Table 1. Perinatal outcome according to a classification based on umbilical artery Doppler

	Type I (n = 23)	Type II (n = 27)	Type III (n = 13)
GA at delivery, weeks, median (range)	36 (26–38)	28 (18–40)	31 (25–37)
Fetal indication for delivery, % (n)	30.4 (7)	70.4 (19)	69.2 (9)
Fetal deterioration in smaller twins, % (n)	8.7 (2)	25.9 (7)	15.4 (2)
Growth arrest in smaller twins, % (n)	3 (13.0)	11.1 (3)	7.7 (1)
Fetal deterioration in larger twins, % (n)	4.3 (1)	7.4 (2)	38.5 (5)
Growth arrest in larger twins, % (n)	0.0 (0)	0.0 (0)	0.0 (0)
Fetal deterioration in both twins, % (n)	4.3 (1)	0.0 (0)	7.7 (1)
Intrauterine both fetal demise, % (n)	0.0 (0)	14.8 (4)	0.0 (0)
Miscarriage, % (n)	0.0 (0)	7.4 (2)	0.0 (0)
IUFD of smaller twins, % (n)	4.3 (1)	29.6 (8)	15.4 (2)
IUFD of larger twins, % (n)	4.3 (1)	22.2 (6)	0.0 (0)
NND of smaller twins, % (n)	0.0 (0)	18.5 (5)	0.0 (0)
NND of larger twins, % (n)	0.0 (0)	11.1 (3)	23.1 (3)
NM of smaller twins, % (n)	4.3 (1)	14.8 (4)	23.1 (3)
NM of larger twins, % (n)	0.0 (0)	11.1 (3)	38.5 (5)

GA = Gestational age; IUFD = intrauterine fetal death; NND = neonatal death; NM = neurological morbidity.

11.5% (3/26) in type I, 32.5% (13/40) in type II and 13.3% (2/15) in type III. All 18 patients with TTTS were treated by laser surgery. This left 63 patients with isolated sIUGR, distributed in 23 type I patients, 27 type II patients and 13 type III patients (table 1).

Median gestational age at delivery was 36 weeks (range, 26–38 weeks) in type I, 28 weeks (range, 18–40 weeks) in type II and 31 weeks (range, 25–37 weeks) in type III. The rate of intrauterine death was 4.3% (1), 29.6% (8) and 15.4% (2) in the IUGR twins, and 4.3% (1), 22.2% (6) and 0.0% (0) in the larger twin (table 1). Delivery was indicated for fetal reasons as defined above in 30.4% of type I cases, 70.4% of type II cases, and 69.2% of type III cases. In the remaining patients delivery occurred due to spontaneous labor or it was indicated for maternal reasons.

Data on postnatal evolution are summarized in table 1. The rate of neonatal mortality in types I, II and III was 0.0% (0), 18.5% (5) and 0.0% (0) among smaller twins, and 0.0% (0), 11.1% (3) and 23.0% (3) among larger twins, respectively. There was no infant death after the neonatal period in any of the three study groups. Neurological morbidity within 6 months after birth, as defined above, was found in 4.3% (1), 14.8% (4) and 23.1% (3) of smaller twins and in 0.0% (0), 11.1% (3) and 38.5% (5) of larger twins in pregnancies defined as type I, II and III, respectively.

When the totality of cases with and without intact survival was analyzed, among the 23 type I twins, 91.3% (21) smaller twins and 95.7% (22) larger twins were defined as having intact survival (IS). Among 27 type II pregnancies, 37.0% (10) smaller and 55.6% (15) larger twins had IS. Finally, among 13 type III twins, 61.5% (8) smaller and 38.5% (5) larger infants were defined as having IS. The distribution of cases within each pregnancy type according to the presence of IS in both fetuses, only one or none are displayed in figure 2.

