RESEARCH ARTICLE

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Oligohydramnios Sequence Revisited in Relationship to Arthrogryposis, With Distinctive Skin Changes

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Thirty cases of arthrogryposis associated with longstanding oligohydramnios were identified among 2,500 cases of arthrogryposis (1.2%) and were reviewed for clinical features and natural history. None had renal agenesis or renal disease. Twenty-two had a history of known rupture of membranes. Only 50% had pulmonary hypoplasia at birth and only two died (7%). Sixty percent (18/30) seemed to have their multiple congenital contractures (MCC) primarily on the basis of compression related to the longstanding oligohydramnios and responded well to physical therapy. On average they did not have intrauterine growth restriction. "Potter" facies and remarkable skin changes were present in all. An excess of males was observed in spite of the lack of genitourinary anomalies. © 2014 Wiley Periodicals, Inc.

Key words: arthrogryposis; multiple congenital contractures; abnormal hair pattern; amniotic fluid leakage; attempted termination of pregnancy; chorionic villus sampling (CVS) compression; deformation; dimple; excess skin; large ears; male excess; multiple congenital anomalies; oligohydramnios; Potter syndrome; pulmonary hypoplasia; redundant skin; renal agenesis; uterine anomaly; webbing

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INTRODUCTION

Oligohydramnios (decreased amniotic fluid for gestational age) was identified in the early 1900s by Pilgrim when it was observed that it lead to changes in the placental surface (placenta nodosum) [Blanc, 1961]. Renal agenesis was later recognized to be frequently associated with oligohydramnios and multiple congenital contractures by Bates [1933], and further expanded upon by Potter [Potter, 1946a,b]. This paper is a review of 30 cases of arthrogryposis (multiple congenital contractures) all without renal agenesis, which experienced longstanding oligohydramnios. The purpose of this paper is to examine the relationship of oligohydramnios to arthrogryposis (multiple congenital contractures) and the secondary and/or tertiary effect on fetal skin.

METHODS

Clinical information on 2,500 individuals with arthrogryposis (multiple congenital contractures) have been collected by the author over a 35-year period. These cases come from clinic visits and consultations, as well as correspondence with physicians and families. Thirty individuals with longstanding oligohydramnios (average five months) were identified. Of these individuals, 20/30 were personally examined in relation to their congenital contractures and other clinical signs. These 30 affected individuals are clearly a biased collection, not representative of the normal or arthrogrypotic population; however, they are being reported in order to raise awareness of their findings and present some interesting questions that they raise. Family, pregnancy, and natural histories were also reviewed. The records and photographs of the 30 individuals were examined, tabulated, and compared to the overall group of cases with arthrogryposis (see Table I).

RESULTS WITH COMMENTARY

Demographics

Both the time of year of birth and the parental age were not unusual compared to the other cases of arthrogryposis. Regarding the length of pregnancy: in one-third of these individuals, the births clustered during the two weeks before and after term. The one third who were born before 36 weeks, were usually premature related to induction

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TABLE I. 30 Cases of Arthrogryposis With Oligohydramnios

No.	Oligohydramnios	Weeks of Pregnancy; Intervention or Oligo noted	Complications of Pregnancy	Weeks of Gestation at Birth	Delivery	Size at Birth	Placenta and Umbilical Cord	Gender	Parental Age M/F	Striking Skin	Limb Position	Mentation	Pulmonary at Birth	Prematurely Related II*	Other Organs	Final Dx
1	ROM	8 weeks	On seizure medication; ROM	32	Breech; C-section	1.4 kg	NR	F	20/28	Deep dimples	Extended arms and legs; Fx at birth; hyperext-ended	Bright		Retinopathy of prematurity	-	ATP and chronic oligo
2	ATP	8 weeks	ATP; UTI Rx; possible twin	31	Breech; C-section	2.4 kg	NR	M	16/17	Posterior hair with tongue of hair on forehead; edema; loose skin	Flattened distal limbs; mild flexion	Hyperactive; normal	Pulmonary hypoplasia	Pneumothorax; required hyperalime-ntation	Hypospadia; cryptorchidism; diathesis and hypoplasia of abdominal muscle	ATP with chronic oligo
3	ROM	9 weeks	ARTs (Clomid); 9 weeks bleed; US fluid around mouth	28	Vertex; C-section	2 lb 1 oz	Long cord	M	32/30	Edema; deep dimples; loose skin	Generalized flexion; dislocated hip	Hyperactive	Croaky voice; hypoplastic limbs	-	abndominal wall muscle; bilateral inguinal hernias	ROM; chronic oligo
4	ATP	11 weeks	ATP; maternal herpes	31	Breech; C-section	1.6 kg	NR	F	31/30	Deep dimples; extra skin; webs	Generalized flexion	Intellectual delay, CP	Respiratory distress at birth	-	Dilated ventricle; pulmonary stenosis; trismus	ATP with chronic oligo
5	Connective tissue; ROM	Early	Back pain; leakage throughout	40	NR	3.3 kg	NR	M	21/-	Loose extra skin; loose joints	Generlized flexion	Normal	NR	-	GI reflux; short palpebral fissure; arachnodactyly; cryptorchidism	Connective tissue, ROM; with chronic oligo
6	Early CVS leakage; ROM	12 weeks	Oligo; post CVS; IUGR	35	Breech; C-section	1.7 kg	Amnion nodosum; long cord around neck; circum-vallate placenta	F	37/-	Cutis mamorata; dimples	Generalized flexion; spatuated hands	Apparently normal	Mild pulmonary hypoplasia; thin diaphragm	-	Umbilical hernia; cord wrapping on leg	Chronic oligo secondary to CVS
7	ATP	12 weeks	ATP; GDM fibroid	36	Vertex; C-section	2.2 kg	3 vessel cord; normal placenta	F	40/41	Dimples; flattened face	Generalized flexion at birth; flattened hands; Fx x2 at birth	Slow	Early respiratory problem	Periventricular echogenic	Required G-tube; trismus	ATP with chronic oligo
8	ROM	12 weeks	Bleeding 1st and 2nd; ROM	30	Breech; vaginal	1.1 kg	NR	M	22/41	Redundant skin	Extended arms; flexed hip and knees; Fx leg at birth	Alert	Pulmonary hypoplasia	Retinopathy of prematurity	Abdominal muscle; pachygyria; mild ventricular enlargement	ROM; chronic oligo
9	ROM	13 weeks	ROM	32	C-section; fetal distress	1.9 kg	NR	M	32/23	Redundant skin; droopy cheeks; deep dimples	Generalized flexion; Fx related to osteopor-osis at birth	Mild develop-mental delay	Pulmonary hypoplasia	Chronic respiratory insufficiency	Needed GJ tube for feeding; decreased facial movement	Prematurity; chronic lung; ROM, chronic oligo
10	ROM	13 weeks	↑ MSAFP; ROM 13 weeks	26	Breech; C-section	900 g	Subchorionic separation	M	24/-	Scar on leg; loose skin; hyperexte-ndable; webs	Generalized flexion; dislocated hip	Normal	Pulmonary hypoplasia; respiratory distress	Retinopathy of prematurity	Shawl scrotum; heart murmur; sacral dimple; bifid uvula; inguinal hernia	ROM; chronic oligo
11	ROM	13 weeks	ARTs triplet; IUGR; GDM	38.5	C-section		MCDA; 2 vessel cord	F	-	Redundant skin; deep dimples	Generalized flexion	Developmental delay	Chronic lung; ↑ AP	-	Moebius; myopathy; G tube; bicuspid aorta	ROM; chronic oligo

TABLE I. (*Continued*)

No.	Oligohydramnios	Weeks of Pregnancy; Intervention or Oligo noted	Complications of Pregnancy	Weeks of Gestation at Birth	Delivery	Size at Birth	Placenta and Umbilical Cord	Gender	Parental Age M/F	Striking Skin	Limb Position	Mentation	Pulmonary at Birth	Prematurely Related II*	Other Organs	Final Dx
12	ROM	16 weeks	Fibroid; trauma to abdomen; 16 weeks; ARTs; leakage	40	Vaginal; vertex	7 lb 12 oz	Placenta previa	F	32/38	Patch of unusual hair; webbing; deep dimples; keloids	Generalized flexion; vertical talus	Bright	↑ AP; short of breath	-	Nasal voice; ptosis; neck pain; decreased facial movement	ROM; chronic oligo
13	ROM	16 weeks	movement; oligo	36	Breech, C-section	4 lb 9 oz	-	M	29/32	Dramatic dimples; 2 hair whorls	Generalized flexion	Bright	-	-	Hemangioma; upper, sacral dimple with hair; tethered cord	ROM, chronic oligo
14	ROM	18 weeks	Bedrest; ROM	34	C-section	4 lb	Long cord	F	29/31	Extra skin	R side flexion; flattened hands and feet	Okay	Wide spaced nipples; early pulmonary distress; ↑ AP	-	facial movement early	ROM; chronic oligo
15	ROM	18 weeks	UTI; ROM	34	Vaginal; breech	3 lb 8 oz	NR	F	27/29	Hirsuit; thin skin; extra skin; webbing	Flexed legs; dislocated hip; short toes	Bright		-	Hemangioma chest	ROM; chronic oligo
16	ROM	~20 chorionic	Twin died at birth	27	Vertex; C-section	1.0 kg	Abruptio placenta; cord normal	F	29/-	Many dimples; webbing; depigmented areas of skin	Generalized flexion	Bright	Severe pulmonary; hypoplastic nipples	Retinopathy of prematurity	Femoral and inguinal hernias; myopia neonatal? Seizures	ROM, chronic oligo; DZ twin
17	ROM	~20 chorionic; oligo	IUGR in 3rd	37	Vaginal	4 lb 2 oz	NR	M	28/30	Two hair whorls; webbing; dimples; mottled skin; redundant skin; large ears	Generalized flexion; torticollis; loose jointed Sprengel's deformity	Normal	Hoarse voice; small chest	-	High palate; Malrotation of gut; inguinal hernia; cleft palate	Possible syndrome; possible mosaicism; effects of chronic oligo
18	ROM; died shortly after birth	21	4 previous Ab; at 4 mo skin infection treated	36	Vaginal; breech	1.6 kg	Cord around neck and long	M	23/-	-	Generalized flexion; asymmetric	-	Pulmonary hypoplasia	-	High palate	Pena-Shokeir phenotype; died 6 mo
19	ROM	21	Bleeding and loss of amniotic fluid; 5 mo	38	-	-	NR	M	-	Extra creases; deep dimples; webbing	Generalized flexion	Bright	Hypoplastic nipples	-	Cryptorchidism; inguinal hernia	ROM; chronic oligo
20	ROM	22 weeks	Fibroid; septate uterus; bleed 12 weeks; 22 weeks ROM; 27 weeks chorionitis	28	C-section	1.2 kg	Marginal placenta; amniotic band at fundus	M	41/38	Double hair whorl; redundant skin	Extended arms; flexed legs; dislocated hips; clubfeet	Bright	Wide nipples; ventilator early	Abnormal muscle	Cryptorchidism; amniotic bands	Amyoplasia with chronic oligo
21	ROM	24 weeks	Twin lost at 6 mo; IUGR; multiple previous Ab	36	Vaginal; vertex	3 lb 13 oz	NR	M	15/16	Thick skin	Trismus; in turned shoulders; flexion of legs; asymmetric	Slow	-	-	Situs inversus; preauricular tag; ectopic lacrimal ducts; accessory nipple	Effects of chronic oligo; syndrome
22	ROM	Late second trimester	Septate uterus; male twin loss; 34 wk ROM noted; oligo	36	Vaginal; vertex	1.8 kg	Placenta attached to uterine scar	M	28/34	Two hair whorls; hemang-ioma; deep dimples	Extended elbow; asymmetric face	Good	-	-	Hemangioma on trunk; cleft foot; transverse defect of toes; tethered cord	Amyoplasia upper limbs; chronic oligo
23	Oligo effects	12 weeks	IUGR	40	C-section; transverse lie	4 lb 14 oz	NR	F	22/23	-	Generalized flexion; rocker bottom feet	Bright	Early respiratory distress; okay by 3 mo	-	Early feeding problems	Secondary effects of oligo

