The prenatal diagnostic in the arthrogryposis multiplex congenita. Presentation of three cases and the systematic revision of the literature

Costin Berceanu[1], Monica M. Cîrstoiu[2], Elvira Brătilă[2], Răzvan Ciortea[3], Sabina Berceanu[1], Simona Vlădăreanu[4]

1. Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania
2. Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania
3. Department of Obstetrics and Gynecology, "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania
4. Department of Neonatology, "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania

All authors have equally contributed to this work.

Abstract

Arthrogryposis Multiplex Congenita (AMC) is a pathology characterised by neuromuscular and connective tissue disorders, leading to the limitation of the foetal joint mobility, muscular contractures and rigidity. The aetiology is variable and multi-factor. In most cases the AMC does not have a genetic determinism, however for 28-30% of the cases, the transmission is genetic, dominant, recessive or related to the X chromosome. The study includes 3 cases, with ages between 26 and 38, with foeti prenatally diagnosed with congenitala. One of the cases presented the recurrence of AMC (a foetus with AMC, the second foetus normal, the foetus included in the study with AMC). The amniocentesis was practiced on two of the cases, normal karyotype 46,XX. The TORCH testing was negative in all cases. The foetal ultrasonographic evaluation pointed out the following aspects – normal foetal growth, polyhydramnios, the fixity of the extremities, the exaggerated flexion of the upper limbs, congenital talipes equinovarus, knee hyperextension (i.e. bilateral genu recurvatum), abnormal position of the fingers, very rare or absent movements of opening and closing the palm, generalised hypokinesia, foetal immobility with no response to stimuli. No other associated malformation has been identified. The systematic ultrasonographic examination, the identification of the associated anomalies and their correlation led to the correct diagnosis of the AMC. The postnatal aspect was obvious and very suggestive, in accordance with the elements identified through ultrasound. The foetal prognostic depends on the associated anomalies, on the gravity of affecting the respiratory function and on the degree of the often moderated, rarely lethal orthopaedic limitation.
Keywords: *arthrogryposis, akinesia, prenatal diagnosis*

Introduction

Arthrogryposis (or arthrogryposis multiplex congenita, AMC) involves a sequence of neurological, muscle and connective tissue disorders, which leads to severe limitation of the joint mobility, contracture and rigidity[1].

The term arthrogryposis comes from a combination of latin and greek words and refers to recurved or arched joints. This term has been used for the first time by Stern in 1923[2].

Arthrogryposis means a complex of symptoms characterised particularly by multiple foetal joint contractures, which are present at birth. The muscular structures in the affected segments are replaced by adipose and fibrous tissue[2-4]. AMC is not particularly a separate entity, but it characterises a number of pathological circumstances, which have as defining elements the limitation of movements and anchylosis of joints in various degrees[5].

The normal development of the foetus in utero requires the mandatory presence of foetal movements. The absence of normal foetal movements, respectively the foetal akinesia, leads to the abnormal positioning of the foetus in utero, joint contractures and many times the occurrence of pulmonary hypoplasia[6].

The association of the elements characteristic to this syndrome, respectively foetal hypokinesia/ akinesia, the limitation of the mobility of foetal joints and abnormal position of the limbs achieves similar phenotypic profiles[6]:

- The association of foetal akinesia - limb deformities,
- The association of foetal akinesia - hypoakinesia,
- The Pena-Shokeir syndrome, type I,
- AMC, and
- The lethal multiple pterygium syndrome.

Although the phenotypic expression is significantly different, there are studies considering the first four concepts to be synonyms[5,7].

Case Report

The study includes 3 cases, with ages between 26 and 38, with foeti prenatally diagnosed with congenital arthrogryposis. One of the cases presented the

Received: *February 05, 2015*
Revised: *March 01, 2015*
Accepted: *May 10, 2015*

recurrence of AMC (i.e. a foetus with AMC, the second foetus normal, the foetus included in the study with AMC). The amniocentesis was practiced on two of the cases. The TORCH testing was negative in all cases.

Discussion

Recent studies show an incidence between 1-3:10 000 births[5,7], although the incidence of hypokinesia/akinesia or the limitation of foetal joints, considered to be isolated, report an even higher incidence, of 1:3000 births[2].

