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Perinatal outcome and clinical features of monochorionic monoamniotic twin gestation

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Abstract

Aim: To clarify perinatal outcomes of monoamniotic (MM) twin pregnancies.

Material and Methods: MM twins delivered in seven tertiary perinatal centers during the last decade were retrospectively evaluated. All pregnant women were scheduled to begin inpatient management at around 24 weeks of gestation and undergo a planned cesarean section beyond 32 weeks. Pregnancy outcomes, prevalence of fetal death and cord entanglement, perinatal mortality and neuromorbidity rate at discharge were examined.

Results: The study group comprised 38 MM twin pregnancies (76 fetuses). Cord entanglement was confirmed in 88% (30/34) of women, and fetal deaths occurred in nine women (eight were both fetal deaths, and one was single fetal death). The cord entanglement accounted for 65% (11/17) of the fetal deaths. The median gestational age at delivery was 31^{+3} weeks, but that for viable infants was 32^{+3} weeks; the median birth weight was 1642 g, the perinatal mortality rate was 2% (1/60), and the neuromorbidity rate was 8% (5/50). The overall survival rate was 75% (57/76).

Conclusion: Perinatal outcomes in our study were relatively good irrespective of high frequency of cord entanglement. Close fetal monitoring may allow MM twin pregnancies to extend gestational age, which may contribute to reduce both fetal death and neonatal morbidity by immaturity, although the best delivery weeks remained undetermined.

Key words: monochorionic monoamniotic twins, perinatal prognosis, umbilical cord entanglement.

Introduction

Monochorionic monoamniotic (MM) twin pregnancy is a relatively rare condition; it has an estimated prevalence of 1 of 1650 to 1 of 93 734 live births.[1,2] A considerably high perinatal loss rate, as high as 45.5%, has been reported in the 1990s.[3] The principal reasons for adverse perinatal outcomes are umbilical cord entanglement, congenital anomalies, preterm delivery, intrauterine growth restriction, and placental vascular

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anastomotic events.[4] In particular, umbilical cord entanglement has been considered to account for 50–65% of perinatal mortality in MM twins.[5,6]

Despite the foregoing, several recent studies of MM twins report a fetal loss rate after 20 weeks of gestation of 13% to 15%[7,8] and a perinatal mortality rate of 17% or less.[7] These studies also report a lower prevalence of cord entanglement for perinatal loss in MM twin gestations.[7]

The aim of this study was to investigate the perinatal prognosis of MM twins as well as the incidence of umbilical cord entanglement. Because the rarity of MM twin pregnancies hampers their analysis, we accumulated MM twin cases that occurred over the last decade at seven tertiary perinatal care centers.

Material and Methods

A retrospective observational study reviewed a series of 38 MM twin pregnancies that were delivered at seven perinatal care centers in Japan between January 2001 and December 2011. The diagnosis of monoamnionicity was made during the first trimester by ultrasound examination. The cases with spontaneous abortion before 14 weeks of gestation, conjoined twins, twin reversed arterial perfusion sequence, and lethal malformations were excluded.

Inpatient management began between 24 and 26 weeks of gestation and a planned cesarean section was performed at 32–34 weeks, unless obstetrical indications mandated earlier delivery. One patient remained on an outpatient basis for personal reasons, despite our recommendation for inpatient care. During hospitalization, fetal heart rate monitoring was performed at least once a day and ultrasound fetal surveillance was conducted at least once a week.

We examined the incidence of intrauterine fetal death (IUFD), presence of umbilical cord entanglement, indication and mode of delivery, gestational age at delivery, birth weight, birth weight discordance, survival rate, and neurological outcome at discharge. Perinatal mortality was defined as the total number of IUFD after 22 weeks of gestation and neonatal death.

Neurological complications diagnosed at discharge were defined as periventricular leukomalacia (PVL), severe intraventricular hemorrhage (grade 3 or 4), or other clinically significant abnormalities such as ventriculomegaly. The causes of fetal death were comprehensively determined by attending obstetricians based on the antenatal clinical course and pathological findings of stillborn infants and placentas.

Results

A total of 38 pregnant women with MM twin pregnancies were included in the study. Table 1 presents baseline characteristics and pregnancy outcomes. Spontaneous abortion occurred in eight women (21%). IUFD occurred in nine women (24%); eight were double fetal demises, the other was a single fetal demise. The presence of umbilical cord entanglement was documented in 34 women (90%). Umbilical cord entanglements were detected antenatally in 25/34 women (74%) and confirmed postnatally in 30/34 women (88%).

Table 2 presents the causes of fetal death. Eleven fetal deaths (65%) were attributed to umbilical cord entanglement. The remaining six fetal deaths were all double IUFDs; they consisted of one pair with twin-to-twin transfusion syndrome, one pair with intrauterine infection, and one pair with unknown etiology.

In 38 MM pregnancies, eight ended in abortion (before 22 weeks) and the remaining 30 MM twins continued gestation after 22 weeks. In 30 MM twins delivered after 22 weeks, planned delivery at 32 to 34 weeks could be performed in 12 women (40%), while 18 women (60%) required earlier delivery of <32 weeks. The indications of earlier delivery of <32 weeks consisted of non-reassuring fetal status (NRFS) in 11 cases, failed tocolysis in three cases, and other indications in four cases. IUFD occurred at 32^{+3} weeks of gestational age in one case.

Table 1 Baseline characteristics and pregnancy outcomes of monoamniotic twin pregnancies

No. pregnancies, *n*	38
Maternal age, median (range)	31 (22–40)
Primipara, *n* (%)	22 (58)
Spontaneous abortion, *n* (%)	8 (21)
Intrauterine fetal death, *n* (%)	9 (24)
Double fetal death, *n* (%)	8 (21)
Single fetal death, *n* (%)	1 (3)
Occurred after 22 weeks of gestation, *n* (%)	1 (3)
Antenatal diagnosis of cord entanglement, *n* (%)	25/34 (74)
Postnatal diagnosis of cord entanglement, *n* (%)	30/34 (88)

Table 2 Causes for 17 fetal deaths

Umbilical cord entanglement, *n* (%)	11 (65)
Twin-to-twin transfusion, *n* (%)	2 (12)
Intrauterine infection, *n* (%)	2 (12)
Unknown, *n* (%)	2 (12)

Table 3 presents the clinical characteristics at birth and short-term prognosis of the infants. The median gestational age at delivery was 31^{+3} (range, 16^{+3}–37^{+0}) weeks and overall survival was 57/76 (76%). For infants delivered after 22 weeks of gestational age, all 60 were delivered by cesarean section, 36 of whom (60%) were delivered by emergency cesarean section. The median gestational age at delivery in 60 infants delivered after 22 weeks was 32^{+3} weeks (range, 25^{+3}–37^{+0}). Fifty-nine (98%) infants were alive at birth; the median birth weight was 1642 g (range: 607–2310) and the median birth weight discordance was 12% (range: 1.3–35.2). Perinatal mortality occurred in one (2%), and two infants expired after the neonatal period. Fifty-seven (95%) infants were alive at discharge and neurological complications at discharge were detected in five infants (8%), including three infants with PVL, one with ventriculomegaly, and one with both PVL and ventriculomegaly. One infant complicated with hypoxic-ischemic encephalopathy (HIE) was delivered from the patient who refused inpatient management; the outcome was an infant death at 11 months of age. The surviving twin from the single IUFD at 32 weeks of gestation had no neurological complications. There were no infants of intraventricular hemorrhage.

Table 3 Clinical characteristics at birth and short-term prognosis of monoamniotic twins

All fetuses	
No. fetuses, *n*	76
Gestational age at delivery, median (range)	31^{+3} (16^{+3}–37^{+0})
Overall survival, *n* (%)	57 (75)
Infants delivered after 22 weeks of gestation	
No. infants, *n*	60
Live birth, *n* (%)	59 (98)
Birth by cesarean section, n (%)	60 (100)
Planned, *n* (%)	24 (40)
Emergency, *n* (%)	36 (60)
Gestational age at delivery, median (range)	32^{+3} (25^{+3}–37^{+0})
Birth weight (g), median (range)	1642 (607–2310)
Birth weight discordance (%), median (range)	12 (1.3–35.2)
Birth weight discordance > 25%, *n* (%)	3 (2)
Perinatal mortality, *n* (%)	1 (2)
Survival at discharge, *n* (%)	57 (95)
Neurological complications at discharge, *n* (%)	5 (8)
Periventricular leukomalacia, *n* (%)	4 (7)†
Ventriculomegaly, *n* (%)	2 (3)†

†One infant had both periventricular leukomalacia and ventriculomegaly.