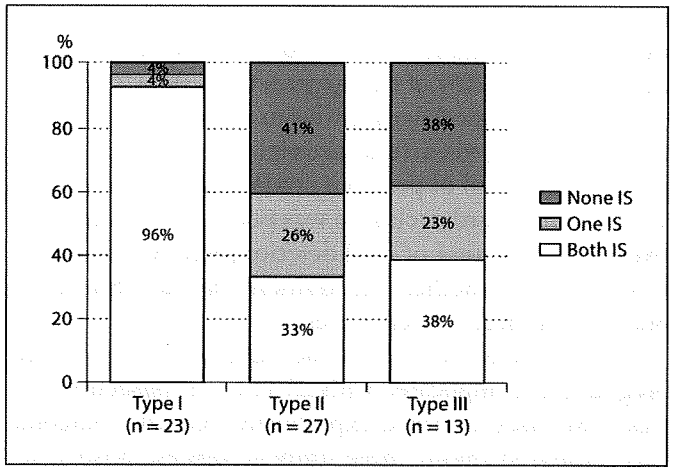

Fig. 2. Pregnancy outcome per mother; the number of infants with intact survival. IS = Intact survival; not IS = death or neurological morbidity.

Discussion

Perinatal prognosis has previously been described for 134 MC twins with sIUGR according to a classification system based on UA Doppler waveforms, with umbilical cord occlusion performed for some cases with abnormal UA based on predicted poor outcome [6]. On the contrary, the present study described perinatal outcomes in a clinical series of cases complicated with sIUGR and managed expectantly with early delivery if warranted, since selective feticide was not applicable due to legal constraints. Among the limitations which must be considered as potential biases in this clinical series is the retrospective nature of the study, and the fact that subjects included patients referred from scattered hospitals, although patients were diagnosed and classified on UA Doppler by specialists at each of the three participating centers. Nevertheless, these results could be of value in clarifying the natural history of twins with sIUGR.

It was noteworthy that the incidence of TTTS before gestational week 26 in the observational period was around one-third in type II cases, while that in type I or III cases was around 12%. This finding could indicate that cases with continuously abnormal UA Doppler in the smaller twin might be at higher risk for TTTS. Type I cases could be relatively protected from TTTS because of a higher number of placental anastomoses, which might allow a more efficient inter-twin blood exchange [3]. Likewise, type III could also be relatively protected from the occurrence of TTTS by the presence of large artery-to-artery anastomoses [6, 10]. Unfortunately, this study did not analyze in detail placental vascular anastomoses preventing any comparison in these respects.

Perinatal outcomes for type I twins were in general favorable, with an intact survival rate in both smaller and larger twins over 90%. The findings are in line with previously reported data [6]. In the light of this evidence, it might seem reasonable that type I patients be managed conservatively until late in gestation. Conversely, type II patients showed the worst prognosis among the three study groups. IS in type II was only 37.0% in smaller twins and 55.6% in larger twins. Of note was the fact that 48.1% of the smaller fetuses showed perinatal death including fetal and neonatal death. Our findings are in line with those of Quintero et al. [4], reporting a high rate of IUFD in type II fetuses managed expectantly. This complication may have remarkable consequences on the outcome of the other twin, due to the risk of acute feto-fetal hemorrhage [11–13]. In a previous report, in utero deterioration of the sIUGR fetus was found in 90.0% of type II [6]. Although in the present study we used a different definition for fetal deterioration, 70% of the type II pregnancies here reported needed delivery due to fetal indications.

The clinical evolution of type III twins presenting with iAREDF has been reported to be atypical. Although sIUGR fetuses differ from type II by failing to show signs of fetal hypoxic deterioration, some sIUGR fetuses may die unexpectedly. More importantly, the proportion of larger twins presenting neurological abnormalities such as PVL may be high in spite of both fetuses being born alive [5, 6]. Only a small number of type III cases were included in the present study. However, the results appear similar to those previously reported [5, 6], with 15.4% of smaller twins presenting IUFD and 38.5% of larger twins showing brain damage.

