What does fetal autopsy unmask in oligohydramnios?

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Abstract

Objective: We aimed to determine the value of autopsy in fetuses with antenatally diagnosed oligohydramnios.

Patients and methods: We evaluated all fetal losses over a period of 6.5 years. Those with oligohydramnios on antenatal scan were critically analyzed. Oligohydramnios was defined as amniotic fluid index of less than five objectively or as an obvious lack of liquor at subjective assessment. A detailed postmortem examination was carried out in all the fetuses after obtaining an informed consent.

Results: Fetal autopsy was conducted in 255 cases. Fifty-five (21.5%) fetuses were diagnosed to have oligohydramnios on antenatal ultrasonography. On analysis of antenatal causes of oligohydramnios, maternal/placental factors were noted in 18%, ultrasound findings known to affect amniotic fluid in 27% while cause remained unidentified in 54.5% of cases. On autopsy, fetal malformations were noted in 61.8% cases, intrauterine growth retardation in 21.8% fetuses and no obvious malformations in 16.3% fetuses. Renal anomalies were noted in 40% cases and non-renal malformations in 21.8% cases.

Conclusion: The postmortem examination helped us to identify the cause of fetal loss in 46 (83.6%) fetuses with antenatal oligohydramnios. A working diagnosis could not have been established without autopsy in 19 (34.5%) cases.

Keywords

Amniotic fluid, anhydramnios, fetal anomalies, genetic counseling, malformation, ultrasonography

History

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Introduction

Normal amniotic fluid quantity is maintained by fetal kidneys, lungs, skin and feto–maternal interphase and is critical for normal development of the fetal respiratory, gastrointestinal and musculoskeletal system. Several fetal and/or maternal factors can lead to a decrease in the amniotic fluid volume or oligohydramnios. Oligohydramnios in turn is associated with significant morbidity and mortality [1,2]. The assessment of amniotic fluid is either subjective or semi-quantitative [3]. Usually the evaluation of amniotic fluid index or single deepest pocket methods are preferred as they are objective methods and decrease the inter-observer variation and are also useful for serial measurements.

Ultrasound between 18 and 22 weeks of gestation is usually carried out in all pregnant women to evaluate fetal anatomy, placental location and amniotic fluid volume [4].

Certain fetal anomalies lead to reduction of amniotic fluid volume and also lead to poor visibility and restricted evaluation of these anatomical structures. Oligohydramnios in turn can lead to deformations in the fetus. There is limited data on precise contribution of postmortem examination in fetuses with oligohydramnios [5,6]. We report on 55 fetuses with oligohydramnios diagnosed antenatally and evaluate the role of autopsy in providing definitive diagnosis in these fetuses.

Patients and methods

Our hospital offers fetal autopsy as a routine clinical service for all fetal losses, which include spontaneous abortions, intrauterine fetal deaths (IUFD)/stillbirths, termination of pregnancies after prenatal diagnosis of major malformations and neonatal death. Institutional ethics committee clearance was taken for this study. Fetuses, either terminated or spontaneously aborted after antenatal diagnosis of oligohydramnios with or without malformation, were examined between October 2008 and March 2015. Oligohydramnios was diagnosed by an amniotic fluid index of less than five or a low liquor at subjective assessment at any gestation [3]. Patient details including family history, antenatal details, consanguinity, and exposure to teratogen were taken. All the cases underwent a detailed postmortem examination.

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Complete postmortem evaluation including fetal autopsy, photography, radiography, external and internal examinations and histopathology of relevant organs was done after written consent from couple or family member. Karyotypes of fetuses were done whenever possible.

We give sonographic and postmortem findings of all cases with antenatal oligohydramnios (Supplementary Table 1). We categorized the cases into three groups based on maternal health and antenatal findings. They are (A) with blood pressure/placenta disorders (maternal/placental reasons), (B) with identified antenatal findings known to affect amniotic fluid and (C) with unidentified antenatal causes of oligohydramnios (Table 1). We then list the renal and non-renal anomalies seen in these fetuses (Table 2). We also looked into the cases of fetal anomalies which were completely masked by oligohydramnios and a working diagnosis could not have been established without fetal autopsy (Table 3).