Discussion

The perinatal mortality rate of MM twins in the present study was 2%, which is far lower than that of older studies;[3] however, it was similar to those reported by Allen *et al.*[5] and Baxi and Walsh[9] (2.8% and 2.4%, respectively). In this context, it is suggested that recent advancements in techniques enable us to diagnose monoamniocity and umbilical cord entanglement antenatally; this is associated with improved outcome.[5,10] Conversely, the overall survival rate in our study was 75%, which was primarily due to spontaneous abortion. Hack *et al.*[7] also reported that MM twin mortality, including fetal deaths during the pre-viable period, was as high as 17% in one of the latest and largest studies.

MM twin pregnancies have two types of potentially hazardous vascular conditions: one is umbilical cord entanglement, and the other is blood flow through placental vascular anastomoses. In the present study, the prevalence of cord entanglement in the cases with fetal death was similar to that of previously reported studies.[6,8] However, Dias *et al.*[11] reported good perinatal outcomes in 18 MM twin pregnancies regardless of antenatal diagnosis of cord entanglement. Determination of the cause of IUFD in MM twin pregnancy may need to be made carefully. Hack *et al.*[7] reported that only two fetal deaths could be attributed to cord entanglement among 14 IUFD MM twin fetuses, while the cause of death for seven fetuses was unknown. In regard to umbilical cord entanglement, which presents in the majority of MM cases,[6,11,12] the prevalence in our series is consistent with that of a recent review (66.2–96.2%).[10] Some investigators have reported that cord entanglements can be detected antenatally in the first half of pregnancy.[9,13] It is theorized that cord entanglements are initially loose, but have the potential to tighten and cause fetal injury or death.[10]

Quinn *et al.*[14] postulated that the transition from loose cord entanglements to complete cord occlusion may be a subacute event that can be predicted and prevented with intermittent monitoring. Reportedly, inpatient management appears to reduce fetal mortality and neonatal morbidity after the period of viability.[5,8,15,16] In our study, one neonate suffered from HIE subsequent to birth under outpatient management; however, we could not determine whether inpatient

management would have prevented this complication. Despite that case, inpatient management from the period of viability onward appears to be reasonable, because emergency delivery was frequently required after 24 weeks, primarily due to an NRFS. Conversely, there was one single IUFD at 32 weeks of gestation under inpatient management. To prevent fetal loss after 32 weeks of gestation, a few studies support elective delivery at 32 weeks.[17,18] However, others do not, in view of the high neonatal morbidity due to prematurity.[11,15] Fetal surveillance to extend the prenatal period is a controversial topic subject to much debate.

Our data revealed a neonatal neuromorbidity rate of 8%, which coincides with previous studies reporting a rate ranging from 5.0–8.7%.[7,15,16] However, the details regarding neurological complications vary slightly in each study. For example, PVL was the most frequent neurological complications in our study, whereas DeFalco *et al.*[16] reported that all were cases of intraventricular hemorrhage. Despite that, the degree of prematurity appears to be critical for neurological prognosis of MM twin infants.

Our study has some limitations. Because it was not a population-based study, the spontaneous abortion rate of MM twins may have been underestimated because cases that occurred before referral to our center would not be included. In addition, the perinatal management strategy, particularly after 32 weeks of gestation, was somewhat different for each case because this was a retrospective, multi-center study.

In conclusion, the management of MM twin gestation aimed for delivery at 32 weeks or more would be advisable. This management should include fetal monitoring and emergency delivery if indicated. However, we could not demonstrate whether it was reasonable to prolong the gestational period past 32 weeks. Further research is indicated in order to establish the optimal timing of delivery for MM twins.

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Disclosure

No author has any potential conflict of interest.

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ORIGINAL ARTICLE

Chorioamniotic membrane separation after fetoscopic laser surgery for twin–twin transfusion syndrome

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ABSTRACT

Objective The purpose of our study was to investigate the incidence of chorioamniotic membrane separation (CMS) after fetoscopic laser surgery and the association between CMS and preterm premature rupture of membranes (pPROM). We also analyzed the risk factors associated with the occurrence of CMS.

Method Retrospective cohort study of 148 patients with twin–twin transfusion syndrome who underwent laser surgery at our institution from March 2003 to December 2009.

Results Chorioamniotic membrane separation occurred in 29 of 148 (19.6%) patients. The presence of CMS strongly correlated with pPROM prior to 28 weeks' gestation. Multivariate analysis of the risk factors of pPROM <28 w showed for CMS an odds ratio (OR) of 7.01 (95% confidence interval (CI): [1.46; 33.60], $p=0.015$). Posterior placentation correlated with the occurrence of CMS (OR: 4.17, 95% CI: [1.39; 12.49], $p=0.01$) and the recipient's deepest vertical pocket (OR: 1.38, 95% CI: [1.03; 1.86], $p=0.03$). There was however no measurable impact of CMS on gestational age at delivery, neither on survival.

Conclusion Chorioamniotic membrane separation occurs in approximately 20% of patients following fetoscopic laser surgery for twin–twin transfusion syndrome and is associated with pPROM <28 w. Posterior location of the placenta coincided with an elevated risk for CMS. © 2012 John Wiley & Sons, Ltd.

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Conflicts of interest: None declared

INTRODUCTION

Twin–twin transfusion syndrome (TTTS), which occurs in 10% of monochorionic twin pregnancies, is associated with high perinatal morbidity and mortality.[1,2] Fetoscopic laser surgery (FLS) improves the outcome of TTTS and has gained worldwide acceptance as the first line of treatment for TTTS between 16 and 26 weeks of gestation.[1,2] However, preterm delivery remains a common problem and may compromise outcome.

Chorioamniotic membrane separation (CMS) is a detachment between the amniotic and chorionic membranes (Figure 1). Although CMS may sometimes occur naturally, it is typically iatrogenic, for example, as a consequence of prenatal diagnostic and therapeutic procedures.[3] CMS is reportedly associated with an increased risk of preterm premature rupture of membranes (pPROM) and preterm labor.[4] CMS can obviously also occur following FLS. However, there have been only few reports on CMS as a perioperative complication of invasive procedures in monochorionic twins with respect to the outcomes of pregnancies among patients with this condition.[5–8]

The purpose of our study was to investigate the incidence of CMS after FLS and the association between CMS and preterm PROM. We also investigated whether we could define risk factors associated with CMS and outcomes of patients with CMS.

METHODS

This was a single center, retrospective cohort study on 178 patients with TTTS who underwent FLS from March 2003 to December 2009. We had follow up on 148 patients until after birth. The diagnosis and staging of TTTS was based on the Quintero staging.[9] All patients provided written consent to undergo FLS. This study was approved by the ethics committee of our institution.

