Table 2 The AUC and the best cutoff value for survival which maximize the difference between the sensitivity and false-positive rate in various representative values of L/T and LHR during gestation

Representative value of L/T and LHR	AUC	Difference between sensitivity and false-positive rate	The best cutoff value
L/T			
The earliest value	0.721	0.347	0.077
The latest value	0.761	0.457	0.107
The minimum value	0.776[a]	0.521	0.080
The maximum value	0.739	0.444	0.142
LHR			
The earliest value	0.735	0.498	1.59
The latest value	0.729	0.441	1.85
The minimum value	0.746	0.476	1.59
The maximum value	0.750[a]	0.459	2.04

AUC area under the ROC curve

[a] Maximum area under the receiver-operating characteristic (ROC) curve

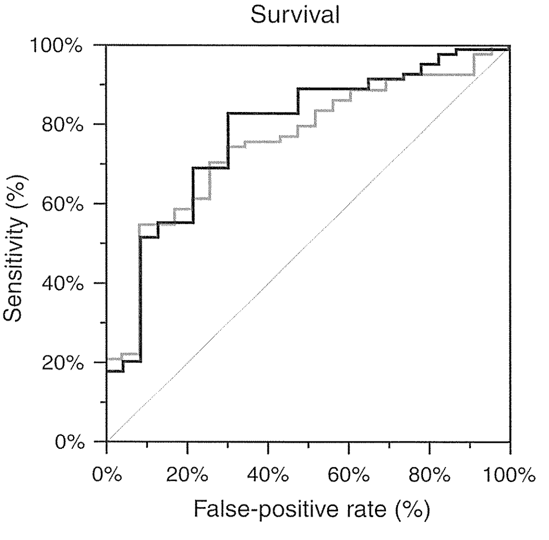

Fig. 3 The ROC curve for discriminating the outcome of survival based on the minimum L/T (*solid line*) and the maximum LHR (*light line*). The AUC for survival in L/T and LHR was 0.776 and 0.750, respectively

reported in normal fetuses [16] and in the fetuses with CDH [11, 15]. The reason for the increase of LHR with the gestational age is due to the difference in the rate of the increase of the lung area and head circumference. Peralta reported that there was a fourfold increase in the LHR between 12 and 32 weeks of gestation in normal fetuses because of these differences [16]. This explains the difficulty in identifying a common cutoff value in LHR which is able to predict the survival, independently of the timing of prenatal assessment. Standardizing the LHR by using the expected LHR has been proposed to provide a constant value throughout period of gestational and thus excellent performance of the ROC curve [15]. However, determining the observed to expected LHR requires the expected LHR in normal fetuses for a standardizing in each population, and thus it has less availability in each population.

On the other hand, the L/T has been reported to be a constant parameter in normal fetuses, [2] and in fact, it had no correlation with gestational age in the survivors or in the patients with intact discharge. The L/T in non-survivors or patients who needed home treatment decreased according to the gestational age, but it may imply that there is a possibility to determine the most powerful measurement point of the L/T to predict poor outcomes. The latest L/T should be theoretically more reliable than the earliest L/T for the prediction of outcome because the L/T had a downward trend in those patients with poor prognosis. In

Table 3 The AUC and the best cutoff value for intact discharge which maximize the difference between the sensitivity and false-positive rate in various representative values of L/T and LHR during gestation

Representative value of L/T and LHR	AUC	Difference between sensitivity and false positive rate	The best cutoff value
L/T			
The earliest value	0.740	0.367	0.080
The latest value	0.784	0.465	0.092
The minimum value	0.798[a]	0.511	0.080
The maximum value	0.729	0.372	0.142
LHR			
The earliest value	0.790	0.474	1.59
The latest value	0.819	0.556	1.72
The minimum value	0.804	0.559	1.59
The maximum value	0.835[a]	0.372	1.79

AUC area under the ROC curve

[a] Maximum area under the receiver-operating characteristic (ROC) curve

Table 4 Patient demographics and the postnatal severity of the fetuses with isolated congenital diaphragmatic hernia in the groups divided by the L/T at 0.080

	n	L/T < 0.080 (*n* = 30)	L/T ≥ 0.080 (*n* = 73)	*p*
Gender (M/F)	103	19/11	39/34	0.390
Side of hernia (left/right)	103	28/2	71/2	0.578
Gestational age at diagnosis (weeks)[a]	103	27.8 ± 5.0	29.0 ± 5.9	0.305
Gestational age at birth (weeks)[a]	103	38.0 ± 1.2	38.0 ± 2.0	0.952
Body weight at birth (kg)[a]	103	2.60 ± 0.50	2.81 ± 0.52	0.063
Polyhydramnios (%)	103	36.7	27.4	0.356
Apgar score at 1 min[a]	101	3.28 ± 1.67	4.88 ± 2.18	<0.001
Apgar score at 5 min[a]	99	4.64 ± 2.04	5.76 ± 2.24	0.024
Highest pre PaO_2 (mmHg)[b]	90	116 (45–237)	266 (177–374)	<0.001
Lowest pre $PaCO_2$ (mmHg)[b]	103	36.7 (29.2–51.4)	31.2 (26.0–43.7)	0.041
Duration of NO inhalation (days)[b]	95	19 (14–40)	8 (5–13)	<0.001
Duration of ventilatory support (days)[b]	103	35 (28–545)	19 (11–31)	<0.001
Duration of O_2 inhalation (days)[b]	103	251 (42–555)	30 (16–53)	<0.001
Need for ECMO (%)	103	33.3	5.5	<0.001
Need for PGE_1 administration (%)	103	60.0	23.3	<0.001
Inoperable cases (%)	103	23.3	5.5	0.013
Over 75% defect of diaphragm (%)	83	89.5	37.5	<0.001
Need for patch closure (%)	92	82.6	36.2	<0.001
Intact discharge rate (%)	103	26.7	82.2	<0.001
Overall survival rate (%)	103	46.7	90.4	<0.001

NO nitric oxide, *ECMO* extra corporeal membrane oxygenation, *PGE_1* prostaglandin E_1

[a] Mean ± standard deviation

[b] Median with interquartile range

fact, the AUC of the latest L/T was greater in comparison to the AUC of the earliest L/T (Table 2). However, the AUC indicated a maximum sensitivity when the L/T was represented by the minimum value during gestation. This may be related to a measurement deviation of L/T and there may be a limit of reliability of this methodology. An earlier assessment of the infants is more desirable to determine the indications for fetal intervention [19, 20]. Neither the LHR nor the L/T may independently be sufficient to determine the indications for fetal intervention; thus, a combination of these and other prenatal factors such as liver position may be necessary, because the liver position has been reported to be one of the most predictive factors [1, 5, 21–23].

Although the LHR increased according to the gestational age in the patients with intact discharge, there is no increase of the LHR in infants without intact discharge. The LHR may be a beneficial indicator for discriminating the favorable patients who can be discharged from hospital without any home treatment. In fact, the best AUC for intact discharge in the LHR was greater than the best AUC for intact discharge in the L/T (Table 3). Interestingly, the most powerful measurement point and accurate cutoff value of L/T for discriminating the outcome of intact discharge was the same value in the same explanatory variable as that used to discriminate the survivors, namely 0.080 in the minimum L/T (Table 3).

