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ORIGINAL ARTICLE

The prognostic factors and the outcome of primary isolated fetal ascites

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Abstract
Purpose The purpose of the present study was to evaluate the prognostic factors and review the outcome of primary isolated fetal ascites.
Methods A retrospective cohort study was conducted for fetuses with primary isolated ascites with a prenatal diagnosis between 1994 and 2009. The patients were divided into the favorable group (Group I) whose ascites were resolved by medical treatment alone and an unfavorable group (Group II) who required surgical intervention after birth due to refractory ascites.
Results There were seven patients in Group I and five patients in Group II. Six of seven patients who developed ascites after 30 weeks' gestation were categorized in Group I, and four of five infants who developed ascites before 30 weeks' gestation were categorized in Group II. There was a negative correlation between the gestational age at diagnosis and the severity of the fetal abdominal distention. In Group II, the ascites resolved in two cases and was reaccommodated in another two cases after surgery. An infant with trisomy 21 received continuous drainage and eventually died of infection.
Conclusions The prognosis of primary isolated fetal ascites can be predicted based on the gestational age at diagnosis and the severity of the fetal abdominal distention.

Keywords Etal ascites · Chylous ascites · Prenatal diagnosis · Fetal intervention · Prognosis

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Introduction

Fetal ascites is frequently recognized as a symptom in non-immune fetal hydrops, which arise in response to numerous causes [1]. Fetal ascites also occurs independently without a fluid accumulation in any other serosal cavities or subcutaneous tissue due to various congenital abnormalities [2–4]. In contrast, the causes of primary isolated fetal ascites are unclear. Most of these fetuses develop chylous ascites after birth [5] which may be caused by either congenital lymphatic dysplasia or abnormal lymphatic drainage [6, 7]. Although the prognosis has been reported to usually be favorable for these infants [5], there are some unfavorable cases with severe chylous ascites that persists after various types of therapy including dietary treatment, total parenteral nutrition (TPN) and surgical intervention [8–10]. However, a few studies have reported the prognostic factors and proposed optimal management of primary isolated fetal ascites [6, 11, 12]. Therefore, a retrospective review of primary isolated fetal ascites was conducted to evaluate the prognostic factors and explore the optimal management both in utero and after birth.

Materials and methods

Study population

A retrospective cohort study was performed for fetuses with primary isolated fetal ascites at the unit of pediatric surgery of Osaka university hospital and Osaka Medical Center and Research Institute for Maternal and Child Health from 1994 through 2009. Isolated ascites was defined as fluid collection in the abdominal cavity without involvement of fluid accumulation in other serosal cavities or subcutaneous tissue. Cases with secondary isolated fetal ascites caused by intrauterine infections, cardiovascular malformations, cardiac arrhythmia, and other fetal malformations such as genitourinary, pulmonary, or gastrointestinal anomalies were excluded from this study. This study was performed in accordance with the rules of both institutional review boards.

Medical and surgical treatment

Our medical treatment strategies and the surgical indications were as described below. Dietary treatment was started with a special diet using either an elemental diet or medium-chain-triglyceride diet in principle, except for the cases with mild ascites that could be started on regular milk. TPN with fasting was performed if the dietary treatment had either no effect or an increase the amount of ascites. TPN was considered from the first if the cases demonstrated severe ascites. Surgical treatment was indicated in order to identify the cause of either lymphatic leakage or abnormal lymphatic drainage at the site of mesenteric root including intestinal malrotation, when refractory ascites had accumulated even after treatment with TPN for more than 4 weeks. When the site of lymphatic leakage could not be identified in spite of Sudan black oral administration, then fibrin glue may be applied at the site that is responsible for the lymphatic leakage.

Collected data and analysis

The onset of fetal ascites was detected by routine ultrasound scans. Prenatal factors such as gestational age at diagnosis, duration of persisting fetal ascites, and the ultrasonographic measured values at third trimester of pregnancy, such as the abdominal circumference (AC), fetal trunk area (FTA), femur length (FL), and amniotic fluid index were reviewed from the medical records. The postnatal factors including sex, gestational age at birth, mode of delivery, Apgar scores at 1 and 5 min, body weight at birth, head circumference at birth, abdominal circumference at birth, need for TPN, need for surgical intervention, details of the surgical procedure, duration of hospitalization, duration of persisting ascites, and final outcome were also collected. Cytological count and chemical analysis of fluid were performed for the identification of chyle in the cases ascites was sampled transabdominally under ultrasound guidance either antenatally or postnatally. The patients were divided according to the clinical course into the favorable group (Group I) whose ascites were resolved by medical treatment alone, and unfavorable group (Group II) who required surgical intervention after birth due to refractory ascites. Prenatal and postnatal prognostic factors were compared between the two groups.

