Care Pathway for Foetal Joint Contractures, Foetal Akinesia Deformation Sequence, and Arthrogryposis Multiplex Congenita

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Mini-Summary

What does this study add to current knowledge?

- The detection of multiple congenital contractures and other sonographic features in arthrogryposis/foetal akinesia deformation sequence (FADS) are often missed prenatally. This article provides a care pathway involving a multidisciplinary team in order to promote early detection, optimize timely counselling during pregnancy and treatment after birth, and to counsel future pregnancies. The proposed care pathway is supported by a flowchart comprised of 8 steps for examination and counselling for foetuses presenting with isolated or multiple contractures.

What are the main clinical implications?

- This article providing a care pathway that can assist prenatal detection of arthrogryposis multiplex congenita and FADS in a structured manner since these conditions are often missed during prenatal ultrasound examination. Moreover, when an underlying diagnosis is found, and parents can be counselled for future pregnancies, so informed reproductive choices can be made.

All participants are members of the Expertise Center on Rare Disease: foetal akinesia deformation sequence and arthrogryposis multiplex congenita.

Keywords

Foetal akinesia · Arthrogryposis multiplex congenita · Prenatal diagnosis · Congenital anomalies

Abstract

Introduction: The majority of arthrogryposis multiplex congenita (AMC) and lethal forms of AMC such as foetal akinesia deformation sequence (FADS) cases are missed prenatally. We have demonstrated the additional value of foetal motor assessment and evaluation in a multidisciplinary team for the period 2007–2016. An applied care pathway was developed for fetuses presenting with joint contracture(s) in one anatomic region (e.g., talipes equinovarus [TEV]), more than one body part with non-progressive contractures and motility (AMC) and with deterioration over time (FADS). **Methods:** The multidisciplinary team of Amsterdam University Medical Centre Expertise Centre FADS and AMC developed the care pathway. Additional tools are provided including a motor assessment by ultrasound examination and a post-mortem assessment form. **Results:** An eight-step care pathway is presented with a proposed timing for prenatal sonographic examination, genetic examinations, multidisciplinary meetings, prenatal and postnatal counselling of the parents by a specialist also treating after birth, and the follow-up of prenatal and postnatal findings with counselling for future pregnancies. **Discussion/Conclusion:** The scheduled serial structural and motor sonographic assessment together with follow-up examinations and genetic analysis should be tailored per prenatal centre per available resources. The multidisciplinary care pathway may pave the way to increase the detection rate and diagnosis of isolated contracture(s), TEV with underlying genetic causes, and the rare phenotypes AMC/FADS and prompt treatment after birth within expertise teams.

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Published by S. Karger AG, Basel

Introduction

Growing awareness has risen that the finding of foetal joint contractures at the structural anomaly scan necessitates additional follow-up examinations to assess possible underlying causes. Joint contractures can differ in severity and prognosis, depending on the extent and underlying cause [1, 2]. Talipes equinovarus (TEV), arthrogryposis multiplex congenita (AMC), and foetal akinesia deformation sequence (FADS; a lethal form of AMC) have a prevalence of 1–3:1,000, 1:3,000–5,000, and 1:13,000 pregnancies, respectively [1, 3]. TEV is a defor-

mity of the foot, resulting in the foot being fixed in adduction, supination, and varus positions [2]. In AMC, the contractures extent to more than one region in the body; in approximately 56%, there is involvement of upper and lower extremity, and 17% have upper extremity involvement alone [4, 5]. FADS is a form of AMC, where the contractures and lack of movement often result in, amongst others, lung hypoplasia, polyhydramnios, flattened facial features, and growth restriction. The outcome of AMC and FADS is dependent on its underlying cause, but in the majority of FADS, it is adverse, varying from need for intensive support to perinatal death [6].

Uni- or bilateral TEV are often isolated anomalies and have a good overall outcome after orthopaedic treatment [7, 8]. The majority of parents confronted with the antenatal suspicion of TEV choose to continue the pregnancy. The counselling is supported by information from follow-up studies, guidelines, and patient organizations [7–14]. Moreover, in about 10%, the finding of prenatal TEV is transient or positional and not confirmed after birth or needing therapy [7]. Nevertheless, parents must be informed that in 33–51%, other anomalies are detected during advanced ultrasound examinations (AUEs), especially in the central nervous system, musculoskeletal system, urogenital tract, or circulatory tract [7, 10]. Isolated contractures in one anatomical region, like TEV or contractures in the arms, can also be the first expression of an underlying genetic/syndromal disorder or acquired anomaly [7, 8]. Although rare, these presenting signs may be the onset of development into multiple contractures in other regions, such as joints of arms and legs, AMC, or FADS.