TABLE I. (*Continued*)

No.	Oligohydramnios	Weeks of Pregnancy; Intervention or Oligo noted	Complications of Pregnancy	Weeks of Gestation at Birth	Delivery	Size at Birth	Placenta and Umbilical Cord	Gender	Parental Age M/F	Striking Skin	Limb Position	Mentation	Pulmonary at Birth	Prematurely Related II*	Other Organs	Final Dx
24	Oligo effects	20 weeks	2 previous spontaneous abortions; migraines early	38	-	8 lb	Vaginal; vertex; long cord	M	38/40	-	Mild scoliosis; extended arms and legs	Bright	-	-	abdominal muscle	Amyoplasia with secondary effects of oligo
25	Oligo effects; post amniocentesis	20 weeks	Post tubal pregnancy; amnio 16 weeks; already oligo	41	Vaginal vertex	2.8 kg	Long cord	M	34/35	Lax skin; thick skin	Asymmetry; Fx femur; extended elbows; flexed hip; scoliosis; neck contractures	Attention deficit disorder	L lung hypoplasia; needed O_2	facial movement	Hydronephrosis resolved; trismus; required G tube; cryptorchidism; needed cranial molding	Chronic oligo post amniocentesis
26	Oligo effects	22 weeks	-	36	Breech; C-section	5 lb 14 oz	NR	M	28/27	-	Extended arms; flexed legs; mainly hands and feet	Bright	-	-	-	Amyoplasia with chronic oligo
27	Oligo effects	26 weeks	Bedrest	38	Vaginal; vertex	7 lb 7 oz	Long cord	M	43/43	Deep dimples; creases on feet	Kyphosis resolved; deep creases on soles; space between 1–2 toes	Speech therapy; okay	-	-	Long umbilicus; myopia; short palpebral fissures; trismus	Chronic oligo effects
28	Oligo effects; died of unknown syndrome	26 weeks	Cystic hygroma noted on US	38	Vaginal; vertex	3rd centile	NR	M	36/-	-	Scoliosis; muscle mass; hypotonia; flexion; prominent heels	-	Pulmonary hypoplasia; pectus; asymmetric chest	-	Cryptorchid; tethered cord; crease over sacrum; ASD; PDA; webbed fingers	Lethal syndrome secondary to pulmonary hypoplasia
29	Oligo effects	? 26 weeks	-	40	Breech; C-section	3.2 kg	NR	M	Young	Sparse hair; webbing	Generalized flexion	Okay	-	-	Shawl scrotum	Chronic oligo effects
30	Oligo effects; unknown syndrome	26 weeks	IUGR; hydronephrosis	32	Breech; C-section	1.7 kg	NR	M	32/-	Coarse hair; dimples; cutis mamorata; posterior hairline	Distal contractures	Developmental delay	Early pulmonary hypoplasia	-	R hearing loss; cortical blindness; hydronephrosis; small kidneys, but adequate; ventricular enlargement; thin corpus callosum; inguinal hernia; microcephaly; craniosynostosis	Syndrome with chronic oligo

NR, no report; ATP, attempted termination of pregnancy; kg, kilogram; CP, cerebral palsy; Fx, fracture.

because of concern for pulmonary hypoplasia or infection related to prolonged rupture of membranes.

Sex Ratio

There is a trend toward an excess of males. A 2:1 ratio was observed as compared to a normal sex ratio in the overall arthrogryposis group. This is not statistically significant (Fisher exact test $P = 0.14$); however, of interest because of the excess of males observed with renal agenesis, oligohydramnios, and arthrogryposis.

Multiple Births

Three individuals reported that a twin had been lost earlier in the pregnancy. One individual was one of dizygotic twins (the other twin dying shortly after birth), and one individual was one of dizygotic triplets (e.g., two of the triplets were monozygotic twins and the affected twin who was part of the triplets was MZ monochorionic diamniotic).

Survival

Only two of these individuals were reported to have died shortly after birth of pulmonary hypoplasia (one from pulmonary hypoplasia and prematurity, and the other with a complex of multiple congenital anomalies). Three individuals had been attempted terminations of pregnancy with continuing of the pregnancies (previously reported in Hall [2012a]) and continual leakage of fluid from the first trimester. One individual was an early chorionic villus sampling (CVS) with subsequent leakage of fluid, one had leakage after a second trimester amniocentesis, and two individuals were born from bicornuate uteri (described as heart shaped with short septums), but these two also had leakage from premature rupture of membranes.

Family Histories

Family histories were essentially negative: one family had a history of multiple spontaneous abortions (this was not one of the mothers with bicornuate uterus). One family had a history of distant relatives with clubfeet and two others had a relative who had worn corrective shoes. One family had a pericentric inversion of chromosome 9 (known to be a polymorphism) which the normal mother transmitted to the affected son.

Deliveries

Seventeen were delivered by Cesarean, of which nine were breech presentation, one was in transverse lie, one was a twin pregnancy, one was a triplet pregnancy, one was fetal distress, and in the other four, the indication was not clear. There were eleven vaginal deliveries, three of which were breech, and in the two other cases, the delivery was not well described.

Maternal Health

In four affected individuals, there had been maternal infertility and fertility drugs were used for the present pregnancy in three individuals. Four mothers had illness during the pregnancy: two gestational diabetes, one severe migraine, and one took seizure medication during the pregnancy. Two other women had uterine fibroids of significant size. Two mothers had septate uteri.

Timing of Decreased Amniotic Fluid

Twenty-two of these affected individuals had history of rupture of membranes (ROM) and chronic leakage of amniotic fluid. Oligohydramnios began as early as eight weeks and often continued until delivery. The average length of leakage from rupture of membranes was 17.8 weeks. The least length of time for leakage of fluid was reportedly as a few weeks; however, this was a pregnancy complicated by a septate uterus from which a twin had been lost previously and the obvious ROM occurred at 34 weeks and the placenta was implanted in a uterine scar with chorionic abruptio placentae. Thus, more than 70% of these individuals historically had prolonged, chronic leakage and rupture of membranes. Pulmonary hypoplasia was present in 15 (50%), and these required respiratory support at birth and in one case for as long as six months. For the other 50%, a small pocket of amniotic fluid (not recognized on ultrasound studies), stress leading to early production of surfactant, or other unknown factors might be enabling pulmonary maturation.

Birth Size

Intrauterine growth restriction (IUGR) has been reported in the past to be associated with longstanding oligohydramnios [Baines and Scott, 1960; Kohler et al., 1970], however, birth size was in general normal for gestational age in these individuals, although there were more individuals below the 50th percentile for weight than above. Length was about the 50th percentile and OFC was about the 50th percentile (except on one syndromic microcephalic child). This near normal weight at birth for gestational age could relate to the presence of edema, since some affected individuals did have pedal edema, in which case the edema resolved shortly after birth. They did have excessively wrinkled skin; however, marked edema or cystic hygroma in utero or after birth were not seen.

Placentas

Placentas in general were not described. There was no information available in 22 individuals. Of eight individuals with descriptions of their placenta: two had placenta previa; one a circumvallate placenta with decreased vascularization, a long cord, and amnion nodosum; one had abruptio placenta with a normal cord; one chronic abruption with attachment to a uterine scar; one case had a marginal placenta; one had subchorionic separation; the triplet, who was one of two monozygotic individuals among the triplets, had a two vessel cord and monochorionic, diamniotic placenta; and one was said to be completely normal with a three vessel cord. Five umbilical cords were noted to be long without comment on the placenta while as noted above, one had a long cord with circumvallate placenta, giving 6/30 pregnancies with long umbilical cords (a relatively large number compared to the overall group of arthrogryposis). Notably, amnion nodosa was only identified in

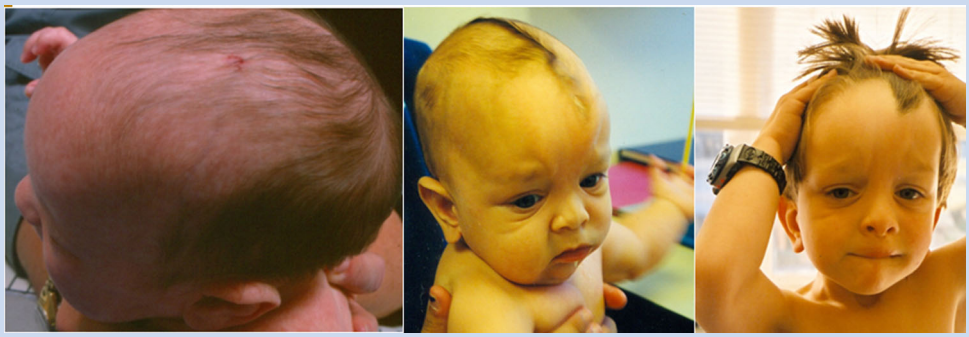

FIG. 1. Note posteriorly placed hairline, dolicocephalic head shape, large ears, thin hair, and hypoplastic mid eyebrow, fullness around the eyes, and the "tongue" of hair onto the forehead.

one case, suggesting some amniotic fluid must have been present in the third trimester, as the kidneys seem to have been functioning normally. However, alternatively, normal fetal kidneys may make some factor that lubricates intrauterine surfaces.