Statistical analyses

The mean and standard deviation or the median and range were used to describe continuous variables, and the frequency was used to describe the categorical data. Either the Wilcoxon rank sum test or Student's t test was used for comparison of continuous variables. The Fisher's exact test was used for analysis of categorical data. Values of $p < 0.05$ were considered significant. The statistical analysis was performed with the JMP software package (Version 8.02; SAS Institute, Inc., Cary, NC, USA).

Results

Twelve fetuses with primary isolated fetal ascites were enrolled in this study. There were six males and six females and the median gestational age at birth was 36.9 weeks' gestation. The treatments after birth and outcomes of these cases are summarized in Fig. 1. The ascites regressed spontaneously without TPN in six infants. TPN was conducted in the other six cases and one of the infants improved after the initiation of TPN. These seven cases were managed only by medical treatment (Group I). The remaining five infants required surgery or continuous drainage due to refractory ascites (Group II) (Fig. 1).

Prenatal and postnatal prognostic factors

The gestational age at diagnosis was significantly earlier in Group II than in Group I. There were no fetuses whose ascites resolved spontaneously prior to delivery. Therefore, the duration of persisting fetal ascites turned out to be longer in Group II in comparison to Group I. There were no differences in the amount of amniotic fluid and head size between the two groups. Both AC and FTA were standardized by dividing them with FL, which were indicators of abdominal distention, and were larger in Group II than in Group I (Table 1). As a result, the severity of abdominal distention or size was thus considered to be poor prognostic factors for primary isolated fetal ascites.

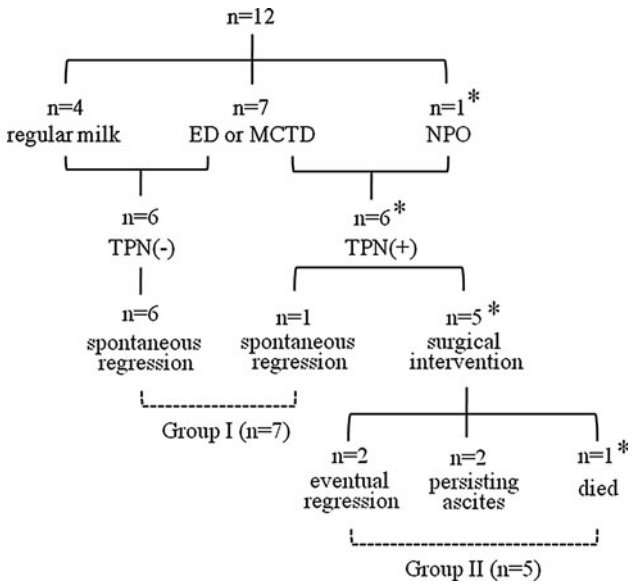

Fig. 1 Overview of the treatments and outcomes after birth for the infants with primary isolated fetal ascites. The *asterisk* indicates a case of continuous drainage alone. *ED* elemental diet, *MCTD* medium-chain-triglyceride diet, *NPO* non per oral, *TPN* total parenteral nutrition

There was a negative correlation between the gestational age at diagnosis and FTA divided by FL, with a correlation coefficient of −0.848. Four out of 5 (80%) infants who developed ascites before 30 weeks' gestation required surgical intervention and two of these, in which the ascites was detected before 20 weeks' gestation had persistent ascites for more than 10 months despite any treatment including repeated surgical procedures. The ascites resolved spontaneously without any surgical intervention in 6 of 7 (86%) patients who developed ascites after 30 weeks' gestation (Fig. 2). There were no significant differences between the two groups in the findings at birth such as sex, gestational age, Apgar scores, body weight, and the measured values of the body including the abdominal circumference (Table 2).

Treatment and outcome

Although six fetuses underwent intrauterine therapeutic paracentesis for an extremely enlarged abdomen, the ascites reaccumulated within a few days in all cases. A cesarean section was performed in five cases because the enlarged abdomen of the fetuses. Three of the six infants who underwent intrauterine therapeutic paracentesis could avoid cesarean section and were delivered transvaginally. The existence of chyle was confirmed in all cases in Group II and three cases in Group I, because abdominal paracentesis was not performed in 4 of 7 cases in Group I (Table 3). Three infants in Group I were started on an elemental diet due to moderate ascites, while the others were started on regular milk. Only one case in Group I needed TPN due to the ineffectiveness of the elemental diet and later showed a good outcome. Four infants in Group II started on either an elemental diet or medium-chain-triglyceride diet due to severe ascites, and all patients of this group, including other non per oral case subsequently needed TPN, and eventually underwent surgery (Fig. 1; Table 3). After Sudan black oral administration, laparotomy was performed to identify the presence of either lymphatic leakage or a lymphatic drainage abnormality in the retroperitoneum or at the site of mesenteric root including intestinal malrotation. However, neither the site of lymphatic leakage nor any abnormal lymphatic drainage was detected during the laparotomy in all surgical cases, Fibrin glue was used in region that were thought to be responsible for the lymphatic leakage in three cases of Group II. The ascites regressed after surgery in two patients in spite of the fact that the lymphatic leakage site could not be identified. Refractory ascites persisted in two patients even after undergoing more than two surgical procedures. An infant with trisomy 21 who received continuous drainage eventually died of infection (Fig. 1). Consequently, the duration of hospitalization and persistent ascites after birth became longer in Group II than in Group I. The morbidity was 60%, and the mortality was 20% in Group II (Table 3).