Focussing on the sonographic detection of AMC and FADS, these phenotypes are often missed prenatally or diagnosed during late gestation, when associated anomalies like micrognathia, foetal growth restriction, polyhydramnios, and suspected lung hypoplasia are more pronounced [15, 16]. In a population (University Children's Hospital, Basel, Switzerland, and BC Children's and Women's Hospital, Vancouver, Canada) of 107 neonatally confirmed arthrogryposis cases published in 2013, 73.8% was not detected during prenatal ultrasound examination [15]. In another population (Shriner Hospitals for Children Montreal, Canada, and Philadelphia, US) of older infants with AMC (mean age 8.25 years, range 1.59–19.23) published in 2019, 85% had clubfeet or clenched hands during the second trimester of pregnancy, but in 53%, AMC was detected prenatally [17]. When applying foetal imaging in a centre of expertise over a period of two decades, sensitivity for detecting arthrogryposis increases

from 66.7% (from 1990 to 1999) to 85.7% (2000–2009) [18]. Recent advice to enhance detection of AMC and FADS emphasized serial sonographic structural anomalies evaluations [19, 20]. Even though it is widely accepted that reduced foetal movement is one of the clinical presentations of AMC and FADS, motility is not yet standardly assessed during prenatal work-up when AMC or FADS is suspected [19, 20]. Our centre has shown the additional value of serial systematic foetal motor assessment. Firstly, demonstrating the distribution of abnormalities in the three motor assessment parameters (differentiation into about 15 different specific movement patterns (SMPs), qualitative performance of especially the most common general movement (GM), and isolated arm and leg movement and quantitative performance of GMs and isolated arm and leg movements) evaluated in 14 FADS foetuses by means of sonographic examinations at 11–30 weeks of gestational age [21]. From the three parameters, abnormal quality was found in all, reduced differentiation into SMPs in 7/14 cases, and reduced quantity in 5/14 cases [21]. In a consecutive 10-year period, the findings were confirmed in 18 FADS foetuses, with ultrasound examination at 20–24 weeks of gestational age, demonstrating abnormal quality in all, abnormal differentiation in 11/18 cases, and reduced quantity in 9/18 cases [22]. In addition, motility of seven foetuses with AMC had normal differentiation into SMPs and quantity in all but suspect or abnormal motility in 4/6 cases [22]. Thirdly, we evaluated the changes based on serial motor assessment at 20–21 of weeks gestational age and 22–23 weeks, together with AUE in case of referral for limb contractures; the 22–23-week sonographic results and genetic results were related to the outcome after birth (evaluated by the multidisciplinary team) [22]. This 2-week interval was selected as this period is reported to demonstrate deterioration in motility and contractures after initially detected [21, 23]. A total of 66 women were evaluated according to our multidisciplinary care pathway, when demonstrating foetal contractures in their foetus at the 20-week gestational age [22]. The first motor assessment changed the initial diagnosis based on structural evaluation in 19/66 cases. The second motor assessment changed the diagnosis based on the second structural evaluation in 3/43 cases and confirmed FADS 7 times as evidenced by deterioration of motility. Postnatally, diagnoses were confirmed as 36 isolated bilateral TEV, 18 FADS, 7 AMC, and 5 bilateral TEV with underlying diseases [22].

Contractures may have an underlying genetic cause. Genetic evaluation has shown an abnormal karyotype in foetuses with TEV without other associated anomalies in

1.5–3.6%, when associated with other anomalies in 10% of unilateral to 15.5% of bilateral TEV [10, 24]. Application of microarray analysis revealed genetic anomalies in 3.9% and 17.5% of foetuses with TEV, without and with other associated sonographic anomalies, respectively; therefore, genetic evaluation should be offered to the parents [25]. The expansion of genetic evaluation possibilities including whole-exome sequencing and soon whole-genome sequencing (WGS) supports further exploration. Hall and Kiefer [26] have dedicated several articles concerning the underlying genetic causes of AMC, and they described 402 associated genes in their 2019 update [27, 28].

