increased 2 weeks after laser surgery. In the present study, a high concentration of maternal serum hCG was seen in TTTS; when laser surgery for TTTS was effective, the concentration of hCG decreased, but when the surgery was ineffective, hCG remained high. Thus, a close association was observed between the concentration of hCG and the condition of TTTS.

It is known that the concentration of hCG in pregnancy reaches a peak between 60 and 80 days after the last menses. At 10–12 weeks, plasma levels begin to decline, and a nadir is reached by about 16 weeks. Plasma levels are maintained at this lower level for the remainder of pregnancy [11]. There are many reports regarding hCG in twin gestations, and most have found that the concentration of hCG is almost 2 MoM [12, 13]. In the present study, the preoperative concentration of hCG in TTTS was 6.34 MoM (interquartile range 3.52–9.86), which is significantly higher than that of normal twin gestations. The reason why high concentrations of maternal serum hCG are seen in TTTS is not known. One hypothesis is that polyhydramnios surrounding the recipient twin may be associated with relatively impaired uteroplacental blood flow that increases the risk of hypoxemia [14]. Unbalanced placental intertwin vascular anastomoses create hypervolemia in one twin (the recipient). This can then lead to polyhydramnios, recipient heart failure and placental edema. The increased maternal serum hCG may reflect the large placental size in TTTS and a change in placental oxygen tension secondary to uteroplacental hypoperfusion [6]. Mirror syndrome refers to a condition of generalized maternal edema, often with pulmonary involvement, that mirrors the edema of the hydropic fetus and placenta [15]. TTTS is one of the diseases associated with mirror syndrome [7, 16], in which hCG is increased [17].

The present study showed that when patients diagnosed with TTTS underwent laser surgery, the concentration of hCG decreased to less than half the preoperative concentration after 2 weeks and further decreased to 1.67 MoM (interquartile range 1.12–2.32), which is considered within the normal range for a twin pregnancy, after 4 weeks. In the recurrent cases, the concentration of hCG either increased or remained unchanged 2 weeks after laser surgery. However, in the recurrent cases that underwent an effective second surgery, the concentration of hCG decreased. Thus, the change in the concentration of hCG after laser surgery could be a marker for the effectiveness of laser surgery. The concentration of hCG 2 weeks after laser surgery could be used as one criterion for determining recurrence of TTTS with polyhydramnios/oligohydramnios. In this study, we excluded the cases in which fetal death occurred after laser surgery, regardless of whether the fetal death was a single death or a double death, due to concerns about the impact on hCG levels. The dynamics of hCG in the single death cases were almost same as in the 2 uneventful surviving cases after laser surgery. The concentration of hCG decreased to less than half the preoperative level after 2 weeks and further reduced to within the normal range of a singleton pregnancy after 4 weeks (data not shown).

Our study has both strengths and limitations. Though there have been some reports that have followed the changes in the concentration of hCG after laser surgery for TTTS, the number of cases studied has been limited [7] and the changes have only been followed for 1 week [6]. The strength of this study is that a considerable number of cases were studied for 1 month after laser surgery. The limitation is that there were only 3 recurrent cases and 1 case that underwent a second surgery. Investigation of more recurrent cases and cases with second surgery should confirm our findings.

In conclusion, we propose the adoption of a control curve of maternal serum hCG after laser surgery. This curve would show the median concentration of hCG in cases with an uneventful course after laser surgery. An excessive concentration of hCG is associated with TTTS, and the concentration of hCG in cases with an uneventful course decreased to less than half the preoperative concentration 2 weeks after laser surgery and to within the normal range 4 weeks after surgery. A close association between the concentration of hCG and the condition of TTTS after laser surgery was observed. hCG could be a useful predictive parameter for the effectiveness of laser surgery in TTTS.

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Ultrasound predictors of mortality in monochorionic twins with selective intrauterine growth restriction

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KEYWORDS: discordant twin; Doppler; monochorionic twin; oligohydramnios; selective intrauterine growth restriction; stuck twin phenomenon; umbilical artery

ABSTRACT

Objectives *The aim of this study was to evaluate the use of ultrasound assessment to predict risk of mortality in expectantly managed monochorionic twin fetuses with selective intrauterine growth restriction (sIUGR).*

Methods *This was a retrospective study of 101 monochorionic twin pregnancies diagnosed with sIUGR before 26 weeks of gestation. All patients were under expectant management during the observation period. At the initial evaluation, the presence or absence of each of the following abnormalities was documented: oligohydramnios; stuck twin phenomenon; severe IUGR $< 3^{rd}$ centile of estimated fetal weight; abnormal Doppler in the umbilical artery; and polyhydramnios in the larger twin. The relationships between these ultrasound findings and mortality of sIUGR fetuses were evaluated using multiple logistic regression analysis.*

Results *Of 101 sIUGR twins, 22 (21.8%) fetuses suffered intrauterine demise and nine (8.9%) suffered neonatal death; 70 (69.3%) survived the neonatal period. Multiple logistic regression analysis revealed that the stuck twin phenomenon (odds ratio (OR): 14.5; 95% CI: 2.2–93.2; P = 0.006) and constantly absent diastolic flow in the umbilical artery (OR: 29.4; 95% CI: 3.3–264.0; P = 0.003) were significant risk factors for mortality.*

Conclusions *Not only abnormal Doppler flow in the umbilical artery but also severe oligohydramnios should be recognized as important indicators for mortality in monochorionic twins with sIUGR. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

The incidence of monochorionic twin pregnancy complicated by selective intrauterine growth restriction (sIUGR) is approximately 11–14%[1–3]; this complication is considered to be indicative of poor outcome for both fetuses[1,3–8] and seems to be caused by unequal placental sharing and placental vascular anastomoses[3,6,7,9]. The characteristics of Doppler waveforms in the umbilical artery (UA) of sIUGR fetuses can be used to classify fetuses into three clinical groups: Type I, normal UA Doppler; Type II, persistent absent or reversed end-diastolic velocity flow (AREDF); and Type III, intermittent AREDF (iAREDF)[6]. Although the prognosis for most Type I fetuses is favorable, many Type II fetuses develop fetal deterioration with a high risk of intrauterine fetal death (IUFD)[6,8]. Among Type III twins with sIUGR, approximately 15% of fetuses die unexpectedly, and 20% of larger twins suffer from parenchymal brain lesions, probably related to fetofetal transfusion via a large arterio-arterial vascular anastomosis[6].

Although the association between abnormal UA Doppler in Type II and Type III fetuses and poor perinatal outcomes in monochorionic twins with sIUGR has been described[6,8], the literature contains limited discussions of other ultrasound prognostic factors that can predict perinatal outcome. Prediction of the risk of acute deterioration and IUFD in sIUGR fetuses, which would facilitate decisions regarding the continuation of pregnancy or selective feticide in previable pregnancies, is therefore essential. The aim of the present study was to clarify the ultrasonographic factors related to poor prognosis in sIUGR twins

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undergoing expectant management. We focused on predicting perinatal mortality, including IUFD and neonatal death (NND), of sIUGR fetuses considered to be at high risk for perinatal death.

METHODS

In this retrospective study, we reviewed a series of 101 monochorionic twin pregnancies diagnosed with sIUGR before 26 weeks of gestation in four tertiary centers in Japan from 2001 to 2009. Cases of monochorionic diamniotic twins with sIUGR were searched using a computerized database; those with an estimated weight below the 10th centile in the smaller twin at 18–26 weeks and that did not develop twin–twin transfusion syndrome (TTTS) were included in the analysis. Perinatal outcome was obtained from the referring physicians if delivery occurred at their facility; however, this information could not be obtained for all cases. Patients provided informed consent (a comprehensive agreement for clinical studies) in all cases, and the study was approved by the Institutional Review Boards of all institutions involved in the study. Sixty-three of the 101 sIUGR pregnancies included in the present study were described in a previous report on perinatal outcome under expectant management[8]. A diagnosis of sIUGR was made if the estimated fetal body weight (EFBW) was below the 10th centile in the smaller twin and above the 10th centile in the larger twin[4,7,8,10]. Cases with TTTS, defined as the presence of polyhydramnios in one twin and oligohydramnios in the other twin[11], or fetal malformation at the time of initial diagnosis, were excluded.

Ultrasound assessment, including fetal biometry and estimation of the amniotic fluid volume, was performed. Severe IUGR in the smaller twin was defined when the EFBW was less than the 3rd centile. The percentage discordance was calculated as (A−B) × 100/A, where A is the EFBW of the larger fetus and B is the EFBW of the sIUGR fetus. Abnormal levels of amniotic fluid in fetuses were defined by the presence of any of the following: isolated polyhydramnios (a maximum vertical pocket (MVP) of > 8 cm in the larger twin); isolated oligohydramnios (an MVP of < 2 cm); isolated stuck twin; or an MVP of < 1 cm[12]. The finding of an isolated abnormal volume of amniotic fluid in the smaller twin had to be accompanied by a normal volume of amniotic fluid in the larger twin. Stuck twin phenomenon was defined as a fixed position of the fetus relative to the uterine wall due to severe oligohydramnios of one twin.