The FLS procedure has been described elsewhere.[2,10] Briefly, all procedures were performed percutaneously under regional or general anesthesia. We utilized general anesthesia in the first 62 patients, whereafter we moved to regional anesthesia to minimize the side effects in pregnant women. An entry site in the maternal abdomen was chosen to allow access to the placental surface through the recipient's sac. We used the

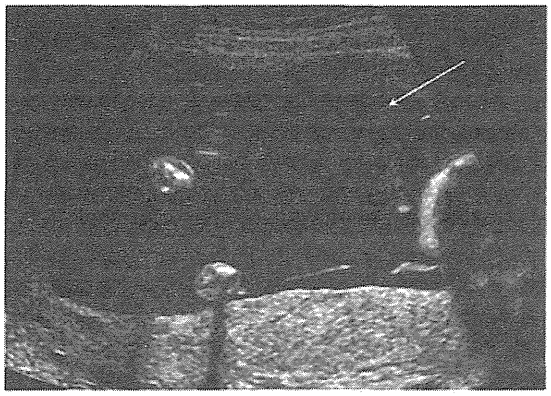

Figure 1 Ultrasound demonstrating chorioamniotic membrane separation noted after laser surgery for twin–twin transfusion syndrome. The white arrow indicates the separated layer

method of direct entry with a diamond-point metal trocar inserted through an 11-Fr (3.4 mm) disposable cannula (RCF-11.0-38-J; Cook Urological Inc., Bloomington, IN) under ultrasound guidance (SD5500; Aloka, Japan). We used a 2.0-mm fetoscope within a 3.0-mm sheath (11630AA/26008AA/11630KH/26161U; Karl Storz, Tuttlingen, Germany). During surgery, saline was infused to prevent coagulation of debris at the tip of the laser fiber and to visualize placental vessels. After the anastomotic vessels were identified and coagulated, amniotic fluid was passively reduced at the end of the procedure. Magnesium sulfate for tocolysis and cefazolin sodium were prophylactically given to all patients. All procedures were done by two operators in alternate shifts.

We reviewed the charts of patients treated with FLS to determine the preoperative obstetrical findings, prior procedures, perioperative findings, and postoperative courses. Postoperatively patients were followed by sonographic examinations every week through the remainder of pregnancy. CMS was defined as an apparent detachment of the amniotic membranes from chorionic membranes. The extent of detachment was not included in the definition of CMS. Preterm PROM was defined as apparent clinical leakage of amniotic fluid from the vagina before 28 and 34 weeks of gestation, which was confirmed by positive nitrazine testing.

We analyzed the risk factors associated with pPROM prior to 28 weeks' gestation as a critical time period in terms of patient outcome. Pearson's chi-squared test and Fisher's exact test were used to compare categorical variables. Wilcoxon's rank sum test and the *t* test were applied to compare means of continuous variables between groups. Univariate and multivariable logistic regression analyses were performed to identify the determinants of CMS and to estimate the effect of CMS on pPROM. A stepwise selection procedure with $p=0.1$ as the entry probability was used to build the multivariable logistic regression model. The odds ratio (OR) for each variable in the final model along with its 95% confidence interval (CI) and *p* value are reported. All statistical analyses were conducted using Statistical Package for the Social Science version 18.0.0 (SPSS Inc., Chicago, IL). Two-sided *p* values of <0.05 were considered statistically significant.

RESULTS

Patient characteristics are shown in Table 1. The mean gestational age at the time of surgery was 21.7 weeks. The number of patients who reached the 28-week and 34-week points was 129 and 67, respectively. Most of the cases (72%) were Quintero stage 3 or 4. CMS occurred in 19.6% of patients. Seventy-six percent of CMS occurred within 2 weeks after surgery; the time at which CMS was found did not correlate with pPROM prior to 28 weeks (data not shown). The incidence of pPROM (<34 w) was 16.2%, and when confined to pPROM prior to 28 weeks' gestation, the incidence was 8.1%.

Next, we analyzed the risk factors related to pPROM prior to 28 weeks (Table 2). Univariate analysis showed that amnioreduction before surgery and the presence of CMS strongly correlated with pPROM prior to 28 weeks. Also, variables such as operative time and amnioinfusion volume affected the outcome. Receiver operating characteristic curve analysis showed an area under the curve of 0.82, and the optimal cut-off value at which a sensitivity of 91% and specificity of 69% were achieved was an amnioinfusion volume of 500 mL. Multivariate analysis of the risk factors of pPROM within 28 weeks' gestation showed that amnioreduction before surgery and the presence of CMS were significant risk factors. ORs were each 30.21 (95% CI: [3.31; 275.73]) and 7.01 (95% CI: [1.46; 33.60]). Gestational age at FLS did not correlate with pPROM prior to 28 weeks.

Table 1 Patient characteristics ($n=148$)

Incidence of CMS	29 (19.6%)
<2 week after surgery	22 (75.9%)
2–4 weeks	7 (24.1%)
≥4 weeks	0 (0%)
Maternal age[a] mean ± SD	31.6 ± 4.5
Parity[b] median (Range)	0 (0–6)
Cervical length before surgery (mm)[a] mean ± SD	30.9 ± 7.8
Amnioreduction before surgery[c]	7 (4.8%)
Preoperative recipient MVP (cm)[a] mean ± SD	10.3 ± 1.9
Location of placenta[d]	
Posterior	87 (58.8%)
Anterior	61 (41.2%)
TTTS stage[c]	
I	25 (16.9%)
II	16 (10.8%)
III	91 (61.5%)
IV	16 (10.8%)
Gestational age at FLS (wk)[a] Mean ± SD	21.72 ± 2.21
Recipient MVP after FLS (cm)[a] Mean ± SD	6.3 ± 1.7
Preterm PROM (<34 wk)[c]	24 (16.2%)
Preterm PROM (<28 wk)[c]	12 (8.1%)
Gestational age at delivery (wk)[a] Mean ± SD	32.6 ± 3.2

[a] *t* test.
[b] Wilcoxon rank-sum test.
[c] Fisher's exact test.
[d] Pearson's χ^2 test.

Table 2 Univariate and multivariable logistic regression models evaluating risk factors associated with preterm PROM (<28 weeks' gestation)

	Univariate analysis			Multivariate analysis[a]		
Covariate	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
Maternal age	1.04	0.91 to 1.19	0.57			
Parity	1.37	0.82 to 2.29	0.23			
Body mass index	1.03	0.87 to 1.23	0.7			
Cervical length before surgery	1.007	0.94 to 1.09	0.85			
Amnioreduction before surgery						
No	1					
Yes	10.92	2.11 to 56.40	0.004	30.21	3.31 to 275.73	0.003
Preoperative recipient MVP	1.09	0.81 to 1.47	0.56			
Location of placenta						
Anterior	1					
Posterior	0.68	0.21 to 2.22	0.52			
TTTS stage						
I	1					
II	0.77	0.06 to 9.22	0.83			
III	0.81	0.15 to 4.29	0.81			
IV	2.65	0.39 to 18.00	0.32			
Anesthesia						
Regional anesthesia	1					
General anesthesia	1.48	0.45 to 4.84	0.52			
Gestational age at FLS (wk)	1.07	0.82 to 1.40	0.61			
Operative time (per 10 min)	1.19	1.02 to 1.40	0.03			
Amnioinfusion volume (per 100 mL)	1.11	1.03 to 1.18	0.004	1.12	1.04 to 1.21	0.004
Amnioreduction volume (mL)	1.001	1.000 to 1.001	0.09			
Intraperitoneal leakage						
No	1					
Yes	1.26	0.15 to 10.90	0.83			
Recipient MVP after FLS	1.12	0.8 to 1.57	0.51			
CMS						
No	1			1.00		
Yes	3.33	0.98 to 11.40	0.06	7.01	1.46 to 33.60	0.015

[a]A stepwise selection with $p=0.1$ as entry probability was used in the multivariate logistic analysis.
The variable history of preterm labor was not included because there was no patient with a history of preterm labor in the preterm PROM (<28 weeks' gestation) group.

We also identified risk factors related to the incidence of CMS (Table 3). Univariate analysis showed that the location of the placenta strongly correlated with the occurrence of CMS. The occurrence of CMS was about four times higher in patients with posterior placentation (OR: 4.17, 95% CI: [1.39; 12.49], $p=0.01$), which was present in half of our cases (87/148, 58.8%). Recipient deepest vertical pocket (DVP) after FLS was also correlated with the occurrence of CMS (OR: 1.38, 95% CI: [1.03; 1.86], $p=0.03$). Gestational age at FLS did not correlate with the incidence of CMS. The incidence of CMS was approximately 20% at any period and did not differ by operator (data not shown).