Filges et al. [4] addressed the need for studies and guidelines to enhance the detection of abnormal motility and multiple contractures to enable physicians and parents to make timely individualized decisions upon continuation of pregnancy. This care pathway is an answer to their call.

The aim of this article was to propose a care pathway in a tertiary foetal medicine centre for early detection, diagnosis, and distinction of foetal contractures; TEV, with or without an underlying cause, AMC, and FADS. The care pathway was developed by a multidisciplinary team of experts to ensure uniform and streamlined care before and after birth and includes dedicated serial structural and motor sonographic assessment, genetic examinations, timely counselling of the parents, follow-up examinations, prompt treatment after birth by an expert team, and counselling for future pregnancies. The follow-up examinations during pregnancy consist of sonographic evaluations and counselling concerning the method of delivery. After birth, the follow-up consists of examinations, treatment, and assessment of developmental milestones from the various disciplines.

Materials and Methods

The care pathway has been developed over the timespan of 25 years. Our multidisciplinary team focusses on detection of AMC/FADS and the underlying causes [21, 22]. Its team consists of obstetricians, child orthopaedic surgeons, geneticists, paediatric neurologists, neonatologists, developmental pathologists, physical medicine and rehabilitation doctors, plastic surgeons, and social workers. In 2015, we became an acknowledged expertise centre on rare disease, specifically FADS and AMC. Since then, multidisciplinary team meetings take place not only for weekly clinical purposes but also every three months for the development of the care pathway including quality evaluation by presenting prenatal diagnosis and outcomes over time, research, and education. All the disciplines mentioned above attributed to the development of the

Table 1. Foetal motor assessment dedicated to normal and FADS characteristics, adapted from Donker et al. [21]

Description		Normal	Abnormal/suspect [†]
<i>Differentiation into SMPs</i>			
Presence, check off	Jaw opening	≥8 SMPs during the 15-min observation <24 weeks of gestational age	Abnormal <8 SMPs in the 15-min observation
GM	Sucking and swallowing		
IAM	Non-nutritive sucking		
ILM	Stretching	Double observation period to 30 min	
Stepping movement	Isolated retroflexion head	in case <3 GMs in 15 min	
Breathing movement	Isolated anteflexion head	Inform parents prior to the observation that in general the longest pause between GMs is 6 min	
Hand-face contact	Isolated rotation head		
Startle	Yawning	between 11 and 19 weeks but up to 15 min can be physiological [28]	
Hiccough	Twitch spine		
<i>Quality GM, IAM, and ILM</i>			
The 6 aspects		GM: variation in the ASPD, fluent movements, and waxing and waning	Suspect GM, IAM, and ILM: no variation in 1–2/6 GM aspects and 1–2/4 IAM/ILM aspects
1. Amplitude varies		If the GMs/IAMs/ILMs are normal, except for the affected joints, the quality is also considered normal with reduced variability in the affected joint	Abnormal GM, IAM, and ILM: no variation in 3 or 4/6 aspects for GM and in 3–4/4 aspects for IAM/ILM
2. Speed varies		IAM/ILM: 1–4 varied; 5 fluent, but, twitches may occur; and 6 not applicable since many short movements occur besides waxing and waning	
3. Participating body parts vary			
4. Direction varies			
5. Fluent movements			
6. Waxing and waning, in- and decreasing activity within one burst of GMs			
<i>Quantity of GM</i>			
		GMs >10th percentile from a normal population 8–40 weeks [35, 36]	GMs, <10th percentile of the age-related normal population [35, 36]
		≥3 GMs in 15 min	<3 GMs in 30 min

SMP, specific movement pattern; FADS, foetal akinesia deformation sequence; GM, general movement; IAM, isolated arm movement; ILM, isolated leg movement. [†]FADS abnormal differentiation, quality, and quantity; abnormal quality with normal/abnormal differentiation and quantity; abnormal quantity, for example, no GMs during age-related sufficient observation period and no possibility to assess differentiation and quality.

care pathway, reporting since 1996, together with the input from patient organizations (i.e., Dutch Clubfeet Association and Spierziekten Nederland) [11, 29]. Ethical approval from our local board was not required since we are describing a care pathway, and no patient data was included.