Cases were monitored using color and pulsed Doppler examination. Fetuses with sIUGR were classified into three groups based on UA Doppler flow: Type I, positive end-diastolic velocity in the UA; Type II, constant AREDF; or Type III, iAREDF, defined as the clear observation of abnormal diastolic flow waveforms following an intermittent pattern within a short interval[6]. Doppler waveforms were recorded using a minimum of three measurements at a free loop in each UA in the absence of fetal or maternal movement. Doppler sampling was performed using a 3.5- or 5-MHz curved array transducer with average spatial peak temporal intensities of < 100 mW/cm^2. The angle of insonation was 0°, or as close to 0° as possible. Ultrasound assessment, including biometry, estimation of amniotic fluid volume and Doppler examination, was performed at diagnosis of sIUGR; however, at least two consecutive examinations confirming the initial findings were required at each institution.

During the observation period, all mothers were under expectant management and selective feticide was not considered to be an option in our clinical setting. The fetal condition, assessed using fetal growth curves, amniotic pocket measurements and Doppler, was monitored by ultrasonography in combination with fetal heart rate monitoring (nonstress test) or fetal biophysical profile at the participating institutions or referring hospitals. Indications for delivery, and the mode of delivery, were at the discretion of the attending physicians; indications for delivery included fetal deterioration (defined by an abnormal fetal heart rate and/or an abnormal biophysical profiling score) and fetal growth arrest for at least 2 weeks after 32 weeks of gestation. Abnormal Doppler waveforms, including reversed flow in the ductus venosus and reversed flow in the UA, were taken into consideration as indications for delivery in some cases; however, they were not used consistently for decisions concerning delivery because of the long duration of the study period.

Statistical analysis

The study outcome was death (including both IUFD and NND in sIUGR fetuses) following ultrasonographic diagnosis of sIUGR. Odds ratio (OR) was used to estimate the risk of IUFD or NND in sIUGR fetuses according to the ultrasound findings. Univariate analyses were used to estimate the crude ORs and their 95% CIs of the ultrasound risk factors, including the presence of AREDF in UA, isolated oligohydramnios, isolated stuck twin, severe IUGR in the smaller twin and isolated polyhydramnios in the larger twin. A multiple logistic regression model for IUFD or NND of the smaller twin was constructed using the variables selected by stepwise selection (significance level for entering into the model: < 0.2). The reported *P*-values were two-sided. Analyses were performed using SAS software version 9.1.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Sonographic measurements were obtained for all 101 pregnancies. The median gestational age at the time of delivery (including stillbirths) was 32 (range: 18–40) weeks. Of all 101 sIUGR twins, 22 (21.8%) fetuses suffered IUFD and nine (8.9%) suffered NND; 70 (69.3%) survived the neonatal period. Of the larger twins, 82 (81.2%) survived, IUFD occurred in 11 (10.9%) and NND occurred in eight (7.9%). Among the 22 cases of IUFD of the smaller twin, IUFD of the larger twin

subsequently occurred in 10 (45.5%) cases. The clinical characteristics of the cases, including perinatal survival of one, both, or neither of the twins, are presented in Table 1.

The associations between each ultrasound factor and mortality on univariate analysis are presented in Table 2. The case distribution, based on UA Doppler waveform, was 31 for Type I, 55 for Type II and 15 for Type III. The mortality of sIUGR twins was 3.2% for Type I, 49.1% for Type II, and 20.0% for Type III. Univariate analysis revealed a strong association between a Type II UA Doppler waveform and mortality of sIUGR fetuses (OR = 28.9; 95% CI, 3.7–227.3; $P < 0.001$). The prevalence of mortality was significantly higher in cases with isolated oligohydramnios than in those without (OR = 2.7; 95% CI, 1.1–6.6; $P = 0.034$). Univariate analysis identified isolated stuck twin phenomenon as a significant risk factor for death (OR = 16.2; 95% CI, 3.3–79.8; $P < 0.001$). In addition, a significant association was observed between severe IUGR and mortality (OR = 3.8; 95% CI, 1.2–11.9; $P = 0.019$). There was a significant difference in the perinatal outcome of twins between those with EFBW discordance ≥ 45% and those with discordance < 45% (OR = 3.5; 95% CI, 1.4–9.0; $P = 0.008$).

Isolated stuck twin phenomenon, UA Doppler in sIUGR fetuses and severe IUGR were selected as explanatory variables for the multiple logistic model (Table 3). The generalized R^2 was 0.33. Isolated stuck twin phenomenon (OR = 14.5; 95% CI, 2.2–93.2; $P = 0.006$) and Type II UA Doppler waveform (OR = 29.4; 95% CI, 3.3–264.0; $P = 0.003$) were significant risk factors for mortality in the sIUGR fetuses (Table 3). Although the risk of mortality for fetuses with severe IUGR was high, the association was not statistically significant (OR = 3.3; 95% CI, 0.9–12.4).

Table 1 Clinical characteristics of monochorionic twin pregnancies with selective intrauterine fetal growth restriction (sIUGR) ($n = 101$)

Characteristic	*Value*
GA at diagnosis (weeks)	20 (18–25)
Discordance in EFBW (%)	38.7 (16.2–77.8)
GA at delivery (weeks)	32 (18–40)
Birth weight of twins with sIUGR (g)	1112 (125–2402)
Birth weight of larger twins (g)	1773 (312–2986)
At least one twin survived	82 (81.2)
Both twins survived	68 (67.3)

Data expressed as median (range) or *n* (%). EFBW, estimated fetal body weight; GA, gestational age.

Table 3 Multiple logistic regression analysis of predictors of mortality in fetuses with selective intrauterine growth restriction (sIUGR)

Predictor	*OR (95% CI)*	P
UA Type II	29.4 (3.3–264.0)	0.003
UA Type III	5.6 (0.4–72.5)	0.186
Isolated stuck twin	14.5 (2.2–93.2)	0.006
Severe IUGR	3.3 (0.9–12.4)	0.084

IUGR, intrauterine growth restriction; OR, odds ratio; UA, umbilical artery.

DISCUSSION

The use of a classification system based on UA Doppler waveforms to predict the perinatal prognosis of monochorionic twins with sIUGR has been previously described[6,8]. Perinatal outcomes for Type I twins are generally favorable, whereas Type II fetuses have the poorest prognosis. In our previous study, which included a subset of the fetuses in the present study, intact survival of

Table 2 Univariate analysis of predictors of mortality in fetuses with selective intrauterine growth restriction (sIUGR)

Predictor	*Survival* (n (%))	*Death* (n (%))	*OR (95% CI)*	P
UA Doppler				
Type I	30 (97)	1 (3)	—	—
Type II	28 (51)	27 (49)	28.9 (3.7–227.3)	< 0.001
Type III	12 (80)	3 (20)	7.5 (0.7–79.4)	—
Isolated polyhydramnios				
No	58 (72)	23 (28)	—	—
Yes	12 (60)	8 (40)	1.7 (0.6–4.6)	0.314
Isolated oligohydramnios				
No	55 (75)	18 (25)	—	—
Yes	15 (54)	13 (46)	2.7 (1.1–6.6)	0.034
Isolated stuck twin				
No	68 (76)	21 (24)	—	—
Yes	2 (17)	10 (83)	16.2 (3.3–79.8)	< 0.001
Severe IUGR				
No	25 (86)	4 (14)	—	—
Yes	45 (63)	27 (38)	3.8 (1.2–11.9)	0.019
Percentage discordance in EFBW				
< 45%	58 (76)	18 (24)	—	—
≥ 45%	12 (48)	13 (52)	3.5 (1.4–9.0)	0.008

EFBW, estimated fetal body weight; OR, odds ratio; UA, umbilical artery.

Type II fetuses was only 37%; with a mortality rate (IUFD or NND) of 48% in this group[8]. In particular, IUFD may be caused by acute fetofetal hemorrhage, which can have profound consequences on the outcome of the surviving cotwin[13–15]. The prevalence of *in-utero* deterioration of Type II sIUGR fetuses ranges from 70 to 90%[6,8]. In terms of mortality of sIUGR fetuses, Type II Doppler waveform was recognized as a predictor of a poor prognosis in the present study (OR = 28.9, compared with Type I Doppler waveform). Approximately 50% of Type II fetuses died on or before the neonatal period, consistent with previously reported results[6,8]. The clinical evolution of Type III fetuses presenting with iAREDF has been reported to be atypical[5,6]. In some cases, sIUGR fetuses may die without any symptoms of hypoxic deterioration, and the larger twin may suffer from neurological abnormalities, even if both fetuses survive. In the present study, Type III fetuses showed a trend for increased mortality, although the association was not significant. We cannot rule out the possibility that the small sample size influenced the lack of significance.