The groups divided by a cutoff value of a minimum L/T of 0.080 demonstrated a significant difference in the postnatal severity including respiratory status, need for

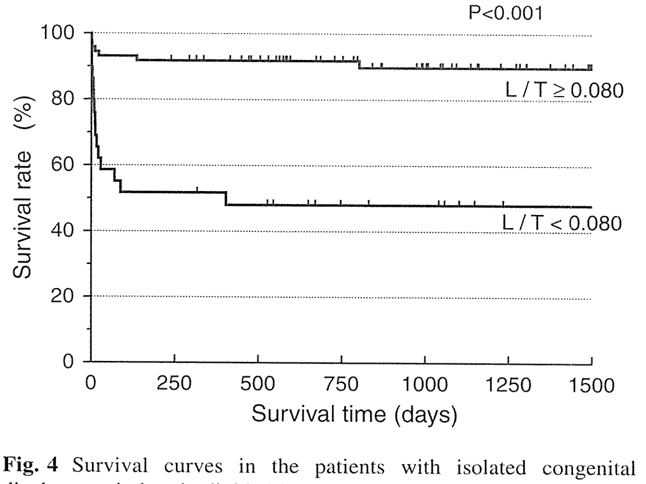

Fig. 4 Survival curves in the patients with isolated congenital diaphragmatic hernia divided by the minimum L/T at 0.080

respiratory support, need for circulatory support, surgical findings, and prognosis, which seems to be reflected in pulmonary hypoplasia. Therefore, the L/T was able to accurately estimate the severity of the infants in the perinatal and perioperative period, and we may be able to develop several different treatment programs in terms of perinatal and perioperative management to adjust for the predicted severity as estimated by the L/T.

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ORIGINAL ARTICLE

Use of the medical information on the internet by pregnant patients with a prenatal diagnosis of neonatal disease requiring surgery

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Abstract
Purpose The purpose of this study was to clarify the current status and the problems associated with using medical information on the internet during pregnancy in patients prenatally diagnosed with fetal abnormalities at a single Japanese institution.
Methods A written, anonymous questionnaire survey was conducted in 155 pregnant patients who had been prenatally diagnosed as having neonatal surgical diseases between January 2000 and December 2009, and their families.
Results Forty-three out of the 75 responding families (57.3%) had used medical information available on the internet during their pregnancy. The availability of information, assessed during 2 year-increments, has increased rapidly in the past 4 years. When the explanation of a physician was compared with the information provided by the internet, the knowledge or impression of the disease was different in 60% of cases and similar in 33% of cases. More importantly, 60% of the patients felt that the information obtained from the internet was more pessimistic than the physician's explanation.
Conclusion The number of pregnant patients who have used medical information on the internet has rapidly increased in the recent years. Subjects who used this information were more likely to experience a sense of anxiety and feelings regarding the seriousness of the disease.

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Keywords Internet · Prenatal diagnosis · Questionnaire survey · Medical information · Neonatal surgery

Introduction

Recently, the patients' use of medical information available on the internet has been spreading rapidly in our country, as well as all over the world. However, careful consideration is necessary for the use of such information, as there are many problems, such as ensuring the reliability of the information, protection of personal information, and the neutrality of the website. When we provide the patients information about a prenatal diagnosis, we occasionally receive questions from pregnant patients and their families based on information obtained from the internet.

Pregnant patients with a prenatal diagnosis of fetal abnormalities may become anxious due to the lack of information. Thus, they may have a tendency to depend on the medical information found in the internet [1, 2], which can affect their feelings and decisions. However, it is not clear how much such patients and their families depend on this medical information, and what kind of problems are caused by this behavior. The purpose of this study was to clarify the current status and the problems associated with the use of medical information available on the internet during pregnancy by patients diagnosed as having a fetus with neonatal surgical diseases.

Patients and methods

A written, anonymous questionnaire survey was conducted in 155 women, including seven who lost a child, whose present addresses were available, who had been prenatally diagnosed as having a fetus with neonatal disease requiring surgery between January 2000 and December 2009, and who had delivered their children, received treatment, and/or were observed at our hospital. The anonymous questionnaires were sent by mail and the responses from those who consented to participate in our survey were compiled. The respondents were questioned regarding the diagnosis of the fetal abnormality, gestational age at diagnosis, whether they had obtained information from the internet or not, the type of information they had obtained, their assessment of the information, their comparison between such information and the explanations provided by their physicians, whether they would wish to use such information if they were faced with the same situation again, and the type of information they would wish to obtain. Our questionnaire mostly involved single-answer questions, with a few multiple-answer questions. This study was approved by our institutional review board (IRB Approval No. 09252).

Results

Demographics of the respondents

The response was obtained from 75 out of 155 (48.4%) pregnant patients or their families. The response rate did not significantly differ between years. The neonatal surgical diseases comprised: 25 with alimentary tract diseases, 14 with a congenital diaphragmatic hernia, 11 with cystic lung disease, 8 with an ovarian cyst, 7 with a tumor, 4 with an abdominal wall defect, and 6 with other diseases. The median gestational age at the first diagnosis of the neonatal surgical diseases was 29 weeks of gestation (between 12 and 39 weeks of gestation). There were 11 patients (14.7%) who were diagnosed before 22 weeks of gestation, the period in which a termination of pregnancy is legally permitted in Japan [3].

Forty-three out of the 75 cases (57.3%) had used medical information from the internet during their pregnancy. The proportion of using the internet for medical information varied between the patients who had fetuses with different diseases. Among the patients who had been diagnosed with a fetal congenital diaphragmatic hernia, 13 patients (93%) had used the internet, in contrast to 9 patients (36%) who had used it among the cases with alimentary tract diseases. Eight out of 11 patients who were diagnosed before 22 weeks of gestation had used medical information from the internet about their children's diseases. Among these, five patients answered that they had experienced difficulty in deciding whether to continue the pregnancy or not, and 4 patients answered that they had referred the information on the internet when deciding whether to continue the pregnancy or not.

The history of internet use and the present desire to use the internet

The proportion of pregnant patients who became pregnant until 2003 and who had used the internet to obtain medical information during their pregnancy was approximately 30%. However, the proportion began to increase among those who became pregnant around 2007, exceeding 90% in the last 2 years (Fig. 1a). On the other hand, the proportion of pregnant patients who would use the internet to obtain medical information, if they were prenatally diagnosed as having a fetus with a neonatal surgical disease exceeded 90% in all of the 2 year increments (Fig. 1b). The 43 patients and their families who had used the internet to obtain medical information were asked about the type of information they had actually referred to and what type of information they would presently use (Table 1). 88% of the subjects had used search engines to search for the information about the diseases. The people who would presently wish to read blogs on the lives of other people, who had children with the same disease was low compared to the number of people who had actually read such blogs. On the other hand, the people who wished to join an internet forum

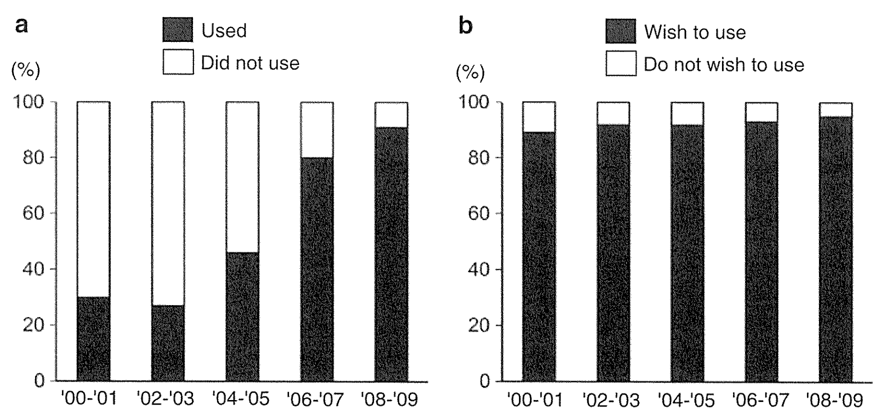

Fig. 1 The proportion of pregnant patients who had used the internet to obtain medical information during their pregnancy (**a**), and the proportion of patients who would use it if they were faced with the same situation (**b**), are shown for 2 year increments

Table 1 The type of internet information that was actually used, and is currently desired, by pregnant Japanese patients with a prenatal diagnosis of a neonatal surgical disease

Type of internet information	Actually used (%)	Presently desire (%)
Using search engines to learn about the disease	88	71
Reading a family blog about a child with the same disease	72	50
Visiting a website of a medical society or institution to learn about the disease	51	67
Reading a medical web dictionary to learn about the disease	49	57
Looking at a personal website to learn about the disease	40	31
Joining a communication site for families who have a child with the same disease	37	55
Checking a website of a hospital to learn about the hospital	35	64
Contacting a family who has a child with the same disease	9	17
Sending an e-mail to a physician or medical institution	2	21

for patients' families and who would wish to contact the family of patients with the same disease was found to have increased compared to the actual use of such forums. Although only one-third of the families had checked hospital websites to learn about the diseases, two-thirds of the people stated that they wished to check them at present. Therefore, the proportion of people who wished to access personal websites tended to decline, while the proportion of people who wished to obtain information from public institutions tended to increase. 21% of the patients answered that they would wish to consult physicians and medical institutions by e-mail [4, 5].

