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Uterine Structural Anomalies and Arthrogryposis—Death of an Urban Legend

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In a review of 2,300 cases of arthrogryposis collected over the last 35 years, 33 cases of maternal uterine structural anomalies were identified (1.3%). These cases of arthrogryposis represent a very heterogeneous group of types of arthrogryposis. Over half of individuals affected with arthrogryposis demonstrated asymmetry and some responded to removal of constraint, 29 of the 33 cases of arthrogryposis whose mother had a uterine structural anomaly could be identified as having a specific recognizable type of arthrogryposis. Only two cases (0.08%) had primarily proximal contractures that returned to almost normal function within 1 year. Craniofacial asymmetry was the most striking finding in these two cases. A quarter of cases had ruptured membranes between 32 and 36 weeks and either oligohydramnios or prematurity. The pregnancy histories of the mothers with uterine structural anomalies were typical in having infertility, multiple miscarriages, and stillbirths. The finding of only two cases which are likely to have multiple congenital contractures on the basis of uterine constraint suggests that it is a very rare primary cause of arthrogryposis. © 2012 Wiley Periodicals, Inc.

Key words: uterine anomalies; bicornuate uterus; arthrogryposis; constraint; deformation; compression; oligohydramnios; multiple congenital contractures

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INTRODUCTION

Arthrogryposis multiplex congenita (AMC) is the term which has been used for nearly a century to describe conditions with non-progressive multiple congenital joint contractures. The conditions that have been described as AMC range from well-known syndromes to non-specific combinations of joint contractures [Hall, 2012]. The shorter term "arthrogryposis" is often used to imply multiple congenital joint involvement and should be reserved for conditions present at birth which are non-progressive and that involve more than one limb or part of the body. The exact pathogenesis of most cases of arthrogryposis is not known, but all involve decreased fetal movement (e.g., fetal akinesia). The suggested mechanisms for decreased fetal movement include abnormalities of nerve structure or function (including both central and peripheral nervous systems), abnormalities of muscles (both structure and function), abnormalities of endplate structure and function, abnormalities of connective tissue, limitations of space or movement within the uterus, intrauterine vascular compromise, maternal illness and exposure to specific drugs or medications. Once fetal akinesia occurs, contractures at involved joints begin to develop, the longer the decreased fetal movement, the more severe the limitation of joint movement and the more likely that pterygia or constraining connective tissue will develop around the joint [Hall, 2012].

Miller et al. [1979] reported the combination of uterine malformation and fetal deformation. They found 14 examples of fetal deformations which they attributed to maternal uterine malformations and constraint of fetal movement. They related the fetal deformities to the molding of fetal tissue as a response to the aberrant constraint. The report emphasized the importance of recognizing that uterine constraint might lead to multiple structural changes. The presenting case in their report died of pulmonary hypoplasia with severe asymmetric deformations, and all of their reported survivors showed restoration toward normal limb function relatively rapidly postnatally. These authors emphasize that early delivery by C-section (which also would identify the specific uterine structural abnormalities) was advantageous. The misshapen head, flattened enlarged ears, small chest, and edema of the limbs which their cases demonstrated were all thought to be secondary to the constraint imposed on the fetuses by being on one side of a bicornuate uterus or caught by a septum. The tip of the nose was depressed in several fetuses which had been in breech position, suggesting the uterine wall had put pressure on the growing nose.

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Early respiratory distress was frequent and thought to be related to decreased respiratory movements in utero because of constraint with subsequent pulmonary hypoplasia.

In their report, the deformations of the survivors were of mild to moderate severity. Normal fetal in utero position was seen, but breech and transverse lies were also frequent. Distal contractures were less severe than proximal contractures. Deformations were considered to be due to extrinsic biomechanical factors, in this case, external uterine constraint. ''The pliable growing fetal tissues were thought to be molded in response to aberrant constraint'' more easily than after birth [Miller et al., 1979]. The authors emphasized that a normal shape of the uterine cavity allows the fetus to move, whereas the structurally abnormal uterus not only provided less space, but also the walls of the abnormal uteri could be expected to be ''deficient in uterine musculature and thus, making it less capable of expanding to accommodate the fetus.''