The significance of ultrasound factors other than UA Doppler have not previously been evaluated with regard to the prognosis of cases with sIUGR. Oligohydramnios is predictive of perinatal death in singleton pregnancies, increasing the mortality rate by 13–47-fold compared to pregnancies with normal amniotic volume[16]. Oligohydramnios is induced by decreased renal perfusion as a result of the redistribution of fetal cardiac output and an increased concentration of antidiuretic hormone, which is, in turn, caused by fetal hypoxemia secondary to placental dysfunction. However, even in monochorionic twins that do not meet the criteria for TTTS, hemodynamic imbalance as a result of placental vascular anastomoses can cause oligohydramnios. Stuck twin phenomenon in monochorionic twin pregnancies, defined as a fixed position of the fetus relative to the uterine wall as a result of severe oligohydramnios of one twin, is also associated with poor perinatal outcome[12,17,18]. In the present study of sIUGR fetuses, isolated oligohydramnios was defined as an MVP of < 2 cm and isolated stuck twin phenomenon was defined as an MVP of < 1 cm[12] without isolated polyhydramnios in the cotwin. Multivariable logistic regression analysis did not identify isolated oligohydramnios in the sIUGR fetus as a significant prognostic factor. In contrast, 10 of 12 cases of isolated stuck twin phenomenon died. Multiple logistic regression analysis showed that isolated stuck twin was a secondary predictor of mortality in sIUGR fetuses (OR = 14.5). Conversely, isolated polyhydramnios of the larger fetus, which might induce premature delivery, was not associated with death.

The severity of growth restriction in fetuses is related to fetal and neonatal outcome[19–21]. Mortality and morbidity are increased among neonates with birth weights at or below the 3rd centile for their gestational age[21]. Severe IUGR, defined as an EFBW less than the 3rd centile, and the percentage discordance between the EFBW of cotwins appeared to be of significant prognostic value for mortality on univariate analysis; however, they were not significant factors in multivariable logistic analysis.

The results of this study indicate that mortality of the sIUGR twin is highest in cases with constant AREDF in the UA as the primary prognostic factor and isolated stuck twin as the secondary prognostic factor. Umbilical cord occlusion for selective feticide has been reported to be an option for Type II and Type III fetuses[22,23]. The application of laser surgery for placental vascular anastomoses has also been noted in preliminary reports of Type II[4] and Type III[10] cases; however, the number of cases in these studies was small and further investigation is necessary. Nevertheless, to prevent acute fetofetal hemorrhage subsequent to IUFD of a sIUGR fetus, these interventions can be considered viable options for Type II pregnancies with severe isolated oligohydramnios.

The present study had several limitations, such as a potential bias in the retrospective study design. Because the study population comprised patients referred from various hospitals, there might have been selection bias towards worse perinatal outcome. Therefore, detailed information on the patient's clinical course was not always available. Furthermore, iAREDV may have been misdiagnosed as constant AREDV in Type II fetuses, as the number of Type III cases in the present series was rather small compared with previous reports[6,7]. Nevertheless, the present results are noteworthy in that they have identified prognostic factors for sIUGR fetuses under expectant perinatal management.

In conclusion, abnormal Doppler findings in the UA and severe isolated oligohydramnios (which we call isolated stuck twin phenomenon) should be recognized as significant predictors for mortality in sIUGR twins. Consequently, fetal intervention might be considered as a management option for fetuses with sIUGR with abnormal Doppler findings and severe oligohydramnios at an earlier gestational age.

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Ultrasound prognostic factors after laser surgery for twin–twin transfusion syndrome to predict survival at 6 months

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Objective To evaluate the significance of ultrasound findings, detected one or two weeks after laser surgery for twin–twin transfusion syndrome, in predicting the mortality at 6 months of age.

Methods Ultrasound evaluation including fetal biometry, amniotic fluid volume estimation and Doppler examination was performed between 7 and 14 days after surgery for 181 cases. The presence of one or more effusions and single fetal death were also determined. Associations between ultrasound findings and mortality at 6 months of age were evaluated using multiple logistic regression analysis.

Results Of the total 181 pairs, 145 (80.1%) donor and 160 (88.1%) recipient twins survived *in utero* for more than 7 days after surgery, and hence were included in the analysis. The survival rate at 6 months was 66.9% for the donor and 80.7% for the recipient twins. Risk factors for death in the donor were the presence of severe intrauterine growth restriction and effusions. In recipients, elevation in the middle cerebral artery peak systolic velocity coincided with fetal death, but this occurred in only three cases.

Conclusion Ultrasound risk factors one week after surgery included severe intrauterine growth restrictions and effusions in the donor twins. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: Doppler; fetal therapy; laser surgery; monochorionic twin; twin–twin transfusion syndrome; ultrasound

INTRODUCTION

Twin–twin transfusion syndrome (TTTS) develops in approximately 10% of cases of monochorionic twin pregnancies and is associated with a poor perinatal prognosis (Lewi *et al.*, 2008). The unbalanced blood flow from the donor to the recipient twin via the intertwin vascular anastomoses may result in profound hemodynamic disturbances in each twin (Diehl *et al.*, 2001; Bermudez *et al.*, 2002). Consequently, severe oligohydramnios occurs in the donor twin and polyhydramnios and cardiac failure occur in the recipient twin. Several recent studies, including a randomized controlled trial, have demonstrated that fetoscopic laser coagulation of placental vascular anastomoses results in a higher survival and lower neurological complication rate, when compared with serial amnioreduction (Ville *et al.*, 1998; Hecher *et al.*, 1999; Quintero *et al.*, 2003; Senat *et al.*, 2004).

The use of ultrasound, which reveals significant perioperative prognostic factors, facilitates the prediction of perinatal outcome of twins after surgery. Detection of absent or reversed end-diastolic flow in the umbilical artery of the donor twin may be the most significant prognostic factor for fetal demise, which frequently occurs within a few days after surgery (Martinez *et al.*, 2003; Cavicchioni *et al.*, 2006; Ishii *et al.*, 2007; Sago *et al.*, 2010). However, even fetuses that survive the acute period, that is, one week after surgery, sometimes die during the fetal or neonatal period (Sago *et al.*, 2010). The clinical features of fetuses that suffer *in utero* or neonatal death one week after surgery remain unknown. This study aimed to identify ultrasound parameters one or two weeks after laser surgery in predicting eventual mortality of fetuses.

METHODS

A total of 181 Japanese women were diagnosed with TTTS, for which they underwent fetoscopic laser surgery. The characteristics and perinatal outcomes of these cases have been previously reported (Sago *et al.*, 2010). TTTS was diagnosed on the basis of the following criteria: (1) the presence of polyhydramnios and a deepest vertical pocket (DVP) of >8 cm in the recipient twin and (2) oligohydramnios and a DVP of <2 cm in the donor twin. All patients were between 16 and 26 weeks of gestation and the Quintero stage of disease was between I and IV (Quintero *et al.*, 1999). Laser surgery was performed using previously described methods (Sago *et al.*, 2010) and

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vascular anastomoses were selectively coagulated (Quintero *et al.*, 1998.). Patients gave their written consent and the study protocol was approved by the institutional review board of each institution.

All mothers with at least one surviving fetus 7 days after laser surgery were examined between 7 and 14 days after the procedure. Ultrasound examination included fetal biometry and amniotic fluid volume estimation. According to the formula given by the Japanese Society of Ultrasound in Medicine (Shinozuka, 2002), an estimated fetal weight of < -2 SD was regarded as a severe intrauterine growth restriction (IUGR). Effusion in one body compartment was defined as the presence of at least one of the following signs: (1) ascites; (2) pleural effusion; (3) pericardial effusion; and (4) skin edema. Furthermore, the presence or absence of a single co-twin death was noted. This was followed by color and pulsed Doppler examination of the umbilical artery (UA), middle cerebral artery (MCA), and *ductus venosus* (DV) of the fetuses. Doppler sampling was performed using a 3.5 MHz or 5 MHz curved-array transducer with spatial peak temporal average intensities lower than 100 mW/cm^2. The high-pass filter was set at the lowest level. During Doppler studies for fetal vessels, the occurrence of absent or reversed end-diastolic flow (AREDF) in UA, elevated peak systolic velocity in the MCA (MCA-PSV), and reversed blood flow during atrial contraction in the DV (DVRF) were regarded as critically abnormal. Flow velocity waveforms were recorded during the absence of fetal breathing and/or movements. Umbilical artery waveforms were recorded at a free loop of the umbilical cord or at the placental cord insertion site. MCA-PSV was measured as described by Mari *et al.* (2000) and a value of >1.5 multiples of median (MoM) using their reference range was considered elevated. The insonation angle between the ultrasound beam and the direction of blood flow was kept as close as possible to 0 degrees. The sample volume for DV was determined from its inlet portion at the umbilical vein.