This is definitely due to the contribution of the foetal ultrasonography in prenatal diagnosis and examiner's experience and training, as well as to the foetus's significantly different phenotypic expression.

In the case of a syndrome with such a complex phenotypic expression, the pathogenesis definitely includes neuromuscular, connective tissue anomalies, myopathies, maternal infections, but not least genetic causes affecting the situses: 5q35, 9p21-q21, 11p15.5(5-7) (Table 1).

AMC has the muscle contracture and limitation of the foetal joint mobility as central, universally recognised element. The term is in fact a descriptive one, and not a diagnostic, the presence of congenital/ prenatal muscle contracture being a suggestive clinical/ultrasound sign, with multiple etiopathogenic substrates and different phenotypic models[2,8].

Multiple etiopathogenic examples are described, which generate the foetal phenotypic model alone or in association, which by the prenatal ultrasound expression and foetal clinical manifestations shall form the correct diagnosis (Table 2).

The ultrasound diagnosis of AMC must be suspected when hypokinesia/akinesia, the limitation of foetal joint mobility, the abnormal position or conformation of the limbs are obvious at foetal examination (Table 3).

Clinically and in terms of ultrasound, 3 subtypes of arthrogryposis multiplex congenita are described[1,8-10]:

- AMC involving only the limbs (distal arthrogryposis),
- AMC involving the limbs and other regions, and
- AMC involving the limbs and the CNS (Neurological arthrogryposis).

The ultrasound diagnosis of the cases with AMC has been established by identifying the following suggestive and/or characteristic signs (Figures 1-4).

- utalipes equinovarus,
- bilateral knee hyperextension,
- fixity of extremities,
- flexion of upper limbs (muscular-joint contracture of the elbow),
- hand clenching (flexion of fingers - overlapping fingers, lack of closing and opening movements in fingers and hands, muscular-joint contracture of radiocarpal joints);
- hypokinesia/foetal akinesia,
- deficient ossification of long bones (osteoporosis),
- polyhydramnios, and
- oligohydramnios.

Table 1 Etiopathology of AMC[6]

The main location of hypokinesia/akinesia	Cause
Brain/Spine	External factors (hypoxia, infection, toxins) Development anomalies (spinal muscular atrophy, olivopontocerebellar hypoplasia)
Peripheral nerves	Defective myelination
Neuromuscular junction	Maternal myasthenia gravis Mutations of the acetylcholine receptor subunits
Striated muscle	Centronuclear/myotubular myopathy Glycogen storage disease (type IV, VII)
Tegument	Restrictive dermopathies
Extrinsic restriction	Extended oligohydramnios, Voluminous uterine leiomyoma
Chromosome anomalies	Trisomy 18, 15 mosaic

Table 2 Etiopathogenic models of hypokinesia/akinesia of AMC

Cited source	Cause	
Bianchi et al.[2]	1. Muscle anomalies	■ Muscular dystrophies ■ Congenital myopathies ■ Amyoplasia
	2. Neurological anomalies	■ CNS malformations ■ Congenital neuropathies ■ Defective or inexistent myelination ■ Exposure to neurotoxic substances
	3. Connective tissue anomalies	■ Anomalies interfering in the development of tendons, bones, cartilages or other connective structures
	4. Mechanical limitation of the intrauterine foetal mobility	■ Uterine leiomyomas ■ Oligohydramnios ■ Amniotic band syndrome ■ Multifetal gestation
Stevenson et al.[8]	1. Muscle deficiencies	■ Multiple myopathies (deficient or absent muscle function)
	2. Neuropathies	■ CNS anomalies ■ Peripheral neuropathies ■ Neuromuscular junction disorders
	3. Connective tissue diseases	■ Connective tissue dysplasia ■ Bone dysplasia subsequent to connective diseases
	4. Limitation of the intrauterine space and constriction	■ Uterine malformations ■ Multiple pregnancy ■ Uterine leiomyomas ■ Oligohydramnios
	5. Vascular injuries	■ Decrease in the foetal-placental vascular flow, in the critical stages of the CNS development, particularly in the first trimester of pregnancy, between 8-14 weeks
	6. Embryo-foetal teratogen exposure	■ Misoprostol, Ergot, Penicillamine, Inhibitors of Angiotensin-convertase, Muscle relaxants ■ Maternal fever and hyperthermia, acidosis, infections ■ Early amniocentesis/Chorionic villus sampling (low risk)
	7. Maternal disorders	■ Maternal neuromuscular disorders (myotonic dystrophy) ■ *Diabetes mellitus* ■ *Myasthenia gravis* ■ Multiple sclerosis ■ Maternal antibodies anti-receptors of the neurotransmitter subunits

