Sonography has become an essential diagnostic tool for imaging in obstetrics. Sonography can identify abnormalities in both structure (i.e., short long bones, cardiac abnormalities) and function (e.g., lack of normal movement of extremities and abnormal cardiovasculature). Assessment of normal function of the musculoskeletal system is an essential part of the prenatal sonographic evaluation. Arthrogryposis multiplex congenita (AMC) is a syndrome that is defined by the abnormal position of two or more joints. The cause of AMC is believed to be decreased fetal movement or fetal akinesia.1

Case Report
A 29-year-old woman presented for a routine second-trimester morphology sonogram at 20 weeks of pregnancy. The first-trimester sonogram was unremarkable. The sonogram revealed an intrauterine pregnancy with multiple fetal anomalies. The arms and hands were abnormally flexed and did not move from this position during the course of the examination (Figures 1–3). Both legs were persistently flexed at the hip and knee. The right leg was notable for the presence of a club foot (Figure 4), and there were additional abnormalities in the position of the toes (Figure 5). The left leg had only a single bone distal to the knee (Figure 6). There did not appear to be a fully formed left foot (Figure 7). The fetal brain was difficult to visualize because of fetal position. The bilateral ventricles were not well visualized at the time of the initial morphology scan but were felt to appear normal at the follow-up examination. The amniotic fluid appeared increased for the gestational age with the maximum

Figure 1. A 3D sonogram demonstrating abnormally flexed arms and hands.

1University of Missouri Women’s and Children, Columbia, MO, USA

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Corresponding Author:
Amy Bildner, RDMS, RDCS, RVT, University of Missouri Women’s and Children, 500 North Keene Street, Columbia, MO, USA.
Email: Bildnera@health.missouri.edu
vertical pocket (MVP) measuring 9.91 cm. A single umbilical artery, hypoplastic nasal bone, and micrognathia were also visualized (Figure 8). There were no obvious cardiac or renal anomalies. A genetic amniocentesis was performed under sonographic guidance, and results demonstrated normal microarray.
The pregnancy was followed with monthly sonograms to assess fetal growth and weekly biophysical profiles (BPP) starting at 32 weeks’ gestation. Weekly umbilical artery Doppler studies were performed because of the finding of intrauterine growth restriction at 34 weeks’ gestation.

At 37 weeks’ gestation, a routine BPP was scored at 2/8 because of inadequate gross body movement, tone, and fetal breathing being observed during the examination. Polyhydramnios was present with a maximum vertical pocket of 8.83 cm and amniotic fluid index of 32 cm. The patient was sent to the labor and delivery area, where the fetal heart tracing was noted to be nonreassuring and cesarean delivery was performed. The surgery was uncomplicated with an estimated blood loss of 800 mL (deemed to be normal). Upon delivery, the infant was brought to the resuscitation room. The infant was placed under a radiant warmer and stimulated but was noted to be limp and breathing spontaneously. Multiple congenital anomalies were appreciated during this initial examination, including contractures in all four limbs and a short left lower limb. Pulse oxygen and a temperature probe were placed. At this time, the infant developed moderate subcostal and supraternal retractions and coarse breathing sounds. The decision was made to transfer the patient to the neonatal intensive care unit due to the infant’s respiratory distress. Otolaryngology was consulted for evaluation and establishment of a definitive airway. The patient did not respond to positive pressure ventilation or continuous positive airway pressure. Intubation was attempted, but secondary to poor jaw opening, a view of the epiglottis was unable to be obtained, and the airway was temporized emergently with a laryngeal mask airway (LMA).

Orthopedics, cardiology, neurology, and genetics consults were recommended. An echocardiogram was performed and revealed a small midmuscular ventricular septal defect (VSD). Also noted was a posterior pulmonary venous confluence with unobstructed drainage into the left atrium. Normal left ventricle systolic function was noted. The VSD and abnormal pulmonary venous anatomy did not seem to be hemodynamically significant at that time. A prenatal sonographic diagnosis of VSDs and pulmonary venous abnormalities can be difficult. Because of the lack of a pressure gradient between the ventricles in utero, small VSDs may not be visible on gray-scale echocardiography.2 Given the patient’s history and presentation, it is likely that her respiratory distress was due to upper airway obstruction/micrognathia given good pulmonary compliance and functionally normal anatomy.

