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Limb Deformations in Oligohydramnios Sequence: Effects of Gestational Age and Duration of Oligohydramnios

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In order to study the pathogenesis of prenatal deformities, we reviewed maternal histories, delivery records, pathology reports, radiographs, and photographs of 90 fetuses with prenatally documented oligohydramnios at gestational ages from 14 weeks to term. The causes of oligohydramnios included premature rupture of membranes (44 cases), fetal renal insufficiency (25 cases), idiopathic (15 cases), and twin–twin transfusion (6 cases). The fetuses were grouped according to gestational age at delivery and duration of oligohydramnios. Sixty-three fetuses (70%) had documented contractures. As expected, contractures were more frequent with earlier onset and longer duration of oligohydramnios. During the 2nd trimester, the frequency of contractures in fetuses with oligohydramnios was 77% compared to 52% in the 3rd trimester (χ^2 = 5.33, 1 *df, P* = .02). Considering all gestational ages together, 57% of fetuses had contractures after less than 2 weeks of oligohydramnios compared to 81% of fetuses with a longer duration of oligohydramnios ((χ^2 = 6.23, 1 *df, P* < .02). The type of contracture varied with gestational age. Clubfoot was the most frequent at all ages, but hand contractures such as camptodactyly were common only in the 2nd trimester while the broad flat hand originally described in Potter sequence was found almost exclusively in the fetuses with oligohydramnios in the 3rd trimester. Of the 63 fetuses with oligohydramnios and contractures, 25 (40%) had either additional malformations or family history that could explain contractures independent of oligohydramnios. Am. J. Med. Genet. 86:430–433, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS: oligohydramnios; limb deformations; contractures; fetal akinesia

INTRODUCTION

Oligohydramnios results in a sequence of effects on the fetus including facial and limb deformations as well as pulmonary hypoplasia. Limb deformities due to oligohydramnios are sometimes difficult to distinguish from those due to intrinsic fetal causes. In order to learn about the effects of oligohydramnios, regardless of cause, on the fetal limbs throughout the 2nd and 3rd trimesters, we chose to include in our study previable fetuses, stillbirths, and DE&C specimens as well as liveborn infants with documented oligohydramnios of at least 24-hr duration. The requirement for documented oligohydramnios eliminated cases with premature rupture of membranes (PROM) but normal amniotic fluid volume in which oligohydramnios sequence would not be expected. The shorter interval allowed us to investigate the cause of contractures in fetuses with relatively brief periods of oligohydramnios. Because fetuses with multiple anomalies were not excluded, the study also provides an estimate of the frequency of other anomalies in fetuses with a history of oligohydramnios or PROM.

MATERIALS AND METHODS

All autopsy, surgical pathology, and placental pathology reports at Magee-Womens Hospital from the 1995 through 1998 were screened for mention of contractures, renal abnormalities, oligohydramnios, or premature rupture of membranes. The mothers' charts were reviewed to determine the cause, time of onset, and duration of oligohydramnios. All cases with clinical

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and/or ultrasound evidence of oligohydramnios at least 24 hr prior to delivery were selected for further study regardless of the cause of the oligohydramnios. Because ruptured membranes sometimes reseal, allowing reaccumulation of amniotic fluid, infants born to women with premature rupture of membranes were included only if there was also ultrasound documentation of oligohydramnios during the 2 weeks preceding delivery. In twin pregnancies, each twin was considered as a separate fetus and included only if oligohydramnios was documented.

For the 90 cases identified, details of maternal and family history were recorded from the mothers' charts. The autopsy or surgical pathology reports of deceased infants or fetuses and medical records of liveborn infants were examined for mention of any malformations, disruptions, or deformities, with special attention to the presence or absence of contractures. In cases where there was any uncertainty, the presence or absence of contractures and other signs of oligohydramnios sequence was confirmed by review of photographs and radiographs obtained at the time of autopsy.