The care pathway consists of eight steps performed by the expertise team members, which enables timing from the first prenatal visit to start of treatment after birth, including counselling moments concerning the underlying cause. Regularly (yearly and on indication more often), the pathway is evaluated and adapted to new insights. Improvement in the possibilities of genetic examination resulted in the following adjustments. Invasive diagnostics for microarray analysis is offered when sonographically isolated TEV is suspected since 2014. Besides microarray, in cases of non-isolated TEV, WES (trio analysis, both parents and DNA from amniotic fluid) is offered, and rapid trio WES analysis (i.e., both parents

and DNA from the amniotic fluid) is used since 2018. The analysis is done in sequential steps in order to limit the chance of detecting incidental findings and to speed up the process [30]. Firstly, a (virtual) FADS gene panel [31] and/or a neuromuscular panel [32] are analysed, and when no (possible) pathogenic variant is detected, this panel examination can be followed by analysis of the whole exome. The type of gene panel depends on factors emerging during the counselling, with consideration to the family history and sonographic findings. In case of post-mortem genetic examination, a FADS/neuromuscular WES panel and in case of no yield, analysis of the whole exome are performed [30]. Since 2019, WES and gene panel testing in foetuses with isolated contractures are offered during the genetic counselling. Clinical expertise with the care pathway had developed, and the unilateral TEV has been included in the pathway since 2018 for the risks of genetic/syndromal disorder; AMC and FADS are similar to foetuses with bilateral TEV. Travel

Table 2. Post-mortem examination and external inspection

External inspection	Notes
Foetal measurements	
Weight	gram
Crown-heel length	cm
Crown-rump length	cm
Head circumference	cm
Biparietal diameter	cm
Inner canthal distance	cm
Outer canthal distance	cm
Philtrum length	cm
Chest circumference	cm
Inter-nipple distance	cm
Abdominal circumference	cm
Hand length	cm
Foot length	cm
Evaluation of the presence of oedema	Yes/no
Hygroma colli versus generalized	Hygroma colli/generalized
Dysmorphic features	
Face	
Flattening nose	Yes/no
Micrognathia	Yes/no
Low position ears	Yes/no
Cleft lip and/or palate	Yes/no
Neck	
Webbing/pterygium	Yes/no
Thorax	
Abnormal shape	Bell-shaped/
Upper extremities	
Contractures in shoulder, elbow, wrist, fingers, and uni-/bilateral	Yes/no range of motion
Other abnormalities (e.g., missing parts and polydactyly)	Yes/no range of motion
Lower extremities	
Contractures in hip, knee, ankle, toes, and uni-/bilateral	Yes/no
Other abnormalities (e.g., missing parts and polydactyly)	Yes/no
Detailed photographic documentation	
Whole-body X-ray	
Anterior-posterior and lateral pictures with focus on the thoracic shape, details of hands and feet, details of contractures, fractures, and other malformations, with measurement of the bone age and of all long bones	

history to countries with endemic Zika was added in 2020 because of the reported association with FADS [33]. Choices for stepwise analysis after birth are performed in line with Dietrich et al. [34].

The quality assessment of the care pathway consists of a yearly presentation of all infants including the follow-up data as recorded in an anonymized database, concerning updates of the information of the various disciplines. Storage of foetal and follow-up examinations of infants with AMC and FADS is recorded in a database to optimize the evaluation of the outcome. The regular orthopaedic follow-up of TEV is until 18 years, until adulthood, according to the Dutch paediatric orthopaedic association club-foot assessment guideline [9]. The multidisciplinary treatment of AMC is until 18 years of age and longer if necessary with the physical medicine and rehabilitation doctor as the main doctor of the team.

Two items are provided in more detail to facilitate similar storage in databases and optimize comparison between cases. Firstly, a record form is presented for the systematic foetal motor assessment, regarding the differentiation into SMPs, qualitative performance, and quantity of movement patterns with normal values in analogy to Donker et al. [21] and Tjon et al. [22]. The record form for the systematic motor assessment is presented in Table 1 [21, 35, 36]. Age-related normal quantitative values are available per SMP [35–38]. The various SMPs remain present throughout gestation and after birth [38]. The qualitative motor assessment of spontaneous GMs is identical to the examination after birth, up to 3 months of age, and demonstrates continuity as reported in other high-risk populations [39, 40]. This assessment is part of the advanced ultrasonographic examination including neurosonography, to assess the brain in axial, coronal, and sagittal planes. Secondly, record