Finally, we determined the outcome of patients with or without CMS (Table 4). Gestational age at pPROM was significantly earlier in patients with CMS (25.6 ± 2.9 vs 29.1 ± 3.1 w, respectively; $p=0.03$). All patients with CMS who developed pPROM prior to 28 weeks' gestation delivered by 32 weeks (data not shown). The rate of pPROM (<34 w) was 24% in the CMS group. Gestational age at delivery and the interval between FLS and delivery did not differ between the two groups. There was also no statistical difference in the survival rate of fetuses after surgery.

DISCUSSION

In this study, the incidence of CMS was approximately 20% among patients with TTTS treated with FLS. Patients with CMS were seven times more likely to rupture membranes prior to 28 weeks. Amnioreduction before surgery also strongly

Table 3 **Univariate and multivariable logistic regression models evaluating risk factors associated with CMS**

	Univariate analysis			Multivariate analysis[a]		
Covariate	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
Maternal age	0.99	0.91 to 1.09	0.86			
Parity	1.12	0.74 to 1.71	0.59			
Body mass index	0.92	0.80 to 1.06	0.24			
Cervical length before surgery (mm)	1.01	0.96 to 1.06	0.8			
Preoperative recipient MVP (cm)	1.03	0.82 to 1.28	0.82			
Location of placenta						
Anterior	1.00			1		
Posterior	3.83	1.36 to 10.81	0.01	4.17	1.39 to 12.49	0.01
TTTS stage						
I	1.00					
II	1.44	0.36 to 5.84	0.61			
III	0.68	0.23 to 1.96	0.47			
IV	0.45	0.08 to 2.59	0.37			
Anesthesia						
Regional anesthesia	1.00					
General anesthesia	1.02	0.44 to 2.32	0.97			
Gestational age at FLS (wk)	0.96	0.79 to 1.15	0.64			
Operative time (per 10 min)	0.92	0.80 to 1.07	0.27			
Amnioinfusion volume (per 100 mL)	1.02	0.96 to 1.08	0.49			
Amnioreduction volume (mL)	1.00	0.999 to 1.00	0.52			
Intraperitoneal leakage						
No	1.00					
Yes	0.43	0.05 to 3.53	0.43			
Recipient MVP after FLS (cm)	1.02	0.98 to 1.05	0.08	1.38	1.03 to 1.86	0.03

[a]A stepwise selection with $p=0.1$ as entry probability was used in multivariate logistic analysis.
The variables history of preterm labor and amnioreduction before surgery were not included because there was no patient with a history of preterm labor or amnioreduction before surgery in the CMS group.

correlated with pPROM prior to 28 weeks. The risk factors for the incidence of CMS were posterior placentation and a larger recipient DVP after FLS. However, gestational age at delivery did not differ with or without CMS, and there was no statistical difference in the survival rate of fetuses.

The incidence of spontaneous CMS has been reported to range from 1/187 to 1/4333.[11–13] However, CMS is more likely after invasive procedures, with a reported incidence of CMS of 10% after amniocentesis.[4,14] Following fetoscopic laser surgery Papanna *et al.* observed a 19.6% incidence of CMS; a

Table 4 **Outcome of patients with or without chorioamniotic membrane separation**

	CMS+ ($n=29$)	CMS− ($n=119$)	*P*
Gestational age at preterm PROM	25.6±2.9	29.1±3.1	0.03
Preterm PROM <28 w	5 (17.2%)	7 (5.9%)	0.06
Preterm PROM <34 w	7 (24.1%)	17 (14.3%)	0.26
Gestational age at delivery (wk)[a] Mean±SD	31.9±4.5	32.7±4.0	0.33
Period from FLS to delivery (d)[a] Mean±SD	72.5±35.5	76.8±33.7	0.54
Survival at 28 days			
0 survivors	3 (10.4%)	7 (5.9%)	0.41
1 survivor	9 (31.0%)	23 (19.3%)	0.26
2 survivors	17 (58.6%)	89 (74.8%)	0.13
At least 1 survivor	26 (89.7%)	112 (94.1%)	0.41

[a]*t* test.

number that was similar in our series.[5] Seventy-six percent of CMS occurred within 2 weeks after FLS.

Chorioamniotic membrane separation is a risk factor for pPROM.[3,4,15–17] In the series of Papanna *et al.*, 70% of patients with CMS developed pPROM (<34 w); however, that was only 24% in our (n=7) series.[5] However, 71% of pPROM occurred prior to 28 weeks of gestation; 17% of these patients had prior CMS. In our series, 12 patients developed pPROM prior to 28 weeks' gestation, and 7 did not have CMS. The occurrence of CMS is, however, a significant risk factor for pPROM prior to 28 weeks (OR = 7.01). In addition, the gestational age at pPROM was significantly earlier in patients with CMS than in those without CMS.

Other risk factors for pPROM prior to 28 weeks' gestation were amnioreduction before FLS and amnioinfusion volume during surgery. Early in the experience, amnioreduction was often performed before referral for FLS. After the establishment of FLS as the first-line treatment for TTTS, there were no further cases of amnioreduction before FLS. The optimal cut-off value of amnioinfusion volume for pPROM prior to 28 weeks' gestation was 500 mL.

Next, we analyzed risk factors associated with the occurrence of CMS. Posterior placentation was four times more likely to be associated with CMS. One report suggested that CMS may be more frequent after amniocentesis in cases in with a posterior placenta.[18] The distance between an entry site and the placenta may be associated with the occurrence of CMS. As the distance extends, membrane tenting may be more likely to occur. In another report, membrane tenting caused CMS upon penetration of the membrane during amniocentesis.[4] We therefore attempt to insert the trocar vertical to the uterine wall to avoid tenting. Theoretically, one might also consider to enter the uterus closer to the margin of the placenta although that compromises visualization of the entire placental surface.

Recipient DVP after FLS was also a risk factor for the occurrence of CMS. Amniotic fluid volume is related to amniotic pressure.[19] Insufficient reduction may leave a higher amniotic fluid pressure, hence leakage through the hole, and as such spreading of the membrane separation – though this is hypothetical. As a limitation, only a direct trocar method was adopted in our center. In the report by Papanna *et al.*, there was no difference in the method of trocar entry (direct trocar method or Seldinger method), but the method of entry may play an important role in the incidence of CMS. In addition, the diameter of the cannula may play an important role in the incidence of CMS. We used only 11-Fr cannulas.

Although CMS is a risk factor for pPROM prior to 28 weeks, and all patients with CMS who developed pPROM prior to 28 weeks' gestation delivered by 32 weeks, there was no difference in the outcome of fetuses with or without CMS. There are two possible reasons for this. In our center, only 8% of patients developed pPROM <28 w, and even in patients with CMS, the rate of pPROM <28 w was only 17%. With such low rate of pPROM, hence preterm birth rate, this may not have caused any measurable difference in the outcome of fetuses.

In conclusion, CMS in TTTS treated by FLS is a frequent complication, and is associated with pPROM prior to 28 weeks' gestation.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Chorioamniotic membrane separation (CMS) after fetoscopic laser surgery (FLS) occurs in 20% of patients and is related to preterm premature rupture of membranes and preterm labor.

WHAT DOES THIS STUDY ADD?

- We confirmed that the incidence of CMS is 20% after FLS.
- Chorioamniotic membrane separation is associated with pPROM prior to 28 weeks' gestation.
- The risk factors related to the incidence of CMS are the location of the placenta and recipient deepest vertical pocket after FLS.

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Original Article

Prognostic factors of congenital diaphragmatic hernia accompanied by cardiovascular malformation

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Abstract ***Background***: Congenital diaphragmatic hernia is associated with cardiovascular malformation. Many prognostic factors have been identified for isolated congenital diaphragmatic hernia; however, reports of concurrent congenital diaphragmatic hernia and cardiovascular malformation in infants are limited. This study evaluated congenital diaphragmatic hernia associated with cardiovascular malformation in infants. Factors associated with prognosis for patients were also identified.

Methods: This retrospective cohort study was based on a Japanese survey of congenital diaphragmatic hernia patients between 2006 and 2010. Frequency and outcome of cardiovascular malformation among infants with congenital diaphragmatic hernia were examined. Severity of congenital diaphragmatic hernia and cardiovascular malformation were compared as predictors of mortality and morbidity.