### Results

Fetal autopsy was conducted in a total of 255 cases over a period of 6 years and 5 months. Fifty-five (21.5%) fetuses were diagnosed to have oligohydramnios on antenatal ultrasound. In this cohort, there were 27 (49%) second trimester fetuses and 28 (51%) third trimester fetuses. There were 27/55 (49%) terminations of pregnancy in view of fetal anomaly, 27/55 (49%) had IUFD with or without anomalies and one (1.8%) neonatal death. Karyotypes could be obtained in six fetuses which were normal. Chromosomal microarray in fetus with a clinical diagnosis of Fraser syndrome did not reveal any pathogenic copy number variations. Diagnoses on autopsy and ultrasound findings of all cases are listed in Supplementary Table 1.

Antenatally maternal and/or placental factors (Category A) contributing to oligohydramnios were found in 10/55 (18%) cases. Of these, 5/55 cases were complicated by gestational

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**Table 1. Classification of cases based on antenatal findings.**

| Etiology                                           | No. of cases (55) |
|----------------------------------------------------|-------------------|
| Maternal/placental factors contributing to oligohydramnios | 10 (18%)          |
| Antenatal findings known to affect amniotic fluid     | 15 (27%)          |
| Unidentified causes of antenatal oligohydramnios      | 30 (54.5%)        |

**Table 2. List of renal and non-renal malformations on autopsy.**

| Malformations                                         | No. of cases (34) |
|-------------------------------------------------------|-------------------|
| **Renal malformations**                               |                   |
| Meckel–Gruber syndrome                                | 3                 |
| Short-rib thoracic dysplasia                          | 1                 |
| Fraser syndrome                                       | 2                 |
| Bladder outlet obstruction                             | 4                 |
| Urorectal septum malformation sequence (URSM)         | 5                 |
| Bilateral renal agenesis                              | 2                 |
| Cystic renal disease                                  | 2                 |
| Hypoplastic kidneys                                   | 1                 |
| Multiple malformations with renal disease (no definitive diagnosis) | 2                 |
| **Other system malformations**                        |                   |
| Central nervous system anomaly                         | 3                 |
| Congenital cystic adenomatoiod malformation of lung    | 1                 |
| Hydrops fetalis                                       | 3                 |
| Club feet                                             | 1                 |
| Cardiac anomaly                                       | 1                 |
| Jarcho–Levin syndrome                                 | 1                 |
| Multiple malformations (no definitive diagnosis)       | 2                 |

**Table 3. Autopsy diagnoses in cases where a working diagnosis was not possible with ultrasonography alone.**

| Autopsy diagnoses                                                                 | No. of cases (19) |
|-----------------------------------------------------------------------------------|-------------------|
| Urorectal septum malformation sequence (two cases associated with omphalocele and truncus arteriosus each) | 5                 |
| Meckel–Gruber syndrome with oligohydramnios sequence                               | 1                 |
| Bilateral renal agenesis                                                           | 1                 |
| Unilateral renal agenesis and contralateral cystic kidney with hemivertebrae       | 1                 |
| Short-rib thoracic dysplasia                                                       | 1                 |
| Venticulomegaly with partial agenesis of corpus callosum                           | 1                 |
| Jarcho–Levin syndrome                                                              | 1                 |
| Fraser syndrome                                                                    | 2                 |
| Cardiac anomaly                                                                    | 1                 |
| Multiple malformations                                                             | 5                 |
hypertension, 3/55 cases had presence of end-diastolic flow in the umbilical artery and history of premature rupture of membrane was noted in 2/55 cases.