Two-thirds of their reported newborn infants had unusual molding of the head in some cases related to breech and transverse positions. Facial deformities occurred in three-fourths, with mandibular asymmetry, and over folded and/or flattened ears. Edema of the limbs occurred frequently, apparently due to proximal obstruction of lymph flow due to compression of the limbs. Limb deformations, including edema and contractures, were present in almost half.

The authors pointed out that pulmonary hypoplasia secondary to space constraint would be the most life threatening feature, although premature rupture of membranes leading to oligohydramnios and premature labor were seen frequently along with the sequelae of prematurity. Two of their cases had amniotic fluid leakage with Potter type facies. The authors point out that oligohydramnios could add to the compression of an abnormally shaped uterus by increasing constaint.

Subsequent to this publication, uterine structural anomalies were often assumed to be responsible for various congenital anomalies and for arthrogryposis. [Graham et al., 1980; Winter et al., 1983; Crabtree et al., 1984; Zlotogora et al., 1985; Martinez-Frías et al., 1998]. However, of course, many other causes of arthrogryposis have been identified since 1979, and many of these have a specific responsible gene identified [Hall, 2012]. Nevertheless, the concept that a uterine anomaly often causes arthrogryposis continues to exist and the author is frequently consulted on such cases.

In 1990, Fahy and Hall reported a retrospective study of pregnancy complications among 828 cases of arthrogryposis. At that time, they identified 2.3% of cases as having uterine abnormalities. This seemed quite consistent with the background rate of 2–4% of uterine anomalies in the general population of women reported by several authors [Ashton et al., 1988; Simón et al., 1991; Raga et al., 1997; Byrne et al., 2000; Grimbizis et al., 2001]. In other words, there did not seem to be an increased occurrence of arthrogryposis in women with bicornuate uterus.

We now have analyzed 2,500 cases of arthrogryposis (including the cases previously reported [Fahy and Hall, 1990]). Sixty percent of these cases have been examined personally; the others come from correspondence and review of hospital and clinic records. They span 35 years of research on arthrogryposis. There is insufficient information on 200 of those cases to be sure there is/was no maternal history of uterine anomaly. Thirty-three mothers were identified to have a uterine anomaly among the 2,300 cases of arthrogryposis (1.3%). Not all of the 2,300 cases of arthrogryposis have had follow up and many were seen prior to the introduction of present day imaging techniques. However, many had C-sections allowing a uterine anomaly to be observed. In fact, more than half of all cases of arthrogryposis have C-sections which would allow the identification of a maternal uterine anomaly. There may be a bias resulting from referred cases where the correspondent wanted to know if the uterine anomaly caused the multiple congenital contractures.

RESULTS

Thirty-three individuals with arthrogryposis were born to mothers with uterine structural anomalies. Table I shows the distribution of types of arthrogryposis in the affected individuals born to mothers with structural uterine anomalies. These were sorted into the recognizable subgroups of arthrogryposis [Hall, 2012] after transient constraint or asymmetry had resolved. Amyoplasia of the classical type, involving all four limbs is the most common specific disorder. Seven cases of Amyoplasia had all four limbs involved and one case had three limbs involvement [Hall et al., 1983a]. Types of distal arthrogryposes were the second most common category [Hall et al., 1982] and central nervous system abnormalities third most common [Hall, 1997]. This fits quite appropriately with the relative incidence of various types of arthrogryposis in the population, suggesting there is nothing special about maternal uterine structural anomalies in association with most types of arthrogryposis [Hall, 1997].

There are 2 of the 33 cases that had multiple congenital contractures at birth which resolved rapidly and probably were related to uterine constraint (0.08%). However, all 31 of the other cases reported here continued to have persistent congenital contractures that required vigorous therapy.