The study outcome was survival at 6 months of age in each twin and the odds ratio (OR) was used to estimate the relative risk of death for each fetus according to the ultrasound findings. Univariate analyses were used to estimate crude ORs and 95% confidence intervals (CIs) of the ultrasound risk factors. A multiple logistic regression model for death at 6 months of age in each twin was constructed using variables obtained by stepwise selection (significance level for entry into the model was <0.2). The reported p values were two-sided and analyses were performed using SAS software version 9.1.2 (SAS Institute Inc., Chicago, Illinois, USA).

RESULTS

Of the total 181 twin sets undergoing laser surgery (Table 1), 145 (80.6%) donor and 160 (88.9%) recipient twins survived for more than 7 days after surgery, and hence were included in the analysis. Ultrasound examination was performed at approximately 8.1 days (range: 7–14) for donor twins and 7.7 days (range: 7–14) for recipient twins. Pregnancy outcomes and perinatal survival rates are shown in Table 2. The median gestational age at delivery was 33 weeks in donor twins (interquartile range: 29.6–36.3 weeks) and 33.1 weeks in recipient twins (interquartile range: 29.6–36.1 weeks). The incidence of preterm delivery and the gestational ages of donors and recipients, respectively, were as follows: 2.8% and 3.1%, <24 weeks; 14.5% and 15.0%, <28 weeks; and 43.4% and 40.6%, ≥34 weeks. Intrauterine fetal death (IUFD) between 7 days and delivery occurred in 8.3% donor and 5.0% recipient twins. The survival rate at 6 months of age was 83.5% for donor and 91.3% for recipient twins.

Univariate logistic regression analysis showed that the significant risk factors for donor death at 6 months of age were the presence of AREDF in UA (OR: 3.03; 95% CI: 1.07–8.58; $p=0.031$), effusion in one body compartment (OR: 3.72; 95% CI: 1.09–12.6; $p=0.043$), and IUGR (OR: 5.33; 95% CI: 1.93–14.75; $p=0.001$) (Table 3). With regard to recipient death, MCA-PSV >1.5 MoM (OR: 4.95; 95% CI: 1.09–22.5; $p=0.058$) was defined as a single prognostic factor (Table 4). Variables such as DVP, DVRF, or single IUFD of the co-twins did not affect the outcomes (Table 3).

In the final multiple logistic model, prognostic factors for donor death were severe IUGR (OR: 6.17; 95% CI:

Table 1—Baseline characteristics ($n=181$)

Maternal age, mean ± SD	31.0 ± 4.5
Nulliparity - no. (%)	100 (55%)
Gestational age at surgery, mean ± SD	21.2 ± 2.5
Location of placenta - no. (%)	
Anterior	89 (49%)
Posterior	92 (51%)
Quintero stage - no. (%)	
Stage 1	14 (8%)
Stage 2	30 (17%)
Stage 3	113 (62%)
Stage 4	24 (13%)

SD, standard deviation.

Table 2—Pregnancy outcomes and survival rates of twins

	Donor ($N=145$)	Recipient ($N=160$)
Gestational age at delivery–weeks		
Median	33.1	33.0
Interquartile range	29.6–36.3	29.6–36.1
Gestational age at delivery, no. (%)		
< 24 weeks	4 (2.8%)	5 (3.1%)
24 to < 28 weeks	17 (11.7%)	19 (11.9%)
28 to < 32 weeks	30 (20.7%)	37 (23.1%)
32 to < 34 weeks	31 (21.4%)	34 (21.3%)
34 to < 36 weeks	16 (11.0%)	17 (10.6%)
≥ 36 weeks	47 (32.4%)	48 (30.0%)
IUFD, no. (%)	12 (8.3%)	8 (5.0%)
NND, no. (%)	6 (4.1%)	5 (3.1%)
Infantile death (<6 months), no. (%)	6 (4.1%)	1 (0.6%)
Survival at 6 months of age, no. (%)	121 (83.5%)	146 (91.3%)

Intrauterine fetal death (IUFD) after ultrasonographic assessment at least 7 days after laser surgery; NND, neonatal death.

Table 3—(a) Crude odds ratio of ultrasound factors for death at 6 months of age in donor twins. (b) Crude odds ratio of ultrasound factors for death at 6 months of age in recipient twins

a)

Variables	Mortality rate in donor twin	OR (95%CI)	*p*
DVP in donor		2.06 (0.77–5.51)	0.145
≤2 cm (*N* = 34)	23.5%		
2 cm < (*N* = 100)	13.0%		
AREDF in UA of donor		3.03 (1.07–8.58)	0.031
AREDF (*N* = 22)	31.8%		
Normal (*N* = 120)	13.3%		
DVRF in donor		2.29 (0.55–9.62)	0.371
DVRF (*N* = 10)	30.0%		
Normal (*N* = 127)	15.7%		
MCA-PSV (MoM)		—	1.000
<1.5 (*N* = 105)	16.2%		
1.5 ≤ (*N* = 3)	0.0%		
Own effusion		3.72 (1.09–12.6)	0.043
Effusion (*N* = 13)	38.5%		
Normal (*N* = 125)	14.4%		
IUFD of co-twin		0.61 (0.07–5.15)	1.000
Presence (*N* = 9)	11.1%		
Absence (*N* = 136)	16.9%		
Severe IUGR		5.33 (1.93–14.75)	0.001
≤ − 2SD (*N* = 53)	30.2%		
2SD < (*N* = 80)	7.5%		

b)

Variables	Mortality rate in recipient twin	OR (95%CI)	*p*
DVP in recipient		1.09 (0.34–3.43)	1.000
8 cm ≤ (*N* = 51)	9.8%		
<8 cm (*N* = 99)	9.1%		
AREDF in UA of recipient		—	1.000
AREDF (*N* = 1)	100.0%		
Normal (*N* = 154)	8.4%		
DVRF in recipient		1.36 (0.16–11.85)	0.563
DVRF (*N* = 9)	11.1%		
Normal (*N* = 143)	8.4%		
MCA-PSV (Mom)		4.95 (1.09–22.51)	0.058
<1.5 (*N* = 113)	8.0%		
1.5 ≤ (*N* = 10)	30.0%		
Own effusion		2.62 (0.50–13.79)	0.239
Effusion (*N* = 11)	18.2%		
Normal (*N* = 141)	7.8%		
IUFD of co-twin		2.52 (0.72–8.81)	0.230
Presence (*N* = 24)	16.7%		
Absence (*N* = 136)	7.4%		

P, *p*-value; OR, odds ratio; CI, confidence interval; DVP, deepest vertiacal pocket; AREDF in UA, absent or reversed end-diastolic flow in the umbilical artery; DVRF, reversed blood flow during atrial contraction in *ductus venosus*; MCA-PSV, peak systolic velocity of middle cerebral artery; MoM, multiples of median; Effusion, defined as when at least one sign, such as ascites, pleural effusion, pericardial effusion and skin edema, was noted; IUFD, intrauterine fetal death; IUGR, intra uterine growth restriction.

2.03–18.73; $p = 0.001$) and effusion in one body compartment (OR: 4.24; 95% CI: 1.09–16.53; $p = 0.037$) (Table 4 (a)). The statistically significant prognostic factor for recipient death was elevated MCA-PSV (OR: 1.21; 95% CI: 1.01–1.46; $p = 0.040$) (Table 4(b)). Interestingly, one of the three recipient twins with elevated MCA-PSV who died had an anemia–polycythemia sequence diagnosed postnatally.

Table 4—(a) Multivariate-adjusted odds ratio of ultrasound factors for death at 6 months of age in donor twins. (b) Multivariate-adjusted odds ratio of ultrasound factors for death at 6 months of age in recipient twins

a)

	Donor (*N* = 126)	
Variables	OR (95%CI)	*p*-value
Own effusion	4.24(1.09–16.53)	0.037
Severe IUGR	6.17(2.03–18.73)	0.001

b)

	Recipient (*N* = 119)	
Variables	OR (95%CI)	*p*-value
MCA-PSV (Mom)	1.21 (1.01–1.46)	0.040
Own effusion	1.22 (0.97–1.55)	0.090

OR, odds ratio; CI, confidence interval; Effusion, defined if at least one sign, such as ascites, pleural effusions pericardial effusion and skin edema was noted; IUGR, intra uterine growth restriction; MCA-PSV, peak systolic velocity of middle cerebral artery; MoM, multiples of median.