The usefulness and comprehensibility of the information on the internet and physicians' explanations

A total of 75.5% of the respondents answered that the internet was useful for learning about the child's disease, while 17.1% answered that it was not useful. A total of 73.2% answered that they had understood more about their child's disease based on the information from the internet, while 98.7% answered that they had understood about their children's disease based on their physician's explanations. With regard to the comprehensibility of the medical information on the internet and the physicians' explanations, 75% of respondents answered that their physicians' explanations were easier to understand, while 5.0% answered that the information on the internet was easier to understand (Fig. 2).

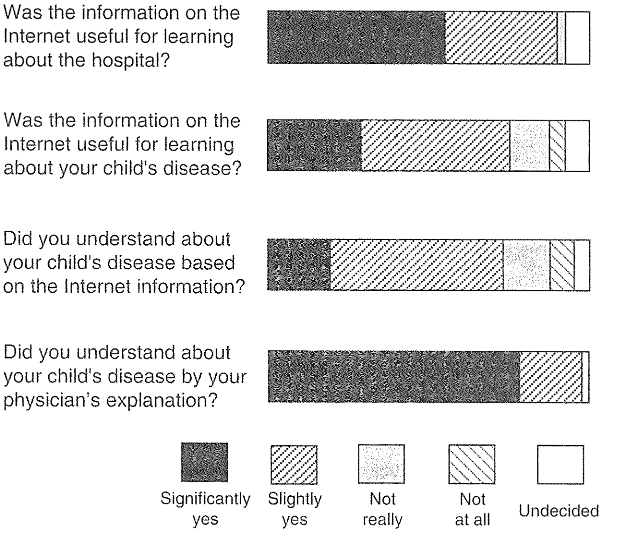

Fig. 2 The usefulness and comprehensibility of the information on the internet and the physician's explanation

Comparison between the information available on the internet and the physicians' explanations

In total, 62.5% of the respondents answered that their knowledge and impression of the disease differed based on the information available on the internet with that provided by their physician's explanation. With regard to the impression of the severity of the disease, 60% had felt the disease to be more severe after viewing the information on the internet, while 17.5% had felt it to be more severe on hearing their physician's explanation. In fact, 73.1% of subjects had felt more anxious upon reading the medical information on the internet, while 24.4% of subjects were more anxious due to their physician's explanation. In contrast, 12.2% of respondents were relieved by the medical information available on the internet, while 63.4% were more relieved due to their physician's explanation. Concerning the degree of anxiety, 65.9% of the subjects had experienced a stronger sense of anxiety over the information on the internet, and 12.2% had experienced a stronger sense of anxiety based on their physician's explanation (Table 2).

Recognition of the medical information on the internet

The proportion of respondents who answered that the medical information on the internet is reliable was 9.5%.

Table 2 Comparison between the information on the internet and the physician's explanation

Did the knowledge or the impression of the disease differ between that on the internet and that of your physician's explanation?	Very different	Slightly different	Almost the same	Same	Undecided
	25.0%	37.5%	32.5%	0.0%	5.0%
Which type of information gave you a more severe impression of your child's disease?	Internet, significantly	Internet, slightly	Almost the same	Physician's explanation, slightly	Physician's explanation, significantly
	35.0%	25.0%	22.5%	7.5%	10.0%
Did you become anxious about your child's disease due to the information on the internet?	Very anxious	Slightly anxious	Slightly relieved	Very relieved	Undecided
	58.5%	14.6%	12.2%	0.0%	14.6%
Did you become anxious about your child's disease due to your physician's explanation?	Very anxious	Slightly anxious	Slightly relieved	Very relieved	Undecided
	17.1%	7.3%	51.2%	12.2%	12.2%

The proportion of respondents who answered that it is unreliable was also 9.5%. A total of 66.2% of the respondents answered that the reliability of medical information on the internet should be judged by the viewer him/herself. The proportion of the respondents who answered that medical information on the internet should be provided by public institutions was 31.1%.

Discussion

The internet is becoming indispensable in daily life for many people throughout the world, and its use has spread rapidly in the recent years. Today, anyone can easily obtain high-level medical information on the web [1, 2, 6]. Under such circumstances, it is a matter-of-course for pregnant patients with a prenatal diagnosis of a fetal abnormality and their families, to use the internet to obtain medical information about their children's diseases. It became apparent through this survey that the use of the internet to obtain medical information has rapidly increased among pregnant patients prenatally diagnosed as having a fetus with a neonatal surgical disease in our country. Although the proportion of internet use was only approximately 30%, 10 years ago, 90% of them answered that they would wish to use it if they were faced with the same situation at present. Therefore, the use of the internet is likely to continue.

Most of the people who responded to our study had used search engines as a way to learn about the diseases. Generally, the search results appear in the order of the frequency of access. However, high-frequency access does not necessarily mean high-level reliability. It is suspected that the users inevitably tend to access the search results in the order of their appearance due to the difficulty for majority of the internet users to judge the reliability of the search results. The accuracy and neutrality of the information on the web is rarely evaluated by impartial observers, even among the websites serving the interests of the public. Furthermore, such information is prone to be subjective and self-righteous, as the information senders take the initiative in framing their websites. It is therefore, difficult for the viewers to judge the reliability of such information. Four out of five pregnant patients who had experienced trouble over deciding whether to continue the pregnancy or not after the prenatal diagnoses answered that they had referred to the information on the web, thus suggesting an increasing need for neutrality and accuracy concerning internet-based medical information that can influence the patients' important decisions [1, 3]. A code of ethics [7] may need to be established in the future to ensure the accuracy of medical information.

As it has become easy for individuals to disseminate information to society through the internet, there are many cases in which people who have developed serious diseases and their families report their experiences under treatment on blogs. Such blogs have the advantage of encouraging other patients with the same diseases and their families. On the other hand, due attention must be paid to the fact that many such blogs report cases of severe illness, which catch the viewers' attention more effectively, thus resulting in a bias, and blogs reporting more severe cases receive higher viewing numbers, making them easier to find using search engines. In addition, it is feared that such blogs may cause the viewers to develop a bias and overly negative images regarding the diseases [3], as reports of severe illness leave a stronger impression than reports about less severe disease. This might be the reason for the lower proportion of subjects who answered that they wished to view the blogs of other people with children who had the same disease, compared to the proportion of people who had viewed such blogs in the past. Internet forums about disease also may lack neutrality and fairness due to their administrators' thoughts, as well as to biases held by some members. Such websites may also suffer from various ethical issues, such as prejudice, slander, and the disclosure of personal information.