Table 3. Post-mortem examination stepwise internal inspection and autopsy procedure

Internal inspection and autopsy procedure	
1.	Evaluation of the situs of all internal body organs
2.	Evisceration
3.	Segmental analysis of the heart-lungs packet
4.	Weight of all organs (thymus, heart, lungs, liver, spleen, adrenals, kidney, and pancreas)
5.	Measurement of the length of the small and large intestines
6.	Oriented embedding of all organs for histological and immunohistochemical analyses
7.	Sampling of skeletal muscle (quadriceps and psoas) for histological and electron microscopy analyses
8.	Brain and spinal cord autopsy (evisceration, fresh weight, fixation, cut, and embedding for histological and immunohistochemical analysis)

forms are presented for the post-mortem examination, highlighting the items for AMC and FADS in line with Oberg et al. [41], Tables 2 and 3. There are 2 differences only, our examination includes no eye muscle samples and includes examination of all organs irrespective of syndromic findings.

The post-mortem examination is performed by a specialized developmental pathologist. Timing of the post-mortem examination is strived to be within 48 h in, and parents provide written informed consent to perform post-mortem examination, with or without brain autopsy. To limit post-mortem autolytic changes, the deceased foetus is kept in a cooled cradle or water basin until post-mortem examination. Evaluation of dysmorphic features is performed together with the clinical geneticist. The pathologist is informed about the request of post-mortem examination to support the planning. Parents are counselled that the autopsy report including muscle biopsy results also supports the interpretation of the genetic data.

Results

The eight time points concerning the appointments for the parents for the various examinations, counselling, and the meetings of the multidisciplinary expertise team are provided for in Figure 1. The first step is described below in more detail. The care pathway is initiated after referral to our tertiary centre when one or more contractures are seen during the 20-week standard anomaly scan. During this first visit, the AUE is performed by a doctor of the expertise centre who counsels the parents and informs about the different steps in the pathway. A maternal and family history is obtained with the following aspects: exposure to medication, recreational drugs, diabetes mellitus, multiple sclerosis and myotonic dystrophy, maternal hyperthermia in the first trimester, infectious disease (rubella, participation in vaccination within Dutch/other national immunization programme is checked, varicella, and Zika), and maternal myasthenia gravis [4]. The parents are referred to the websites from

the different patient organizations for additional information [11, 29, 42–45]. The parents are offered consultation by the clinical geneticist for invasive diagnostics, performing karyotype and microarray analysis or trio WES. We advise counselling by the orthopaedic surgeon after the second AUE in cases of stable contractures and motility, moreover after obtaining the results of the genetic testing. The multidisciplinary team meeting is within a week after the first AUE, when no new insights arise during this meeting the parents are informed about the results of the meeting at the second AUE. When parents are referred to our centre before or after the 20-week scan, the same care pathway is applied with adapted time points.

The joint team effort in the stepwise approach is to detect the underlying cause and support counselling for the current and future pregnancies. Additionally, the expertise team members who are involved during pregnancy will continue treatment from the neonatal period throughout childhood and into adulthood. The main doctor of the expertise team after birth is the physical medicine rehabilitation doctor in cases of AMC/FADS and the orthopaedic surgeon in cases of stable contractures in one region (e.g., TEV).

Discussion and Conclusion

This study provides a care pathway for fetuses with joint contractures suspected at the structural anomaly scan at 20 weeks. The flowchart describes a suggested

Fig. 1. Multidisciplinary care pathway of isolated joint contractures, TEV, AMC, and FADS after referral to our tertiary centre from the 20-week foetal structural anomaly scan performed by the expertise team. AMC, arthrogryposis multiplex congenita; FADS, foetal akinesia deformation sequence; TEV, talipes equinovarus; AUE, advanced ultrasound examination.

(For figure see next page.)

eight-step follow-up plan, including serial sonographic evaluation of structural and motor anomalies, to enhance the distinction between stable contractures in one region, multiple contractures in more than one region (AMC), and the deterioration into an often lethal phenotype of AMC and FADS. It provides personalized counselling and follow-up examination to enhance decision-making for the parents during pregnancy and prenatal diagnostic possibilities for future pregnancies and postnatal treatment planning. After the birth prompt, treatment of the infant is started by the same team members who provided prenatal counselling. The transparent timing of examinations and multidisciplinary set-up supports care professionals and parents during the waiting time for the results of the underlying cause and thus prognosis of the anomaly. The care pathway facilitates timely counselling as termination of pregnancy is regulated by law in any case up to 24 weeks of gestational age in the Netherlands. Possibilities to terminate pregnancy at later gestational ages in other countries may influence the timing of the serial ultrasound examinations to later in pregnancy.