Table 3 Ultrasound semiology of AMC

Foetal anomalies detectable in ultrasound for the prenatal diagnosis of AMC	■ Knee hyperextension ■ Uni or bilateral talipes equinovarus ■ Fixity of extremities ■ Flexion of upper limbs (frequently) ■ Hand clenching (flexion of the fingers, lack of opening and closing movements in fingers and hands) ■ Hypokinesia/foetal akinesia ■ Deficient ossification of long bones (osteoporosis) ■ Polyhydramnios ■ Oligohydramnios ■ Ventriculomegaly ■ Vermian agenesis ■ Renal anomalies ■ Lissencephaly ■ CNS anomalies ■ Agenesis of the corpus callosum ■ Cystic hygroma or NT " ■ Facial defects* ■ Microcephaly* ■ Cataract*
**Anomalies particularly occurring in neurological arthrogryposis*	

The first ultrasound signs that drew attention on the musculoskeletal contracture were the abnormal position of the limbs and foetal hypokinesia/akinesia during the examination, even under the conditions of an ultrasound study lasting 45-60 minutes. AMC may be associated with many foetal malformations, but the thorough and serious ultrasound examination did not identify major respiratory, kidney, central nervous system disorders or facial defects. Taking into account the heterogeneity of manifestations, the associated

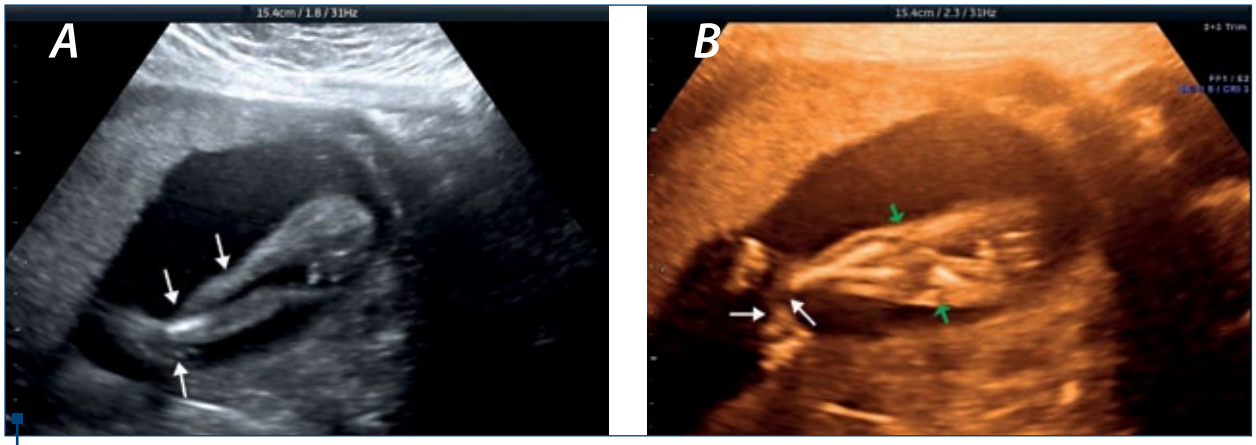

Figure 1. A. Image on longitudinal section in sagittal plane, proving the unilateral talipes equinovarus, right leg (white arrows), and excess of amniotic fluid. B. Sagittal image proving the unilateral talipes equinovarus, right leg (white arrows), knee hyperextension (green arrows), fixity of legs (personal collection)