One of the resolving cases had a persistant facial palsy, but the limbs became normal. Both resolving cases initially had significant asymmetry, particularly of the craniofacies. Two-thirds of the other 31 cases had mild asymmetric changes suggesting constraint may have made their contractures more severe. In all of these cases, the asymmetry mostly resolved shortly after birth.

Table II shows the types of uterine anomalies which the mothers of affected children were reported to have. Systems for categorizing

TABLE I. Types of Arthrogryposis Among the 33 Cases Reported

Amyoplasia	8
Distal arthrogryposis	7
Distal arthrogryposis IIE	3
Central nervous system dysfunction	5
Lower limb only	1
Upper limb only	2
Connective tissue disorder	2
Lethal syndrome with multiple anomalies	1
Unknown type of arthrogryposis	2
Rapidly resolving	2

TABLE II. Types of Uterine Structural Anomalies Present in 33 Mothers of the Reported Cases

Bicornuate	1
Septated	11
Subseptated	9[a]
Not defined	12

[a]One case had reconstructive surgery prior to the pregnancy.

uterine structural anomalies have evolved over the years. Recently with improving imaging (particularly ultrasound and MRI) much better definition of the type of uterine structural anomaly is possible [Holden and Hart, 1983; Byrne et al., 2000; Woelfer et al., 2001; Alborzi et al., 2002; Airoldi et al., 2005; Braun et al., 2005; Jayasinghe et al., 2005; Ghi et al., 2009; Gubbini et al., 2009; Bermejo et al., 2010]. The newer systems reflect the many variations of Müllerian development [Falls, 1956; Holmes, 1956; Jones, 1981; Woelfer et al., 2001; Lev-Toaff et al., 2003; Rackow and Arici, 2007; Ghi et al., 2009; Gubbini et al., 2009].

Two-thirds of these 33 cases were ascertained after 1990 when ultrasound became readily available. Eighty-five percent of the cases had C-sections which would allow definition of the specific uterine structural anomaly. However, in 12 cases, the specific uterine abnormality was not defined, only described as a "bicornuate uterus." One subseptated uterus had had corrective surgery prior to the pregnancy. Thus, the reported uterine structural anomalies in Table II are placed in rather broad categories (however, no cases of arcuate and unicornuate uterus were seen). In addition, the distribution fits with that seen in the general population regarding the frequency types of uterine anomalies [Ashton et al., 1988; Woelfer et al., 2001; Airoldi et al., 2005; Rackow and Arici, 2007; Ghi et al., 2009; Gubbini et al., 2009; Bermejo et al., 2010]. There was only one case identified of a true bicornuate uterus.

In about one-third of the 31 cases of persistent arthrogryposis, there was obvious asymmetry and proximal limb involvement. These affected individuals had some resolution during the first year leaving a recognizable form of arthrogryposis albeit different from case to case. In another-third, there was very mild asymmetry with only mild resolution of contractures over the first year. In the final-third, there appeared to be no effect of uterine constraint on the affected fetus.

In the case where the mother had true separate horns, there was definite constraint although the child appeared to have Amyoplasia (four limb involvement) after the constraint effect resolved. In this case, there was marked hyperextension of the spine with gastroschisis at birth. However, among the other 30 non-resolving cases, the type of uterine anomaly did not seem to make a difference to the type or amount of constraint.

Review of the pregnancy histories of these 33 mothers demonstrated a rather remarkable overall history of increased miscarriage, stillbirth, and infertility consistent with what is seen in uterine anomalies in general [Van Dongen, 1956; Kurland and Rosengart, 1960; Maneschi et al., 1993; Raga et al., 1997; Proctor and Haney, 2003; Papp et al., 2006]. Five women were being treated for infertility by in vitro fertilization or fertility drugs. Eight women had had multiple miscarriages and/or stillborn fetuses (as many as five prior to the affected infant). Two mothers were documented to have had a normal child on the right side and then an abnormal child on the left. Nine families had had normal children prior to the affected pregnancy. Five families had normal children subsequent to the affected child without treatment of the uterine anomaly.