Craniofacial Features (see Table I)

Although Potter described molding of the head and face with frequent asymmetry, this was not a common feature in these individuals with arthrogryposis and oligohydramnios without renal anomalies. Instead, there was frequently a dolicocephalic head (probably associated with being in breech position for prolonged in utero periods), and prominent foreheads with posteriorly placed hairline, such that the hairline usually began about where the ears were placed (Figs. 1–3). Two individuals had striking "tongues" of hair protruding anteriorly in the midline from the posteriorly placed hairline forward to where the "normal" position for the hairline would have been.

All 30 individuals with oligohydramnios and arthrogryposis had typical "Potter facies". The face was often flattened. In particular, the nose tip was flattened and upturned. The tip and columellar often remained hypoplastic after birth resulting in a somewhat

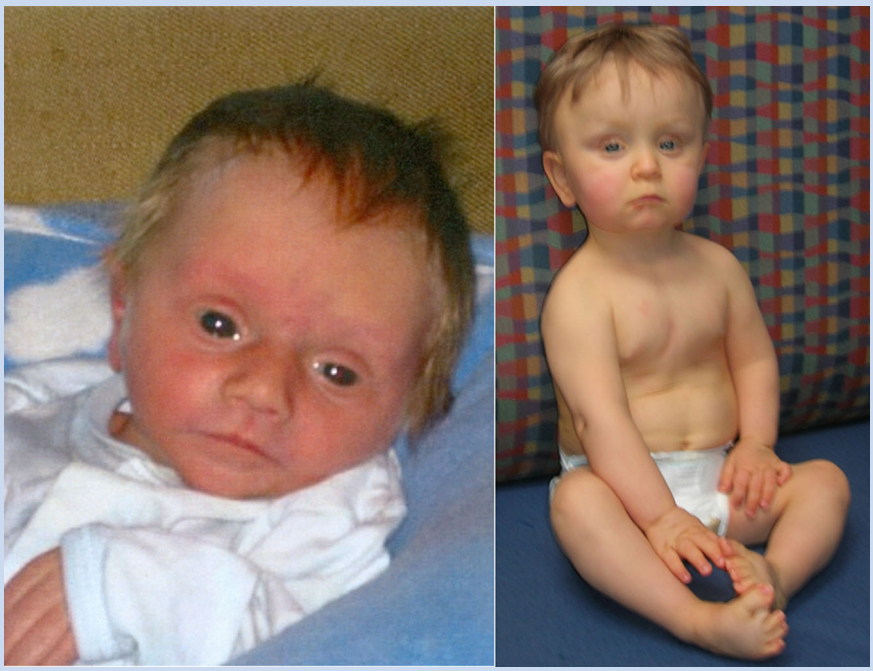

FIG. 2. Note eyes appear deep-set, hairline is posteriorly placed, and prominent forehead.

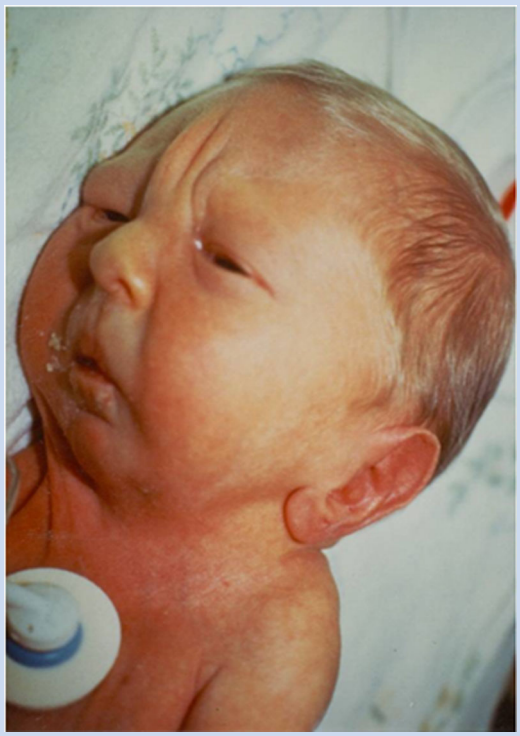

FIG. 3. Note vertical wrinkles, between the eyes, large ears, and crease below the lips.

beaked shaped nose as the bridge grew (Fig. 4). The columella was almost always quite short (Fig. 5). The nasal root was most often flat at birth, but in at least half the cases, the root of the nose rose after compression was released, giving a high bridge at a later time in life (as is seen in fetal akinesia sequence) [Hall, 2009].

There were characteristic long epicanthal folds running downward and outward from the inner canthus giving a crease below the lower eyelid (Figs. 1 and 6). There was almost always an increased distance between the inner canthi; however, true ocular hypertelorism was not seen. The eyelids were often quite puffy. The eyes developed a deep-set appearance after the puffiness resolved (Fig. 2). The eyebrows were often sparse, particularly medially (Figs. 3 and 5). Later in life as the eyebrows became more obviously hypoplastic medially they could be quite flared at the medial border (Fig. 7). The medial portion of the eyebrow was laterally displaced, often with deep furrows and excessive skin (Figs. 3 and 6) between the median borders of the eyebrow.

The ears almost always appeared large and flattened, posteriorly angulated, and pressed against the head (Figs. 1 and 4) (however, folded normally). Only in one individual did one ear later become somewhat prominent. The ears were almost always (if measured) above the 97th percentile at birth and later in childhood. They usually had little apparent cartilage in the newborn period. It developed over the first two years.

The jaw was almost always micrognathic with a receding chin (Fig. 4). A prominent depression between the lower lip and the chin was always present in the newborn period (Figs. 2,4 and 6). Subsequently the jaw usually grew and could even appear large by one year of age; however, the crease below the lower lip usually persisted. The vermilion of the lips was well developed. The corners of the mouth were often down turned in the newborn period (Figs. 2 and 5).

There was usually somewhat decreased movement of the face in the newborn period. Vertical creases between the eyebrows were frequent (Fig. 3). The philtrum could be flat in the newborn period, but usually developed normal pillars. The neck almost always appeared short with extra skin at birth, suggestive of post fetal nuchal edema (which had not been observed in utero, except in one individual, when there had been in utero scanning), and occasionally the neck skin had actual webbing (Figs. 4 and 8).

The Skin

The skin was quite remarkable in these children with oligohydramnios and multiple congenital contractures. In the newborn period, it often appeared thin with little subcutaneous fat (Figs. 5, 9, and 14). The subcutaneous blood vessels could often be seen and the skin was sometimes described as having cutis mamorata (Fig. 9). At an older age, the skin was almost always described as soft and hyperextensible with excessive creases. Extra skin and skin creases were often

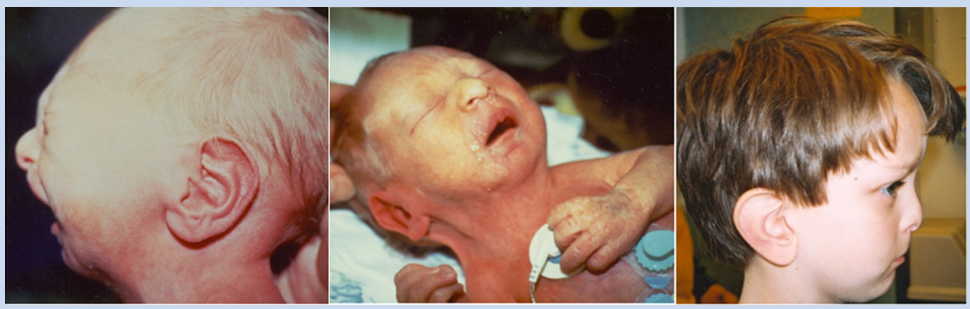

FIG. 4. Note micrognathia, short columella, short upturned nose, somewhat beaked nose, large ears, short appearing neck with webbing, spade shape to hand.

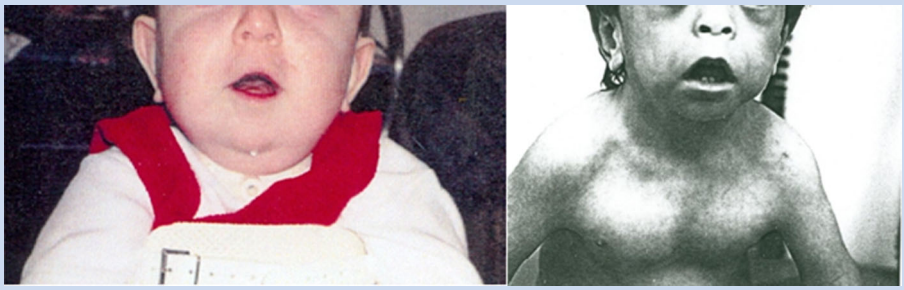

FIG. 5. Note short columella, creases under eyes, tented mouth, and short appearing neck.

present in many areas (Fig. 7). It was particularly striking on the forehead, on the face and neck (Figs. 3 and 7), and along the limbs where the skin seemed to "hang off" the limb (Figs. 8 and 10). The face appeared prematurely aged. By six or eight years of age as the children developed, they seemed to "grow into their skin" and appear more normal.

Occasionally, there was increased webbing in areas, such as the neck, axillia, groin, and elbow (Figs. 4,8 and 11). Mild syndactyly could be present particularly with the spade-like, flattened hands and feet (Fig. 12).

Skin healing seemed to be normal although scars could be wide they were not thickened.

One individual had streaky hypopigmentation of the skin.

Dimples

The "usual" dimples of arthrogryposis were seen overlying the joints with congenital contractures. However, in these cases, they were almost always very deep and quite large when overlying the limb joints where there was limitation of movement (Fig. 13). Dimples also occurred in areas not usually seen in arthrogryposis, such as buttocks (one case), sacrum (five cases), the chest (three cases), and sternum (three cases), and even along the inner arm (Fig. 11).