Results: Cardiovascular malformation was identified in 76 (12.3%) of 614 infants with congenital diaphragmatic hernia. Mild cardiovascular malformation was detected in 19 (33.9%) and severe cardiovascular malformation in 37 (66.1%). Their overall survival rate at discharge was 46.4%, and the survival rate without morbidity was 23.2%. Mortality and morbidity at discharge were more strongly associated with severity of cardiovascular malformation (adjusted OR 7.69, 95%CI 1.96–30.27; adjusted OR 7.93, 95%CI 1.76–35.79, respectively) than with severity of congenital diaphragmatic hernia.

Conclusions: The prognosis for infants with both congenital diaphragmatic hernia and cardiovascular malformation remains poor. Severity of cardiovascular malformation is a more important predictive factor for mortality and morbidity than severity of congenital diaphragmatic hernia.

Key words cardiac anomaly, diaphragmatic hernia, liver herniation, prognostic factor.

In recent years, outcomes in patients with isolated congenital diaphragmatic hernia (CDH) have markedly improved because of advances in perinatal management. Some studies have reported overall survival and intact survival rates exceeding 80% and 60%, respectively.[1–3] However, CDH is also known to be associated with other congenital malformations. Cardiovascular malformation (CVM) is found in 10–20% of infants with CDH.[4,5] Some reports have shown higher mortality rates in infants with both CDH and CVM than in those with CDH alone.[6,7]

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Many prognostic factors, such as liver herniation, lung-to-head ratio, Apgar score, and pulmonary artery size, have been previously evaluated for their association with isolated CDH. These factors are important for counseling of parents or management in the perinatal period.[8–12] However, in infants with both CDH and CVM, the association of the severity of these conditions with mortality and morbidity remains uncertain. This study evaluated the incidence and outcome of CDH associated with CVM and factors influencing the prognosis for infants with CDH and CVM were also examined.

Methods

This study was approved by the ethics committees of the National Center for Child Health and Development, Nagoya University Hospital, Osaka University Graduate School of Medicine, Hyogo College of Medicine, Osaka Medical Center and Research

Institute for Maternal and Child Health, Osaka University Hospital and Graduate School of Medical Sciences, and Kyushu University. A questionnaire was distributed to the departments of pediatric surgery and/or tertiary perinatal care centers of 159 educational hospitals. The survey inquired about infants with CDH born between 2006 and 2010. Of the 159 institutes invited to participate, 109 (68.8%) responded to the questionnaire. Of these, 26 institutes reported no CDH cases and 11 refused to participate in the survey, although some cases of CDH were treated at these institutes. Thus, the final sample included 72 institutes in which 614 CDH cases were treated during the study period.

Data from the CDH survey were combined with data from a nationwide survey conducted in Japan. All infants described as having cardiac defects were selected for review. Infants with patent foramen ovale, atrial septal defects, patent ductus arteriosus, and hemodynamically insignificant vascular malformation (including right aortic arch) were excluded from the review. The incidence of CVM among infants with CDH identified in the hospital survey was examined.

Factors influencing mortality and morbidity in infants with both CDH and CVM were assessed using multivariate analysis. Infants with trisomy 13 or trisomy 18 and those who received palliative care after birth were excluded from the analysis of prognostic factors. Severe CVM was defined as hemodynamically significant heart disease requiring surgical intervention. Severe CDH was defined as liver herniation. In infants with more than two CVM, the anomaly most likely to affect outcome was adopted. In addition, survival without morbidity was defined as no need for respiratory support, including oxygen supplementation, tube feeding, parenteral nutritional support, or vasodilation.[3]

All data were analyzed using the statistical software program Stat Flex for Windows version 6.0 (Artec, Osaka, Japan). Univariate analysis was performed to identify differences between survivors and non-survivors and differences between infants with and without morbidity at discharge or death. The χ^2-test, Fisher's exact test, the 2-sample test, and the Mann–Whitney nonparametric test were selected as appropriate. Multiple logistic regression analysis was performed to evaluate the association of CDH and CVM severity with mortality and morbidity. Mortality was defined as death during hospitalization. Statistical significance was set at $P < 0.05$.

Results

CVM was identified in 76 of the 614 (12.3%) infants. Life-limiting genetic defects were identified in 14 infants (trisomy 13, $n = 4$; trisomy 18, $n = 10$). Palliative care for severe CVM, trisomy 21, heterotaxia, or tracheal stenosis was administered in six cases, and full intervention was required in 56 cases. Mild CVM was detected in 19 (33.9%) of these 56 infants and severe CVM in 37 (66.1%) (Fig. 1).

Details of the 76 infants with CVM are provided in Table 1. Ventricular septal defect (VSD) was identified in four of the infants with trisomy 13 or trisomy 18, three infants with tetralogy of Fallot (TOF) and double-outlet right ventricle (DORV) with right ventricular outflow tract obstruction (RVOTO), and four

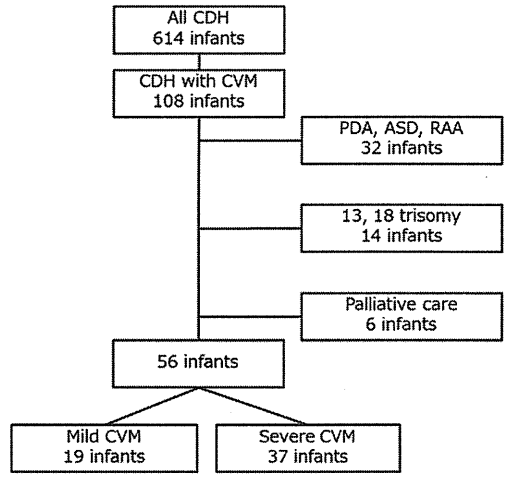

Fig. 1 Diagram summarizing the study population. ASD, atrial septal defect; CHD, congenital diaphragmatic hernia; CVM, cardiovascular malformation; PDA, patent ductus arteriosus; RAA, right aortic arch.

infants with DORV without RVOTO. The majority of infants with mild CVM had VSD ($n = 14$, 73.7%).

The overall survival rate at discharge of the infants with CVM who required full intervention was 46.4% (26/56). This rate for those with mild CVM and severe CVM was 77.8% (14/18) and 31.6% (12/38), respectively. The overall usage rate of extracorporeal membrane oxygenation (ECMO) and nitric oxide inhalation (iNO) were 8.9% (5/56) and 71.4% (40/56), respectively. On the other hand, the overall survival rate without morbidity at discharge was 23.2% (13/56). For those with mild and severe CVM, this rate was 50.0% (9/18) and 10.5% (4/38), respectively. Morbidities at discharge included use of supplemental oxygen ($n = 10$), tube feeding ($n = 6$), and vasodilation ($n = 4$). No ventilation, tracheostomy, or total parenteral nutrition was required at discharge for any of the patients.

Univariate analysis revealed that severe CVM was found significantly more frequently in non-survivors than in survivors (86.7% vs 46.2%, $P = 0.001$). However, no significant difference between survivors and non-survivors was observed for the other variables (including liver herniation, which was used to represent severity of CDH) (Table 2). Severe CVM was significantly more frequent in infants with morbidity at discharge or in non-survivors than in survivors without morbidity at discharge (79.1% vs 30.8%, $P = 0.001$) (Table 3). The adjusted OR for mortality in infants with CDH associated with CVM was 7.69 (95%CI 2.00–30.27) for infants with severe CVM and 0.49 (95%CI 0.12–1.91) for those with liver herniation. Morbidity in infants with CDH associated with CVM was calculated as 7.93 (95%CI 1.76–35.79) for those with severe CVM and 0.82 (95%CI 0.15–4.63) for those with liver herniation (Table 4).