Pregnancy Complications

The majority of pregnancies concluded within 2 weeks of term, however, eight had premature rupture of membranes. Six of these delivered between 33 and 36 weeks and five of these had neonatal respiratory distress.

Pregnancies were often complicated by abnormal fetal position: nine were in breech, five in transverse position, and one was a face presentation (all had cesareans). In the other 18 pregnancies, there was nothing unusual about fetal position, however, 12 of these infants were delivered by cesarean and only six were delivered vaginally. Four pregnancies reported staining of the amniotic fluid. As noted above, five infants had significant neonatal respiratory distress—including one with vocal cord paralysis. Two infants died; one with multiple congenital anomalies not recognized as a known syndrome and one from prematurity and respiratory compromise.

Other complications of pregnancy included: one-third had fairly significant bleeding in the first trimester, one had polyhydramnios at 36 weeks, and one had severe oligohydramnios during the last part of the pregnancy after rupture of membranes. The mothers of eight affected children were known to have uterine anomalies prior to the affected pregnancy.

With regard to prenatal diagnosis of arthrogryposis, only six fetuses were diagnosed as having arthrogryposis prior to delivery. Documentation of prenatal ultrasonography was not present in many of the other cases, although it was clearly done in at least 12 additional cases where the diagnosis of arthrogryposis was missed.

Five mothers had twins diagnosed by ultrasound (on the other side of the uterus) which then went on to die early in the pregnancy (prior to 12 weeks) and to be reabsorbed. One child was part of a dizygotic twin pregnancy (the other twin being normal). Not all placentas were examined, but five records recorded marginal placenta, placenta previa, placenta acreta, small placenta, and placenta abruptia.

Family History

Family histories are of interest in that only one family had a secondary relative with clubfoot, none with dislocated hips, one with neural tube defect, one family reported family members with "loose joints," and one reported two third degree relatives with abdominal wall defects (not the family with gastroschisis). Two mothers reported other family members with many miscarriages, and two mothers reported a family history of stillborns. One mother had a sister said to have a "bicornuate uterus" and one mother was a 47,XXX/45,X mosaic.

Demographic Data

There were 17 males and 16 females in this study. Neonatal death occurred in one male and one female. The parents of the 33 cases were older than the overall groups of arthrogryposis parents and had an average mean maternal age of 32 and paternal age 34. It

should be noted that these pregnancies range from 1970 to the present time.

The births have taken place across the spectrum of the years; however, there appear to be fewer births between April and September than would be expected. This is in keeping with what is seen in the overall arthrogryposis group.

Birth weights were less than 50th centile, but not significantly below the 3rd centile for gestation, averaging about 25th centile. Again, this is in keeping with what is generally seen in various types of arthrogryposis.

Unusual Anomalies

Five cases had hyperextension of the spine at birth. This is known to occur in arthrogryposis, however, this number would be 10 times what is seen in the overall group of 2,500 and is likely related to the maternal uterine anomaly and space constraint. These cases are listed in Table III. Two seem to be related to the fetal body being caught under a uterine septum. Four of these cases of hyperextension also had rather marked asymmetry.

Other interesting or unusual anomalies observed in these cases are listed in Table IV. The only features that seem somewhat increased as compared to the overall group of arthrogryposis are facial compression (particularly upturned tip of the nose), edema of distal limbs, and true hemangiomas. Three cases had structural central nervous system abnormalities which appear to be by chance. One mother had gestational diabetes and hypothyroidism. She also had Factor V Leiden deficiency. A surprising anomaly is the presence of four cases who have double hair whorls and three of these also have true hemangiomas on various parts of their bodies.

DISCUSSION

This review of a large number of cases of arthrogryposis looking specifically for uterine anomalies does not find an increase incidence of uterine anomalies among the mothers of babies born with arthrogryposis (multiple congenital contractures). In fact, if anything there would appear to be a low rate of uterine anomalies compared to that which has been reported in the general population. It is possible this reflects having incomplete histories at the time the cases of arthrogryposis were referred.