DISCUSSION

Ultrasound detectable prognostic features that predict 6-month survival in donor and recipient twins and which are obtained more than a week after laser surgery have not been elucidated earlier, although this information might be important when referring a patient back after laser surgery. In contrast, earlier studies have logically focused on perioperative sonographic indicators (Martinez *et al.*, 2003; Cavicchioni *et al.*, 2006; Ishii *et al.*, 2007; Sago *et al.*, 2010). According to the results of our previous study (Sago *et al.*, 2010), 13.3% donor twins and 6.1% recipient twins died within 7 days after surgery, while 69.1% donor twins and 82.9% recipient twins survived for more than 6 months.

Regarding the donor twins, a preoperative AREDF in UA is a negative predictor for fetal or neonatal survival (Martinez *et al.*, 2003; Cavicchioni *et al.*, 2006; Ishii *et al.*, 2007; Sago *et al.*, 2010), which may be associated with a small placental territory and/or vascular anastomoses (Chang *et al.*, 2006). On the other hand, AREDF in UA presented immediately after surgery correlate with perinatal outcome (Martinez *et al.*, 2003; Cavicchioni *et al.*, 2006). AREDF in the UA one week or more after laser surgery was neither predictive of donor death in previous studies (Martinez *et al.*, 2003; Cavicchioni *et al.*, 2006) nor in this one. Actually most donor deaths occurred within 7 days after laser surgery (Ishii *et al.*, 2007). Early donor death has often been explained by a drastic change in circulating blood volume. The presence of AREDF becomes less predictive later on, as the latter probably is more an indicator of the degree of growth restriction, which on itself may be an independent predictor of perinatal death. In the present study, the presence of severe IUGR rather than AREDF was indeed an independent predictor of survival. This has also been shown previously

in singletons (Kramer *et al.*, 1990; Spinillo *et al.*, 1995; McIntire *et al.*, 1999).

A second predictor of late donor death was the presence of one or more effusions. This has been earlier explained to be caused by a sudden increase in peripheral or placental vascular resistance causing an increased afterload. They were explained to be caused by an increase in umbilical venous blood flow volume after arrest of the intertwin transfusion process, leading to a relative increase in fetal volemia (Mahieu-Caputo *et al.*, 2000; Gratacos *et al.*, 2002a, 2002b; Ishii *et al.*, 2004). In a previous study by Gratacos *et al.*, in nine out of ten donor twins who developed hydropic signs, this disappeared within 14 days after surgery, whereas it worsened and the donor twin resulted in death in another case (Gratacos *et al.*, 2002b). In the present study, 13 donor twins had hydropic signs, of whom five (38.5%) actually died. The exact pathophysiologic mechanism of persisting hydrops remains unknown, hence the difference in results cannot be explained.

For recipients, postoperative MCA-PSV >1.5 MoM was predictive of the outcome, which may be indicative of fetal anemia. Preoperative-elevated MCA-PSV of the recipient twins was earlier reported as a risk factor for IUFD 24 h after laser surgery for TTTS (Kontopoulos and Quintero, 2009), whereas postoperative elevation of the MCA-PSV usually is benign and transient (Ishii *et al.*, 2008). In the present study, elevation of MCA-PSV more than 7 days after surgery was documented in seven patients, which normalized in six. The only one where it did not eventually died. Elevated MCA-PSV has also been earlier tied to subsequent fetal death in growth-restricted fetuses (Mari *et al.*, 2007). These authors speculated that an increased MCA-PSV indicated an increased blood flow to the brain through an elevated left cardiac output and increased placental vascular resistance. Because we did not have detailed assessment of the fetal hemodynamic status, including cardiac output, we cannot speculate on this particular feature. As only three of ten recipient twins with postoperative elevated MCA-PSV eventually died, this might not make it a significant prognostic factor.

In summary, factors that predict perinatal outcome between 7 and 14 days after laser surgery are different from those in the preoperative or immediate postoperative period. In this study, we have shown that the presence of severe IUGR and one or more effusions in the donor twin more than one week after laser surgery are predictive of the perinatal outcome of the donor. Such findings put the donor fetus at risk, which warrants a more close surveillance, and eventually in the viable period may lead to a more active management.

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ORIGINAL ARTICLE

The Japanese experience with prenatally diagnosed congenital diaphragmatic hernia based on a multi-institutional review

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Abstract
Purpose To review the recent Japanese experience with prenatally diagnosed congenital diaphragmatic hernia (CDH) based on a multi-institutional survey.
Methods A multicenter, retrospective cohort study was conducted on 117 patients born between 2002 and 2007 with isolated prenatally diagnosed CDH. All patients were managed by maternal transport, planned delivery, immediate resuscitation and gentle ventilation. The primary outcome measurements were the 90-day survival and intact discharge. The examined prenatal factors included gestational age (GA) at diagnosis, lung-to-head ratio (LHR), lung-to-thorax transverse area ratio (L/T) and liver position. Physical growth and motor/speech development were evaluated at 1.5 and 3 years of age. Data were expressed as the median (range).
Results The mean GA at diagnosis was 29 (17–40) weeks. The LHR and L/T were 1.56 (0.37–4.23) and 0.11 (0.04–0.25), respectively. There were 48 patients with liver up. The mean GA at birth was 38 (28–42) weeks. The 90-day survival rate and intact discharge rate were 79 and 63%, respectively. Twelve patients had major morbidity at discharge, and 71% of these patients had physical growth or developmental retardation at 3 years of age.
Conclusion This multicenter study demonstrated that the 90-day survival rate of isolated prenatally diagnosed CDH was 79%, and that subsequent morbidity remained high.

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A new treatment strategy is needed to reduce the mortality and morbidity of severe CDH.

Keywords Congenital diaphragmatic hernia · Gentle ventilation · Prenatal diagnosis · Fetus · Multicenter study

Introduction

Congenital diaphragmatic hernia (CDH) is one of the most challenging anomalies faced by pediatric surgeons and neonatologists. During the past few decades, many innovative techniques, including high-frequency oscillation (HFO), inhaled nitric oxide (NO), extracorporeal membrane oxygenation (ECMO) and gentle ventilation (GV), have been introduced for the treatment of CDH [1, 2]. Additionally, prenatal diagnosis has also made a contribution to the improvement of the outcome of CDH [3, 4]. In many high-volume centers, immediate start of gentle ventilation following planned delivery has become the standard strategy for the treatment of prenatally diagnosed CDH. Despite these advances in fetal and neonatal care, mortality and morbidity remain high in a subset of severe CDH. To offer appropriate information to the family before birth, and to develop a multi-institutional consensus on selection criteria for fetal intervention, it is necessary to analyze the most recent outcomes of prenatally diagnosed CDH. This study was conducted to review the modern experience of prenatally diagnosed CDH treated in five Japanese centers dedicated to this condition.

Materials and methods

A multicenter retrospective study was conducted on 117 patients born between 2002 and 2007 with isolated prenatally diagnosed CDH. Patients with associated life-threatening or chromosomal anomalies were excluded. The participating centers included three children's medical centers and two university hospitals. All patients were managed by maternal transport, planned delivery, immediate resuscitation and gentle ventilation. To achieve GV, the goals of the blood gas parameters were set at $PaCO_2$ < 60–70 mmHg and pre-ductal SpO_2 > 90%. Once these gas data were obtained, ventilator settings, including FiO_2 and mean airway pressure (MAP), were decreased promptly. The upper limit of MAP was set at 18–20 cmH_2O. In each center, HFO, NO and ECMO were available from the entry criteria of each patient. Diaphragmatic repair was performed when respiratory and circulatory stabilization was achieved. The goal of the preoperative stabilization was appropriate blood pressure to keep diuresis and appropriate blood gas data (PaCO2 < 60–70 mmHg, pre-ductal SpO2 > 90%).

This study was approved by the institutional review board of the participating centers (the approved number of subjects was 314).

We reviewed the charts of all patients and their mothers to collect the following data.

Prenatal data

The prenatal data examined included gestational age (GA) at diagnosis, the presence of polyhydramnios, initial lung-to-head ratio (LHR), initial lung-to-thorax transverse area ratio (L/T) and liver position (liver up/liver down). When LHR or L/T was measured several times, the earliest data were analyzed as the initial data.

Postnatal data

Data abstracted postnatally included: GA at birth; birth weight; sex; side of defect; mode of delivery; Apgar score at 1 min; use of NO, HFO and ECMO; highest MAP; duration of mechanical ventilation; duration of oxygen supplementation; date of surgery; need for patching; date of discharge; and significant morbidity at discharge. Significant morbidity included the need for respiratory support (supplemental oxygen, mechanical ventilation), nutritional support (tube feeding, parenteral nutrition) or circulatory support (use of vasodilators).