Many of the respondents felt that the knowledge or the impression that they obtained from the internet differed from those provided through their physician's explanation. It has been clarified that the information on the web is likely to be less comprehensible, present the disease as more severe, and cause more anxiety compared to a physician's explanation. The information on the web, which was obtained to ease anxiety through learning more about the diseases [1], conversely resulted in increased anxiety. Since the anxiety of many respondents decreased on hearing their physician's explanations, a proper explanation by a physician seems to be very important for subjects with a prenatal diagnosis of a neonatal surgical disease. Those who had previously used the internet to obtain information showed a stronger tendency to desire information from public institutions, such as medical institutions and academic societies, rather than from personal websites. As many people also answered that information about diseases should be provided by public institutions, academic societies and medical institutions should therefore, play an even more important role in the future by providing accurate medical information on the web.

Along with receiving proper explanations by a physician and accurate medical information from public institutions, some of the new websites, nevertheless do sometimes provide useful information for pregnant patients. Websites providing peer-reviewed collaborative information and the forums providing accurate medical information on the web may gradually result in an improvement in the quality of medical information available on the web. Strong warnings that medical information on the web may be misinterpreted by people not familiar with a special medical field and websites, which stress the importance of carefully interpreting medical information, may help to avoid misunderstandings by pregnant patients and their families.

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ORIGINAL ARTICLE

Reliability of the lung to thorax transverse area ratio as a predictive parameter in fetuses with congenital diaphragmatic hernia

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Abstract

Purpose An accurate prenatal assessment of the patients' severity is essential for the optimal treatment of individuals with congenital diaphragmatic hernia (CDH). The purpose of this study was to clarify the reliability of the lung to thorax transverse area ratio (L/T) as a prenatal predictive parameter.
Methods A multicenter retrospective cohort study was conducted on 114 isolated CDH fetuses with a prenatal diagnosis during the period between 2002 and 2007 at five participating centers in Japan. The relationship between the gestational age and the L/T was analyzed. The most powerful measurement point and accurate cutoff value of the L/T was determined by an analysis of a receiver operating characteristic curve, which was verified by comparing the patients' severity.
Results There was a negative correlation between the gestational age and the L/T in the non-survivors, and no correlation in the survivors. There were significant differences in the parameters which represented the patients' severity including the respiratory and circulatory status, the surgical findings, and the final outcomes between the groups divided at 0.080 in the minimum value of the L/T during gestation.
Conclusion The L/T was not strongly influenced by the gestational age, and it was found to be a reliable prenatal predictive parameter in fetuses with isolated CDH.

Keywords Congenital diaphragmatic hernia · Prenatal diagnosis · Predictive parameter · Prognostic factor · Pulmonary hypertension · Severity

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Introduction

Postnatal mortality and morbidity of fetuses with congenital diaphragmatic hernia (CDH) mainly depends on the severity of the pulmonary hypoplasia. An accurate prenatal assessment of pulmonary hypoplasia is essential to plan an optimal treatment strategy for individual cases before birth. Many prenatal prognostic parameters, which are estimated by ultrasonography or MRI, such as fetal lung size [1–4], liver or stomach position [5–7], signal intensity of the fetal lungs [8], and pulmonary artery blood flow [9] have been previously proposed by various investigators. The lung area to head circumference ratio (LHR) [1, 10] and the lung to thorax transverse area ratio (L/T) [2, 11] are the predictive parameters in which the fetal lung size is measured by ultrasonography. However, several investigators have been skeptical about the reliability and usefulness of LHR in predicting the outcome of the fetuses with CDH [12–14]. It is necessary for the LHR to be standardized by the normal values obtained from normal fetuses, because the LHR increases significantly with gestational age in fetuses with CDH [11, 15] as well as in normal fetuses [15, 16]. Therefore, the LHR value is no longer considered independently predictive of survival [6]. In contrast, L/T was originally reported to be a constant parameter throughout the gestational period in the normal fetuses [2]. However, it is unclear whether the L/T changes significantly with gestational age in fetuses with CDH [15]. The purpose of this study was to clarify the reliability of the L/T by an analysis of the change in the L/T with gestational age and to identify the most accurate cutoff value of the L/T for a prediction of patients' postnatal severity in isolated CDH.

Materials and methods

Study population

This multicenter retrospective cohort study included the prenatally diagnosed, isolated CDH fetuses that were born at five participating centers during the period between January 2002 and December 2007. The National Center for Child Health and Development, Kanagawa Children's Medical Center, Osaka Medical Center and Research Institute for Maternal and Child Health, Kyushu University Hospital, and Osaka University Hospital participated in this study. Patients with serious associated anomalies such as major cardiac anomaly and unfavorable chromosomal abnormalities were not included in this study. Cases with bilateral diaphragmatic hernia and cases where neither the LHR nor L/T was measured were also excluded from this study. All patients were inborn and managed by immediate resuscitation followed by neonatal intensive care including gentle ventilation with high-frequency oscillatory ventilation. To successfully carry out the gentle ventilation strategy, the goals of the arterial blood gas data were set at $PaCO_2 < 70$ mmHg and preductal $SpO_2 \geqq 90\%$/preductal $PaO_2 \geqq 70$ mmHg. Once these gas data were obtained, the ventilator settings including FiO_2 and the mean airway pressure decreased immediately. Inhaled nitric oxide (NO) was used in the patients with persistent pulmonary hypertension of the newborn. This study was approved by the institutional review board of each participating center.

Collected data

The primary outcome measures were the overall survival, which was defined as surviving until the end of the observation period, and intact discharge, which was defined as being discharged from the hospital without any need for home treatment such as ventilatory support, oxygen administration, tube feeding, and parenteral nutrition. The postnatal factors including the Apgar scores at 1 and 5 min, highest PaO_2 and lowest $PaCO_2$ in the pre-ductal artery within 24 h after birth, duration of NO inhalation, duration of ventilatory support, duration of oxygen inhalation, need for extra corporeal membrane oxygenation (ECMO), need for prostaglandin E_1 administration [17], surgical findings and survival time were also collected. The L/T and the LHR were measured at the transverse section containing the four-chamber view of the heart by ultrasonography. The L/T was defined as the area of contralateral lung divided by the area of the thorax [11]. The LHR was defined as the ratio of the contralateral lung area, which was the product of the longest two perpendicular linear measurements, to the head circumference [1, 18]. The L/T and the LHR values were collected up to three measurement times according to the gestational age at diagnosis; the earliest measurement before 30 weeks of gestation, the earliest measurement between 30 and 35 weeks of gestation, and the earliest measurement after 35 weeks of gestation.

Analysis of relationship and determination of cutoff value in L/T and LHR

The relationship between the gestational age with the L/T and the LHR was analyzed by subgroups divided according to the outcomes. Logistic regression models were used with the survival and intact discharge as response variables to explore the most powerful measurement point of the L/T and LHR for a prediction of outcomes. The explanatory variables were the earliest value, the latest value, the minimum value, and the maximum value during the gestation. Then the receiver operating characteristic (ROC) curves was calculated to examine the performance of each value. The area under the ROC curve (AUC) was used as an index of global performance, with an AUC of 0.5 indicating no discrimination ability. The efficacy of a screening test is dependent not only on its overall accuracy assessed by the AUC, but also on the consequences of misclassification associated with sensitivity and specificity. The point maximizing the difference between the sensitivity and the false-positive rate was evaluated as the most accurate cut off point of L/T and LHR for discriminating the survival and intact discharge. The patients' postnatal profiles, including the parameters which represented the severity concerning respiratory status, circulatory support, surgical findings, and prognosis, were compared between the groups divided at the accurate cutoff value to assess the usefulness of the adequate cutoff value of appropriate L/T.