Some constraint and compression may occur because of the uterine anomalies and was possibly seen in a third to two-thirds of cases. At least a half of these were suggestive only because of asymmetry. Mild asymmetry is actually quite common in arthrogryposis in general. The third of these cases, which appears to have more marked asymmetry and involvement of proximal joints with rapid resolution back to a more normal range of movement, may have been mildly affected by uterine constraint during the pregnancy.

Almost all of these cases can be diagnosed as having a specific type of arthrogryposis. Only two cases of this collection of 33 had their contractures resolve completely over the first year. These two cases would be in keeping with the cases reported by Miller et al. [1979] as primarily due to the constraint of the abnormal uterus. This would represent an extremely rare occurrence: 0.08% of this collection of cases with arthrogryposis.

Pregnancy histories of infertility, multiple miscarriages, prematurity, and stillbirths suggest the possibility of a uterine anomaly [Van Dongen, 1956; Kurland and Rosengart, 1960; Golan et al., 1992; Maneschi et al., 1993; Raga et al., 1997; Proctor and Haney, 2003; Papp et al., 2006], and were seen in the pregnancy histories of these mothers. Ideally, the uterine anomaly would be recognized prior to a pregnancy, treated if appropriately [Candiani et al., 1990; Heinonen, 1997; Grimbizis et al., 2001; Sinha et al., 2006], and thereafter probably not contribute to fetal deformation.

It is important to point out that there are several familial forms of uterine structural abnormalities as well as the inherited combination of uterine and urinary tract structural anomalies [Nykiforuk,

TABLE III. Newborns With Spinal Hyperextension in Cases of Arthrogryposis With Maternal Uterine Anomalies

Gender	Arthrogryposis diagnosis	Uterine anomaly	Outcome
Male	CNS dysfunction Facial asymmetry Respiratory problem at birth	Uterus with "thick partial septum" which "caught" the fetus at the waist	C-section at 33 weeks Moderate improvement in contractures by 14 months
Female	Three limb Amyoplasia Thin abdominal muscles	Non-specific subseptated uterus post myomectomy	C-section at 33 weeks typical of Amyoplasia
Male	Distal Arthrogryposis IIE	Subseptate uterus Transverse lie under septum Small placenta and thin cord	C-section at term Slow improvement of contractures with physical therapy
Male	Compression	Septate uterus Oligohydramnios Cranial molding	C-section at term Complete resolution by 2 years through physical therapy
Female	Four limb Amyoplasia with gastroschisis	True bicornuate uterus	C-section at term Typical of Amyoplasia

TABLE IV. Anomalies Among the 33 Cases of Arthrogryposis With Maternal Uterine Anomalies

Expected anomalies seen with constraint documented on these 33 cases	
Asymmetry	11
Squashed craniofacies	11
Depressed tip of nose	3
Edema of limbs	5
Respiratory distress early	8
Small chin	4
Anomalies often seen in Arthrogryposis in general, observed among these 33 cases	
Trismus	5
Torticollis	5
Cord wrapping of limb	4
Amniotic bands	2
Syndactyly or small digit	6
True hemangiomas	4
Cranial suture synostosis	2
Eye	
Esotropia	1
Ptosis	1
Cataracts	1
Deafness/hearing loss	1
GI and abdominal wall	
Gastroschisis	1
Decreased abdominal wall muscle	1
Diaphysis rectus	2
Umbilical hernia	3
Skin	
Double hair whorl	4
Scalp defect	1
Skin tag	1
Extra nipple	1
Sacral dimple	1
Limb	
Polydactyly of foot	1
Cleft foot	1
Radial clubfeet	1
Fracture at birth	3
Kyphosis	3
CNS—Structural anomalies	3

1938; Polishuk and Ron, 1974; Kurtz et al., 1980; Biedel et al., 1984; Stone et al., 2000; Cho et al., 2005; Uliana et al., 2008] in which fetal deformation might be expected to occur secondary to maternal uterine constraint. As well, there are syndromes and chromosomal anomalies in which uterine structural anomalies are known to occur [Shanks, 1956; Reece et al., 1982; Stone et al., 2000; Puvabanditsin et al., 2003; Ramirez and Lammer, 2004; Cho et al., 2005; Forzano et al., 2005; Mohan et al., 2006; Uliana et al., 2008]. Two of the 33 cases in this series have a history suggestive of a genetic form of uterine anomaly in mother.