In a subgroup analysis, the survival rate of infants with VSD was 72.2% (13/18); however, that of infants with the other CVM was <50%. No infants with hypoplastic left heart syndrome (HLHS) survived. In contrast, the intact survival rate in infants

Table 1 Types of cardiac defects observed in patients with CDH and CVM

n	13, 18 trisomy	Palliative care	Full intervention		Overall CVM
			Severe CVM	Mild CVM	
	14	6	37	19	76
VSD	4	2	5	14	25 (32.9%)
TOF or DORV with RVOTO	3	–	8	1	12 (15.8%)
DORV without RVOTO	4	–	4	–	8 (10.5%)
CoA or IAA	1	–	4	3	8 (10.5%)
HLHS	–	1	6	–	7 (9.2%)
SV	1	2	4		7 (9.2%)
PS or PA	–	–	1	1	2 (2.6%)
AVSD	1	–	1	–	2 (2.6%)
TAPVR	–	–	1	–	1 (1.3%)
TGA	–	–	1	–	1 (1.3%)
Truncus arteriosus	–	1	–	–	1 (1.3%)
TA	–	–	1	–	1 (1.3%)
TV dysplasia	–	–	1	–	1 (1.3%)

AVSD, atrioventricular septal defect; CDH, congenital diaphragmatic hernia; CoA, coarctation of the aorta; CVM, cardiovascular malformation; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interruption of the aortic arch; PA, pulmonary atresia; PS, pulmonary stenosis; RVOTO, right ventricular tract obstruction; SV, single ventricle; TA, tricuspid valve atresia; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

with VSD was 38.9% (7/18). The intact survival rate in infants with other CVM was very low (Table 5).

Discussion

Results of this report showed that CVM was concurrent with CDH in 12% of infants included in this study during this period. Ninety percent of infants with CVM (except those with trisomy 13 and trisomy 18) underwent full intervention. Despite this intervention, overall and intact survival rates at discharge were extremely poor (46% and 23%, respectively). VSD was the most common cardiac defect, and left-sided heart disease and conotruncal anomalies, such as TOF and DORV, were also common. Severe CVM was more closely associated with mortality and morbidity at discharge than liver herniation, which represented severe CDH in this study. The survival rate of infants with VSD was about 70%; however, less than 50% of infants with other types of CVM survived. In addition, even infants with VSD had low intact survival rate.

Table 2 Clinical characteristics of survivors and non-survivors. Data are presented as mean values ± SD or median values and (Q1–Q3)

Variables	Survivors	Non-survivors	*P*
Number of infants	26	30	
GA (wk)	37.7 ± 2.0	36.9 ± 2.9	0.254
BW(g)	2259 ± 517	2447 ± 623	0.229
Apgar score at 1 min	3 (2–5)	3 (2–4)	0.172
Apgar score at 5 min	5 (3–6)	5 (3–6)	0.418
Female	13 (50.0%)	17 (56.7%)	0.618
Vaginal delivery	6 (23.1%)	4 (13.3%)	0.738
Prenatal diagnosis	20 (76.9%)	25 (83.3%)	0.547
CDH left	24 (92.3%)	27 (90.0%)	1.000
Liver herniation	8/26 (30.8%)	7/26 (26.9%)	0.760
Severe CVM	12 (46.2%)	26 (86.7%)	0.001

BW, birthweight; CDH, congenital diaphragmatic hernia; CVM, cardiovascular malformations; GA, gestational age.

In various studies, the prevalence of CVM ranges from 8 to 13 per 1000 live births.[13,14] However, a recent study suggested a much higher prevalence of CVM (50 per 1000 live births).[15] The

Table 3 Clinical characteristics of infants according to status at discharge. Data are presented as mean values ± SD or median values and (Q1–Q3)

Variables	Survival without morbidity	Survival with morbidity or death	*P*
Number of infants	13	43	
GA (wk)	37.4 ± 1.6	37.2 ± 2.7	0.787
BW(g)	2158 ± 535	2421 ± 584	0.154
Apgar score at 1 min	4 (3–6.3)	3 (2–4)	0.047
Apgar score at 5 min	5 (5–7)	5 (2.3–6)	0.068
Female	8 (61.5%)	22 (51.1%)	0.511
Vaginal delivery	1 (7.7%)	9 (20.9%)	0.424
Prenatal diagnosis	11 (84.6%)	34 (79.1%)	0.721
CDH left	12 (92.3%)	39 (90.7%)	1.000
Liver herniation	3/13 (23.1%)	12/39 (30.8%)	0.733
Severe CVM	4 (30.8%)	34 (79.1%)	0.001

BW, birthweight; CDH, congenital diaphragmatic hernia; CVM, cardiovascular malformations; GA, gestational age.

Table 4 Association of severity of CVM and CDH with status at discharge (multivariable logistic regression). Variables were adjusted for gestational age, prenatal diagnosis, and Apgar score at 1 min

Variables	Mortality		Morbidity	
	Adjusted OR	95%CI	Adjusted OR	95%CI
Severe CVM	7.69	2.00–30.27	7.93	1.76–35.79
Liver herniation	0.49	0.12–1.91	0.82	0.15–4.63

CVM, cardiovascular malformation.

Table 5 Survival rates with and without morbidity at discharge for infants with CDH according to presence and type of cardiac defect

		n	Survivors	Survivors without morbidity
CDH with CVM	Overall	56	26 (46.4%)	13 (23.2%)
	Severe	38	12 (31.6%)	4 (10.5%)
	Mild	18	14 (77.8%)	9 (50.0%)
VSD		18	13 (72.2%)	7 (38.9%)
TOF or DORV with RVOTO		9	3 (33.3%)	1 (11.1%)
DORV without RVOTO		5	2 (40.0%)	1 (20%)
CoA or IAA		7	3 (42.9%)	2 (28.6%)
HLHS		6	0	0
SV		4	2 (50%)	0
PS or PA		2	1 (50%)	1 (50%)
AVSD		1	0	0
TAPVR		1	0	0
TGA		1	1 (100%)	0
TA		1	1 (100%)	1 (100%)
TV dysplasia		1	0	0

AVSD, atrioventricular septal defect; CDH, congenital diaphragmatic hernia; CoA, coarctation of the aorta; CVM, cardiovascular malformation; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interruption of the aortic arch; PA, pulmonary atresia; PS, pulmonary stenosis; RVOTO, right ventricular tract obstruction; SV, single ventricle; TA, tricuspid valve atresia; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

present study detected a frequency of CVM associated with CDH of about twice as high as that in the general population. The frequency of this study (12%) was similar to that identified by the Congenital Diaphragmatic Hernia Study Group (CDHSG) (10.5%).[5] In the assessment of types of CVM, VSD was the most common in both studies (this study 32%, CDHSG study 42%). The frequency of left-sided heart disease, including HLHS, was 28% in the CDHSG study, which was higher than that identified in the present study (19.7%). Some reports have shown a lower frequency of left-sided heart disease in Asia than in Western countries. Thus, the discrepancy between our results and those of the CDHSG study may be because of differences in race.[15,16] In Japan, left-sided heart disease accounts for about 3% of all CVM, which suggests that the frequency of left-sided heart disease associated with CDH is extremely high, even in the Japanese population.[15,17]

In a study of major structural non-cardiac anomalies identified with CVM, Miller *et al.* reported a frequency of 15% for left-sided heart disease associated with all congenital anomalies. In another study, the frequency of left-sided heart disease associated with CDH was reported as 27%.[18] The higher incidence of left-sided heart disease may reflect the limited flow through the left side of the heart due to direct compression of herniated structures and decreased pulmonary blood flow caused by lung compression. In the present study, all infants with left-sided heart disease also had left-sided CDH, which supports this theory.[19,20]

In this study, numerous conotruncal anomalies, such as TOF and DORV, were observed, accounting for about 30% of all CVM. Trisomy 13 and trisomy 18 have been strongly associated with conotruncal anomalies.[21] Our sample included 14 infants with trisomy 13 and trisomy 18, half of whom had TOF or DORV. This may be one of the causes of the high frequency of conotruncal anomalies.

Many studies have reported associations between the prognosis for patients with isolated CDH and several predictors, such as lung-to-head ratio, liver herniation, low birthweight, Apgar score, pulmonary artery diameter, and best PaO_2 value.[8–12,22] This study found no association between liver herniation (used to represent severe CDH) and mortality and morbidity. However, the results indicated that severity of CVM was an independent risk factor for mortality and morbidity at discharge.