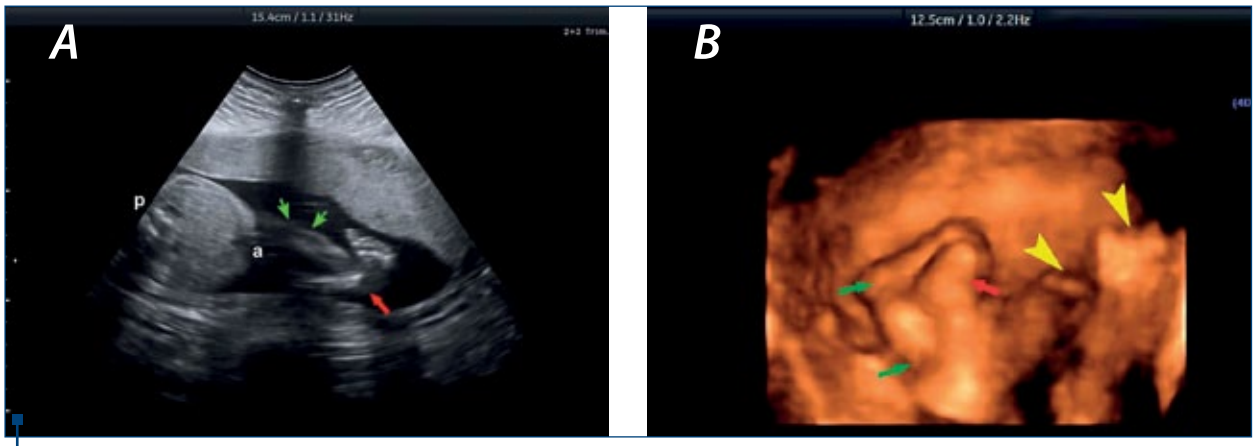

Figure 2. A. Cross image (a-anterior, p-posterior) proving unilateral talipes equinovarus, right leg (red arrow), fixity of the knees (green arrows) and ankles. B. Three-dimensional reconstruction of the upper and lower limbs proving unilateral talipes equinovarus, right leg (red arrow), fixity of the knees and ankles, knee hyperextension (green arrows), fixity of the wrists and finger joints, fixed flexion of the fingers - overlapping fingers (yellow arrows), (personal collection)

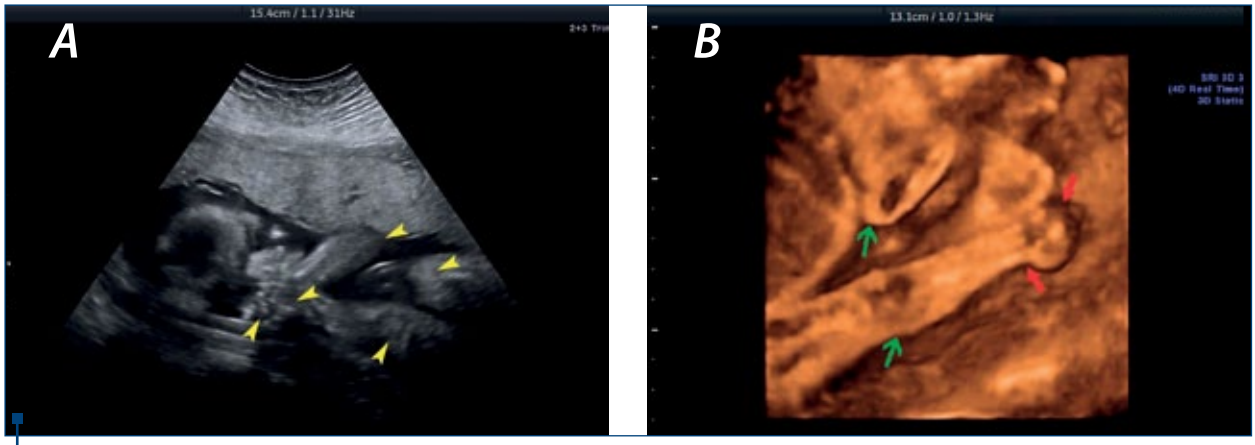

Figure 3. A. Image proving the fixed flexion of the elbows, hands and knees (yellow arrows), oligohydramnios. B. Three-dimensional reconstruction of the lower and upper limbs proving unilateral talipes equinovarus, right leg (red arrows), fixity of the knees and ankles, knee hyperextension, fixed flexion of the elbows (green arrows), (personal collection)