Statistical analysis

The median and interquartile range or the mean and standard deviation were used to describe continuous variables; frequency and percentages were used to describe the categorical data. Either the Wilcoxon rank sum test or Student's t test was used for comparison of continuous variables. Fisher's exact test was used for analysis of categorical data. The log-rank test and Kaplan–Meier method were used to compare the duration of respiratory managements and survival time. p values of less than 0.05 were considered to indicate statistical significance.

Results

The L/T or LHR were measured at least one time in 114 patients with isolated unilateral fetal CDH who were managed in the participating centers in the study period. Eighty-seven infants (73.3%) were alive until the end of the observation period and 74 infants (64.9%) were discharged from the hospital without any home treatment. The median survival time of the survivors was 1,052 (595–1,496) days, and the median survival time of the non-survivors was 12 (2–57) days. Among them, the L/T was measured 211 times in 103 patients, the LHR was measured 200 times in 100 patients and both of them were measured simultaneously 168 times in 89 patients.

Relationship between L/T and LHR with gestational age

No correlation was observed between the gestational age and the L/T in survivors, although there was a negative correlation between those variables in non-survivors. On the other hand, there were positive correlations between the gestational age and the LHR both in survivors and non-survivors (Fig. 1; Table 1). A negative correlation was observed only between the gestational age and the L/T in infants who died or needed home treatment. On the contrary, a positive correlation was recognized only between the gestational age and the LHR in patients with intact discharge (Fig. 2; Table 1).

Determination of most appropriate cutoff value in L/T for discriminating the outcome

The AUC for discriminating the survivors demonstrated the maximum when the minimum value of the L/T was applied (Table 2). In contrast, the AUC for discriminating the survivors demonstrated the maximum when the maximum value of LHR was applied (Table 2). The difference between the sensitivity and the false-positive rate was maximized with the cutoff value of 0.080 for the minimum L/T and with the cutoff value of 2.04 for the maximum LHR (Table 2). The best AUC in the L/T was greater than the best AUC in the LHR (Table 2; Fig. 3). The AUC for discriminating the intact discharge also demonstrated a maximum when either the minimum value of the L/T was applied or the maximum value of LHR was applied (Table 3). The difference between the sensitivity and the false-positive rate of the minimum L/T was also maximized with the cutoff value of 0.080 (Table 3).

Comparison of the patients' severity in each predictive group divided by the cutoff value of the L/T

The patients were divided into two predictive groups according to the cutoff value of 0.080 in the minimum value of the L/T. Although there was no significant difference in the patients' demographic profiles between the two groups, there were statistically significant differences in the respiratory status such as Apgar scores, arterial blood gas data, and the duration of respiratory support, in the necessity of circulatory support such as ECMO and prostaglandin E_1 administration, in the surgical findings such as operability, diaphragmatic defect size and the need for patch closure and in the final outcomes (Table 4). There was also a significant difference in the survival curve between the two groups (Fig. 4).

Discussion

Although the original definition of the L/T was calculated from both areas of the contralateral lung and ipsilateral lung [2], the L/T was calculated as the ratio of the contralateral lung area to the thorax area in this study, as it has been used in the measurement of the LHR and has also been reported previously in the measurement of the L/T [11]. It seems to

Fig. 1 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia by survival and non-survivors. The *open circles* and *dashed regression line* (LHR = 0.344 + 0.00677GA) represent the survivors and the *closed squares* and *solid regression lines* (L/T = 0.187 − 0.000434GA, LHR = 0.386 + 0.00455GA) represent the non-survivors. *GA* gestational age

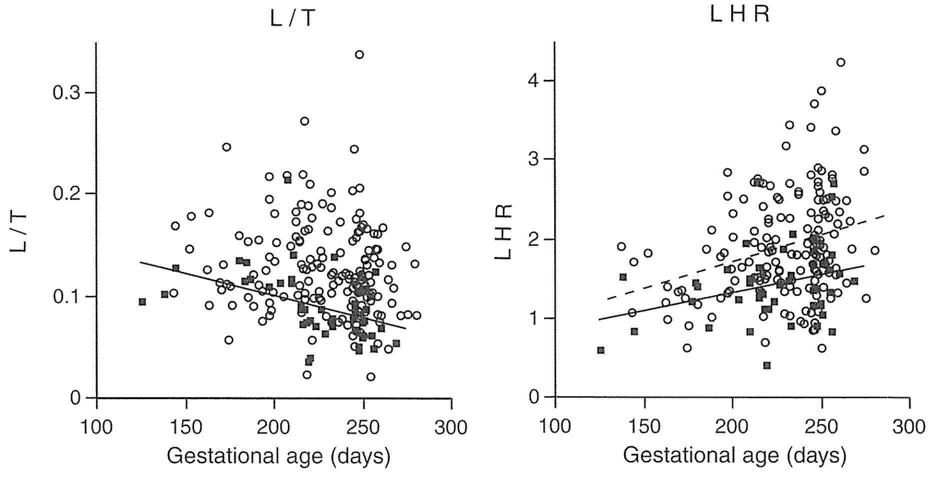
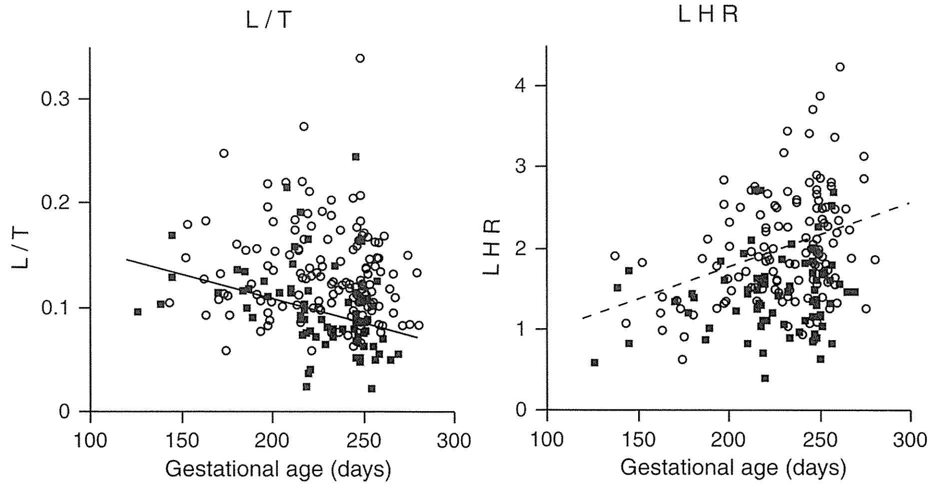


Table 1 Relationship between the gestational age, the lung to thorax transverse area ratio (L/T), and the lung area to head circumference ratio (LHR) in the fetuses with congenital diaphragmatic hernia according to survival and intact discharge

Outcome	Gestational age with L/T			Gestational age with LHR		
	n	CC	*p*	*n*	CC	*p*
Survival	166	−0.141	0.056	151	0.296	<0.001
Non-survival	45	−0.411	0.001	49	0.301	0.022
Intact discharge	139	−0.113	0.163	126	0.356	<0.001
Died or needed home treatments	72	−0.343	0.001	74	0.172	0.109

CC correlation coefficient

Fig. 2 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia according to intact discharge and non-intact discharge. The *open circles* and *dashed regression line* (LHR = 0.159 + 0.00796GA) represent the infants with intact discharge and the *closed squares* and *solid regression line* (L/T = 0.201 − 0.000469GA) represent the infants without intact discharge. *GA* gestational age



be reasonable to use only the contralateral lung area for determination of the L/T, because the ipsilateral lung is invisible in many cases at the transverse section containing the four-chamber view of the heart because of cranial dislocation of the ipsilateral lung [11]. There is also a possibility of over-estimation in measuring the ipsilateral lung area because of the close similarity of ultrasonographic appearance of the ipsilateral lung and the intestine or spleen. A manual tracing of the limit of the lungs, which is conducted in the measurement of the L/T, has been reported to be the most reproducible measurement rather than a multiplication of lung diameters for the assessment of lung area [16, 18].