Hair

The hair was thin and fine at birth, but often became coarse and even curly by 2–3 years of age (Figs. 1 and 4). One individual had excessive hair around a dimple, and another was described as hirsute at birth. Four cases had two occipital hair whorls, and two had patches of light colored hair in the forelock area. However, the most unusual aspect was the hairline, as noted above, which was posteriorly placed together with a prominent forehead (Figs. 2 and 14).

Other

Nipples were unusual in several individuals: with an extra nipple in three, hypoplastic nipples in three (Figs. 5 and 14), and wide set nipples in five (Figs. 10 and 14).

Preauricular skin tags were observed in one individual and a preauricular pit was seen in another.

FIG. 6. Note telecanthus, posterior hairline, crease below the lower lip (all the same child at different ages), and how eyes become deep-set overtime.

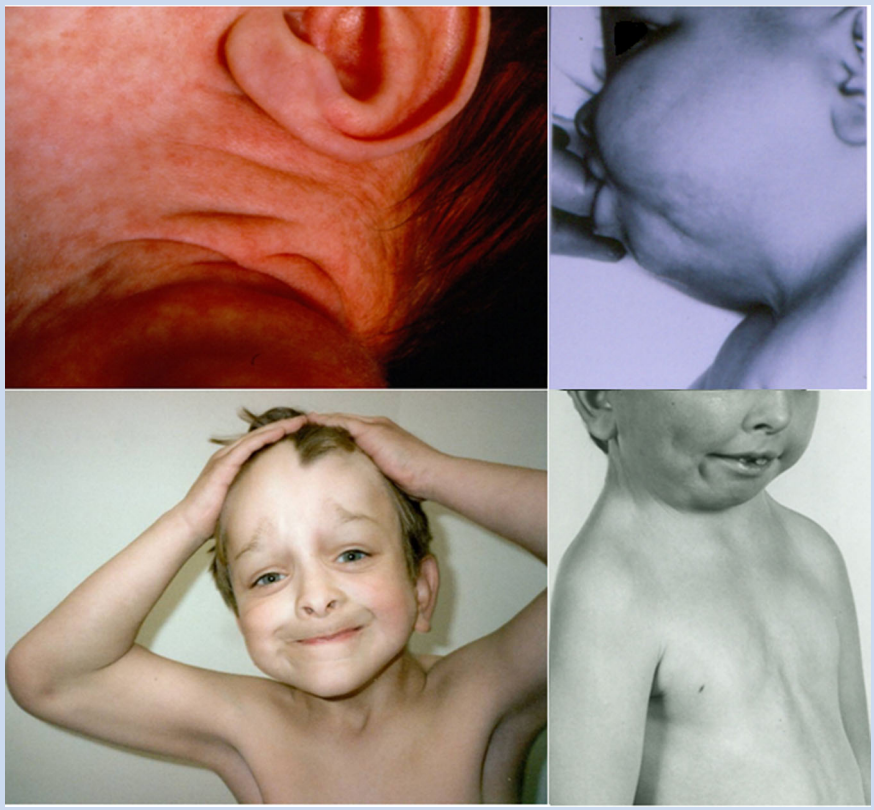

FIG. 7. Note skin creases in the neck, facial creases and dimples, loose skin on arms and around neck, and mild webbing.

Congenital Contractures

The limbs were usually held in flexion at birth. The hands and feet were often edematous and spade-like, and sometimes quite remarkably flattened (whether the foot was in equinovarus or in flexion) (Figs. 10 and 14). While true shortening of the digits was rare, the fingers often appeared short in relation to the width of the palm (Fig. 12). The nails were intact except in the one case of amniotic bands. If there had been cord wrapping or banding, there was often striking edema distally.

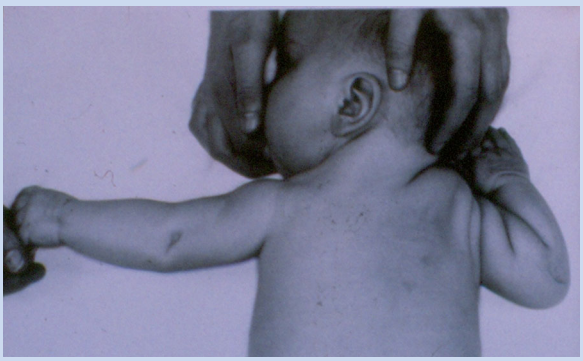

FIG. 8. Note "extra skin", deep dimples, webbing, and large ear.

The proximal contractures usually "worked out" quite rapidly (except in the four cases with contractures typical of Amyoplasia). The hands and feet often took longer to respond to therapy, however they were usually quite functional by the age of five or six years of age. There could be overlapping fingers, but usually the fingers are extended rather than clenched. There were often deep longitudinal creases on the soles and palms (similar to those seen in Trisomy 8 mosaicism) accentuated by the loose skin. Some individuals developed a crouching stance (Fig. 10).

As in the case of compression with uterine anomalies or fibroids, release of the external compression usually leads to fairly rapid normalization of contractures. However, in contrast to infants who were constrained due to uterine anomalies and fibroids, asymmetry of contractures was rarely seen in these cases of oligohydramnios.

Pulmonary Hypoplasia

Moderate to severe pulmonary hypoplasia was seen in half of these individuals. This was almost surely related to not having enough amniotic fluid to "breathe" in utero, and thereby allow the lungs to develop normally. Compression of the chest because of the oligohydramnios probably accentuated the retarded lung development and prematurity accentuated these two factors. No information

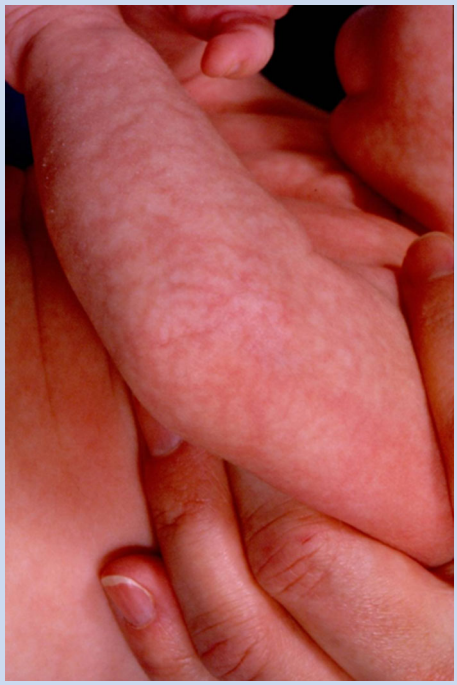

FIG. 9. Note subcutaneous vessels and cutis mamorata appearance in newborn.

documenting fetal breathing in utero was available on any of these cases. Many of the children with pulmonary hypoplasia at birth ended up with chronic lung disease and were more susceptible to upper respiratory infections (URIs) later in childhood. These individuals with pulmonary hypoplasia frequently had relatively weak respiratory efforts in the newborn period requiring early support. Many required gauvage feeding or J or G-tubes during the first year of life to avoid aspiration and because of lack of adequate suck.

Natural History and Other Anomalies

Seven of these affected individuals were born prior to routine ultrasound studies in pregnancy; however, all were recognized prior to birth to have oligohydramnios. These children with oligohydramnios and arthrogryposis were relatively well grown at birth (e.g., had a reasonably good birth weight) as compared to the cases of oligohydramnios related to renal agenesis [Potter, 1946a; Jeffcoate and Scott, 1959; Baines and Scott, 1960]. Once the congenital joint contractures were mobilized, and if any had been present, the edema had resolved, these individuals all grew above the 10th percentile for height and weight. In fact, most were close to the 50th centile.

The abnormal features were often striking at birth, but the children seem to grow toward normal as they mobilize and increase their joint, body, and facial movement, and in general, have a much better outcome of their contractures than the average case of arthrogryposis or Amyoplasia [Hall et al., 2014].

Other anomalies (see also Table II), which were present in these 30 individuals included: one individual had malrotation of the gut, six individuals had generalized decreased musculature of the abdominal wall (without specific renal defects), six males had cryptorchidism (two of which also had shawl scrotums), and three individuals had inguinal hernias. One individual had loss of the ends of digits; together with amniotic bands. There was a cleft of the foot in one individual with Amyoplasia and a scar on back of the leg in a different individual. Five had fractures of long bones at the time of birth (a common finding in arthrogryposis and probably related to osteopenia because of decreased movement in utero). Four had

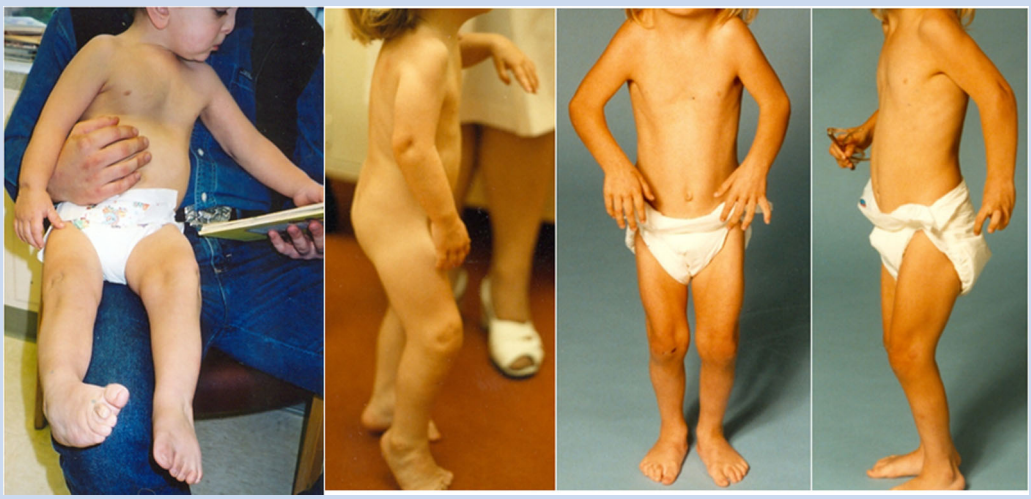

FIG. 10. Note flattened hands and feet, crouching stand, and deep dimples.