The study cases were grouped according to gestational age at delivery and duration of oligohydramnios. Duration of oligohydramnios was based on clinical evidence of rupture of membranes or ultrasound documentation, whichever occurred first. In cases with severe renal anomalies, oligohydramnios was assumed to be of over 2 weeks duration, even if no ultrasound evidence was available for that time period.

RESULTS

We identified 90 fetuses with documented oligohydramnios at least 24 hr before delivery. Eight fetuses were delivered before 16 weeks, 22 at 16 to 20 weeks, 35 at 20 to 24 weeks, and 25 after 24 weeks gestation. Overall, 44 fetuses had oligohydramnios due to PROM and/or chronic placental abruption, 25 fetuses had renal insufficiency, 15 had idiopathic oligohydramnios, and 6 had oligohydramnios due to twin–twin transfusion.

Contractures were noted after as little as 1 day of oligohydramnios, and were common in all groups (15/22 = 68% at <1 week, 9/20 = 45% at 1–2 weeks), but the highest rate of contractures (39/48 = 81%) occurred after >2 weeks. In the 2nd trimester, 50/65 (77%) of fetuses with oligohydramnios had contractures compared to only 13/25 (52%) in the 3rd trimester ($\chi^2 = 5.33$, 1 *df*, $P = .02$). The frequency of contractures was approximately the same for each 1-month period within the 2nd trimester (6/8 at <16 weeks, 17/22 at 16–20 weeks, and 27/35 at 20–24 weeks). The type of contractures was dependent on gestational age. Clubfoot was the most frequent contracture at all ages, occurring in two thirds of 2nd-trimester fetuses and half of 3rd-trimester fetuses. Camptodactyly was most frequent in the youngest fetuses (53% at <20 wks, 34% at 20–24 weeks, and 20% at >24 weeks, $\chi^2 = 6.95$, 2 *df*, $P < .05$). The broad, flat hands described in the original reports of Potter sequence were found almost exclusively in the 3rd trimester (0 at <20 weeks, 1/35 = 3% at 20–24 weeks, 7/25 = 27% at >24 weeks). Other risk factors such as multiple anomaly syndromes or siblings affected with contractures in the absence of oligohydramnios were identified in 25/63 (40%) of fetuses with contractures and none of the 27 without contractures. The fetuses with other anomalies included 2 with chromosomal disorders (trisomy 21, isotetrasomy 9p), 11 with other known syndromes (Meckel–Gruber, multiple pterygium, caudal regression (5), amniotic bands (3), VACTERL) and 10 with isolated nonrenal malformations or multiple anomalies not suggestive of any known syndrome. Of those with a positive family history, 1 had a monozygotic twin with contractures despite polyhydramnios, 1 (who also had an abdominal wall defect) had a dizygotic twin with contractures despite normal amniotic fluid, and 1 had a previous sib with fetal hypokinesia sequence.

DISCUSSION

Amniotic fluid is necessary for fetal development. Fetuses with insufficient fluid volume often develop oligohydramnios sequence, characterized by facial compression (loose skin folds, especially beneath the eyes, flattened and beaked nose, large, flat ears), pulmonary hypoplasia, and positional deformities such as asymmetric club feet, major joint contractures, and broad, flat hands with redundant skin. Although oligohydramnios (or Potter) sequence was initially described in neonates with renal anomalies [Potter, 1946], other causes of oligohydramnios such as premature rupture of membranes (PROM) or uteroplacental circulatory disorder lead to the same final result [Graham, 1988; Thomas, 1974]. Several previous studies have been focused on the duration of ruptured membranes necessary to produce anomalies, especially pulmonary hypoplasia, in liveborn premature infants. Nimrod et al. [1984] reported pulmonary hypoplasia in 9% and skeletal abnormalities in 12% of premature infants with prolonged premature rupture of membranes (PPROM) for more than 1 week prior to delivery. Eight of the 9 cases of lung hypoplasia occurred in infants with rupture of membranes prior to 26 weeks of gestation. Contractures were also more common in infants with earlier onset and longer duration of PROM. Thibeault et al. [1985] studied preterm infants with PROM for more than 5 days. Only half had documented oligohydramnios, and in this group, 2/3 had positional limb deformities and 91% required assisted ventilation. In another study [Rotschild et al., 1990], pulmonary hypoplasia was noted in only 14/88 infants with PROM longer than 7 days and occurring before 29 weeks of gestation. The relatively low incidence of lung hypoplasia is probably due to inclusion of cases with normal amniotic fluid volume despite PROM. Skeletal anomalies were found primarily in cases with severe oligohydramnios of extended duration. McIntosh and Harrison [1994] found compression deformities in 21% of preterm infants with PROM at least 4 days prior to delivery. The infants with compression deformities had a median PROM duration of 28 days compared to only 7 days for the infants without deformities, but contractures were observed as early as 4 days after ROM in some fetuses. Recently, Kurkinen-Raty et al. [1998]