In this study, the survival rate of infants with mild CVM was about 80%, the same as that for isolated CDH (84%) in our survey.[23] On the other hand, the survival rate of infants with severe CVM was about 30% and of infants without morbidity was just 10%. This result suggests that the prognosis remains poor in infants with CDH concurrent with CVM despite improvements in outcomes in cases with isolated CDH. Furthermore, in our survey, the usage rates of ECMO and iNO in all CDH were 7.0% and 56.2%, respectively.[23] The usage rates among infants with both CDH and CVM tended to be higher than those among all CDH.

The survival rate was relatively favorable in infants with VSD (72%) but not in infants with other types of CVM (<50%). In infants with VSD, cyanosis rarely develops. However, in infants with univentricular anatomy, DORV, and pulmonary stenosis, cyanosis could develop easily even without CDH. Furthermore, in such patients, hypoxia could get worse because of presence of CDH. It may be one of the causes that infants with CDH and such types of CVM have poorer prognosis than those with VSD.

In this study, none of the six infants with HLHS survived. Termination of labor and palliative care after birth may be considered in cases associated with HLHS. Although the survival rate of infants with VSD was favorable, only 40% of infants were discharged from hospital without morbidities. This may be important information for parents of infants with this defect.

Completion of Fontan circulation is difficult for infants with CVM in whom biventricular repair is also difficult. Residual pulmonary hypertension complicates this situation. Therefore, 3- or 5-year survival rates may be lower than the survival rate at discharge used in this study. To our knowledge, no previous cases have been reported of survival in infants with cavopulmonary anastomosis and CDH. Long-term follow up in patients with these conditions is required.

This study has several limitations. First, detailed information regarding treatment was not included. This study was based on data from a retrospective national survey of infants with CDH that did not include this information. Second, severity of CVM was defined on the basis of hemodynamic significance. However, this decision may have differed between facilities, and thus, assessment of disease severity may not have been uniform. Third, the end-point of the study was at discharge; therefore, intracardiac surgery had not yet been performed in some infants. Thus, the actual mortality and morbidity rates may have been poorer than those reported in this study. Finally, the number of cases

may be insufficient for accurate evaluation of prognostic factors. The lung-to-heart ratio and pulmonary artery size are useful for assessing severity of CDH; however, data on these parameters were available for only about 20 infants included in this study. Thus, liver herniation was used as an index of CDH severity.

Despite these limitations, the results of this study demonstrate that the frequency of CVM among infants with CDH in Japan is similar to that in Western countries. Mortality and morbidity rates remain unfavorable despite improvements in perinatal management. The severity of CVM is important to the prognosis for patients who have these conditions concurrently. Further study is needed to determine factors influencing prognosis depending on the type of CVM.

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RESEARCH LETTER

Stomach herniation predicts fetal death or non-reassuring fetal status in gastroschisis at late pregnancy

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Advances in neonatal intensive care and the development of parenteral nutrition have reduced the infant mortality rates associated with gastroschisis from 60% in the 1960s to 3–10% at present.[1] On the other hand, a disturbingly high incidence of intrauterine fetal death (IUFD) during the third trimester has consistently been reported, with a rate in the range of 1.6–12.5%.[2–4] A high incidence (22–43%) of a non-reassuring fetal status (NRFS), suspected by abnormal cardiotocogram, has also been reported.[4,5] Therefore, strict fetal surveillance for fetal gastroschisis has been recommended. Although numerous studies have been undertaken to determine what findings on the antenatal ultrasound examination may predict the postnatal outcomes,[6–8] few have assessed the findings associated with IUFD or NRFS. The objective of this study was to elucidate such antenatal findings.

We identified 24 cases of fetal gastroschisis, which were diagnosed antenatally, all delivered at our hospital between July 2003 and July 2012. We excluded four cases of induced and one case of spontaneous abortion all before 22 weeks of gestation. In the 19 cases, which were expectantly managed during pregnancy, check up with ultrasonography was performed every 2 weeks until 34 weeks of gestation after diagnosis. After 34 weeks, ultrasonography was performed once a week, and a nonstress test was performed twice a week until delivery. In all cases, elective cesarean section was scheduled near term. The timing of the cesarean delivery was determined on the basis of obstetric indications. This retrospective study was conducted with the approval of the institutional review board of the National Center for Child Health and Development in Japan.

We classified the 19 cases into two groups, that is, either complicated by IUFD or NRFS ($n=7$) or cases with reassuring fetal status (RFS) ($n=12$). In the IUFD/NRFS group, there was one fetal death at 34 weeks of gestation and six cases undergoing emergency cesarean section due to NRFS. The RFS group consisted of 12 cases all delivered by scheduled cesarean section. We compared prenatal (e.g., stomach herniation,[9] bowel dilatation,[6] oligohydramnios,[10] and polyhydramnios[7]) and postnatal parameters (e.g., size of the wall defect,[3] birth weight,[8] and intestinal complications) between the two groups. The antenatal findings on ultrasound, which were related to outcome, were limited to those obtained within a week prior to the delivery. Stomach herniation was defined as herniation of the major part of the fetal stomach through a defect in the anterior abdominal wall. Bowel dilatation was defined as an intestinal diameter of greater than 20 mm.[6] Small for gestational age was defined as a birth weight of the infants of less than the tenth percentile for our country. The two study groups were compared by the use of the Fisher's exact test for categorical variables or t-tests for continuous data. The distributions of continuous data were normal except for birth weight, in which Welch's t-test was used. All reported p-values were two-sided. The level of significance was set at $p<0.05$. Data are presented as means ± SD (range) or the case number (percentage).

The mean maternal age was 24.7 ± 6.5 (17–41 years), the mean gestational age at diagnosis was 25.3 ± 4.9 (15–32 weeks), the mean gestational age at birth was 35.8 ± 1.0 (33.9–38.1 weeks), and the mean birth weight was 2124 ± 316 (1702–2918 g). In total, there were two neonatal deaths due to pneumonia and postoperative sepsis, all occurred in the RFS group. The overall survival was 84% (16/19 cases; one fetal and two neonatal deaths). No significant gastrointestinal or neurological complications were seen in the 16 survivors. Comparisons between the IUFD/NRFS group and RFS group are summarized in Table 1. Stomach herniation was seen on antenatal ultrasonography in five cases (71%) of the IUFD/NRFS group and only in one case (8%) of the RFS group ($p=0.019$). At birth, stomach herniation was present in all seven cases of the IUFD/NRFS group, while it was present in only three cases (25%) of the RFS group ($p=0.005$).

Robinson *et al.*[9] reported two cases of fetal gastroschisis with stomach herniation and notching of the umbilical arterial Doppler waveform, suggestive of cord compression. One of two cases resulted in NRFS. While we found a significant relationship

Table 1 **Comparison of characteristics and prenatal/postnatal parameters between the intrauterine fetal death/non-reassuring fetal status group and reassuring fetal status group.**

	IUFD/NRFS (7 cases)	RFS (12 cases)	*p* value
Maternal age (year)	26.0 ± 8.3 (19–41)	23.9 ± 5.5 (17–38)	0.518
Primipara	3 (43%)	8 (67%)	0.593
GA at diagnosis (weeks)	24.3 ± 5.0 (15–29)	23.0 ± 4.9 (18–32)	0.559
Antenatal US			
Stomach herniation	5 (71%)	1 (8%)	0.019
Bowel dilatation	3 (43%)	3 (25%)	0.757
Oligohydramnios	1 (14%)	0	0.737
Polyhydramnios	1 (14%)	0	0.737
GA at birth (weeks)	35.4 ± 1.0 (34.0–36.9)	36.0 ± 1.0 (33.9–38.1)	0.209
Birth weight (g)	1921 ± 116 (1702–2069)	2242 ± 338 (1836–2918)	0.009
SGA	4 (57%)	5 (42%)	0.860
Sex (male)	2 (29%)	6 (50%)	0.673
Major axis of defect (mm)	40.0 ± 11.7 (20–45)	33.2 ± 9.4 (25–50)	0.257
Stomach herniation at birth	7 (100%)	3 (25%)	0.005
Intestinal complications			
Atresia	1 (14%)	2 (17%)	1
Malrotation	2 (29%)	3 (25%)	1
Volvulus	0	1 (8%)	1
Rupture	0	1 (8%)	1

