion for the incidence of different types of chromosomal anomalies detected at birth in fetuses with a prenatal diagnosis of isolated clubfeet.

Table S4: Sub-group analysis according to the laterality of talipes (unilateral vs bilateral).

Figure legends

Figure 1. Systematic review flowchart.

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.

Table 1. General characteristics of the included studies.

Author	Year	Country	Study design	Prenatal imaging	Gestational age at diagnosis	Outcomes observed	Stratification according to laterality of the defect	Fetuses (n)	Isolated clubfoot (n)	Unilateral (n)	Bilateral (n)
Sharon Weiner[24]	2017	Israel	Retrospective	Ultrasound	II-III trimester	Anomalies at birth, abnormal karyotype, CMA, mortality, surgical outcome, neurodevelopmental outcome, siagnostic accuracy	Performed	109	76	43	33
Viaris de le Segno[25]	2016	France	Retrospective	Ultrasound	II trimester	Anomalies at birth, abnormal karyotype, mortality, diagnostic accuracy	Performed	90	56	19	37
Seravalli[26]	2015	Italy	Retrospective	Ultrasound	II-III trimester	Diagnostic accuracy	Not performed	858	672	NR	NR
Gat[27]	2015	Israel	Retrospective	Ultrasound, MRI	II-III trimester	Anomalies at follow up, anomalies at MRI	Performed	28	14	NR	NR
Toufaily[28]	2014	United States	Retrospective	Ultrasound	II-III trimester	Anomalies at birth, mortality	Not performed	208	83	NS	NS
Hartge[29]	2012	Germany	Retrospective	Ultrasound	I-II-III trimester	Abnormal karyotype, mortality, surgical outcome	Not performed	106	41	16	25
Nemec[30]	2012	Austria	Retrospective	Ultrasound, MRI	II-III trimester	Anomalies at MRI, anomalies at birth	Performed	44	19	4	15
Sharma[31]	2011	United Kingdom	Retrospective	Ultrasound	I-II-III trimester	Abnormal karyotype, mortality, diagnostic accuracy	Not performed	174	83	44	39
Glotzbecker[32]	2010	United States	Retrospective	Ultrasound	NS	Mortality, diagnostic accuracy	Not performed	83	83	NS	NS
Lauson[14]	2010	Canada	Retrospective	Ultrasound	II-III trimester	Anomalies at follow up, abnormal karyotype, mortality, surgical outcome,	Performed	65	65	25	40

						neurodevelopmental outcome, diagnostic accuracy					
Canto[33]	2008	Spain	Retrospective	Ultrasound	II trimester	Anomalies at birth, abnormal karyotype	Not performed	42	28	13	29
Offerdal[34]	2007	Norway	Prospective	Ultrasound	I-II-III trimester	Abnormal karyotype, mortality, diagnostic accuracy	Not performed	69	27	8	19
Cohen-Overbeek[35]	2006	The Netherlands	Retrospective	Ultrasound	II-III trimester	Mortality, surgical outcome, diagnostic accuracy	Performed	57	20	6	14
Bar-On[36]	2005	Israel	Retrospective	Ultrasound	II-III trimester	Anomalies at follow up, anomalies at birth, surgical outcome, diagnostic accuracy	Not performed	52	40	NR	NR
Mammen[16]	2004	United States	Retrospective	Ultrasound	I-II-III trimester	Abnormal karyotype	Not performed	87	27	16	11
Bakalis[37]	2002	United Kingdom	Retrospective	Ultrasound	II trimester	Anomalies at birth, mortality, neurodevelopmental outcome, diagnostic accuracy	Not performed	107	55	25	26
Keret[38]	2002	Israel	Retrospective	Ultrasound	II-III trimester	Surgical outcome	Not performed	51	51	NS	NS
Carroll[39]	2001	United Kingdom	Retrospective	Ultrasound	II-III trimester	Mortality, surgical outcome, diagnostic accuracy	Not performed	76	35	NR	NR
Malone[40]	2000	United States	Retrospective	Ultrasound	II-III trimester	Anomalies at birth, abnormal karyotype, diagnostic accuracy	Not performed	51	51	32	19
Tillet[41]	2000	United Kingdom	Retrospective	Ultrasound	II trimester	Anomalies at birth, surgical outcome, diagnostic accuracy	Not performed	14	14	NR	NR
Rijhsinghani[42]	1998	United States	Retrospective	Ultrasound	II-III trimester	Anomalies at birth, abnormal karyotype, mortality, diagnostic accuracy	Not performed	35	7	NR	NR
Katz[43]	1999	Israel	Retrospectiv	Ultrasound	II-III trimester	Abnormal karyotype,	Not performed	13	10	NR	NR

			e			mortality, surgical outcome, diagnostic accuracy					
Treadwell[44]	1999	USA	Prospective	Ultrasound	II-III trimester	Mortality, diagnostic accuracy	Not performed	61	20	NR	NR
Woodrow[45]	1998	Australia	Retrospective	Ultrasound	II trimester	Anomalies at birth, abnormal karyotype, mortality, surgical outcome, diagnostic accuracy	Not performed	17	17	NR	NR
Shipp[46]	1998	United States	Retrospective	Ultrasound	II-III trimester	Anomalies at birth, abnormal karyotype, mortality, surgical outcome, neurodevelopmental outcome, diagnostic accuracy	Not performed	68	68	NR	NR