The present study found that the LHR were increased according to the gestational age both in the subgroups of survivors and non-survivors, as it has been previously

Table 2 The AUC and the best cutoff value for survival which maximize the difference between the sensitivity and false-positive rate in various representative values of L/T and LHR during gestation

Representative value of L/T and LHR	AUC	Difference between sensitivity and false-positive rate	The best cutoff value
L/T			
The earliest value	0.721	0.347	0.077
The latest value	0.761	0.457	0.107
The minimum value	0.776[a]	0.521	0.080
The maximum value	0.739	0.444	0.142
LHR			
The earliest value	0.735	0.498	1.59
The latest value	0.729	0.441	1.85
The minimum value	0.746	0.476	1.59
The maximum value	0.750[a]	0.459	2.04

AUC area under the ROC curve

[a] Maximum area under the receiver-operating characteristic (ROC) curve

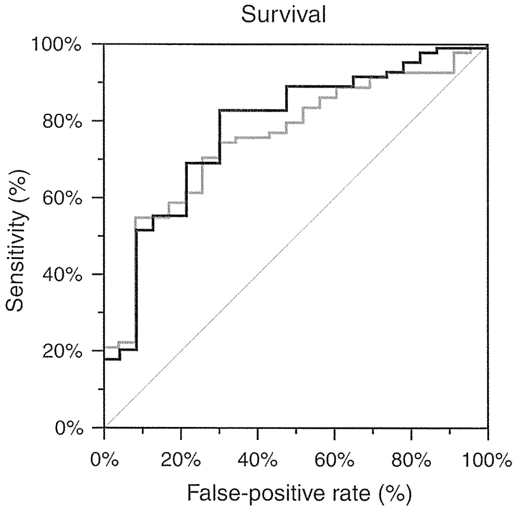


Fig. 3 The ROC curve for discriminating the outcome of survival based on the minimum L/T (*solid line*) and the maximum LHR (*light line*). The AUC for survival in L/T and LHR was 0.776 and 0.750, respectively

reported in normal fetuses [16] and in the fetuses with CDH [11, 15]. The reason for the increase of LHR with the gestational age is due to the difference in the rate of the increase of the lung area and head circumference. Peralta reported that there was a fourfold increase in the LHR between 12 and 32 weeks of gestation in normal fetuses because of these differences [16]. This explains the difficulty in identifying a common cutoff value in LHR which is able to predict the survival, independently of the timing of prenatal assessment. Standardizing the LHR by using the expected LHR has been proposed to provide a constant value throughout period of gestational and thus excellent performance of the ROC curve [15]. However, determining the observed to expected LHR requires the expected LHR in normal fetuses for a standardizing in each population, and thus it has less availability in each population.

On the other hand, the L/T has been reported to be a constant parameter in normal fetuses, [2] and in fact, it had no correlation with gestational age in the survivors or in the patients with intact discharge. The L/T in non-survivors or patients who needed home treatment decreased according to the gestational age, but it may imply that there is a possibility to determine the most powerful measurement point of the L/T to predict poor outcomes. The latest L/T should be theoretically more reliable than the earliest L/T for the prediction of outcome because the L/T had a downward trend in those patients with poor prognosis. In

Table 3 The AUC and the best cutoff value for intact discharge which maximize the difference between the sensitivity and false-positive rate in various representative values of L/T and LHR during gestation

Representative value of L/T and LHR	AUC	Difference between sensitivity and false positive rate	The best cutoff value
L/T			
The earliest value	0.740	0.367	0.080
The latest value	0.784	0.465	0.092
The minimum value	0.798[a]	0.511	0.080
The maximum value	0.729	0.372	0.142
LHR			
The earliest value	0.790	0.474	1.59
The latest value	0.819	0.556	1.72
The minimum value	0.804	0.559	1.59
The maximum value	0.835[a]	0.372	1.79

AUC area under the ROC curve

[a] Maximum area under the receiver-operating characteristic (ROC) curve

Table 4 Patient demographics and the postnatal severity of the fetuses with isolated congenital diaphragmatic hernia in the groups divided by the L/T at 0.080

	n	L/T < 0.080 (*n* = 30)	L/T ≥ 0.080 (*n* = 73)	*p*
Gender (M/F)	103	19/11	39/34	0.390
Side of hernia (left/right)	103	28/2	71/2	0.578
Gestational age at diagnosis (weeks)[a]	103	27.8 ± 5.0	29.0 ± 5.9	0.305
Gestational age at birth (weeks)[a]	103	38.0 ± 1.2	38.0 ± 2.0	0.952
Body weight at birth (kg)[a]	103	2.60 ± 0.50	2.81 ± 0.52	0.063
Polyhydramnios (%)	103	36.7	27.4	0.356
Apgar score at 1 min[a]	101	3.28 ± 1.67	4.88 ± 2.18	<0.001
Apgar score at 5 min[a]	99	4.64 ± 2.04	5.76 ± 2.24	0.024
Highest pre PaO_2 (mmHg)[b]	90	116 (45–237)	266 (177–374)	<0.001
Lowest pre $PaCO_2$ (mmHg)[b]	103	36.7 (29.2–51.4)	31.2 (26.0–43.7)	0.041
Duration of NO inhalation (days)[b]	95	19 (14–40)	8 (5–13)	<0.001
Duration of ventilatory support (days)[b]	103	35 (28–545)	19 (11–31)	<0.001
Duration of O_2 inhalation (days)[b]	103	251 (42–555)	30 (16–53)	<0.001
Need for ECMO (%)	103	33.3	5.5	<0.001
Need for PGE_1 administration (%)	103	60.0	23.3	<0.001
Inoperable cases (%)	103	23.3	5.5	0.013
Over 75% defect of diaphragm (%)	83	89.5	37.5	<0.001
Need for patch closure (%)	92	82.6	36.2	<0.001
Intact discharge rate (%)	103	26.7	82.2	<0.001
Overall survival rate (%)	103	46.7	90.4	<0.001

NO nitric oxide, *ECMO* extra corporeal membrane oxygenation, *PGE_1* prostaglandin E_1

[a] Mean ± standard deviation

[b] Median with interquartile range

fact, the AUC of the latest L/T was greater in comparison to the AUC of the earliest L/T (Table 2). However, the AUC indicated a maximum sensitivity when the L/T was represented by the minimum value during gestation. This may be related to a measurement deviation of L/T and there may be a limit of reliability of this methodology. An earlier assessment of the infants is more desirable to determine the indications for fetal intervention [19, 20]. Neither the LHR nor the L/T may independently be sufficient to determine the indications for fetal intervention; thus, a combination of these and other prenatal factors such as liver position may be necessary, because the liver position has been reported to be one of the most predictive factors [1, 5, 21–23].

Although the LHR increased according to the gestational age in the patients with intact discharge, there is no increase of the LHR in infants without intact discharge. The LHR may be a beneficial indicator for discriminating the favorable patients who can be discharged from hospital without any home treatment. In fact, the best AUC for intact discharge in the LHR was greater than the best AUC for intact discharge in the L/T (Table 3). Interestingly, the most powerful measurement point and accurate cutoff value of L/T for discriminating the outcome of intact discharge was the same value in the same explanatory variable as that used to discriminate the survivors, namely 0.080 in the minimum L/T (Table 3).