We identified antenatal ultrasound findings in fetus known to affect amniotic fluid (Category B) in 15/55 (27%) cases. All these cases had renal anomalies. The antenatal findings in these cases were as follows: bladder outlet obstruction (five cases), multi-cystic/poly cystic kidneys (four cases), megalocystis (two cases), non-visualization of kidneys (two cases), enlarged and echogenic kidneys and hydronephrosis in one case each. On postmortem evaluation in these cases, there was Meckel–Gruber syndrome in three cases, bladder outlet obstruction in four cases, urorectal septum malformation (URSM) sequence in two cases, cystic renal disease with unilateral renal agenesis in two cases and bilateral renal agenesis, Fraser syndrome, short-rib thoracic dysplasia and multiple congenital anomalies in one case each.

In 30/55 (54.5%) cases, antenatal causes of oligohydramnios remained unidentified (Category C) (Table 1). In this category, postmortem examination revealed anomalies in 15 cases, intrauterine growth retardation (IUGR) in six cases, fetal deformation secondary to oligohydramnios in two cases and no obvious malformation in seven cases. The anomalies in this category were as follows: URSM sequence in three cases, Dandy–Walker malformation/vermian hypoplasia in two cases, unexplained hydrops fetalis in two cases, multiple malformations (with renal anomaly in two) in four cases and bilateral renal agenesis, Fraser syndrome, cystic adenomatoid malformation of lung and Jarcho–Levin syndrome in a case each.

Overall, autopsy revealed fetal malformations in 34 (61.8%) cases and intrauterine growth retardation in 12 (21.8%) fetuses. Hence, the postmortem examination helped us to identify the overall cause of fetal loss in 46/55 (83.6%) fetuses with antenatal oligohydramnios. Seventeen (62.9%) of the 27 cases with intrauterine fetal death had anomalies on autopsy. Also, structural and/or vascular abnormalities of placenta were evident in five cases with intrauterine growth retardation. No obvious cause of fetal loss could be identified in nine (16.3%) fetuses.

Predominant renal anomalies were noted in 22 (40%) cases while other system malformations were noted in 12 (21.8%) cases (Table 2). Malformation syndromes were noted in 17 cases, Dandy–Walker malformation/vermian hypoplasia in two cases, unexplained hydrops fetalis in two cases, multiple malformations (with renal anomaly in two) in four cases and bilateral renal agenesis, Fraser syndrome, cystic adenomatoid malformation of lung and Jarcho–Levin syndrome in a case each.

Oligohydramnios markedly limited the fetal assessment on antenatal ultrasonography in 19/55 (34.5%) of fetuses. A working diagnosis would not have been possible without autopsy in these cases (Table 3). Notably, five cases had URSM sequence among them.

Discussion

The etiopathogenesis of oligohydramnios is very heterogeneous and can arise as a result of number of maternal or fetal factors. The incidence of oligohydramnios has been reported in 1–8.6% of pregnancies [7–12]. It is often associated with significant morbidity and mortality as it interferes with normal pulmonary development and survival. Though pregnancies with isolated oligohydramnios do not always carry a risk of poor fetal outcome, presence of associated anomalies predicts an unfavorable outcome. Often ultrasound examination of fetuses with oligohydramnios is technically difficult due to fetal crowding and poor visibility. Hence, we aimed to evaluate the contribution of fetal autopsy in pregnancies complicated by oligohydramnios. This study forms part of our ongoing work on fetal autopsy [13].

This is the second largest study analyzing the importance of autopsy in fetuses with antenatally diagnosed oligohydramnios after the earlier report by Scott and Goodburn [14]. They reported on 60 autopsies with oligohydramnios sequence (five fetuses had external assessment instead of formal autopsy) to assess the range of pathological lesions associated with second trimester oligohydramnios.

The present study revealed higher fetal malformations rate of 61.8% (34/55) when compared to other series on oligohydramnios which report an incidence range of 7–37% [7,15–18]. This could be attributed to the study population which comprised mainly of pregnancies which were referred in view of fetal anomalies or IUFD along with oligohydramnios, thus introducing a selection bias. However, the rate of anomalies in cases with intrauterine fetal death too was found to be higher, 62.9% (17/27) than the previous reports (31% and 39.2%) [7,15]. The anomalies were found in this subset of fetuses are heterogeneous on postmortem examination, though many of them had renal involvement as well. This subgroup appears to have highest yield on postmortem evaluation.