Orthopedics confirmed findings of severe contractures (Figure 9). The right arm appeared to be well developed with good range of motion of the shoulder and elbow. The left upper extremity was smaller than the right. Shoulder range of motion appeared to be adequate; however, the left elbow had limited range of motion from full extension to about 40° of flexion. There were flexion contractures of the wrist and fingers (Figures 10 and 11). Five fingers were present bilaterally. The right leg appeared clubbed with cavus abductus and equinus deformity (Figure 12). The left leg was dysplastic. There appeared to be a knee and a proximal segment of the tibia with a foot that was void of any bone or cartilage (Figures 13 and 14).

Radiographs of the arms and legs further confirmed these findings. The right humerus and forearm bones were completely formed and appeared normal in size. Radiographs of the right lower arm/hand revealed ulnar deviation of the second through fifth proximal phalanges.
There were flexion contractures of the second and fifth interphalangeal joints with diffusely hypoplastic distal phalanges. Radiographs of the left arm demonstrated a hypoplastic arm and forearm bones (Figure 15). The arm and forearm were asymmetrically shorter and thinner compared with the contralateral side. There were flexion contractures at the metacarpophalangeal joints. There were flexion contractures of the second and fifth interphalangeal joints with diffusely hypoplastic distal phalanges. Radiographs of the left arm demonstrated a hypoplastic arm and forearm bones (Figure 15). The arm and forearm were asymmetrically shorter and thinner compared with the contralateral side. There were flexion contractures at the

**Figure 10.** Postnatal image of the left arm demonstrating flexion contractures of the elbow, wrist, and fingers.

**Figure 11.** Postnatal image of the left wrist demonstrating flexion contractures of the wrist.

**Figure 12.** Postnatal image of the left and right legs. A short left limb and clubbed right foot is demonstrated in this postnatal image.

**Figure 13.** Postnatal image of the dysplastic left leg that felt void of any bone or cartilage.
left wrist and distal interphalangeal joints with hypoplastic/malformed distal phalanges (Figure 16). There appeared to be a hypoplastic first metacarpal. Additional radiographs of the lower extremities revealed severe pes cavus of right lower extremity with dorsiflexion of the calcaneus and abnormally increased calcaneal pitch angle (Figure 17). A radiograph of the right foot was also obtained. The right foot was plantarflexed and inverted with abnormally positioned toes (Figure 18). The left lower leg radiograph demonstrated a femur and the proximal segment of tibia and fibula as well as a dislocated left hip (Figure 19).

Neurology recommended pediatric magnetic resonance imaging (MRI) of the brain because of poor visualization of the lateral ventricles in utero and multiple fetal anomalies. The MRI demonstrated extensive bilateral supratentorial cortical abnormalities with predominant pattern of pachygyria. There was also focal polymicrogyria involving the left insula suggestive of closed-lip

Figure 14. Postnatal image of the dysplastic left leg.

Figure 15. Radiograph of the dysplastic left arm and forearm with flexion contractures at the wrist.

Figure 16. Radiograph of the left hand demonstrating flexion contractures of the wrist and distal interphalangeal joints with hypoplastic/malformed distal phalanges.

Figure 17. Radiograph of the right lower leg demonstrating severe pes cavus with dorsiflexion of the calcaneus and abnormally increased calcaneal pitch angle.
schizencephaly involving the inferior right frontal gyrus, right insula, and superior temporal lobe. Schizencephaly is defined by abnormal clefts in the cerebral hemispheres and can affect one or both sides of the brain.

Genetics further examined the patient. The patient was found to have dysmorphic facies, micrognatia, syndactyly of the toes, and camptodactyly of the fingers. Except for occasional recreational marijuana use and prenatal vitamins, the patient denied any prescription or over-the-counter medications, alcohol, infections, or other potential teratogens. Genetics recommended a whole exome sequencing. Whole exome sequencing evaluates all exomes in the genome. It is able to detect genetic disorders that would not be detected by a microarray. Because of the potential for misinterpretation of the results and the increased cost, whole exome sequencing is not recommended as first-line genetic testing in obstetrics. It can be useful in cases such as this with multiple fetal anomalies and a normal microarray. The whole exome sequencing came back with normal results. Therefore, it is difficult to combine these findings under a single unifying diagnosis. However, they are most consistent with a diagnosis of AMC.