The groups divided by a cutoff value of a minimum L/T of 0.080 demonstrated a significant difference in the postnatal severity including respiratory status, need for

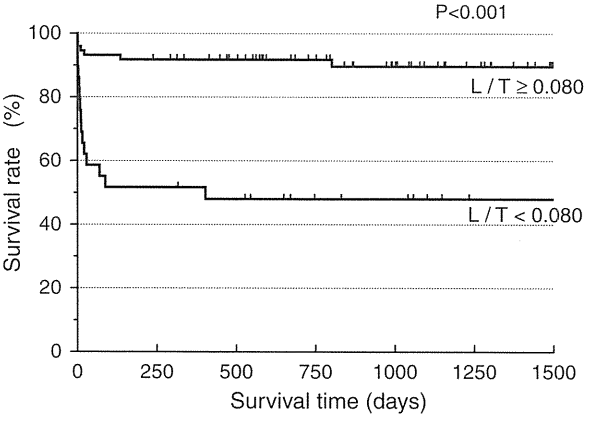


Fig. 4 Survival curves in the patients with isolated congenital diaphragmatic hernia divided by the minimum L/T at 0.080

respiratory support, need for circulatory support, surgical findings, and prognosis, which seems to be reflected in pulmonary hypoplasia. Therefore, the L/T was able to accurately estimate the severity of the infants in the perinatal and perioperative period, and we may be able to develop several different treatment programs in terms of perinatal and perioperative management to adjust for the predicted severity as estimated by the L/T.

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ORIGINAL ARTICLE

Interleukin 6 and interleukin 8 play important roles in systemic inflammatory response syndrome of meconium peritonitis

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Abstract
Purpose Meconium peritonitis is caused by an intestinal perforation that may occur in the fetus, followed by severe chemical peritonitis, resulting in high morbidity.
Methods We have experienced six patients with meconium peritonitis. Cystic drainage was performed soon after birth for all patients. We investigated the concentrations of several cytokines and a chemokine (interleukin 8) in the ascites from the six patients with meconium peritonitis. In two patients we also measured the serum cytokines and chemokine level just after birth.
Results Interleukin 6 and interleukin 8 concentrations were very high in the cyst or ascites just after birth. In the serum taken from two patients, the levels of interleukin 6 and interleukin 8 were also high. In five patients who underwent drainage of cysts after birth, systemic inflammation could not be completely suppressed before curative surgery.
Conclusions Interleukin 6 and interleukin 8 play important roles in the inflammatory response syndrome associated with meconium peritonitis, and drainage of cystic fluid did not completely suppress this inflammation. To lessen the high morbidity of meconium peritonitis, efforts should be made to suppress the inflammatory response using new treatment strategies, such as administration of steroids or anti-cytokine therapy to supplement cystic drainage.

Keywords Meconium peritonitis · Systemic inflammatory response syndrome · Fetal inflammatory response syndrome · Interleukin 6 · Interleukin 8

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Introduction

Meconium peritonitis is a fetal inflammatory response syndrome (FIRS) [1] that is triggered by meconium leaking into the peritoneal cavity in the fetus. If such chemical inflammation continues after birth, it is called systemic inflammatory response syndrome (SIRS) and makes patient care more difficult. A high morbidity rate of meconium peritonitis is reported even today [2]. However, precisely which cytokines and chemokines are involved in this inflammation remain to be elucidated, and only one experimental report has previously suggested a role for tumor necrosis factor-α [3]. We report herein our investigation of the concentrations of several cytokines and chemokines in the ascites and serum taken from six patients with meconium peritonitis and elucidate their potential roles in the systemic inflammation in these patients.

Materials and methods

We have experienced six patients with meconium peritonitis since 1993. One patient died soon after birth because he was complicated with a diaphragmatic hernia and had severe pulmonary hypoplasia. The other five patients were classified as having giant cystic type meconium peritonitis. In all six patients, ascitic or cystic fluids were drained soon after birth and centrifuged at 5,824 g for 10 min; supernatants were kept at −80°C until examination. In two patients, blood samples were also taken just after birth, and these were also kept at −80°C until use. Five patients underwent curative surgery at 5–25 days of age, and they all had ileal atresia and short bowels. In one patient, severe peritonitis caused by methicillin-resistant *Staphylococcus aureus* occurred after curative surgery, and additional peritoneal drainage was needed. Ascites and serum were taken from this patient after surgery and kept at −80°C until they were analyzed.

The following cytokines and a chemokine [interleukin 8 (IL-8)] were measured using commercially available ELISA kits: interleukin 1β (IL-1β), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ).

Results

Profiles of the six patients and the degree of inflammation after birth

The patient profiles are shown in Table 1. Four patients were male and two were female. Patient 2 was not diagnosed antenatally, but five patients were diagnosed as having meconium peritonitis while in utero. Patient 3 died soon after birth because he also had a diaphragmatic hernia and severe pulmonary hypoplasia. The gestational age of the six patients at birth ranged from 34 to 40 weeks and 3 days. Their body weight varied between 2,425 and 3,700 g (including the volume of the peritoneal cyst). All six cases except case 3 were giant cystic types; case 3 was an adhesive type with massive had ascites. The cystic fluids or ascites were drained at 0–2 days after birth, and the serum C-reactive protein (CRP) level was monitored as an indicator of systemic inflammation (Fig. 1). Curative surgery was performed at 5–25 days of age. All patients except in case 3 had ileal atresia and had shorter bowels (the small intestine ranged from 70 to 130 cm in length) compared with age-matched normal neonates. The five patients who underwent surgery are all still alive.

Table 2 shows laboratory data immediately after birth indicating the level of systemic inflammation. White blood cell counts were high, from 18,000 to 32,500/mm^3 in all patients. The serum CRP level was high in patients 1, 2, and 4 (17.4, 2.33, and 4.38 mg/dl, respectively) and mildly elevated in patients 3, 5, and 6 (0.49, 0.3, and 0.8 mg/dl, respectively). Erythroblast counts indicated the level of inflammation, which was high in patients 2 and 4 (12% and 75.6%, respectively).

Concentrations of cytokines and a chemokine in cystic or ascitic fluid and serum that were collected after birth (Tables 3, 4)

In the cystic or ascitic fluids, IL-6 and IL-8 were present at very high concentrations (IL-6 level, 393–31,800 pg/ml; IL-8, 35.2–11,000 pg/ml). The levels of these two cytokines did not correlate with the disease term (from gestational age at diagnosis to gestational age at birth) and also were not correlated with the serum whole blood cell (WBC) and CRP levels, as shown in Table 2. IL-1β was mildly elevated, from 8 to 348 pg/ml. TNF-α was at very low levels in most patients. IFN-γ, IL-2, IL-4, and IL-10 were all almost below the level of detection. In patients 2 and 6, IL-10 was mildly elevated, which suggested that an antiinflammatory response had occurred in these patients [4]. In patients 2 and 4, the serum cytokine and chemokine levels were measured. IL-6 and IL-8 were high, whereas IL-1β and TNF-α were mildly elevated.

Increases and decreases of systemic inflammation after cystic drainage

Figure 1 shows CRP changes before and after curative surgery in case 2. The CRP level fluctuated after cystic drainage, but it never came down below the normal value.