As the outcome of MC pregnancies with sIUGR and abnormal UA Doppler seems to be clearly unfavorable, some sort of intervention could be considered for these cases at the time of diagnosis. Umbilical cord occlusion for selective feticide has been extensively reported as an option for complicated or discordant MC twins [14, 15], and this procedure could be considered as an option for type II and III pregnancies. However, the use of this technique may be controversial. Selective feticide reduces by definition the survival rate to 50%, and in some cases the remaining twin can also present perinatal death or neurological morbidity [14]. For this reason, and particularly in countries such as Japan where feticide is usually ethically unacceptable, the application of laser coagulation for placental communicating vessels may be an option. The overwhelming advantage that this therapy represents for TTTS [9] has not been reproduced in preliminary clinical series reporting the use of laser placental coagulation in type II [4] or type III cases [4, 16]. Although the number of cases included in these studies has so far been small and further experience may be required, the results suggest that laser may increase the chances of fetal death of the smaller twin, but it might protect the larger twin from the consequences of fetal death of the IUGR fetus [4, 16].

In conclusion, clinical evolution and perinatal outcome with expectant management was different in MC twins with sIUGR classified according to the type of UA Doppler flow in the sIUGR fetus. In general, the outcome in MC twins with sIUGR and abnormal umbilical artery Doppler was markedly poor under expectant management, while normal Doppler seemed to be associated with a good prognosis. Fetal intervention such as cord

occlusion or laser therapy might be considered as a management option for sIUGR cases with abnormal Doppler findings, but the benefit of this options remains to be evaluated in further clinical studies.

Acknowledgement

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Fetal arrhythmia: Prenatal diagnosis and perinatal management

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Abstract

The importance of managing fetal arrhythmia has increased over the past three decades. Although most fetal arrhythmias are benign, some types cause fetal hydrops and can lead to fetal death. With the aim of improving the outcome in such cases, various studies for prenatal diagnosis and perinatal management have been published. Detailed analysis of the type of arrhythmia *in utero* is possible using M-mode and Doppler echocardiography. In particular, a simultaneous record of Doppler waveform at the superior venous cava and the ascending aorta has become an important and useful method of assessing the interval between atrial and ventricular contractions. Common causes of fetal tachycardia (ventricular heart rate faster than 180 bpm), are paroxysmal supraventricular tachycardia (SVT) with 1:1 atrioventricular (AV) relation and atrial flutter with 2:1 AV relation. Of fetal SVT, short ventriculo-atrial (VA) interval tachycardia due to atrioventricular reentrant tachycardia is more common than long VA interval. Most fetuses with tachycardia are successfully treated *in utero* by transplacental administration of antiarrhythmic drugs. Digoxin is widely accepted as a first-line antiarrhythmic drug. Sotalol, flecainide and amiodarone are used as second-line drugs when digoxin fails to achieve conversion to sinus rhythm. Fetal bradycardia is diagnosed when the fetal ventricular heart rate is slower than 100 bpm, mainly due to AV block. Approximately half of all cases are caused by associated congenital heart disease, and the remaining cases that have normal cardiac structure are often caused by maternal SS-A antibody. The efficacy of prenatal treatment for fetal AV block is limited compared with treatment for fetal tachycardia. Beta stimulants and steroids have been reported as effective transplacental treatments for fetal AV block. Perinatal management based on prospective clinical study protocol rather than individual experience is crucial for further improvement of outcome in fetuses with tachycardia and bradycardia.

Key words: fetal arrhythmia, fetal echocardiography, prenatal diagnosis, prenatal treatment.

The importance of managing fetal arrhythmia has increased over the past three decades. Fetal arrhythmia is often found during fetal heart monitoring or routine prenatal ultrasound examination. Although most fetal arrhythmias are benign, some cause fetal hydrops and can lead to fetal death.[1,2] To improve the outcome in such cases, various studies of prenatal diagnosis and perinatal management have been published. Up-to-date knowledge of effective methods of diagnosing fetal arrhythmia and the selection of appropriate perinatal treatment is crucial for managing affected fetuses. In the present paper, we summarize the current method of prenatal diagnosis and perinatal management of fetal arrhythmia based on recent publications.