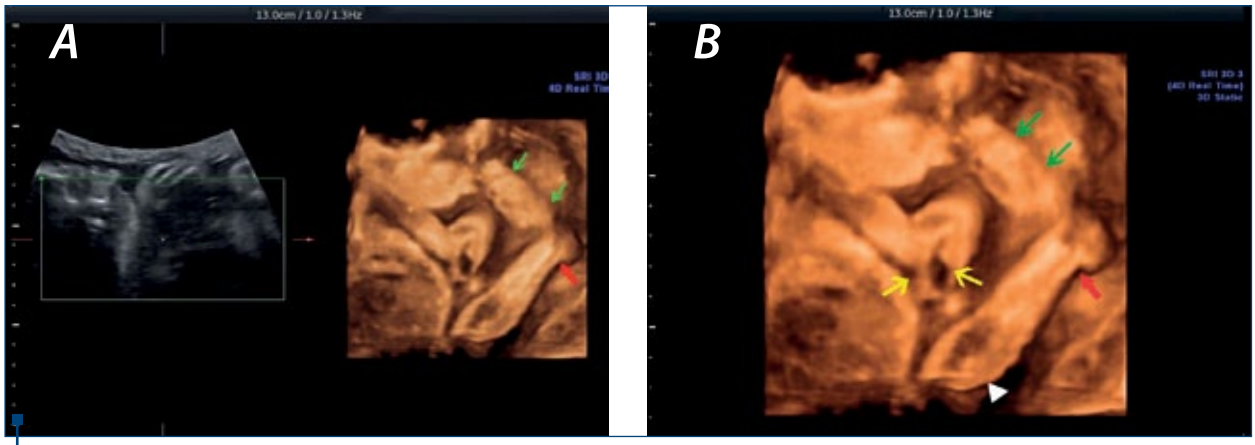

Figure 4. Three-dimensional reconstruction of the lower and upper limbs proving unilateral talipes equinovarus, right leg (red arrows), left leg in normal position (green arrows), fixed hyperextension of the thighs (white arrow), fixed flexion of the right elbow (yellow arrows), (personal collection)

anomalies and the ultrasound expression thereof, the differential diagnosis of AMC is required to be performed (Table 4).

Although the differential diagnosis of this anomaly can be done with more than 150 malformations that are associated with musculoskeletal contracture, the abnor-

Table 4 Differential diagnosis of AMC

Freeman-Sheldon Syndrome (Distal arthrogryposis, type 2A)[1,2,11]	■ Characteristic facies ■ Flexion and ulnar deviation of the fingers ■ talus verticalus
Congenital contractual arachnodactyly (Beals Syndrome)[1,8,11]	■ ear deformities ■ finger contractures
Pena-Shokeir Syndrome[2,8]	■ severe intrauterine growth restriction ■ short umbilical cord ■ pulmonary hypoplasia ■ micrognathia ■ facial defects
Antley-Bixler Syndrome[1,8,12]	■ abnormal shape of the head ■ micrognathia ■ craniosynostosis ■ foetal hypokinesia
Lethal multiple pterygium syndrome[1,6]	■ cystic hygroma ■ flexion/ contracture of the limbs ■ foetal hypokinesia
Smith-Lemli-Optitz Syndrome[1,8,13]	■ microcephaly ■ heart malformations ■ genital ambiguity ■ syndactyly ■ polycystic/hypoplastic kidney/hydronephrosis ■ intrauterine growth restriction
Amniotic band syndrome[1]	■ hypokinesia ■ facial/limb deformities
Cerebro-oculo-facio-skeletal Syndrome[1,2,8]	■ severe facial anomalies ■ generalised contracture ■ severe CNS anomalies ■ recessive autosomal transmission
Amyoplasia[2,8,14]	■ symmetrical contracture (all 4 limbs) ■ characteristic position of the limbs ■ marked reduction of the muscle mass ■ moderate micrognathia
Genetical anomalies[1,2,7]	■ Trisomy 18, 9, 10, Deletion 4p (Wolf-Hirschhorn Syndrome), Triploids

mal position of the limbs or foetal hypokinesia/akinesia, we present in this study herein the essential differential diagnosis of AMC in terms of ultrasound semiology. Due to the association of AMC with multiple genetic syndromes, the foetal karyotype has been done in all cases (1 retrospective case), revealing 2 cases of 46,XX and 1 case of 46,XY. The foetal prognosis depends on the degree of functional musculoskeletal impotence and gravity of the related anomalies. Due to the heterogeneity of manifestations, on the one hand, and multiple types of expressing the musculoskeletal contracture on the other hand, with various forms of specific postnatal manifestations, the