Discussion

AMC is rare, with a prevalence of 1 in 3000 live births with equal gender ratios. The term arthrogryposis is derived from the Greek word meaning “curved or hooked joints.” Contractions range in severity from a clubbed foot to the lethal Pena-Shokeir phenotype, which is characterized by facial anomalies, multiple joint contractures, polyhydramnios, intrauterine growth restriction, and pulmonary hypoplasia. Fetal movement can be recognized with sonography by 8 to 9 weeks’ gestation; however, contractures are difficult to identify in the first trimester. The most common time to diagnose contractures is during the second trimester. Arthrogryposis is often an incidental finding. A club foot is the most common isolated finding identified during a routine second-trimester sonogram, with a prevalence of 1 in 500 live births. If one joint contracture or anomaly is noted, a comprehensive evaluation of all limbs and joints should be performed. The differential diagnosis is broad, and the workup includes a recommendation for invasive genetic testing (microarray and karyotype analysis); complete anatomic survey with assessment for vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities; and a family history. Some cases are identified only later in pregnancy, when a sonogram is urged because of decreased fetal movement. In this setting, it may be reasonable to defer genetic testing until after delivery.

Although the diagnosis of AMC is more common in the second and third trimester, there are reports of affected fetuses demonstrating anomalies in the first trimester. In a study of 27 cases of lethal congenital arthrogryposis, 26% of the fetuses presented with nuchal edema during second- or third-trimester sonography examinations. Of these cases, two had previously demonstrated nuchal translucency thickness of greater than the 99th percentile for gestational age during the first-trimester sonogram. Based on these limited findings, it may be important to consider lethal arthrogryposis in the differential diagnosis, given a thickened nuchal translucency. This highlights the importance of counseling
patients that in the setting of a thickened nuchal translucency and normal microarray on chorionic villus sampling or amniocentesis, there remains an increased risk of adverse perinatal outcome.7

The pathogenesis of AMC is unknown. The condition has been reproduced in animal models by “viruses, neuromuscular blocking agents, hyperthermia and limb immobilization.”1,4,5 In an early animal study from 1969, chickens and rats were immobilized early in fetal development.8 This led to multiple anomalies, including intrauterine growth restriction, generalized contractures, shortened extremities, pulmonary hypoplasia, shortened and premature gut, and craniofacial changes.9 These anomalies are features of the lethal Pena-Shokeir phenotype of arthrogryposis.5 Broadly speaking, the differential diagnosis can be thought of in terms of extrinsic (oligohydramnios) and/or intrinsic (neurologic) insult resulting in a loss of muscle mass that produces connective tissue around the joint and causes fixation.4,5,8 Oligohydramnios may be due to early rupture of membranes, fetal renal agenesis, or bladder outlet obstruction. Fetal neurologic insult can be caused by a number of factors, including infection (cytomegalovirus, toxoplasmosis, or Zika virus), fetal cerebral vascular accident resulting in schizencephaly or porencephaly, aneuploidy, and or a number of syndromic conditions, the most common of which is spinal muscular atrophy type I Werdnig-Hoffmann disease. Recurrence risk depends on the underlying etiology. For example, spinal muscular atrophy (SMA) is inherited in an autosomal recessive pattern, and carrier parents would have a 25% risk of having another affected child. Genetics consultation and individualized assessment of recurrence risk is recommended.

The etiologies of AMC can be separated into subcategories, as a way of producing differential diagnosis.4 This includes neurologic diseases, connective tissue defects, muscle abnormalities, limitations in utero, intrauterine fetal vascular compromise, and maternal disease.1,4,5,8 Neurologic anomalies comprise 70% to 80% of cases of AMC.1,4,5 The most common neurologic anomaly is anterior horn cell disease and SMA.1,4 Maternal myasthenia gravis has been reported to cause decreased fetal movement due to the transfer of acetylcholinesterase receptor antibodies across the placenta. Other muscular disorders that may cause AMC include but are not limited to muscular dystrophy, myopathies, myositis, and mitochondrial disorders.4 Regardless of the underlying mechanism, fetal motion is vital for appropriate growth of fetal joints. A lack of motion triggers a collagenic response around the joints, causing contractions or joint fixations.4 Syndromes that may cause joint fixation and are most commonly associated with AMC include Larsen dysplasia, Beal contractual arachnodactyly, and pterygium syndrome.4 Insufficient blood supply to the fetus during utero can also cause contractures. Inadequate blood supply can lead to fetal hypoxia, which leads to fetal cell death, most commonly anterior horn cell death.4 This cell death causes damage in the neurons, muscles, and bones and as a result develops multiple contractures.4 Lastly, maternal disease such as multiple sclerosis, myotonic dystrophy, diabetes mellitus, and infection have all been closely associated with akinesia or AMC.4