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History of Managing Fetal Arrhythmias

Prenatal recognition and treatment of fetal tachycardia began in the 1970s. After the first report of prenatal diagnosis using M-mode echocardiography was published in 1980 by Kleinman *et al.*,[3] many reports of prenatal treatment of fetal tachycardia using various types of antiarrhythmic drugs were published in the 1980s. In the 1990s, researchers were more focused on refractory cases.[4–6] To enable a more detailed prenatal diagnosis, measurement of the ventriculo-atrial (VA) interval was reported in 1998,[7] and the magnetocardiogram was introduced as a useful modality.[8] In the 21st century, researches began to focus on better strategies to manage fetal arrhythmia by conducting multicenter trials with larger numbers of patients.[9]

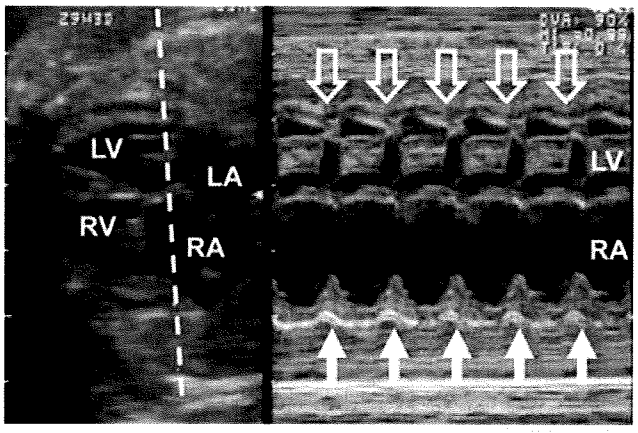

Figure 1 Simultaneous M-mode recording of both ventricles and atria. M-mode recording in a fetus with supraventricular tachycardia reveals 1:1 relation of atrial (closed arrow) and ventricular contraction (open arrow) with a ventricular rate of 210 bpm. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Definition and Method of Prenatal Diagnosis

There are three types of fetal arrhythmias.[1,2] The most common form is irregular heartbeat, mainly caused by ectopic beats. When the ventricular rate is faster than 180 bpm or slower than 100 bpm, such fetal arrhythmia is classified as fetal tachycardia or fetal bradycardia, respectively. Detailed analysis of the type of arrhythmia *in utero* is possible using M-mode and Doppler echocardiography.

M-mode echocardiography

An M-mode trace of ventricular and atrial motion demonstrates cardiac rhythm and rate. A simultaneous record of both ventricular and atrial contractions with a four-chamber view is especially useful for assessing the relation of atrioventricular (AV) mechanical connection in fetuses with arrhythmias, and can determine the mechanism causing the fetal arrhythmia (Figs 1,2).[1,2]

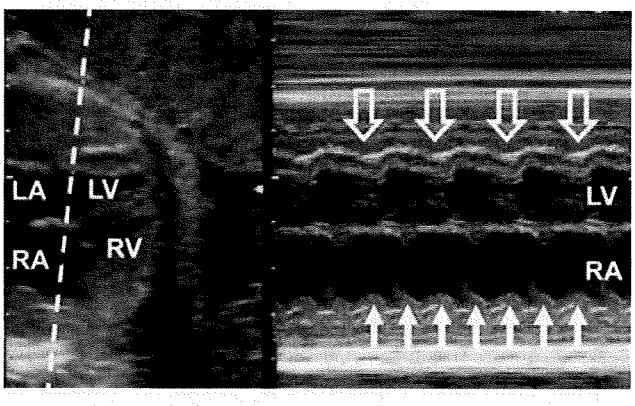

Figure 2 M-mode recording in a fetus with atrial flutter and 2:1 atrioventricular conduction, with an atrial (closed arrow) rate of 510 bpm and a ventricular (open arrow) rate of 255 bpm. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Doppler echocardiography