compared 78 premature infants with rupture of membranes greater than 24 hr before delivery to 78 controls matched for gestational age, but without prolonged rupture of membranes. The infants with prolonged premature rupture of membranes (PPROM) had a higher incidence of contractures (8% vs. 0%) and pulmonary hypoplasia (12% vs. 0%) relative to controls. Within the PPROM group, the infants with contractures had a median duration of ROM 54 days prior to delivery compared to 7 days for the infants without contractures. The differing rates of contractures among these studies presumably reflect differences in the frequency and severity of oligohydramnios as well as differences in the type of skeletal deformities that were counted.

Limb contractures and lung hypoplasia occur not only when fetal movement is limited by oligohydramnios, but also when fetal akinesia is due to intrinsic neuromuscular abnormalities. Fetuses with severe neuromuscular abnormalities usually fail to swallow and develop polyhydramnios, which predisposes to PROM. Distinguishing oligohydramnios sequence from fetal akinesia due to intrinsic neuromuscular abnormalities may be difficult if a mother with unrecognized polyhydramnios presents with oligohydramnios following rupture of membranes. Although contractures caused by neuromuscular abnormalities tend to be more symmetrical than those due to oligohydramnios and the facial appearance is different [Rodriguez and Palacios, 1991], akinesia due to neuromuscular anomalies may be difficult to distinguish from that due to compression, especially when examination of the brain is limited as in dilation and curettage specimens or macerated stillbirths. Of particular concern is the situation in which a fetus is noted to have contractures after only a few days of oligohydramnios. The distinction between oligohydramnios sequence due to PROM and fetal akinesia sequence due to intrinsic neuromuscular anomalies may be vital for assessment of recurrence risk and planning for prenatal diagnosis of subsequent pregnancies.

Our data show increasing frequency of contractures in younger fetuses with longer duration of oligohydramnios in accord with previous studies, but the total incidence of contractures is higher (63/90 = 70%). This can be attributed in part to early gestational age because 72% of our subjects were delivered in the 2nd trimester. Another factor contributing to the high incidence of contractures in our study is the exclusion of subjects without documentation of oligohydramnios. Our results are similar to those of Thibeault et al. [1985] who found contractures in two thirds of their subjects with documented oligohydramnios. Other investigators reporting fewer skeletal deformities provide no information on the incidence or severity of oligohydramnios in their subjects. Furthermore, because 97% of our subjects had an autopsy, documentation of all anomalies including contractures may be more complete.