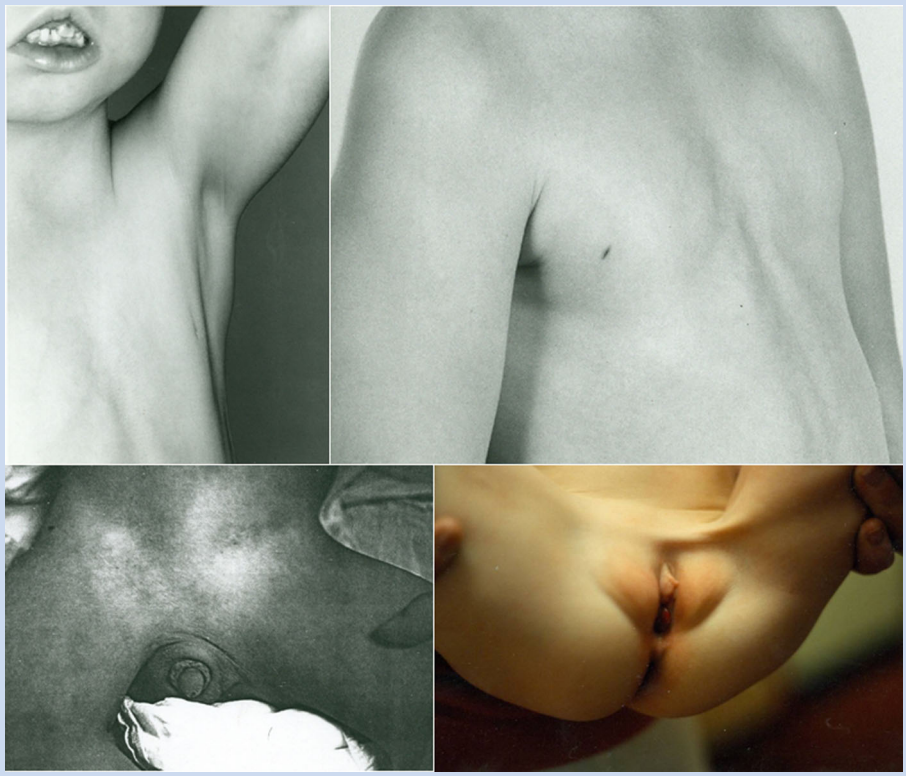

FIG. 11. Note inner arm crease, chest crease, hypoplastic nipples, shawl scrotum, and inguinal webbing.

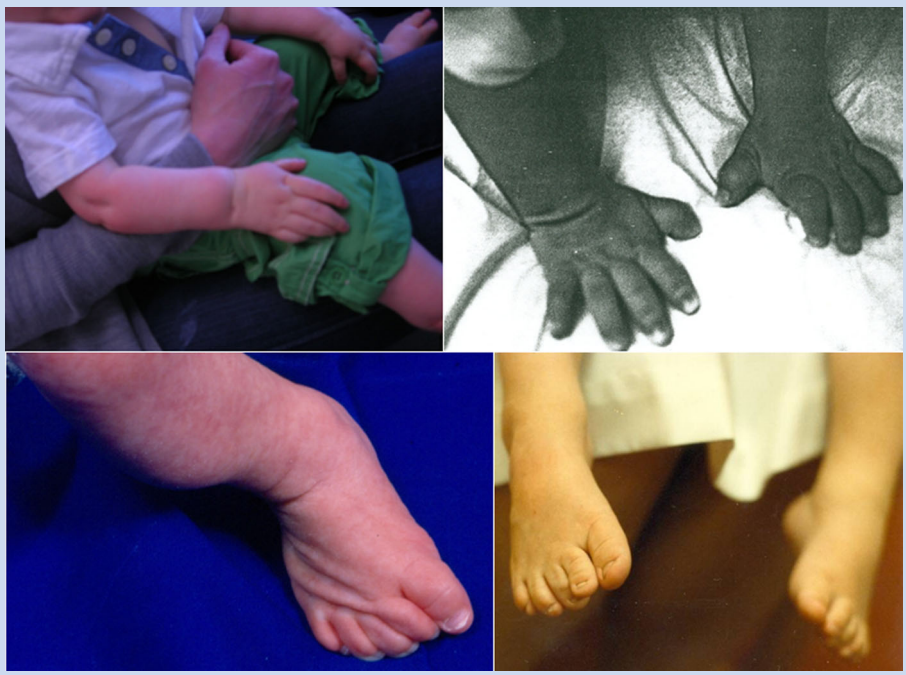

FIG. 12. Note the flattening of hands and feet (even in older child), short digit appearance, and dimples.

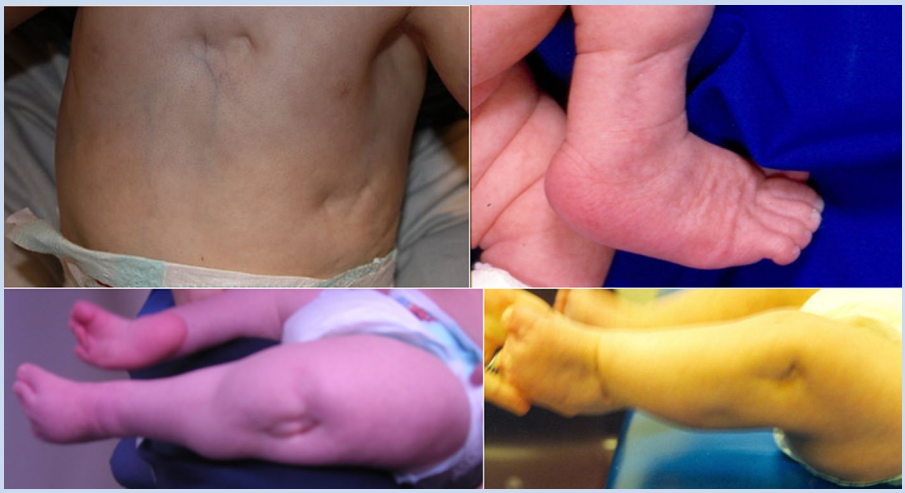

FIG. 13. Note excessively deep and large dimples and unusual positioning.

significant cord wrapping with depressions on the limb in the area of cord wrapping at birth, which is seen with decreased limb movement [Hall et al., 2014]. Three had true congenital vascular malformations (hemangiomas).

Only, one male had mild renal anomalies with somewhat small kidneys and hydronephrosis at the time of birth, which have not created a problem since then and was unlikely to be the cause of the oligohydramnios. Another had hydronephrosis in utero, which resolved by birth. Four had cardiac abnormalities; one of which had situs inversus as part of an unusual syndrome, another had pulmonary stenosis, the third had bicuspid aortic valve, which was associated with heart failure in the newborn period, but subsequently has not been a problem and a fourth had ASD and PDA and died related to pulmonary hypoplasia. Another child had a heart murmur that disappeared.

One syndromic child had premature fusion of cranial sutures. Two had what was described as "croaky" voices. Several had strabismus. Two had myopia. Five had significant developmental delay (17%)—in two of whom there had been a failed attempted termination of pregnancy [Hall, 2012a]. Two of the others with developmental delay had central nervous system structural abnormalities. However, one of the cases with developmental delay had normal CNS imaging. Three other children who appeared to be normal intellectually had structural central nervous system abnormalities, including one with periventricular leukomalacia and pachygyria in the newborn period, and two had a tethered spinal cord.

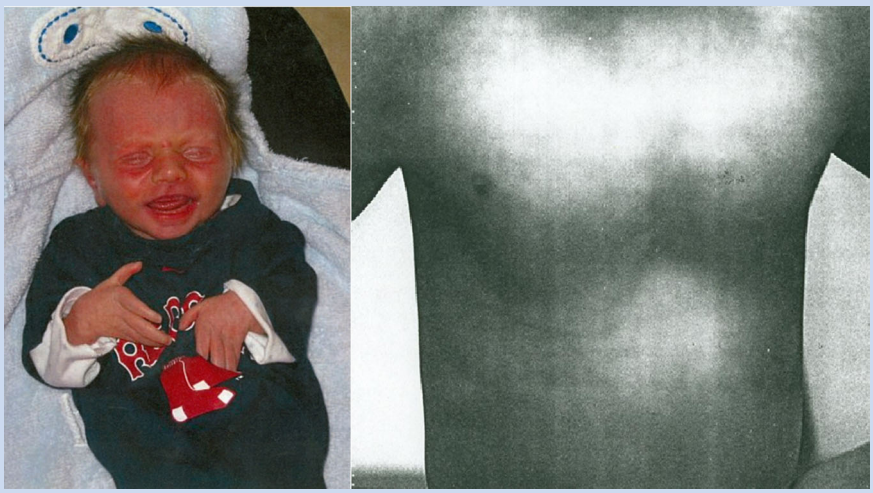

FIG. 14. Note dry flaky skin, flattened hands, laterally placed small nipples, and sternal depression.

TABLE II. List of Clinical Features in 30 Cases of Arthrogryposis and Oligohydramnios

Cranio-facial (Potter syndrome)
- Micrognathia → receding chin
- Tip of nose flattened (absent cartilage?)
- Short columella → "beak shaped" nose
- Epicanthal folds → above and below eye creases
- Telocanthus
- Eyes appear deep set
- Crease below lip
- Wrinkles between eyes
- Prominent forehead
- Dolicocephalic (molded head probably related to breech position)

Skin
- Thin initially (lacks subcutaneous tissue)
- Blood vessels at surface
- Dry and wrinkled (adds to aged appearance)
- Soft, hyperextensible, doughy, loose
- Excessive skin on limbs, neck, groin – "grow into" over years
- Extra creases on face
- Deep long dimples in unusual places – chest, inner arm, sacrum, and buttocks
- Resolving edema?
- Webbing (axilla, neck, groin)

Hair
- Posterior hair line (prominent forehead)
- Thin initially, then coarse
- "Tongues" of hair down to forehead from posteriorly placed hairline
- Eyebrows hypoplastic and laterally displaced

Ears
- Large, greater than 97th centile
- Squashed, flat
- Cartilage
- Simple folding
- Appear low set

Unusual types of contractures
- Primarily flexion contractures
- Spade-like flattened hands & feet
- Deep large dimples
- Quite responsive to physical therapy

The cause of arthrogryposis appeared to be primarily related to oligohydramnios and compression in 18 of these cases because of their rapid response to physical therapy. Two individuals died because of pulmonary hypoplasia with features of fetal akinesia sequence, one of these with a complex set of multiple congenital anomalies. The 10 other individuals with oligohydramnios had ongoing contractures. Four appeared to have Amyoplasia (diagnosed on the basis of clinical features, positioning and lack of responses to physical therapy)—three with four-limb involvement, one with upper limbs only. Of the remaining six, three individuals had residual contractures associated with attempted termination of pregnancy, one was related to early CVS, and two appeared to have unknown syndromes with ongoing contractures.