Physical growth (height and body weight) and motor/speech development were evaluated at 1.5 and 3 years of age. Height or body weight less than −2SD was defined as physical growth retardation. The inability to walk alone was defined as motor developmental retardation. The inability to speak more than 3 words at 1.5 years or to talk normally at 3 years was defined as speech developmental retardation.

Outcome measures

The primary outcomes of the study were 90-day survival and intact discharge. Intact discharge was defined as discharge from the hospital without any of the significant morbidities mentioned above.

Comparisons

To investigate the prognostic factors, comparisons of the prenatal and postnatal data were made between the 90-day survivors and 90-day non-survivors.

Statistical analyses

Data were expressed as the median with the range. The statistical significance of differences was determined by Fisher's exact probability test or the chi-square test for categorical data and the Wilcoxon-test for continuous data. Differences with a P value of <0.05 were considered as significant.

Results

Prenatal data

The GA at diagnosis was 29 (17–40) weeks, and 24 patients had polyhydramnios. The initial LHR was 1.55 (0.37–4.23) and the initial L/T was 0.11 (0.04–0.25), measured at 31 (18–40) weeks. There were 48 patients with liver up and 69 patients with liver down.

Table 1 Postnatal data

Postnatal data	Median (range), *n* (%)
Gestational age at birth (weeks)	38 (28–42)
Birth weight (kg)	2.78 (1.04–4.04)
Sex	
Male	63 (53.9)
Female	54 (46.2)
Mode of delivery	
Vaginal	55 (47.0)
C-section	62 (53.0)
Apgar score at 1 min	4 (1–9)
HFO	
Yes	116 (99.1)
No	1 (0.9)
NO	
Yes	94 (80.3)
No	23 (19.7)
ECMO	
Yes	19 (16.2)
No	98 (83.8)
Highest MAP (cmH_2O)	14 (12–15)[a]
Side of the defect	
Left	109 (93.2)
Right	6 (5.1)
Bilateral	2 (1.7)
Diaphragmatic repair	
Yes	104 (88.9)
No	13 (11.1)
Age at repair (hours)	69 (26–101)[a]
Diaphragmatic closure	
Direct	54 (51.9)
Patch	50 (48.1)
Survivors	
Duration of mechanical ventilation (days)	20 (11–101)[a]
Duration of O_2 supplementation (days)	32 (17–54)[a]

[a] Median (interquartile range)

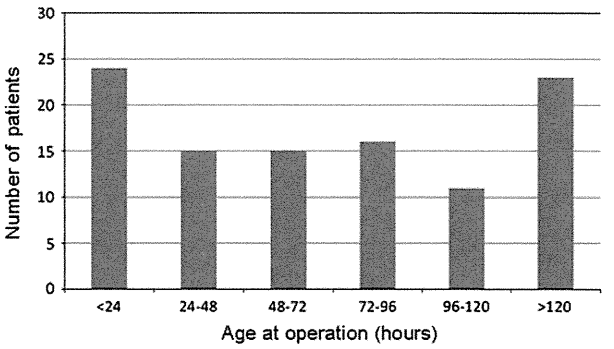

Fig. 1 Age distribution at surgery (hours). Each *bar* indicates the number of patients every 24 h after birth

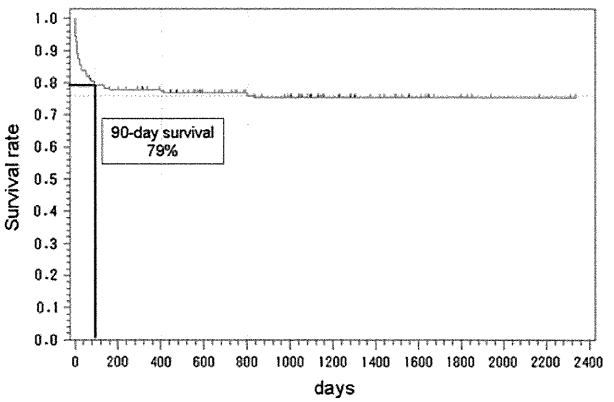

Fig. 2 The survival curve reached a plateau at 90 days. The 90-day survival rate was 79%

Postnatal data

The patients' postnatal characteristics are shown in Table 1. The GA at birth was 38 (28–42) weeks, and the birth weight was 2.78 (1.04–4.04) kg. The mode of delivery was vaginal in 55 patients and cesarean section in 62 patients. HFO was used in 116 patients (99%) and NO in 94 patients (80%). ECMO was used in 19 patients (16%); 7 of these patients survived for 90 days and 2 patients had an intact discharge. The highest MAP was 14 (12–15) cmH_2O. The side of the diaphragmatic defect was left in 109 patients, right in 6 patients, and bilateral in 2 patients. Diaphragmatic repair was performed in 104 patients (direct closure: 54 patients; patch closure: 50 patients); closure was conducted at a median of 69 h after birth. Figure 1 shows the number of patients who underwent diaphragmatic repair every 24 h after birth. The timing of surgery was almost equally distributed up to more than 120 h.

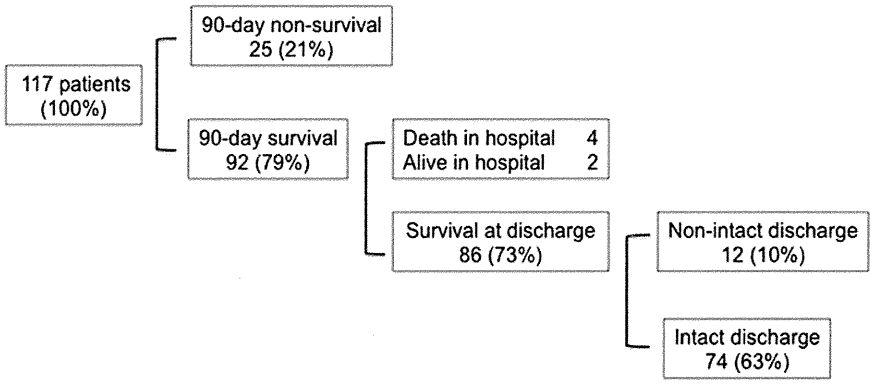

Fig. 3 Summary of the outcomes

Table 2 Comparisons of the incidence of physical growth and motor/speech retardation (intact discharge vs. non-intact discharge)

	Intact discharge ($n = 74$)	Non-intact discharge ($n = 12$)	p
1 year and 6 months			
Any retardation	44% (26/59)	80% (8/10)	0.045
Physical growth	24% (14/59)	60% (6/10)	0.029
Motor/speech	30% (18/59)	70% (7/10)	0.029
3 years			
Any retardation	27% (10/37)	71% (5/7)	0.036
Physical growth	16% (6/37)	57% (4/7)	0.037
Motor/speech	19% (7/37)	43% (3/7)	0.323

Table 3 Comparisons of prenatal data, birth weight and gestational age at birth between 90-day survivors and non-survivors

	90-day survivors ($n = 92$)	90-day non-survivors ($n = 25$)	p
GW at diagnosis (weeks)	29.0 ± 5.8	27.3 ± 5.4	0.249
Polyhydramnios	23% (17/91)	41% (7/24)	0.261
LHR	1.772 ± 0.703	1.273 ± 0.435	0.004
L/T	0.126 ± 0.043	0.096 ± 0.040	0.006
Liver up	28% (26/92)	88% (22/25)	<0.001
Birth weight	2.743 ± 0.526	2.700 ± 0.488	0.404
GA at birth (weeks)	38.0 ± 2.1	37.6 ± 1.7	0.127

Data are expressed as the mean ± SD

Among the survivors, the median duration of mechanical ventilation and O_2 supplementation were 20 and 32 days, respectively.

Outcome measures

Figure 2 shows the overall survival curve, which reached a plateau at 90 days. The 90-day survival was 79% (92/117). Among the survivors, six patients did not qualify for hospital discharge: four patients died in the hospital after 90 days of age, and two patients were still alive in the hospital at the age of 18 and 24 months. Therefore, 86 patients (73%) survived to discharge, including 12 with some major morbidities. Finally, the rate of intact discharge was 63% (74/117). These results are summarized in Fig. 3.

The details of the major morbidities at discharge in 12 patients are as follows:

supplemental O_2: 5;
supplemental O_2 + vasodilator: 2;
supplemental O_2 + tube feeding: 1;
supplemental O_2 + mechanical ventilation + tracheostomy: 1;
tube feeding: 3.

In the 12 non-intact discharge patients, the rate of physical or developmental retardation was 80% at 1.5 years and 71% at 3 years of age. In contrast, in the intact discharge patients, the rate of physical or developmental retardation was significantly lower (Table 2).