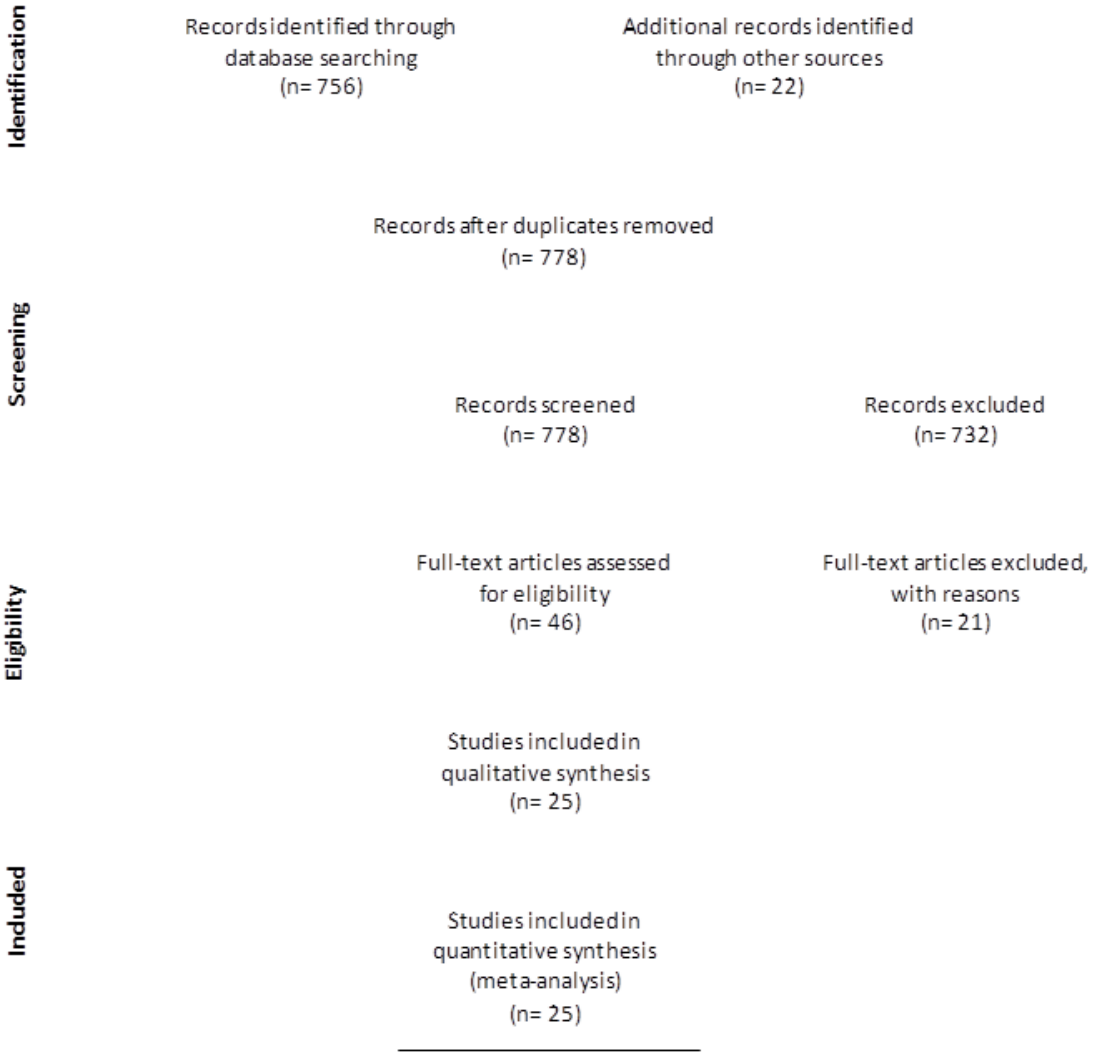
Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for cohort studies; a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

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	□	□	□

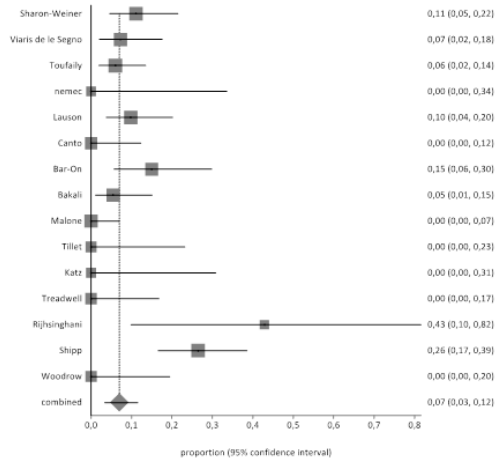
Table 3: Pooled proportion for the outcomes explored in this systematic review in fetuses with a prenatal diagnosis of isolated talipes.

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	12	9/267	3.6% (1.7-6.2)	7
Abnormal CMA analysis	1	0/2	0 (0-84.2)	-
Mortality				
Intra-uterine 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
Non-surgical 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

MRI, magnetic resonance imaging; CMA, Chromosomal microarray analysis.



Associated anomalies detected at birth



Abnormal karyotype