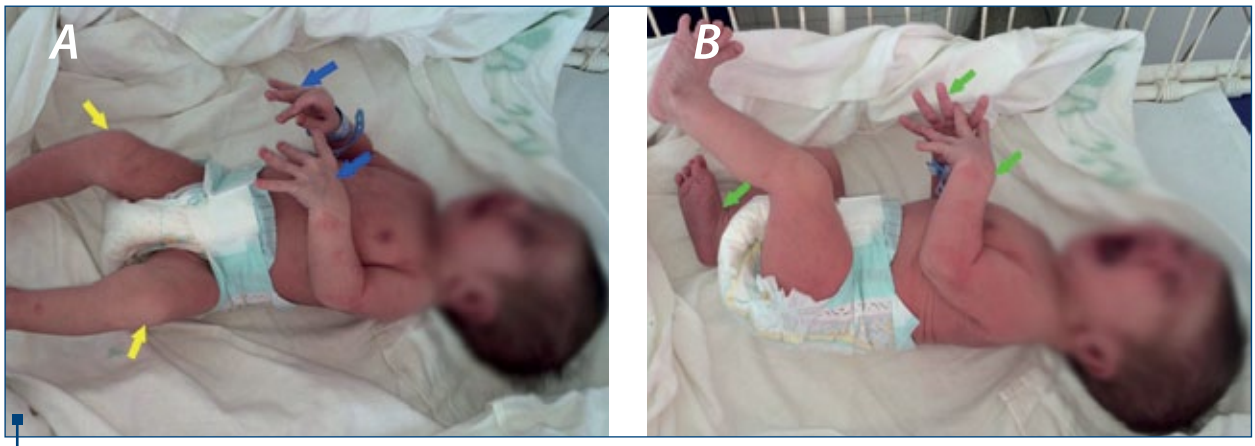

Figure 5. Images demonstrating fixed flexion of the elbows and hands (blue arrows), fixed hiperextension of the knees (yellow arrows), right talipes equinovarus, muscular contractures and rigidity (personal collection)

complete and accurate diagnosis is almost impossible to be stated at prenatal stage (Figure 5)[2,15-17].

The maternal factors that may influence the foetal prognosis in AMC are infections, fever, hyperthermia, exposure to teratogens or the uterine tumours[2].

Maternal myasthenia gravis is a factor that significantly deteriorates the foetal prognosis in the cases with AMC[2,6].

The associated anomalies, particularly the prenatal prediction of the postnatal respiratory insufficiency, due to pulmonary hypoplasia, renal agenesis, severe malformations of the CNS or genetic anomalies are severe or even lethal foetal prognosis factors[2,18,19].

AMC is a prenatal diagnosis with very varied phenotypic expression, with dominant autosomal transmission, in distal congenital arthrogryposis, while in the other forms of AMC the transmission is recessive or related to chromosome X[1,19-23].

Although the risk of recurrence is low[7], our study includes two recurrent cases at the same couple of progenitors, a case with AMC, female (46,XX), a second child, perfectly healthy, female and the third child, AMC, male (46,XY).

Conclusions

Arthrogryposis involves a sequence of neurological, muscle and connective tissue disorders, which leads to severe limitation of the joint mobility, contracture and rigidity. AMC has the muscle contracture and limitation of the foetal joint mobility as central, universally recognised element. AMC is in fact a descriptive term, and not one for diagnosis, with multiple etiopathogenic substrates and different phenotypic models. The ultrasound diagnosis of AMC must be suspected when hypokinesia/akinesia, the limitation of foetal joint mobility, the abnormal position or conformation of the limbs are obvious at foetal examination. The foetal prognosis depends on the degree of functional musculoskeletal impotence and gravity of the related anomalies. Although the risk of recurrence is low, our study includes two recurrent cases at the same couple of progenitors, in a pathology with an incidence that is also low. ■