HISTORIC PERSPECITIVE (SEE TABLES III AND IV)

In 1946, Potter eloquently defined the clinical features/phenotype of children born with non-functional kidneys [Potter, 1946a,b]. They often had oligohydramnios and arthrogryposis as well as some very specific cranio-facial features, pulmonary hypoplasia, changes in the skin, and the presence of contractures. The craniofacial features have become known as "Potter" facies and include long epicanthal folds, creases above and below the eyes, flattened nose, large ears, additional facial creases particularly between the eyebrows and under the lower lip, and small jaw. She also suggested these changes might be related to oligohydramnios noting a lack of amniotic fluid had been frequently reported in newborns with renal dysfunction and that the features could arise from the compromise of fetal space in oligohydramnios. Only one third of her cases had arthrogryposis and half had other multiple congenital anomalies in addition to renal agenesis [Potter, 1946a,b]. She also reported an excess of affected males. She considered the facial, ear, and pulmonary features to be involved in some type of common genetic mechanism associated with renal dysplasia.

In 1959, Jeffcoate and Scott reviewed their experience with polyhydramnios and oligohydramnios, noting that amniotic fluid was not static and appeared to come from a number of sources depending on the stage of pregnancy [Jeffcoate and Scott, 1959]. They postulated that the amount of fluid and its content depended on rates of formation versus rates of removal. They noted that oligohydramnios was far less frequent than polyhydramnios. Up until that time, the reported cases of oligohydramnios were apparently all, or almost all related to renal agenesis or severe renal dysplasia. These authors reported three cases with normal urinary tracts, which they thought were related to chronic leakage of amniotic fluid. Being pathologists, they emphasized the presence of amnion nodosum with longstanding oligohydramnios. They also noted for the first time that growth restriction occurred in these fetuses only in the third trimester. Among their potential explanation (as most of their cases had renal anomalies) was that the fetus depends on a fluid environment for growth, in other words, the liquor distended and stimulated the uterus to enlarge allowing the fetus the freedom of movement necessary for its growth. They did not mention the possibility of renal growth factors, but did rule out toxicity from renal failure noting that urea and electrolyte levels in newborn blood of babies without kidneys was normal at birth (and as we know, it is cleared by the mother until birth).

In 1960, Baines and Scott summarized their 50 cases of urinary tract agenesis and dysplasia [Baines and Scott, 1960]. Prior to the advent of ultrasound, they suggested that "a small for dates uterus" and the "failure to record rupture of membranes" were useful clinical signs to suspect oligohydramnios. Sixty percent of their cases were in breech and all their liveborn babies died of pulmonary hypoplasia. They emphasized the presence of the intrauterine growth restriction, "amnion nodosum," distinctive facial characteristics and noted specific skin and joint findings. They described the skin as dry, "redundant, often loose and wrinkled giving in some cases, an appearance of "premature senility". Joint contractures

TABLE III. 30 Cases of Arthrogryposis With Oligohydramnios Compared to Oligohydramnios and Renal Agenesis

	These 30 Cases With Arthrogryposis and Long Standing Oligohydramnios	Oligohydramnios [Nimrod et al., 1984; Thibeault et al., 1985; Rotschild et al., 1990; McIntosh and Harrison, 1994; Christianson et al., 1999]	Potter Sx Renal Agenesis [Potter, 1946a; Jeffcoate & Scott, 1959; Baines and Scott, 1960]
Pulmonary Hypoplasia	50%	80%	100%
IUGR	No	50%	100%
Craniofacies	100%	60%	80%
MCC	100%	50%	~60%
Die in Newborn	7%	25% (do well if survive)	100%
Responses to Physical Therapy	Surprisingly good	Good if survive	†
Males	2:1	4:3	85% male

were present in 72% of their cases, including clubfeet, flexion contractures of knees and elbows, and "spade like" hands. They describe the hands as "broad and clumsy with redundant skin on the dorsum, while the fingers were relatively short in relation to the width of the palm".

In 1962 Blanc et al. [1962] reported on 30 cases with oligohydramnios, reviewed previously reported cases of oligohydramnios and re-emphasized that renal anomalies were common. Overall, 43% of their cases had arthrogryposis.

Baines and Scott [1960] and subsequently Kohler et al., [1970] re-examined the non-renal features seen with chronic oligohydramnios. They pointed out that when premature rupture of membranes is the source of oligohydramnios, then pulmonary hypoplasia, infection, and compression deformations often lead to death in utero and/or premature delivery and postnatal death. They reported that both polyhydramnios and oligohydramnios might be associated with congenital anomalies; however, they suggested that most of the anomalies seen with oligohydramnios could be considered secondary deformations to the lack of space constraining fetal movement seen with oligohydramnios. Occasionally, multiple congenital anomaly syndromes were observed to also manifest oligohydramnios, such as in COFS [Preus et al., 1977] and Trisomy 7 mosaicism [Yunis et al., 1980; Pflueger et al., 1984] either because of lack of production of normal amounts of amniotic fluid or because of premature rupture of membranes. Similarly, compressive abnormalities were noted to be the rule in ectopic

TABLE IV. Previous Studies of Arthrogryposis and Oligohydramnios (All Note That Earlier in Gestation and the Longer Exposure Leads to Worse Contractures)

	Arthrogryposis	Pulmonary Hypoplasia	Died	Skin Changes Noted
Potter, [1946a] – all 20 renal agenesis	30%	100%	100%	++
Baines and Scott, [1960] – all 50 urinary tract anomalies	72%	100%	100%	+++
Blanc et al., [1962] – 30 cases of amnion nodosa	43%	53%	100%	+++
Nimrod et al., [1984] – all 100 ROM	12%	9%	17%	?
Manivel et al. [1989]	58%	24%	32%	+++
Thibeault et al., [1985] – all 76 ROM preterm with renal anomalies	28%	26%	41%	?
Rotschild et al., [1990] – all 88 oligohydramnios	20%	16%	20%	?
McIntosh and Harrison, [1994] – 117 ROM & oligo	21%	9%	20%	?
Christianson et al., [1999] – mixed 90 cases of oligohydramnios	70%	12%	100%	+++
Present study	100%	50%	7%	++++

ROM, rupture of membranes.

pregnancies and occasionally could also be seen with longstanding fetal edema [Williams et al., 1977].

In 1974 Thomas and Smith identified cases with "Potter syndrome features" without renal agenesis and cases of renal agenesis without "Potter syndrome features" [Thomas and Smith, 1974]. They drew together concepts from animal work [DeMyer and Baird, 1969; Poswillo, 1972; Singh et al., 1974], clinical observations, pathological studies and the growing body of work on amniotic fluid dynamics to hypothesize the "oligohydramnios tetrad"; in other words, four clinical signs which were observed when oligohydramnios was present either from defects of urinary output or chronic leakage of amniotic fluid. The non-renal features of Potter syndrome were considered to be related to fetal compression secondary to oligohydramnios. The four features of the oligohydramnios tetrad were as follows: 1) fetal growth deficiency, 2) pulmonary hypoplasia, 3) Potter facies, and 4) limb positioning defect (and contractures). In the same issue of the Journal of Pediatrics as the Thomas and Smith report, Potter (who had obviously reviewed the paper) wrote a commentary suggesting it was likely not to be that simple [Potter, 1974]. She had already emphasized that there must be a genetic/developmental relationship between the findings in the kidneys, ears, lungs, and craniofacial changes, foreshadowing the importance of growth factors and cytokines during embryonic and fetal in utero growth.

Oligohydramnnios, both chronic and late onset, is not a rare finding in pregnancy now that ultrasound has become routine [Keirse and Meerman, 1978; Schmidt et al., 1982; Hill et al., 1983; Dicker et al., 1984; Benacerraf, 1990]. Intraperitoneal saline infusion may improve the development of intra-abdominal organs [Nicolini et al., 1989] and MRI helps to define the status of fetal kidneys. The etiology and significance; however, of oligohydramnios is not always clear. It would appear that long standing oligohydramnios has many etiologies and several implications for the fetus. The changing dynamics and source of amniotic fluid also create different scenarios at different periods of gestation [Underwood et al., 2005; Harman, 2008]. However, there is a consensus that the earlier the onset and the longer it is present, the more likely that oligohydramnios will be associated with pulmonary hypoplasia and arthrogryposis [Thibeault et al., 1985; Palacios and Rodriguez, 1990; Rotschild et al., 1990; Rodríguez and Palacios, 1991; McIntosh and Harrison, 1994; Christianson et al., 1999].

There are excellent reviews of oligohydramnios related to renal and non-renal pathogenesis that identify the multiple etiologies of oligohydramnios. These include renal agenesis [Bates, 1933; Potter, 1946a,b; Jeffcoate and Scott, 1959; Blanc, 1961; Blanc et al., 1962; Passarge and Sutherland, 1965; Fantel and Shepard, 1975; Grunnet and Bale, 1981; Benacerraf, 1990; Kadhim et al., 1993], obstructive uropathies (prune belly syndrome) [Pramanik et al., 1977; Manivel et al., 1989], early CVS (chorionic villus sampling) [Cheng et al., 1991], twin-twin transfusion [Blanc et al., 1962], macerated feti [Blanc, 1961; Blanc et al., 1962], intrauterine infection [Blanc, 1961], attempted termination of pregnancy [Hall, 2012a], premature rupture of membranes [Blanc et al., 1962; Kohler et al., 1970; Perlman et al., 1976; Naeye and Peters, 1980; Thibeault et al., 1985; Tibboel et al., 1990; Levine et al., 1996; Christianson et al., 1999], ectopic pregnancy [Guha-Ray and Hamblin, 1977; Williams et al., 1977; Stevens, 1993; Pricop et al., 2000], twinning [Mauer et al., 1974] and placental anomalies [Ohyama, 1991]. Oligohydramnios may be associated with many syndromes, including NTD, Sirenomelia [Kohler, 1972], Meckel syndrome [Chen, 2007], COFS syndrome [Preus et al., 1977], Beckwith-Wiedemann syndrome [Watanabe and Yamanaka, 1990] as well as idiopathic oligohydramnios [Christianson et al., 1999].