Discussion

Fetal ascites is generally a part of the symptoms in cases with nonimmune fetal hydrops, which refers to fluid collection in at least two body cavities or to fluid collection in

Table 1 Prenatal findings of the infants with primary isolated fetal ascites

	Group I ($n = 7$)	Group II ($n = 5$)	p
Gestational age at diagnosis (days)[a]	225 (192–250)	196 (127–216)	0.016
Duration of persisting fetal ascites (days)[a]	36 (13–60)	60 (37–137)	0.016
Amniotic fluid index (cm)[b]	18.0 ± 7.89	22.1 ± 8.15	0.393
BPD/FL[b]	14.7 ± 0.79	15.4 ± 0.69	0.127
HC/FL[b]	4.9 ± 0.40	5.4 ± 0.48	0.108
AC/FL[b]	5.4 ± 0.53	6.4 ± 0.94	0.037
FTA/FL[b]	1.3 ± 0.25	1.8 ± 0.42	0.038

BPD biparietal diameter, *FL* femur length, *HC* head circumference, *AC* abdominal circumference, *FTA* fetal trunk area

[a] Median with range

[b] Mean ± standard deviation

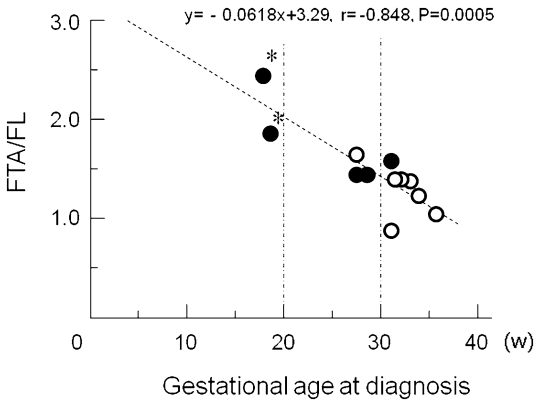

Fig. 2 The relationship between the gestational age at diagnosis and fetal trunk area (FTA) divided by femur length (FL) indicated a negative correlation with a correlation coefficient of −0.848. The *open circles* represent the infants in Group I and the *closed circles* represent the infants in Group II. The *asterisk* shows the cases persisting ascites after surgical intervention

one cavity plus diffuse subcutaneous edema. The etiology of nonimmune fetal hydrops include numerous causes such as chromosomal anomalies, intrauterine infections, cardiac failure, and structural anomalies of various organs [1]. Fetal ascites sometimes occur independently without a fluid accumulation in any other serosal cavities or subcutaneous tissue. Favre et al. [3] analyzed a large series, focusing on nonimmune fetal ascites, and reported that the fetal ascites accompanied by fetal hydrops had more unfavorable prognosis in comparison with isolated fetal ascites without an association of hydrops. Several investigators have reported that these isolated fetal ascites are often caused by cardiac [13], renal [14], gastrointestinal [15], pulmonary [16] and metabolic disorders [17]. The prognosis for these cases is mostly favorable, although the presence of isolated fetal ascites is a rare diagnosis and work-up should be followed to ensure a proper diagnosis as most of the cases are associated with other abnormalities [18].

In contrast, isolated fetal ascites occasionally occurs primarily without any evident underlying causes. Although the mechanisms of primary isolated fetal ascites is not fully understood, most of these fetuses result in chylous ascites after birth [5, 11]. The causes of congenital chylous ascites are congenital lymphatic dysplasia [7], obstruction of lymphatic vessels [10], and leakage from lymph ducts [6, 7]. Although the prognosis of these infants is usually favorable [5], there are some unfavorable cases with severe chylous ascites [19], and the prognostic factors of primary