The type of contractures varies with gestational age. Clubfeet are frequent regardless of gestational age or duration of oligohydramnios, but the type of hand abnormality is dramatically age-dependent. Potter's original report on renal agenesis [1946] described clubfeet but made no mention of the hands. Thomas [1974], who was the first to document that Potter sequence results from oligohydramnios of any cause, used the term "spadelike" to describe the broad, flat hands in oligohydramnios sequence. We observed this type of hand frequently in 3rd trimester cases, especially those with oligohydramnios lasting more than 2 weeks (5/10 with renal disease, 2/6 with other causes of prolonged oligohydramnios). In 2nd-trimester fetuses, the clinical picture is different with frequent hand contractures, primarily camptodactyly. Typical "Potter hand" is extremely rare in the 2nd trimester, even in fetuses with renal insufficiency. Our only observation of Potter hand in the 2nd trimester was in a 20-week fetus with caudal dysgenesis and bilateral renal agenesis, but 6/14 other 2nd-trimester fetuses with renal insufficiency had camptodactyly. This finding is important because the combination of camptodactyly and equinovarus feet has traditionally been associated with the fetal akinesia sequence [Graham, 1988]. Our observation of camptodactyly in 2nd-trimester fetuses with various causes of oligohydramnios, including renal disease, suggests that the initial response to oligohydramnios may include camptodactyly, but with increasing size of the fetus and increasing duration of oligohydramnios the hand may become broad and flat with loose skin. In the 2nd trimester, camptodactyly cannot be used to distinguish between akinesia due to neuromuscular anomalies and that due to oligohydramnios.

Twinning is a risk factor for oligohydramnios due to PROM and/or twin–twin transfusion. Thirteen infants from 11 twin pregnancies (8 monozygotic, 2 like-sex dichorionic, 1 unlike sex pair) were included in our study. Six were twin–twin transfusion donors while 7 (including two recipients of twin–twin transfusions) had PROM. Only 3 of the twin pairs (the two with PROM in the twin–twin transfusion recipient and one pair with simultaneous PROM in both sacs) were concordant for oligohydramnios, but only the 2 donor twins had contractures. One monozygotic pair with twin–twin transfusion was concordant for contractures even though only 1 fetus had oligohydramnios, and the unlike sex pair was also concordant for contractures even though only 1 twin had oligohydramnios. Twinning clearly increases the risk of oligohydramnios, but among the twins with documented oligohydramnios, the incidence of contractures was not significantly different from that in singletons (8/13 = 61% in twins vs. 51/77 = 66% in singletons).

A total of 25 fetuses with oligohydramnios had at least one additional risk factor that might explain the observed contractures. Two twin pairs (1 MZ, 1 DZ) were concordant for contractures, but not for oligohydramnios, 1 had a non-twin sib with fetal akinesia, and 23 had nonrenal malformations including 13 with recognizable conditions (5 caudal dysgenesis, 3 amniotic bands, 1 trisomy 21, 1 isotetrasomy 9p, 1 Meckel, 1 lethal multiple pterygium, 1 VATER), 6 with malformations not a recognized syndrome, and 4 with apparently isolated malformations (limb deficiency, diaphragmatic hernia, abdominal wall defect, congenital heart disease). The fetus with abdominal wall defect had a DZ twin with contractures, but no abdominal

wall defect and no oligohydramnios. Among fetuses with additional malformations or a family history of malformations, the incidence of contractures was 24/25 = 96% compared to 35/65 = 54% among those without additional risk factors. This observation suggests that such risk factors may account for a significant proportion of all observed contractures.

Although the incidence of contractures increases with earlier onset and longer duration of oligohydramnios, occasional contractures are observed after as little as 24 hr of documented oligohydramnios. Possible explanations include underestimation of the duration of oligohydramnios and/or heterogeneity of cause for the contractures. Even in infants with oligohydramnios, contractures may be due to other causes as suggested by the nonrenal malformations or family histories documented in 28% of our cases overall, but in 40% of those with contractures. The type of contracture, especially in the hands depends on gestational age. In the 2nd trimester the broad, flat Potter hand is rare while camptodactyly, which has traditionally been attributed to neuromuscular akinesia, is common in 2nd-trimester fetuses with oligohydramnios sequence. Even in fetuses with well-documented oligohydramnios, detailed evaluation and investigation for other possible causes are necessary to distinguish between oligohydramnios sequence and fetal akinesia sequence due to neuromuscular abnormalities of the fetus.

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