Martinez-Frías et al. [1998] saw four times higher rate of congenital anomalies in infants born to women with bicornuate uterus. Nasal hypoplasia, omphalocele, limb deficiency, teratoma, and acardiac anencephaly were specifically noted to be increased in their study. She reported only two cases of limb contractures, among her 38 cases of maternal bicornuate uterus when compared to the control group of almost 27,000 cases of mothers of children with congenital anomalies with normal uteri. This may reflect that not all cases of bicornuate uterus were actually diagnosed.

The present study was aimed at identifying whether and how often uterine structural anomalies are associated with arthrogryposis (multiple congenital contractures), whether the uterine structural anomalies caused the arthrogryposis and what unique or specific features arthrogryposis caused by the constraint of a uterine anomaly might have.

It would appear that uterine anomalies rarely are the primary cause of arthrogryposis—<0.1% of the time. However, it also appears that as many as two-thirds of cases of arthrogryposis who were in utero in a uterus with a structural anomaly may show some minor signs of constraint which then resolve within the first year and reveal the underlying specific type of arthrogryposis.

Primarily proximal limb contractures, rapid resolution of the limb contractures with physical therapy over the first year, and marked asymmetry (particularly of the craniofacies) are associated with uterine anomaly constraint. Upturned small flattened nose, hand and foot edema, misshapen asymmetric skull and face, large ears, and spinal hyperextension may be seen with in utero constraint either related to uterine anomaly or oligohydramnios. Premature rupture of membranes appears to occur with increased frequency in the presence of uterine anomalies and was seen among these cases. Severe oligohydramnios is associated with (and was in two of these cases) pulmonary hypoplasia.

The finding of five cases of spinal hyperextension is worth noting since it is a rare finding among arthrogryposis cases in general (less than 1.4%), but represents 15% of these 33 cases. Spinal hyperextension in arthrogryposis almost surely relates to a fetus with decreased in utero movement getting caught and constrained at a specific stage of development by limitation of fetal movement secondary to oligohydramnios or by a uterine structural anomaly. The important point here is that the fetus with spinal hyperextension would likely suffer spinal cord damage without C-section.

Is it possible that a uterine anomaly predisposes to arthrogryposis in other ways than constraint? Since the wall of a uterus with a structural anomaly may have less endometrium, muscle or vascular supply, a uterine structural anomaly may predispose to abnormal implantation, and subsequently to abnormal placenta and vascular supply which could in turn predispose to arthrogryposis and intrauterine growth retardation. These data do not seem to support that possibility. However, the one case of uterine repair prior to conception of the child with arthrogryposis could be related.

Bicornuate uteri may be at increased risk for twin pregnancies [Tompkins, 1962; Green et al., 1979; Ahram et al., 1984; Narlawar et al., 2003; Singhal et al., 2003; Arora et al., 2007] (possibly via superfetation) particularly with assisted reproductive technologies and IVF [Barmat et al., 1996; Aruh et al., 2005; Suh et al., 2005]. Twin pregnancies appear to have an increased risk for arthrogryposis, particularly of the Amyoplasia type [Hall et al., 1983b]. Five of these mothers reported "vanishing twins" during their pregnancies and one pregnancy was a dizygotic twin.

Thus in summary, the "urban legend" that maternal uterine structural anomalies cause arthrogryposis seems to be untrue.

Rather maternal uterine structural anomalies appear to occasionally increase the severity of limb contractures in a fetus with already existing arthrogryposis.

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