Table 2 Findings of the infants with primary isolated fetal ascites at birth

	Group I ($n = 7$)	Group II ($n = 5$)	p
Sex (M/F)	3/4	3/2	1.000
Gestational age at birth (weeks)[a]	37.0 ± 0.98	36.6 ± 0.75	0.423
Apgar score at 1 min[a]	8.1 ± 0.69	7.8 ± 1.09	0.715
Apgar score at 5 min[a]	8.3 ± 0.76	9.0 ± 0.0	0.064
Body weight at birth (kg)[a]	2.92 ± 0.30	3.05 ± 0.34	0.504
Head circumference at birth (cm)[a]	33.6 ± 1.23	33.5 ± 0.96	0.860
Abdominal circumference at birth (cm)[a]	35.8 ± 5.84	38.4 ± 3.64	0.456
AC/HC[a]	1.1 ± 0.18	1.1 ± 0.09	0.508

HC head circumference, *AC* abdominal circumference

[a] Mean ± standard deviation

Table 3 Treatments and outcome for the fetuses with primary isolated ascites

	Group I ($n = 7$)	Group II ($n = 5$)	p
Fetal abdominal paracentesis	2	4	0.242
Cesarean section	1	4	0.072
Confirmation of chyle	3	5	0.080
Dietary treatment	3	4	0.198
Total parenteral nutrition	1	5	0.015
Surgical intervention	0	5	0.001
Duration of hospitalization (days)[a]	17 (4–40)	79 (18–95)	0.023
Duration of persisting ascites (days)[a]	25 (5–81)	238 (64–966)	0.005
Morbidity	0	3	0.046
Mortality	0	1	0.417

[a] Median with range

isolated fetal ascites have not been fully elucidated because of its small population.

Therefore, a retrospective review of primary isolated fetal ascites was conducted to evaluate the prognostic factors. The results demonstrated that the most important prognostic factor was the gestational age of onset for fetal ascites. In fact, 86% of the patients who had fetal ascites detected after 30 weeks' gestation regressed without surgical intervention. In contrast, 80% of the infants who developed fetal ascites before 30 weeks' gestation eventually required some kind of surgical intervention. In particular, two patients whose ascites were detected before 20 weeks' gestation experienced the chylous ascites more than 10 months after birth, despite treatment, including repeated surgery. In addition, there was a negative correlation between the gestational age at diagnosis and the severity of the fetal ascites, which was also a prognostic factor of primary isolated fetal ascites. These results indicated that the gestational age of the onset of fetal ascites may suggest the etiology or mechanism of fetal ascites, because congenital chylous ascites is caused by several types of lymphatic abnormalities [11, 20], and the type of lymphatic abnormalities determines the outcome [5, 7].

The development of the lymphatic system commences after 5 weeks' gestation and will be completed by 16 weeks' gestation [21]. Therefore, the appearance of fetal ascites before the complete formation of lymphatic system suggests the abnormal development of the lymphatic system, and the appearance after the formation of this system suggests an accidental abnormality in the lymphatic system. Ascites detected after 30 weeks' gestation in the current series were more likely to regress spontaneously with medical treatment alone. These facts implied that fetal ascites that appeared later in pregnancy may be caused by a localized occlusion or leakage of a lymphatic duct, and thus, often regresses spontaneously [5] or will respond to conservative therapy using a medium-chain-triglyceride diet or TPN [22]. The involvement of lymphatic abnormalities may be greater in the fetuses with ascites detected between 20 and 30 weeks' gestation than in the later onset cases. Even though conservative treatments may be ineffective in these cases [8], surgical intervention may be effective and indicated. An exploratory laparotomy may therefore improve ascites due to adhesion of the lymphatic leakage area [8, 23] and decrease the chyle flow [24], even if no responsible lesion is identified during the surgery.

In contrast, ascites noticed before 20 weeks' gestation were refractory and persisted despite various types of treatment. Surgical correction of the lymphatic system or adhesive therapy may be ineffective for these intractable ascites because these cases may be closely correlated with a congenital defect in the development of the lymphatic system [25]. More aggressive surgical therapy such as a peritoneovenous shunt may be required in such intractable cases, though this procedure has a higher incidence of serious complications, such as sepsis [26]. Intrauterine paracentesis had no effect on preventing an enlarged abdomen because of rapid reaccumulation of the ascites. However, intrauterine therapeutic paracentesis is useful for avoiding cesarean section by reducing the abdominal size over a short term and to ensure the safe delivery of the baby [26]. This procedure was performed in six fetuses and avoided cesarean section in two of them.

One major limitation of this study was that this retrospective study consisted of a small series of single institutions. However, primary fetal ascites is uncommon as a cause of isolated fetal ascites, which is rare in the fetal ascites diagnosed before birth [18], and thus, the study has generalizable information which is useful to practitioners for predicting the prognosis. In the present study, the prognosis of primary isolated fetal ascites can therefore be predicted by the gestational age at the time of diagnosis and it may be possible to estimate the optimal management for these fetuses both in utero and after birth based on these prognostic factors.

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