Data are presented as mean ± SD (range) for continuous data and number of cases (percentage) for categorical data.
IUFD, intrauterine fetal death, GA, gestational age, NRFS, non-reassuring fetal status, RFS, reassuring fetal status, US, ultrasonography, SGA, small for gestational age.

between stomach herniation and the occurrence of IUFD/NRFS, we could not assess the relationship of the umbilical arterial Doppler wave forms and outcome, because it was not measured in all cases. We found no significant difference in the presence of oligohydramnios or the size of the abdominal wall defect, which were earlier reported as an increased fetal risk in gastroschisis.[3,10] We did not find a significant difference in the incidence of bowel dilatation,[6] polyhydramnios,[7] small for gestational age,[8] or intestinal complications. The birth weight was significantly lower in the IUFD/NRFS group ($p=0.009$). Obviously, babies of the IUFD/NRFS group were potentially delivered earlier than in the other group because of fetal distress, but no significant difference was seen in the gestational age at birth. We did not find differences in the occurrence of fetal growth restriction.

The limitation of this study was its retrospective nature and its small number of patients, and that it is based on findings obtained late in pregnancy. We could not address the time-course from the onset of the stomach herniation to the onset of IUFD or NRFS. In the case of IUFD, the stomach was not herniating at 32 weeks of gestation, however, it was at the time of still birth in 34 weeks of gestation. Further prospective studies with frequent antenatal ultrasonography and cardiotocography are required to confirm this result and to determine this is predictive of poor outcome. In their absence, we conclude that stomach herniation is a possible risk factor for IUFD or NRFS in gastroschisis at late pregnancy.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Sudden fetal death and a non-reassuring fetal status are more frequent in fetal gastroschisis. Many studies were undertaken to determine what findings may predict postnatal outcome, but few assessed the findings related to the fetal risk.

WHAT DOES THIS STUDY ADD?

- Fetal gastroschisis with stomach herniation is associated with a high risk of fetal death or non-reassuring fetal status.

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Letter to the Editor

Fetal pulmonary thrombosis

We report a rare case of fetal pulmonary thrombosis with a structurally normal heart. A 44-year-old woman, gravida 2 para 1, was referred to our center at 25 weeks' gestation. Fetal ultrasonography revealed hydrops with bilateral pleural effusion, pericardial effusion, skin edema and ascites. The fetus had a structurally normal heart and no extracardiac anomalies. Thoracocentesis was performed at 25 + 4 weeks' gestation. The cell content of the fetal pleural fluid revealed a lymphocyte percentage of 99%, suggesting chylothorax.

Thoracoamniotic shunting was performed using a double-basket catheter (Hakko Co., Japan) at 26 + 2 weeks' gestation. After a third shunting at 29 + 3 weeks, uterine contractions could not be suppressed by a combination of ritodrine hydrochloride and magnesium sulfate. Following adequate counseling, indomethacin as a suppository was used for tocolysis at a dose of 50 mg every 8 h. Three days later, the right atrium and ventricle of the fetus gradually dilated, and mild tricuspid regurgitation was observed. Indomethacin treatment was discontinued immediately, however, markedly decreased blood flow in the pulmonary artery and the ductus arteriosus were sequentially demonstrated by Doppler echocardiography at 30 + 1 weeks (Figure 1). A dilated main pulmonary artery with mild valve regurgitation was also observed. Although fetal hydrops markedly improved after a fourth shunt procedure at 30 + 4 weeks, blood flow in the pulmonary artery and the ductus arteriosus did not resume, and right ventricular failure did not improve. At 31 + 3 weeks the mother went into labor and an emergency Cesarean section was performed, with delivery of a 1686-g male infant. The neonate died 3 h after birth as a result of hypoxia and metabolic acidosis.

Postmortem examination revealed a hypertrophic right ventricular wall and a severely dilated main pulmonary artery due to occlusion by an organizing thrombus

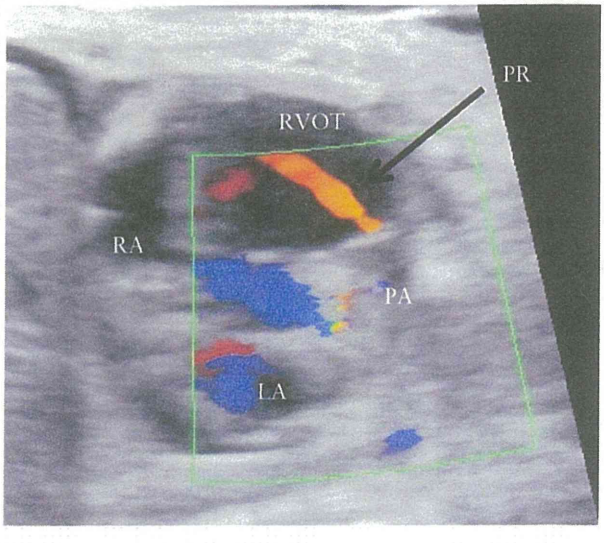

Figure 1 Color Doppler ultrasound image of a fetus with chylothorax and hydrops at 30 weeks' gestation, showing absence of blood flow in the pulmonary artery (PA) and ductus arteriosus. Dilation of the main PA and mild pulmonary regurgitation (arrow, PR) can also be seen. LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract.

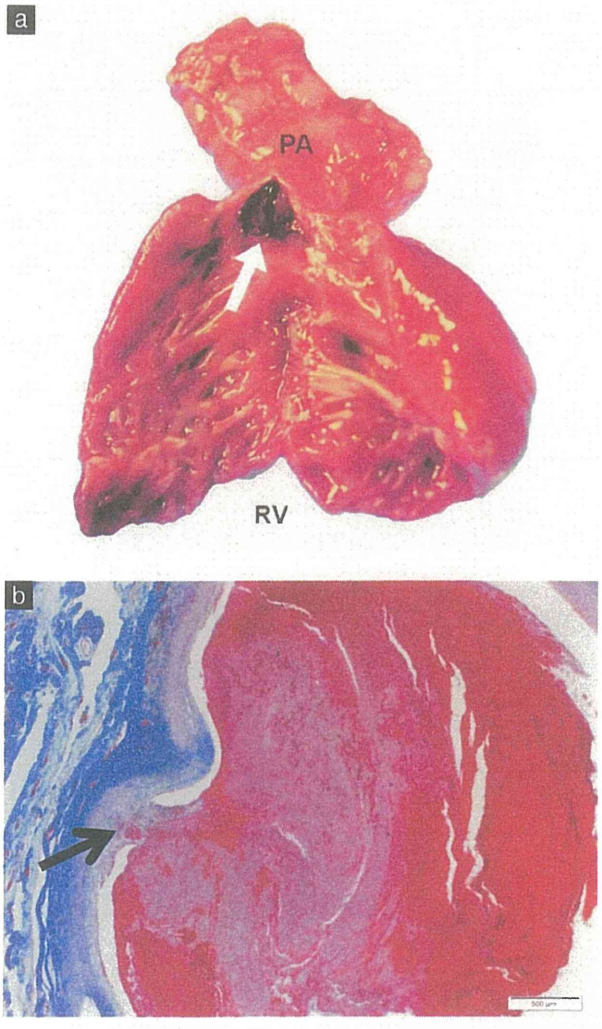

Figure 2 (a) Postmortem image of the heart of a fetus with chylothorax and hydrops, showing hypertrophic right ventricle (RV) and severely dilated main pulmonary artery (PA) due to occlusion by organizing thrombus (arrow). (b) Photomicrograph of dilated main PA showing presence of mural thrombus partly adhered to arterial wall (arrow), as highlighted by Masson's trichrome stain. Bar, 500 μm.