With the knowledge of the low prenatal detection of AMC/FADS, we have to inform parents of fetuses with contractures at the 20-week scan about various aspects at the first check-up. We discuss with the parents that although at the first ultrasound examination the TEV or contracture elsewhere may seem isolated, an advanced ultrasound follow-up examination is recommended to detect associated anomalies and progression over time with amongst others development into AMC/FADS. This is in line with Di Mascio et al. [24], who reported 8% associated anomalies at follow-up and another 7% at birth. Whereas AMC and FADS are often missed prenatally, TEV is often detected at prenatal ultrasound examination with a still improving detection rate [10]. Implementation of the care pathway for all fetuses with contractures, such as uni- or bilateral TEV, opens possibilities to reach more fetuses with AMC and FADS. Collaboration with patient organizations dedicated to clubfeet and AMC will enable further improvement of the care pathway.

We are the first to introduce a systematic motor assessment in the evaluation of joint contractures to evaluate the functional expression of the central nervous system with age-related normative data and data of fetuses with FADS and AMC. Earlier reports on motor assessment in case of FADS and AMC applied various methods concerning differentiation in SMPs (specified for body parts), qualitative assessment, quantitative assessment, and age-related duration of observation time [23]. The knowledge on the various aspects of motility explains that stable con-

tractures and motility observed 2 weeks after initial contractures can be considered as reassuring [22, 23]. Moreover, it elucidates why mothers of fetuses with AMC reported no movements in only 3/36 and abnormal movements in 11/36 since systematic motor assessment showed abnormal movement quantity in half of the FADS and none of the AMC (small) population [17, 22].

The additional value of genetic testing is also emphasized. The field of clinical genetics is rapidly evolving, and therefore, data on prevalence of anomalies found with new techniques are needed. Introducing WGS into diagnostics of daily practise is approaching. This technology can replace WES and array, making it a more complete diagnostic test. However, WGS should only be implemented when it is an improvement on costs, quality, and/or diagnostic yield [46–48]. The implementation of WES and WGS has increased the probability of detecting unsolicited or incidental findings. Counselling by a clinical geneticist is therefore essential before requesting WES or WGS, to take care of the informed consent, as well as discuss the results with the parents, especially as the outcome of the WES/WGS may have important implications for other family members. Finally, prenatal diagnostics might be recommended for future pregnancies. A pilot registry for children with AMC by Dahan-Oliel et al. [17] showed that genetic testing was not performed consistently and when performed often inconclusive. They emphasized the importance of performing genetic tests prenatally [17]. By performing these examinations prenatally, we hope to get a diagnosis before birth. The medical workup for diagnosis after birth as well as feeding problems are considered the reasons for on average two weeks hospitalization but can have a negative psychological effect interrupting parent-infant attachment and can delay treatment [17, 49].

Despite the serial ultrasound examination, genetic evaluation, and multidisciplinary approach, we still have to inform parents about the limitations of our evaluation. Even within the population of stable contractures in one region, in 5% (3/60), an underlying disease became evident at the follow-up, in line with the earlier findings of 7% reported by Di Mascio et al. [21, 24]. These results however concerned the period before the application of prenatal WES.

In our care pathway, we did not include foetal MRI. This imaging technique is suggested by Adamo et al. [20] and Niles et al. [19] in addition to ultrasound examination to get more information about potential brain anomalies and lung hypoplasia during the 2nd or 3rd trimester of pregnancy. On the other hand, Niles et al. [19] also

mentioned the limitations of foetal MRI for certain regions concerning costs, time, and expertise. In our centre with available experts on the systematic application of multiplanar neurosonography, the necessity of foetal MRI is limited and restricted to indications after neurosonography, as recommended by the International Society of Ultrasound in Obstetrics and Gynaecology [50, 51]. When foetal neurosonography is not possible, MRI may be helpful.