With regard to the relations of liver position and outcomes, the 90-day survival rate was 54% (26/48) in liver up and 96% (66/69) in liver down. The intact discharge rate was 29% (14/48) in liver up and 87% (60/69) in liver down. There were significant differences ($p < 0.05$) in the rate of 90-day survival and intact discharge between liver up and liver down patients.

Comparisons

There were no differences in GA at diagnosis, the incidence of polyhydramnios, birth weight and GA at birth between the 90-day survivors and 90-day non-survivors. The initial LHR and L/T were significantly higher in 90-day survivors compared to non-survivors. The incidence of liver up was significantly higher in 90-day non-survivors (Table 3).

Discussion

This is the first Japanese multicenter study of prenatally diagnosed CDH managed by planned delivery and followed by GV. Because five high-volume centers participated in this study, the data from a large series of prenatally diagnosed CDH could be collected in a comparatively short period. As most of the new strategies for CDH treatment, including HFO, NO, ECMO and GV, were introduced in the 1990s, all patients in this study were treated based on these established modern treatments throughout the study period. Therefore, this study should have revealed the most current outcomes for prenatally diagnosed CDH with minimal historical bias.

Our outcomes were somewhat better than the data from the large CDH study group registry in the USA, which noted a 70.5% "survival to discharge" of 1,222 infants born between 1995 and 2006 with prenatal diagnosis [5]. In most of the previous reports, including the CDH study group, "survival to discharge" was taken as the primary outcome. However, the rescue of more severely affected patients resulted in more patients with severe morbidities, including long-term respiratory support, nutritional support and circulatory support. In this study, a total of 12 patients were discharged with major morbidities (9 on respiratory support, 4 with tube feeding and 2 receiving vasodilators). Our results indicate that significant numbers of CDH patients are alive with major morbidities, resulting in poor quality of life. Thus, survival to discharge does not accurately reflect the treatment results if quality of life is taken into account. Because the overall survival curve reached a plateau at 90 days, 90-day survival does seem to be a good index to evaluate the short-term outcomes of CDH.

Our data have also shown that the rate of physical or developmental retardation at 1.5 and 3 years of age in the intact discharge patients was lower compared to the non-intact discharge patients. This suggests that intact discharge is a useful index to predict the long-term outcome of CDH.

This study has also clarified the latest treatment policy. With regard to the timing of delivery, the median gestational weeks at planned delivery was 38 weeks (range 28–42). According to the CDH study group, infants born at 37–38 weeks, compared with those born at 39–41 weeks, had less use of ECMO and a trend toward a higher survival rate was found among infants born through elective cesarean delivery [5]. Because the degree of pulmonary hypoplasia and vascular abnormalities become relatively more severe as gestation progresses [6, 7], there may be a potential benefit from delivering infants with CDH early. Although the best timing of delivery is unclear, 38 weeks is the most common and may be an appropriate timing for delivery of fetuses with CDH.

With regard to the mode of delivery, our data showed that cesarean section was likely to be selected in severe cases. Although the best mode of delivery remains unclear in prenatally diagnosed CDH, recent data have suggested that elective cesarean delivery may be associated with greater rates of survival without ECMO [8]. A prospective randomized trial is needed to determine the best mode of delivery for fetuses with CDH.

The timing of surgery also remains controversial. Some centers delay surgery until physiologic stabilization has occurred, while others prefer early surgery immediately after birth [3]. As a result, the timing of surgery was almost equally distributed to up to 120 h after birth in this study. Our data showed that the timing of surgery was not related to the survival rate. This lack of importance may be due to the progress made in the postoperative medical management of the patients.

With regard to the mode of ventilation, HFO was used immediately after birth in almost all cases. HFO has become the first-line ventilator mode for CDH in Japan. While ECMO was used in 19 patients, only 2 patients who were on ECMO had an intact discharge. Because of the advances in neonatal respiratory care, the role of ECMO has become limited in the treatment of prenatally diagnosed CDH in comparison to the past. A prospective randomized study may be necessary to determine if ECMO can improve the outcome of prenatally diagnosed CDH.

Our data have revealed that the initial LHR and L/T were significantly higher in 90-day survivors compared to 90-day non-survivors. Because of the wide distribution of LHR and L/T in each group, it is difficult to determine a cutoff to distinguish fetuses with expected poor outcome from fetuses with good outcome. Although LHR has been the most common method for lung assessment, there are several reports that have described that LHR is not a reliable predictor of outcome in fetuses with CDH [9–11]. According to our data, liver position was strongly correlated with 90-day survival as well as LHR and L/T. It is important to consider these factors together to predict outcomes of prenatally diagnosed CDH more precisely. In addition to LHR, L/T and liver position, measurement of other prognostic factors, such as total fetal lung volume [12], herniated liver volume [13, 14] and the observed to expected normal mean for gestation (o/e) LHR [15], are also required to establish an entry criteria for fetal intervention.

A major limitation of this study is the late diagnosis. The initial measurement of LHR and L/T were conducted at 31 weeks of gestation. Although L/T is consistent during gestation [16], LHR increases with gestation. It is therefore preferable to use o/e LHR to obtain a gestation-independent prediction of survival [15]. This fact should be considered when using our data as a selection criterion for fetal

intervention, which is currently being performed at 26–28 weeks' gestation.

The present study has demonstrated that a significant number of CDH patients are alive with major morbidities, despite good survival rate. A new treatment strategy, including fetal intervention, is therefore needed to reduce the mortality and morbidity of severe CDH.

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Re-evaluation of stomach position as a simple prognostic factor in fetal left congenital diaphragmatic hernia: a multicenter survey in Japan

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KEYWORDS: congenital diaphragmatic hernia; fetus; gentle ventilation; liver; stomach

ABSTRACT

Objectives *To document outcome and to explore prognostic factors in fetal left congenital diaphragmatic hernia (CDH).*

Methods *This was a multicenter retrospective study of 109 patients with prenatally diagnosed isolated left CDH born between 2002 and 2007. The primary outcome was intact discharge, defined as discharge from hospital without major morbidities, such as a need for respiratory support including oxygen supplementation, tube feeding, parenteral nutrition or vasodilators. All patients were managed at perinatal centers with immediate resuscitation, gentle ventilation (mostly with high-frequency oscillatory ventilation) and surgery after stabilization. Prenatal data collected included liver and stomach position, lung-to-head ratio, gestational age at diagnosis and presence or absence of polyhydramnios. Stomach position was classified into four grades: Grade 0, abdominal; Grade 1, left thoracic; Grade 2, less than half of the stomach herniated into the right chest; and Grade 3, more than half of the stomach herniated into the right chest.*

Results *Overall intact discharge and 90-day survival rates were 65.1% and 79.8%, respectively. Stomach herniation was classified as Grade 0 in 19.3% of cases, Grade 1 in 45.9%, Grade 2 in 13.8% and Grade 3 in 21.1%. Multivariate analysis revealed that liver position was the strongest prognostic variable for intact discharge, followed by stomach position. Based on our results, we divided patients into three groups according to liver (up vs. down) and stomach (Grade 0–2 vs. Grade 3) position. Intact discharge rates declined significantly from liver-down (Group I), to liver-up with stomach Grade 0–2 (Group II), to liver-up with stomach Grade 3 (Group III) (87.0%, 47.4% and 9.5% of cases, respectively).*

Conclusion *Current status and outcomes of prenatally diagnosed left CDH in Japan were surveyed. Stomach herniation into the right chest was not uncommon and its grade correlated with outcome. The combination of liver and stomach positions was useful to stratify patients into three groups (Group I–III) with different prognoses.*

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is one of the most challenging anomalies for pediatric surgeons and neonatologists. The rate of prenatal detection has been increasing over time, and is now over 50%[1–3]. A recent survey by the Japanese Association of Pediatric Surgeons reported that 73.5% of neonatal CDH cases in Japan had been diagnosed prenatally[4]. Prenatal detection allows management at experienced centers and avoidance of inadvertent events such as pneumothorax, distention of

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the gastrointestinal tract or resuscitation failure. This has improved the outcome of patients diagnosed prenatally, but limitations have led to an ongoing debate regarding the role of fetal intervention.

The prognosis of a patient with prenatally diagnosed CDH is estimated from several factors, including liver position and measurement of contralateral lung size (i.e. lung-to-head ratio (LHR) or lung-to-thoracic ratio). Stomach position, whether herniated into the chest or not, was formerly used as a factor for prediction of prognosis[5–7]. We reported previously an observation that stomach herniation into the right chest is an ominous sign in fetal left CDH[8]. In this study, we investigated the prognostic value of stomach position using a new grading system.