Table 1 Profile of six patients with meconium peritonitis

Case	Sex	Fetal diagnosis	Gestation	Body weight (g)	Drainage (days)	Curative surgery (days)	Length of small intestine (cm)	Prognosis
1	M	32 weeks	40 weeks, 3 days	2,920	0–2	25	70	Alive
2	F	–	35 weeks, 0 day	3,700	0.1	5	75	Alive
3[a]	M	33 weeks	35 weeks, 2 days	2,698	0	–	?	Dead
4	M	28 weeks, 2 days	34 weeks, 0 day	2,425	1	16	130	Alive
5	F	28 weeks	36 weeks, 5 days	2,748	0.1	20	110	Alive
6	M	30 weeks	36 weeks, 1 day	2,448	0	5	120	Alive

[a] Case 3 was complicated with diaphragmatic hernia and the patient died at 2 days of age of pulmonary insufficiency and generalized edema

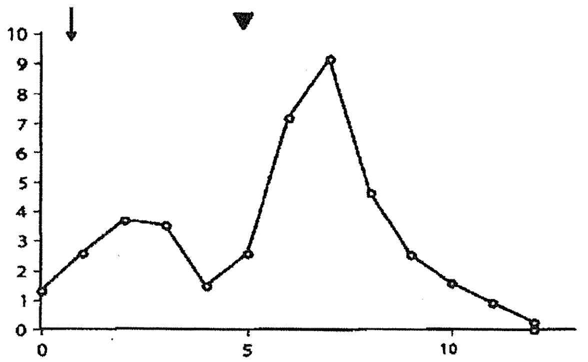

Fig. 1 C-reactive protein (CRP) change in patient 2. Just after birth, the CRP level was 2.33 mg/dl (*y*-axis). After cystic drainage, it fluctuated, but never came down to the normal value. After curative surgery on day 5 after birth (*x*-axis), the CRP level increased as high as 9.0 mg/dl, but decreased thereafter. *Arrow* cystic drainage, *arrowhead* curative surgery

Table 2 Inflammatory states after birth in six patients

Case	Term from diagnosis to birth	WBC[a] (/mm^3)	CRP[a] (mg/dl)	Erythroblasts[a] (%)
1	8 weeks, 3 days	32,500	17.4	0
2	–	29,700	1.33	12
3	2 weeks, 2 days	18,000	0.49	
4	5 weeks, 5 days	15,400	4.38	75.6
5	8 weeks, 5 days	28,800	0.3	
6	6 weeks, 1 day	25,600	0.8	

WBC whole blood count, *CRP* C-reactive protein

[a] Blood samples were taken just at birth

The other four patients (cases 1, 4, 5, and 6) also showed fluctuations in their CRP levels after drainage, and none of them came down below the normal value (data not shown). We concluded that cystic drainage could attain reduction of the local levels of cytokines and the chemokine but could never completely control systemic inflammation caused by meconium peritonitis.

Discussion

In the past few decades, meconium peritonitis has been considered to be a severe, complicated disease with a very high mortality rate [5, 6]. Recently, antenatal diagnosis and progress in treatment have decreased the mortality rate [7, 8], but the morbidity rate is still high because the severe inflammatory response may continue after birth and cause complications [2].

FIRS is a relatively novel concept, but it is now becoming widely accepted by neonatologists and obstetricians [1], and it is closely related to the presence of cytokines such as IL-6 and IL-8 [9, 10]. Meconium peritonitis may be a typical FIRS manifestation at the early stage of the disease in the fetus when one considers its fetal pathophysiology. Meconium is a strong inducer of inflammation via the complement system and the CD14 molecule on macrophages [11]. In the fetus, TNF-α and IL-1β secreted by peritoneal macrophages might play an important role in triggering the inflammatory response in meconium peritonitis [3].

Our present data showed that the inflammatory response continued after birth, and that the patients had varying degrees of inflammatory responses at birth. In other words, the patients with meconium peritonitis are in SIRS just after birth, and suppressing this inflammatory response is very important for successful treatment after birth. Our data also showed that after birth, IL-6 and IL-8 played key roles in inflammation, in contrast to IL-1β and TNF-α, which were suggested to play important roles in experimental meconium peritonitis [3]. We hypothesize that IL-1β and TNF-α work in the fetus to induce an inflammatory reaction in the peritoneal cavity, and that such an inflammatory reaction can result in the formation of a pseudocyst. IL-6 and IL-8 may amplify the inflammation initiated by IL-1 and TNF-α. In some patients, the IL-10 level was increased slightly in the cyst, thus suggesting that these patients may have had antiinflammatory response syndrome (CARS) [4], but even in these

Table 3 Concentration of cytokines and chemokine in cystic fluids

Case	TNF-α (pg/ml) (<5)	IL-1β (pg/ml) (<10)	IL-6 (pg/ml) (<4)	IL-8 (pg/ml) (<2)	IFN-γ (IU/ml) (<0.1)	IL-2 (U/ml) (<0.8)	IL-4 (pg/ml) (<6)	IL-10 (pg/ml) (<5)
1	6	348	1,120	11,000	<0.1	<0.8	–	<2.0
2	<5.0	38	31,800	1,800	<0.1	<0.8	<2.0	9
3	<5.0	16	7,800	591	<0.1	<0.8	<2.0	<2.0
4	23.2	8	393	35.2	0.3	<0.8	–	<2.0
5	<5.0	30	566	8,220	0.2	<0.8	<2.0	<2.0
6	<5.0	2.89	5,200	6,650	0.2	<0.8	–	25

Numbers in parentheses indicate normal value in human blood

TNF-α tumor necrosis factor-α, *IL* interleukin, *IFN-γ* interferon-γ

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Table 4 Concentration of cytokines and chemokines in serum after birth

Case	TNF-α (pg/ml)	IL-1β (pg/ml)	IL-6 (pg/ml)	IL-8 (pg/ml)
1	–	–	–	–
2	1.8	2.1	154	66
3	–	–	–	–
4	3	1.13	38.4	104
5	–	–	–	–
6	–	–	–	–

patients, the systemic inflammation still continued, as indicated by the WBC count and CRP level.

The IL-6 and IL-8 concentrations in the cysts did not correlate with the disease term (from first diagnosed gestational age to birth age), or with the serum inflammatory markers such as WBC and CRP in our five patients, although the reasons for this lack of correlation were not clear. We speculate that the inflammatory responses in a fetus may vary according to the process of formation of the pseudocyst wall (this process is likely different in each patient), and once formed, this pseudocyst wall may work as a seawall to prevent the overflow of cytokines into the bloodstream in some patients, whereas in other patients, the wall did not work, leading to severe systemic inflammation. Another important fact was that the IL-6 and IL-8 levels were high in all six patients, but their absolute concentrations varied. Again, the reason for this was not clear, but we speculated that IL-6 and IL-8 were produced by the activated macrophages and neutrophils attracted by the first inflammation evoked by TNF-α and IL-1β. If the adhesive and fibrous pseudocyst wall was promptly formed after first inflammation, it might be difficult to attract macrophages and neutrophils into the cysts, thereby preventing the inflammatory cascade from effectively producing IL-6 and IL-8. In contrast, if the pseudocyst was formed gradually by a necrotic intestinal wall, the wall would have been fragile and easily attracted macrophages and neutrophils into the cyst, allowing the inflammatory cascade to proceed to induce high levels of IL-6 and IL-8. However, these theories are just speculation, and more data are needed to a demonstrate reasonable explanation for these observed differences.

Cystic drainage was reported to be valuable to control the inflammation because it worked to reduce cytokine levels [12], but such treatment alone could not suppress the inflammation completely, as shown by our present data. Therefore, a more effective and stronger anti-cytokine treatment is needed to control SIRS after birth. Steroids are among the promising therapeutic candidates [13]. Other candidates, as apparent from our data, are anti-IL-6 agents [14]. It will be important and valuable to use these medications in the future to control SIRS in meconium peritonitis patients, and this may reduce the morbidity of the disease.

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Congenital anterior neck cysts classified as 'thyroglossal anomalies'

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The most frequent congenital anterior neck cyst is the thyroglossal duct remnant cyst and the second most frequent is the dermoid cyst.[1,2] A dermoid cyst in the anterior neck is considered to have arisen from abnormal invagination of the surface ectoderm that forms the face and neck.[3] A thyroglossal duct remnant cyst is caused by failure of obliteration of the thyroglossal duct when it descends from the foramen cecum to the infrahyoid region in early embryologic life. In this context, both congenital lesions are etiologically distinct but are considered by some to have a close relationship, and such lesions are sometimes collectively called 'thyroglossal anomalies'.[4–7]

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