Interestingly, pulmonary cartilage appears to be under developed in renal aplasia [Itoh and Itoh, 1988], but not necessarily in other oligohydramnios situations. If oligohydramnios persists throughout a pregnancy and particularly in late pregnancy, the lungs are usually not able to develop sufficiently to sustain life [Perlman et al., 1976]. There are many animal studies in mice [Singh et al., 1974; MacIntyre et al., 1995], guinea pigs, rats [DeMyer and Baird, 1969], and Macacas [Poswillo, 1972] demonstrating the secondary effects of oligohydramnios. With the development of ultrasound, careful measurements of amniotic fluid and chest size became part of a prenatal ultrasound examination in humans [Naeye and Peters, 1980; Philipson et al., 1983].

By 1983, Moessinger recognized that lack of fetal movement (fetal akinesia) played a key role in the development of the oligohydramnios tetrad features since many of these signs could be seen when myo-neural dysfunction occurred. They could even occur in the presence of polyhydramnios if no movement of the fetus was present. He listed: 1) growth deficiency, 2) pulmonary hypoplasia, 3) short umbilical cord, 4) limb positional defects, and 5) facial anomalies as part of the "Fetal Akinesia Deformation Sequence" [Moessinger, 1983]. He emphasized that if any one of those features were present the others should be looked for (both structural and functional). Short gut (6) can be added to the list, since if in utero swallowing does not occur, then the gut appears not to lengthen and become functionally mature frequently resulting in polyhydramnios.

In 1991, Rodriguez and Palacio, as neonatologists doing newborn respiratory research were interested in pulmonary development. They honed the concept still further distinguishing etiologies of muscular or neurogenic weakness from those related to compression of the fetus [Palacios and Rodriguez, 1990; Rodríguez and Palacios, 1991]. They separated the specific features into categories primarily related to weakness, lack of movement or compression. They emphasized the possibility of multiple combinations, which could help to identify the primary mechanism(s) involved (see Fig. 15).

DISCUSSION

Many interesting questions arise from analysis of these 30 individuals with arthrogryposis and oligohydramnios. For instance, why is fetal skin so responsive to contact and pressure in later pregnancy? It is known that the amnion responds to chronic oligohydramnios with the production of amnion nodosa [Blanc, 1961]. In the present cases, it appears that the subcutaneous tissue was often deficient and that there was overgrowth of the skin (dermis and epidermis) itself. It is possible that the overgrowth is in response to transient edema in the subcutaneous space, but it seems much more complicated than that since generalized edema was not seen prenatally or at birth in

these cases. Smith [1979] proposed four mechanisms to produce excessive fetal skin: intrinsic pressure (such as edema), extensive pressure from rubbing against the uterine wall, malformations of skin as in cutis laxa giving an abnormal response to normal pressure, and idiopathic as may be seen in various forms of dwarfing [Smith, 1979].

Keeping in mind developmental and genetic mechanisms, mechanical transduction to skin cells from intrinsic or extrinsic pressure in utero could lead to the production of cytokines/growth factors which could lead to the growth of more skin. This process could be akin to the thickening seen in callous formation in areas of repeated external pressure after birth.

The extra creases in the skin of the chin and under the eyes are probably related to the presence of excessive skin prior to birth or possibly resolving fetal edema. They are quite characteristic and last for a long time after birth. The epicanthal folds and telecanthus are striking and consistently present at birth. The lateral displacement of the eyebrows suggests, together with the posterior displacement of the hair, that something different is occurring with regard to hair patterning because of the lack of amniotic fluid/and or pressure on the skin during fetal development.

Most of these individuals were mildly or moderately dolicocephalic, probably responded to in utero molding from their breech position. The continuing prominent forehead also suggests that the skull (bone and cartilage) respond to pressure with overgrowth (possibly in a protective way). Craniosynostosis, which might have been expected from external pressure occurred in only one syndrome case.

The hairline was very remarkable, and was characteristically posteriorly placed behind the prominence of the forehead. The hair was usually quite thin and wispy for the first two or three years and then became quite curly and coarse. This type of secondary coarseness, of course, is thought to occur in relation to the fetal scalp edema as seen in Noonan syndrome and Cardiofaciocutaneous syndrome. There is no history of scalp edema in the present cases.

The presence of dimples at joints or points of skin contact to immobiled joints is common in arthrogryposis in general. The dimples are thought to relate to the overlying skin attaching to the joint tissue when there is no or markedly decreased fetal movement of the joint or decreased subcutaneous tissue. However, the dimples in these affected individuals are both deep and much larger than usually seen in arthrogryposis. In addition, they are present in unusual areas, but all areas where there could have been pressure on the skin in the presence of oligohydramnios.

The ears are overgrown, which has been thought in the past to be related to in utero pressure on the developing cartilage, causing mechanical transduction in the cartilage tissue with overgrowth. However, the ears of these children at birth are characteristically very soft and seemed to actually lack normal amounts of cartilage at birth. Similarly, the tip of the nose in these cases seemed to have hypoplastic cartilage, was undergrown and was upturned with a short columella. Some authors have suggested that the nose has been squashed against the uterine wall in the presence of oligohydramnios, however, even in the individuals without pulmonary hypoplasia (who must have had a pool of amniotic fluid around the nose and/or the mouth in order for the lungs to be able to "breathe" in utero) there are short upturned noses. Are fetal tissue specific growth factors or their receptors involved in this cartilage undergrowth of the nose as compared to the overgrowth seen in the ears?

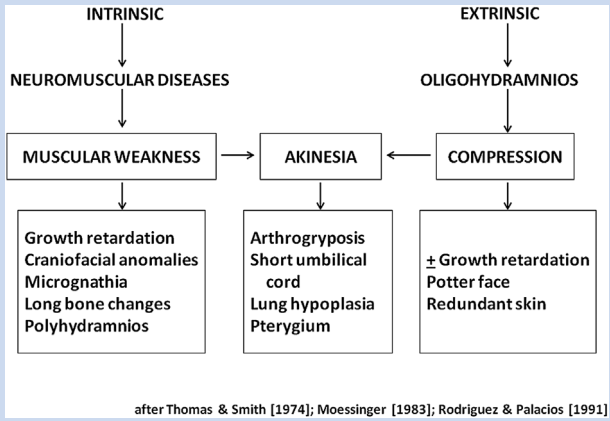

FIG. 15. After Rodriguez and Palacios, Oligohydramnios sequence related to fetal akinesia.

The flattening of the face and the micrognathia appear to be related to fetal pressure and lack of space to grow. The congenital contractures appear to relate to the lack of room to move and are almost always held in flexion; however, in general without some other underlying cause, quite responsive to physical therapy after birth. Facial movement and appearance normalized over the first few years, as disuse muscle atrophy is overcome. The frequent flattening of the hands and feet usually persists into older childhood. Christianson et al., [1999] point out the spade like hands and feet are a third trimester phenomenon. Why do some of the deformations persist and others resolve?

Although clearly a selected subgroup of a larger arthrogryposis collection, why is there a trend toward an excess of males? It is understandable that there would be an excess of males in Potter syndrome since there is a higher occurrence of renal abnormalities in males. Most of the reviews of outcome of oligohydramnios not involving renal agenesis do not mention sex ratio; however, both Nimrod et al., [1984] and Thibeault et al., [1985] also had an excess of males apparently with normal birth weights (Table IV). In the case of oligohydramnios and arthrogryposis, perhaps the excess of males is because males are somewhat larger during fetal development, and therefore, more easily compromised, but it also suggests that there may be X-linked or gender related factors involved in the maintenance of fetal membranes or amniotic fluid. See Tables III and IV for comparisons of these 30 individuals with other reports of oligohydramnios.

The pulmonary hypoplasia appears to relate to the lack of available amniotic fluid allowing the fetus to "breathe in and out" in utero, thus failing to allow normal pulmonary development in utero. In addition, body/chest compression from lack of fluid in the presence of increasing body size may make it more difficult for the lungs to expand. However, why do these individuals with oligohydramnios and arthrogryposis actually do so well after birth? As noted above, it is surprising that half of these individuals, who

sustained longstanding oligohydramnios, appear to have normal lung development at birth. It is unclear what protective factors were at work. Itoh and Itoh [1988] found lack of pulmonary cartilage in renal agenesis, which may contribute to pulmonary hypoplasia in such cases, but not in other types of pulmonary hypoplasia, suggesting fetal renal growth factors are at work. In addition, the normal renal tissue may provide some as yet unidentified growth factor.

The good news in those individuals who seem to have their contractures on the basis of oligohydramnios is, that if they survive pulmonary hypoplasia, and have no central nervous system defect (70%), they seem to do quite well [Hoekstra and de Boer, 1990].

The third of these individuals with oligohydramnios and arthrogryposis who were premature have all the risks and outcomes of prematurity, in this case, including five who have retinopathy of prematurity and chronic lung disease.

The long-term natural history of these individuals with oligohydramnios and arthrogryposis is still not known. The four cases related to Amyoplasia can be expected to have outcomes similar to the natural history of Amyoplasia [Hall et al., 2014]. The outcome for the two surving individuals with unknown syndromes are not clear. Oligohydramnios may well be part of the syndromes.

Mental development seems to be related to the risks of prematurity, the cases with attempted termination of pregnancy, CNS malformations, and the unusual syndromes included in this summary.

Prenatal diagnosis of oligohydramnios can be made by ultrasound and if necessary followed by transvaginal scanning [Keirse and Meerman, 1978; Schmidt et al., 1982; Dicker et al., 1984; Benacerraf, 1990] to assess the actual amount of fluid. The care of such pregnant women is now clear [Chen, 2007; Waters and Mercer, 2009].

Among this overall group, most individuals (74%) with oligohydramnios and multiple contractures were related to early rupture of membranes; however, eight (20%) had no history of ROM. Two of these had Amyoplasia, two had syndromes, which may have oligohydramnios as part of these conditions, and four had oligohydramnios for unknown reason with resolution of contractures occurring rapidly during the first few years.

Overall these individuals have done surprisingly well in view of previous reports of oligohydramnios with and without renal anomalies (see Tables II and III) [Nimrod et al., 1984; Mercer and Brown, 1986; Hoekstra & de Boer, 1990; Rotschild et al., 1990; Tibboel et al., 1990; McIntosh and Harrison, 1994]. In addition, they are reasonably well grown, which appears to be true of most cases of oligohydramnios on a non-renal basis. This suggests that the maturing fetal kidney produces a growth factor(s) important for normal growth in the third trimester.