METHODS

A retrospective chart review was conducted on all isolated prenatally diagnosed CDH patients born during the period 2002–2007 at the National Center for Child Health and Development, Kanagawa Children's Medical Center, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka University Hospital or Kyushu University Hospital. We included in the study cases with presence of a left-sided CDH without associated life-threatening or chromosomal anomalies. All patients delivered at our centers and neonates were managed by immediate resuscitation followed by neonatal intensive care, including gentle ventilation mostly with high-frequency oscillatory ventilation (HFO) and preoperative stabilization. All institutions had extracorporeal membrane oxygenation (ECMO) and nitric oxide (NO) inhalation capability, which were initiated according to the clinical decisions of each team; indication criteria were not defined prospectively. This study was approved by the institutional review boards of all participating centers.

Prenatal data

The following data were collected for each patient: gestational age at diagnosis, presence or absence of polyhydramnios (maximum vertical pocket ≥ 8 cm), position of fetal liver and stomach, and LHR measured on maternal admission. Only those cases with obvious liver herniation (more than one-third of the left thoracic space occupied by the liver) on prenatal imaging studies were grouped as 'liver-up', eliminating questionable cases. Position of the stomach was categorized as: Grade 0, abdominal; Grade 1, left thoracic; Grade 2, less than half of the stomach herniated into the right chest; and Grade 3, more than half of the stomach herniated into the right chest (Figure 1). The lung area was measured by multiplication of the longest diameter of the lung by its longest perpendicular diameter in the cross-sectional plane at the level of the four-chamber view of the heart.

Postnatal data

Data collected postnatally included sex, gestational age at birth, birth weight, mode of delivery, Apgar score at 1 min, need for HFO, NO inhalation, ECMO and patch repair. Major morbidities at discharge, such as a need for respiratory support including oxygen supplementation, tube feeding, parenteral nutritional support or vasodilators, were recorded.

Outcomes

The primary and secondary outcomes were intact discharge (defined as discharge from hospital without any need for respiratory support including oxygen supplementation, tube feeding, parenteral nutritional support or vasodilators to control pulmonary hypertension) and 90-day survival rate.

Statistical analysis

Data are reported as median (range) or frequency (percentage). Univariate analyses were performed using chi-square, Fisher's exact and Cochran–Armitage tests. Crude odds ratio (OR) and 95% CIs for intact discharge failure, including death, were calculated. Multiple logistic regression analysis was also performed to estimate the OR of the prenatal variables adjusting for correlation among them. We used a stepwise selection method (variable selection criteria, $P < 0.20$) to select the variables correlated with intact discharge failure. All reported P-values are two-sided and not adjusted for multiplicity. $P < 0.05$ was considered statistically significant. Data were analyzed with SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

The characteristics of the 109 patients with isolated left CDH managed by the five participating centers between January 2002 and December 2007 are summarized in Table 1. The distribution of liver and stomach positions is shown in Figure 2. Almost all (67/69) of the liver-down patients had stomach Grades 0–2, while more than half (21/40) of the liver-up patients had stomach Grade 3.

With respect to therapeutic interventions used after birth, all except one patient ($n = 108$, 99.1%) were ventilated with HFO. Inhaled NO was administered in 87 (79.8%) patients. ECMO was used in 16 (14.7%) patients, only four of whom survived to discharge, two with oxygen supplementation. Surgery to repair the diaphragm was performed in 98 (89.9%) patients, of whom 46 (46.9%) required patch repair.

At 90 days of postnatal life, 22 patients had died and 87 (79.8%) were alive. After 90 days, only four patients died (at 92, 136, 403 and 802 days) and only two patients were still in hospital at the time of the survey. Eighty-one patients survived to discharge, including 10 patients

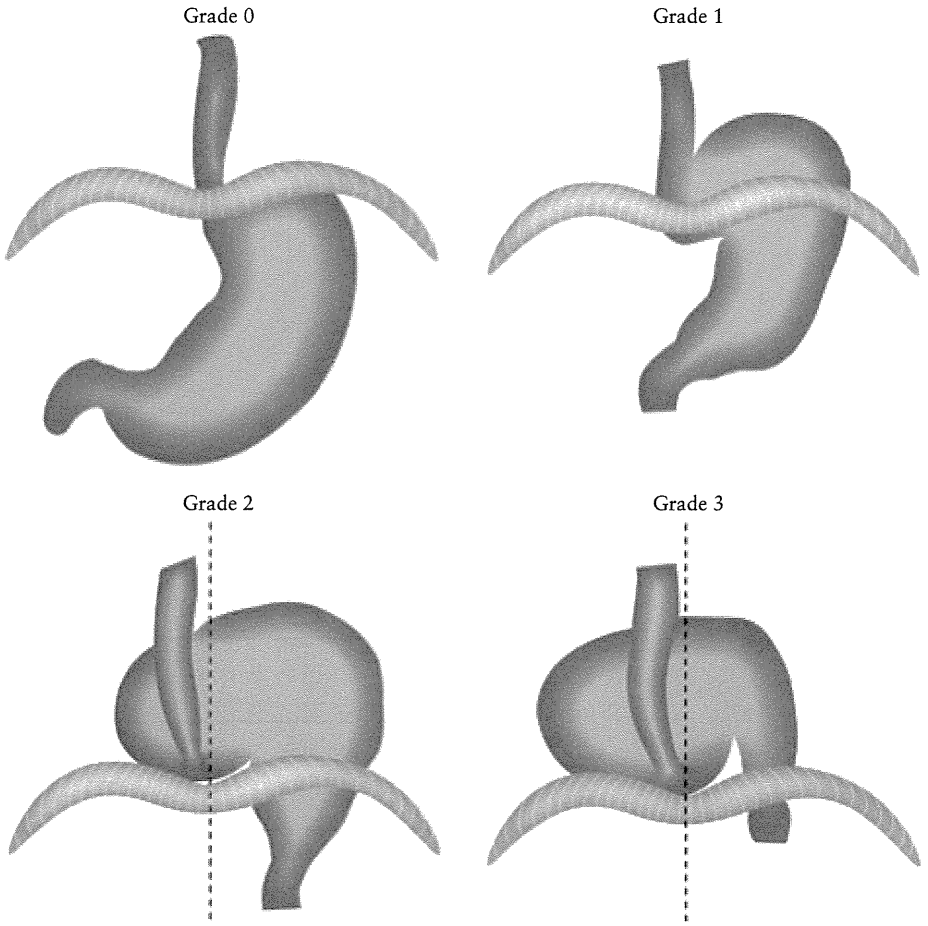

Figure 1 Schematic diagrams showing the four grades of stomach position in patients with left congenital diaphragmatic hernia. Stomach position was categorized as Grade 0, abdominal; Grade 1, left thoracic; Grade 2, less than half of the stomach herniated into the right chest; and Grade 3, more than half of the stomach herniated into the right chest.

with some major morbidities (seven patients required oxygen supplementation, four required tube feeding and two required vasodilators). Thus, the rate of intact discharge was 65.1% (71/109).

The results of univariate analysis are shown in Table 2 and those of multivariate analysis are in Table 3. Adjusted ORs of liver position and stomach position for intact discharge failure were statistically significant. While the OR of LHR was not statistically significant, the magnitude of this risk was not negligible. Adjusted ORs of these three variables became less significant than the crude ORs because they confounded each other.

Stomach position grade was also correlated with the need for patch repair, the need for patch repair being 0% (0/20) for Grade 0, 46% (22/48) for Grade 1, 62% (8/13) for Grade 2 and 94% (16/17) for Grade 3 ($P < 0.001$).

Based on these results, we divided patients into three groups according to liver (up vs. down) and stomach (Grade 0–2 vs. Grade 3) position (Figure 3). Intact discharge rates declined significantly from Group I (liver-down), to Group II (liver-up with stomach Grade 0–2), to Group III (liver-up with stomach Grade 3) (87.0%, 47.4% and 9.5% of cases, respectively).

DISCUSSION

This multicenter study has revealed the outcomes of prenatally diagnosed left CDH managed at perinatal centers with immediate resuscitation and gentle ventilation: a 90-day survival rate of 79.8% and an intact discharge rate of 65.1%. The results compare favorably with reports from leading centers of the world[9,10], considering that patients were all diagnosed prenatally and had relatively low birth weight. Our results reflect the current status in Japan as a whole, compared with previous reports that reflected smaller, single centers[11,12].

A new concept for prognostic evaluation of CDH, intact discharge, was introduced in this study. Intact discharge was defined as discharge from hospital without any respiratory, nutritional or circulatory support. Previously, studies had been focused mainly on therapies that reduce perinatal and neonatal mortality of CDH[13–15]. However, it is well known that to save the lives of the more severely affected patients results in a significant increase in survivor morbidity[16–18]. Intact discharge may serve in counseling the parents and could be an important goal of prenatal intervention. Whether patients with intact discharge have