References

1. Benacerraf B. Ultrasound of the Fetal Syndromes, Second Edition. Churchill Livingstone Elsevier, 2008, 362-5.
2. Bianchi DW, Crombleholme TM, D'Alton ME, Malone FD. Fetology-Diagnosis and Management of the Fetal Patient, Second Edition. McGraw-Hill Medical, 2010, 697-704.
3. Shapiro F, Specht L. The diagnosis and orthopedic treatment of childhood spinal muscular atrophy, peripheral neuropathy, Friedreich ataxia and arthrogryposis. J Bone Joint Surg Am 1993, 75, 1699-714.
4. Beals RK. The distal arthrogryposes: a new classification of peripheral contractures. Clin Orthop Relat Res 2005, 435, 203-10.
5. Callen PW (Editor). Ultrasonography in Obstetrics and Gynecology, 5th Edition. Saunders Elsevier, Philadelphia, 2008, 123.
6. Rodeck CH, Whittle MJ (Editors). Fetal Medicine - Basic Science and Clinical Practice, Second Edition. Churchill Livingstone Elsevier, 2009, 191.
7. Pelinescu Onciul D, Vlădăreanu R. Anomalii fetale diagnostic și conduită. Editura Medicală Antaeus, București, 2007, 261-89.
8. Stevenson RE, Hall JG. Human Malformations and Related Anomalies, Second Edition, Oxford University Press, New York, 2006, 925-33.
9. Hall JG, Vincent A. Arthrogryposis. In: Neuromuscular Diseases of Infancy, Childhood, Adolescence - A Clinician's Approach. Jones H, De Vivo DC, Darris BT. Heinemann, Amsterdam, 2002, 123.
10. Sung SS, Brassington AM, Krakowiak PA et al. Mutations in TNNT3 cause multiple congenital contractures: a second locus for distal arthrogryposis type 2B. Am J Hum Genet 2003, 73, 212.
11. Bonilla-Musoles F, Machado LE, Osborne NG. Multiple congenital contractures (congenital multiple arthrogriposis). J Perinat Med 2002, 30, 99-104.
12. Witters I, Moerman P, Fryns JP. Fetal akinesia deformation sequence: a study of 30 consecutive in utero diagnoses. Am J Med Genet 2002, 113, 23-8.
13. Murphy JC, Neale D, Bromley B et al. Hypoechogenicity of fetal long bones: a new ultrasound marker for arthrogryposis. Prenat Diagn 2002, 22, 1219-22.
14. Ruano R, Dumez Y, Dommergues M. Three-dimensional ultrasonographic appearance of the fetal akinesia deformation sequence. J Ultrasound Med 2003, 22, 593-9.
15. Borglen L, Amiel J, Viollet L et al. Survival motor neuron gene deletion in the arthrogryposis multiplex congenita-spinal muscular atrophy association. J Clin Invest. 1996, 98, 1130-2.
16. Chen CP. Arthrogryposis of the wrist and ankle associated with fetal trisomy 18. Prenat Diagn 2005, 25, 423-5.
17. Smith DW, Drennan JC. Arthrogryposis wrist deformities: results of infantile serial casting. J Pediatr Orthop 2002, 22, 44-7.
18. Bianchi DW, Van Marter LJ. An approach to ventilator dependent neonates with arthrogryposis. Pediatrics 1994, 94, 682-6.
19. Nowlan NC. Biomechanics of foetal movement. Eur Cell Mater 2015, 29, 1-21.
20. Rossor AM, Oates EC, Salter HK et al. Phenotypic and molecular insights into spinal muscular atrophy due to mutations in BICD2. Brain. 2015, 138(Pt 2), 293-310.
21. Dicke JM, Piper SL, Goldfarb CA. The Utility of Ultrasound for the Detection of Fetal Limb Abnormalities - a 20 year Single Center Experience. Prenat Diagn 2015, 35(4), 348-53.
22. Patil SJ, Rai GK, Bhat V et al. Distal arthrogryposis type 5D with a novel ECEL1 gene mutation. Am J Med Genet A 2014, 164A(11), 2857-62.
23. Drury S, Boustred C, Tekman M et al. A novel homozygous ERCC5 truncating mutation in a family with prenatal arthrogryposis--further evidence of genotype-phenotype correlation. Am J Med Genet A 2014, 164A(7), 1777-83.