The strength of our care pathway is the strict organization within time slots of our multidisciplinary team to perform the investigations, referrals, and counselling. We are aware of the privileges we have in the Netherlands regarding early referrals thanks to our health care system, the knowledge, and experience in our centre. Parts of the steps in our care pathway may not be feasible in other centres because of lack of expertise for instance concerning the foetal motor assessment, logistics, or costs. In that case, at least serial AUE including neurosonography and careful evaluation of contractures, facial profile, cardiothoracic ratio, and amniotic fluid with counselling and offering of amniocentesis are recommended. If possible, a 15-min recording of the motility can be performed, to assess the quality of the movement. This care pathway is an example to use as a guideline in case the phenotypes AMC or FADS are suspected and include the isolated contractures in one region as they can be the onset of AMC/FADS. It also supports decision-making on the place of delivery in case of AMC or FADS in a tertiary centre.

The limitation is that the knowledge of the foetal motility on rare diseases like FADS and AMC is still based on a restricted number of fetuses despite our long-lasting experience. We strive to extend our present database into an international database with AMC and FADS cases including the prenatal structural and motor assessment, phenotype descriptions, postnatal findings, genetic and paediatric, or post-mortem findings [21, 22]. Filges et al. [4] and Dahan-Oliel et al. [17] have called for an international database for AMC to get a better understanding of AMC. To optimize the database, the importance of applying corresponding definitions of AMC is emphasized in a Delphi consensus study [52]. Participation in the European Reference Network for rare diseases, especially the Transversal cross-ERN Pregnancy and Family Planning on rare diseases Working Group, may support the international effort of an international database. The transparency within the database should support colleagues to identify similar phenotypes of affected fetuses and new found genetic abnormalities and in addition stimulate ap-

plication of the guideline. To assess the efficiency of the care pathway, we will continue to report on prenatal and postnatal results, presently halfway the third decade, 2017–2026. Various aspects of teaching foetal motor assessment are explored including an e-learning to facilitate more health care professionals with experience in foetal motility to implement this in their care pathway. Our effort to implement the care pathway in other centres is in line with the initiative of the European Reference Network on rare inherited and congenital anomalies (ENRICA), calling for standardized prenatal ultrasound assessment of the foetus with congenital diaphragmatic hernia. In the rare disease congenital hernia diaphragmatica, not only is the detection rate higher, 70% than the reported 26.2% for AMC, but also the outcome is dependent on the follow-up in a perinatal tertiary set-up [15, 53].

In conclusion, the care pathway for foetal contractures is meant to provide a clear stepwise multidisciplinary approach to increase the detection rate and diagnosis prenatally of isolated contractures, TEV, AMC, and the lethal form FADS, including serial structural and systematic foetal motor assessment. The implementation of this proposed pathway by a dedicated expertise team optimizes prenatal and postnatal follow-up, care, and counselling during pregnancy; treatment after birth throughout childhood; and counselling for future pregnancies, tailored per tertiary centre. The tailoring is depending on factors such as resources and knowledge. Future research on an international register facilitates comparison of knowledge and education on theoretical and practical gaps, to overcome differences between centres and countries.

Acknowledgments

We would like to thank R. Boekestijn from the foundation board of the patient organization, the Dutch Clubfeet Association and R. Jansen from the working group AMC of the patient organization Spierziekten Nederland for assessing the care pathway [1, 2]. We would like to thank C.S. Kee for her activities as social worker in our care pathway.

Statement of Ethics

An ethics statement was not required for this study type, no human or animal subjects or materials were used.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

All funding was provided by Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Obstetrics and Gynaecology, Amsterdam Movement Sciences, De Boelelaan 1117, Amsterdam, Netherlands.

Author Contributions

Jill K. Tjon, Marianna Bugiani, Melinda Witbreuk, and Johannes A. van der Sluijs contributed to writing, analysis, and interpretation of article. Gita M.B. Tan, Marjan M. Weiss, Laura A. van de Pol, Mirjam M. van Weissenbruch, Annemieke I. Buizer, Margriet H.M. van Doesburg, Petra C.A.M. Bakker, Bloeme J. van der Knoop, Ingeborg H. Linskens, and Johanna I.P. de Vries contributed to writing, analysis, and revising of article.

Data Availability Statement

No data were obtained, writing this article. Any data concerning the development of the care pathway is available through the author.

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