Isolated IUGR was found in 12/55 (21.8%) fetuses. In a recent systematic meta-analysis, birth weights as well as perinatal mortality have been found to be strongly associated with oligohydramnios [2]. However, it was concluded that precise outcome cannot be predicted for individual pregnancies complicated by oligohydramnios.

In our series, genitourinary tract anomalies were noted in 22 (40%) cases (including six cases with syndromes) comparable with the previous reports. As anticipated, these anomalies are the most frequent anomalies associated with oligohydramnios, described previously in similar series [14,15,19]. Scott and Goodburn [14] observed renal anomalies in 28 (46.6%) cases and no renal anomalies in 27 (45%). Various studies have highlighted the role of fetal autopsy and histopathological examination to discern the definitive etiology of the various renal malformations for providing definitive recurrence risk [6,20].

A working diagnosis could not have been possible in 2/10 cases in category A and 7/15 cases in category B. In category C, 10/30 cases received a working diagnosis on postmortem evaluation only. Overall, critical evaluation of the contribution of fetal autopsy and comparison of cases of oligohydramnios with cases of normal amniotic fluid was carried out. Though in 27/55 (49%) cases, a diagnosis was possible by antenatal ultrasound findings, in 19/55 (34.5%) fetuses oligohydramnios markedly limited the fetal assessment on antenatal ultrasonography (Table 3). While in cases with
normal amniotic fluid, a working diagnosis by antenatal ultrasound was possible in 63% of cases and in 22% of cases a diagnosis was made after postnatal evaluation only.

URSM sequence was the most common malformation (9%) in our series (detailed autopsy findings are provided in Supplementary Table 1). It is usually associated with oligohydramnios when there is an absence of perineal opening. In two of these fetuses, only the presence of oligohydramnios was noted on prenatal ultrasound while the other two had megacystis with hydrenephrosis. One of these fetuses had umbilical cyst with URSM which was mistaken for anterior abdominal wall defect antenatally. Patil et al. [21] correlated antenatal ultrasound with autopsy findings of URSM. They found non-visualization of bladder, bilateral hydronephrosis or multicystic kidneys as the antenatal presentation while URSM could be diagnosed only on autopsy.

URSM sequence is a rare entity with defect in the embryonic development of caudal mesoderm leading to malformations of urogenital tract and hindgut development. The severity and subtypes of URSM sequence vary and are classified into complete and incomplete types [22]. All our cases had complete URSM sequence. The overall incidence is one in 50 000–250 000 neonates [23]. However, in a recent survey [24], the prevalence of partial URSM has been found to be 2.8 per 100 000 total births. Several cases have been reported from India earlier [21,25,26]. Recurrence of URSM in sibs was also reported raising the possibility of a genetic etiology [25]. Though several theories have been postulated on pathogenesis of the condition, exact mechanism remains unknown till date.

Seven well-defined monogenic syndromes including Meckel–Gruber, Fraser, short-rib thoracic dysplasia and Jarcho–Levin could be ascertained in our series, which aided in providing definitive genetic counseling and risk of recurrence to the family. Two cases of intracranial malformations (Dandy–Walker malformation/variant) were diagnosed at ultrasound, but could not be confirmed by autopsy due to maceration of brain. However, additional malformations were noted on autopsy.

The study is retrospective and looks into a specific subgroup of families who sought fetal autopsy. Hence we do not have data on maternal factors that influence the amniotic fluid volume, specifically maternal hypertension during pregnancy. Karyotype and chromosomal microarray could be done in only limited cases due to the unavailability of appropriate samples and financial constraints.

We conclude that fetal autopsy aids to determine the etiology in substantial proportion of pregnancies complicated by low amniotic fluid volume. Renal anomalies were the most commonly observed anomalies in these fetuses. URSM sequence is a common cause of oligohydramnios that is difficult to visualize antenatally.

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Declaration of interest

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Supplementary material available online