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REFERENCES

Baines AD, Scott JS. 1960. Renal agenesis and severe urinary tract dysplasia: A review of 50 cases, with particular reference to the associated anomalies. Br Med J 1:841–846.

Bates GS. 1933. Bilateral renal agenesis in the fetus, associated with oligohydramnios. Am J Ostetr Gynecol 25:41–50.

Benacerraf BR. 1990. Examination of the second-trimester fetus with severe oligohydramnios using transvaginal scanning. Obstet Gynecol 75:491–493.

Blanc WA. 1961. Vernix granulomatosis of amnion ("amnion nodosum") in oligohydramnios: Lesion associated with urinary anomalies, retention of dead fetuses, and prolonged leakage of amniotic fluid. New York State J Med 61:1492–1496.

Blanc WA, Apperson JW, McNally J. 1962. Pathology of the newborn and of the placenta in oligohydramnios. B Sloane Hos Women Columbia Presbyt Med 8:51–64.

Chen CP. 2007. Meckel syndrome: genetics, perinatal findings, and differential diagnosis. Taiwan J Obstet Gynecol 46:9–14.

Cheng EY, Luthy DA, Hickok DE, Hollenbach KA, Resta RG, Mahony BS, Luthardt FW. 1991. Transcervical chorionic villus sampling and midtrimester oligohydramnios. Am J Obstet Gynecol 165:1063–1068.

Christianson C, Huff D, McPherson E. 1999. Limb deformations in oligohydramnios sequence: Effects of gestational age and duration of oligohydramnios. Am J Med Genet 86:430–433.

DeMyer M, Baird I. 1969. Mortality and skeletal malformations from amniocentesis and oligohydramnios in rats: Cleft palate, clubfoot, microstomia, and adactyly. Teratology 2:33–38.

Dicker D, Samuel N, Feldberg D, Goldman JA. 1984. The antenatal diagnosis of Potter syndrome (Potter sequence). A lethal and not-so-rare malformation. Eur J Obstet Gynecol Reprod Biol 18:17–24.

Fantel AG, Shepard TH. 1975. Potter syndrome. Nonrenal features induced by oligoamnios. Am J Dis Child 129:1346–1347.

Grunnet ML, Bale JF Jr. 1981. Brain abnormalities in infants with Potter syndrome (oligohydramnios tetrad). Neurology 31:1571–1574.

Guha-Ray DK, Hamblin MH. 1977. Arthrogryposis multiplex congenita in an abdominal pregnancy. J Reprod Med 18:109–112.

Hall JG. 2009. Pena Shokeir Phenotype (Fetal akinesia deformation sequence) Revisited. Birth Defects Res A 85:677–694.

Hall JG. 2012a. Arthrogryposis (multiple congenital contractures) associated with failed termination of pregnancy. Am J Med Genet 158A:2214–2220.

Hall JG, Aldinger KA, Tanaka KI. 2014. Amyoplasia revisited. Am J Med Genet A in press.

Harman CR. 2008. Amniotic fluid abnormalities. Semin Perinatol 32:288–294.

Hill LM, Breckle R, Wolfgram KR, O'Brien PC. 1983. Oligohydramnios: Ultrasonically detected incidence and subsequent fetal outcome. Am J Obstet Gynecol 147:407–410.

Hoekstra JH, de Boer R. 1990. Very early prolonged premature rupture of membranes and survival. Eur J Pediatr 149:585–586.

Itoh K, Itoh H. 1988. A study of cartilage development in pulmonary hypoplasia. Pediatr Pathol 8:65–81.

Jeffcoate TN, Scott JS. 1959. Polyhydramnios and oligohydramnios. Can Med Assoc J 80:77–86.

Kadhim HJ, Lammens M, Gosseye S, Gadisseux JF, Evrard P. 1993. Brain defects in infants with Potter syndrome (oligohydramnios sequence). Pediatr Pathol 13:519–536.

Keirse MJ, Meerman RH. 1978. Antenatal diagnosis of Potter syndrome. Obstet Gynecol 52:64S–67S.

Kohler HG. 1972. An unusual case of sirenomelia. Teratology 6:295–301.

Kohler HG, Peel KR, Hoar RA. 1970. Extramembraneous pregnancy and amniorrhoea. J Obstet Gynaecol Br Commonw 77:809–812.

Levine D, Kilpatrick S, Damato N, Callen PW. 1996. Dolichocephaly and oligohydramnios in preterm premature rupture of the membranes. J Ultrasound Med 5:375–379.

MacIntyre DJ, Chang HH, Kaufman MH. 1995. Teratogenic effects of amniotic sac puncture: A mouse model. J Anat 186:527–539.

Manivel JC, Pettinato G, Reinberg Y, Gonzalez R, Burke B, Dehner LP. 1989. Prune belly syndrome: Clinicopathologic study of 29 cases. Pediatr Pathol 9:691–711.

Mauer SM, Dobrin RS, Vernier RL. 1974. Unilateral and bilateral renal agenesis in monoamniotic twins. J Pediatr 84:236–238.

McIntosh N, Harrison A. 1994. Prolonged premature rupture of membranes in the preterm infant: A 7 year study. Eur J Obstet Gynecol Reprod Biol 57:1–6.

Mercer LJ, Brown LG. 1986. Fetal outcome with oligohydramnios in the second trimester. Obstet Gynecol 67:840–842.

Moessinger AC. 1983. Fetal akinesia deformation sequence: An animal model. Pediatrics 72:857–863.

Naeye RL, Peters EC. 1980. Causes and consequences of premature rupture of fetal membranes. Lancet 1:192–194.

Nicolini U, Santolaya J, Hubinont C, Fisk N, Maxwell D, Rodeck C. 1989. Visualization of fetal intra-abdominal organs in second-trimester severe oligohydramnios by intraperitoneal infusion. Prenat Diagn 9:191–194.

Nimrod C, Varela-Gittings F, Machin G, Campbell D, Wesenberg R. 1984. The effect of very prolonged membrane rupture on fetal development. Am J Obstet Gynecol 148:540–543.

Ohyama M. 1991. An infant having Potter facies without pulmonary hypoplasia after prolonged oligohydramnios due to a placental mass. Eur J Pediatr 150:859.

Palacios J, Rodriguez JI. 1990. Extrinsic fetal akinesia and skeletal development: A study in oligohydramnios sequence. Teratology 42:1–5.

Passarge E, Sutherland JM. 1965. Potter's syndrome: Chromosome analysis of three cases with Potter's Syndrome or related syndromes. Am J Dis Child 109:80–84.

Perlman M, Williams J, Hirsch M. 1976. Neonatal pulmonary hypoplasia after prolonged leakage of amniotic fluid. Arch Dis Child 51:349–353.

Pflueger SM, Scott CI Jr, Moore CM. 1984. Trisomy 7 and Potter syndrome. Clin Genet 25:543–548.

Philipson EH, Sokol RJ, Williams T. 1983. Oligohydramnios: Clinical associations and predictive value for intrauterine growth retardation. Am J Obstet Gynecol 146:271–278.

Poswillo D. 1972. Experimental first-trimester amniocentesis in nonhuman primates. Teratology 6:227–234.

Potter EL. 1946a. Bilateral renal agenesis. J Pediatr 29:68–76.

Potter EL. 1946b. Facial characteristics of infants with bilateral renal agenesis. Am J Obstet Gynecol 51:885–888.

Potter EL. 1974. Oligohydramnios: Further comment. J Pediatr 84:931–932.

Pramanik AK, Altshuler G, Light IJ, Sutherland JM. 1977. Prune-belly syndrome associated with Potter (renal nonfunction) syndrome. Am J Dis Child 131:624–672.

Preus M, Kaplan P, Kirkham TH. 1977. Renal anomalies and oligohydramnios in the cerebro-oculofacio-skeletal syndrome. Am J Dis Child 131:62–64.

Pricop M, Tomoşoiu C, Feurdean M, Gafencu C, Muscă S, Slătineanu S, Daniil C. 2000. Abdominal pregnancy. Case report, review of the literature. Rev Med Chir Soc Med Nat Iasi 104:139–142.

Rodríguez JI, Palacios J. 1991. Pathogenetic mechanisms of fetal akinesia deformation sequence and oligohydramnios sequence. Am J Med Genet 40:284–289.

Rotschild A, Ling EW, Puterman ML, Farquharson D. 1990. Neonatal outcome after prolonged preterm rupture of the membranes. Am J Obstet Gynecol 162:46–52.

Schmidt W, Schroeder TM, Buchinger G, Kubli F. 1982. Genetics, pathoanatomy and prenatal diagnosis of Potter I syndrome and other urogenital tract diseases. Clin Genet 22:105–127.

Singh S, Mathur MM, Singh G. 1974. Congenital anomalies in rat foetuses induced by amniocentesis. Indian J Med Res 62:394–401.

Smith DW. 1979. Commentary: redundant skin folds in the infant–their origin and relevance. J Pediatr 94:1021–1022.

Stevens CA. 1993. Malformations and deformations in abdominal pregnancy. Am J Med Genet 47:1189–1195.

Thibeault DW, Beatty EC Jr, Hall RT, Bowen SK, O'Neill DH. 1985. Neonatal pulmonary hypoplasia with premature rupture of fetal membranes and oligohydramnios. J Pediatr 107:273–277.

Thomas IT, Smith DW. 1974. Oligohydramnios, cause of nonrenal features of Potter's syndrome, including pulmonary hypoplasia. J Pediatr 84:811–814.

Tibboel D, Gaillard JL, Spritzer R, Wallenburg HC. 1990. Pulmonary hypoplasia secondary to oligohydramnios with very premature rupture of fetal membranes. Eur J Pediatr 149:496–499.

Underwood MA, Gilbert WM, Sherman MP. 2005. Amniotic fluid: Not just fetal urine anymore. J Perinatol 25:341–348.

Watanabe H, Yamanaka T. 1990. A possible relationship between Beckwith-Wiedemann syndrome, urinary tract anomaly and prune belly syndrome. Clin Genet 38:410–414.

Waters TP, Mercer BM. 2009. The management of preterm premature rupture of the membranes near the limit of fetal viability. Am J Obstet Gynecol 201:230–240.

Williams J, Gordon LP, Rosenberg HS, Rudolph AJ. 1977. Oligohydramnios syndrome and intra-abdominal pregnancy. J Pediatr 90:158–160.

Yunis E, Ramírez E, Uribe JG. 1980. Full trisomy 7 and Potter syndrome. Hum Genet 54:13–18.