Management and treatment of AMC must be initiated as early as possible to achieve optimal results. The primary long-term treatment goal is improved joint mobility and attaining the best quality of life, whether independent daily living or social involvement.1,9 Each treatment plan is exclusively tailored to each patient and most often includes a team of pediatricians, orthopedic surgeons, geneticist, occupational/physical therapists, and a case manager.5 With surgical and therapy treatments available, significant improvements in mobility and joint function are possible. Casting or splinting is the most common treatment option. This involves repositioning the affected limb into the most normal position achievable and then immobilizing it for long periods of time. This process is repeated every 1 to 2 weeks or as recommend by occupational/physical therapist to increase range of motion. If repositioning and immobilization fail to move the involved extremity to a normal position, surgery may be recommended. Most commonly, contractures are an isolated finding; however, in more extreme cases, contractures are associated with lethal genetic disorders (Trisomy 18, Trisomy 13 Pena-Shokeir syndrome) and therefore have a poor prognosis. In this particular case, the infant received progressive thermoplastic splints. The left wrist was placed in a neutral position with the digits in extension. The right hand was also splinted to improve alignment and structural integrity. Routine passive range of motion numerous times per day with therapy was also performed. The right leg was casted, and the infant was placed in a Pavlik harness due to findings of bilateral hip dysplasia.

Conclusion

Prenatal diagnosis of AMC is made based on fetal sonographic findings. The very subtle abnormally postured limbs can be difficult to visualize, and therefore fetal movement is important to visualize during routine examinations. The differential diagnosis for AMC is broad and requires a substantial diagnostic workup. Establishment of an underlying etiology is essential to inform families regarding prognosis, arrange for appropriate treatment, and provide an estimation of recurrence risk for future pregnancies.
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References
1. What statement best defines arthrogryposis multiplex congenita (AMC)?
   a. Believed to be caused by increased fetal movement
   b. Biophysical profiles document gross body movement
   c. Syndrome defined by the abnormal position of two or more joints
   d. Differential diagnosis is narrow and requires a limited diagnostic workup

2. Which subcategory of AMC etiologies comprise 70% to 80% of cases?
   a. Connective tissue defects
   b. Intrauterine fetal vascular compromise
   c. Maternal disease text
   d. Neurologic anomalies

3. In cases of AMC, what is the most common isolated finding identified during a routine second-trimester sonogram with a prevalence of 1 in 500 live births?
   a. Club foot
   b. Nuchal edema
   c. Renal anomalies
   d. Cardiac defects

4. Although the pathogenesis of AMC is unknown, which fetal neurologic infection insult can cause factors leading to AMC?
   a. Fetal cerebral vascular accident
   b. Aneuploidy
   c. Porencephaly
   d. Cytomegalovirus

5. Which genetic test is not recommended as the first-line genetic testing in obstetrics because of its increased cost and the potential for misinterpretation of results?
   a. First-trimester translucency measurement
   b. Whole-exome sequencing
   c. Genetic amniocentesis
   d. Microarray
6. Which maternal disease has been reported to cause decreased fetal movement due to the transfer of acetylcholinesterase receptor antibodies across the placenta?
   a. Myasthenia gravis  
   b. Muscular dystrophy  
   c. Mitochondrial disorders  
   d. Myositis

7. The differential diagnosis may be due to which extrinsic (oligohydramnios) insult?
   a. Zika virus  
   b. Schizencephaly  
   c. Bladder outlet obstruction  
   d. A syndromic condition

8. In this case study, which extremity was spared severe contractures?
   a. Left upper extremity  
   b. Right upper extremity  
   c. Left lower extremity  
   d. Right lower extremity

9. What response from a lack of fetal motion contributes to contractions or joint fixations?
   a. Limb repositioning  
   b. Growth restriction  
   c. Collagenic response around joints  
   d. Mid-muscular ventricular septal defect

10. What is the purpose of placing an infant in a Pavlik harness?
    a. Treat bilateral hip dysplasia  
    b. Place extremity in a neutral position  
    c. Add structural integrity to spinal column  
    d. Adjust plantarflexion