Recently, a simultaneous record of Doppler waveforms at the superior venous cava (SVC) and the ascending aorta (aAo) was introduced as a useful method of assessing cardiac arrhythmias (Fig. 3).[10,11] The beginning of reverse flow at the SVC created by atrial contraction and the beginning of forward flow at the aAo created by ventricular contraction are interpreted as the beginning of P and QRS wave by electrocardiogram (ECG), respectively. Using Doppler waveform, the relation and time intervals of the atrial and ventricular contractions can be measured.[12,13] The pulmonary vein and the pulmonary artery,[14] or the innominate vein and the aortic arch can also be used as alternative methods of assessing simultaneous venous and arterial waveforms.[12]

Another method of measuring AV conduction time interval is the simultaneous record of left ventricular inflow and outflow waveforms.[2] Although this method is relatively easy, AV contraction relation cannot be assessed once the tachycardia begins because E wave, first peak, and A wave, second peak of the inflow pattern cannot be distinguished in this condition.

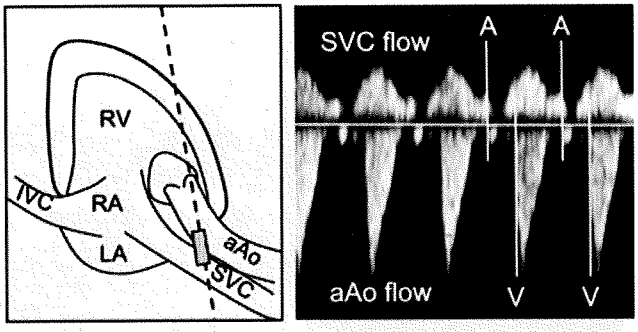

Figure 3 Simultaneous Doppler trace of the ascending aorta (aAo) and the superior vena cava (SVC). Beginning of reverse flow at SVC (A) and forward flow at aAo (V) represent the timing of atrial and ventricular contraction, respectively. IVC, inferior vena cava; LA, left atrium; RA, right atrium; RV, right ventricle.

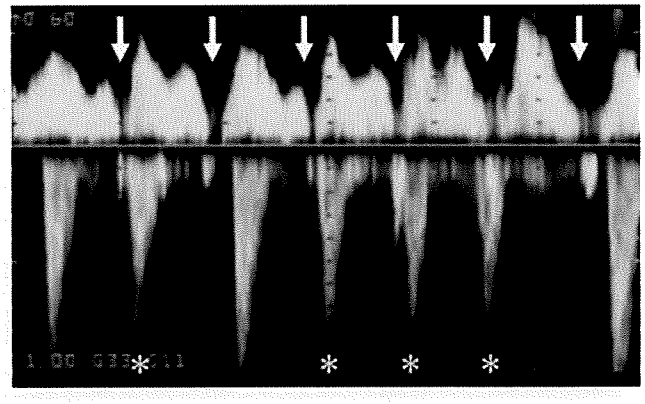

Figure 4 Simultaneous Doppler trace of the ascending aorta and the superior vena cava in a fetus with ventricular or junctional tachycardia reveals regular atrial contraction with reversal flow at the superior vena cava (arrows) and faster ventricular contraction (asterisk).

Simple measurement of the time length of A wave may be another method to screen the prolongation of AV interval.

Tissue Doppler echocardiography, which can demonstrate detail timing of myocardial contraction, is a useful tool for evaluating fetal arrhythmia.[13,15] Because the tissue Doppler method has become available in the equipment used currently, this technique may become part of routine examination in the near future to diagnose fetal arrhythmias.

Tachycardia

Prenatal diagnosis

Fetal tachycardia is diagnosed when the fetal ventricular heart rate is faster than 180 bpm.[1,2,11] Common causes of fetal tachycardia are paroxysmal supraventricular tachycardia (PSVT) and atrial flutter (AFL). There are other rare types of fetal arrhythmias, such as ventricular tachycardia (VT), junctional tachycardia, and multiforcal atrial tachycardia (MAT). Fetal tachycardia is classified based on the relation of the AV contraction observed by fetal echocardiography. Fetal PSVT has a 1:1 AV relation (Fig. 1). Fetal AFL has a very fast atrial heart rate, such as 400 or 500 bpm, and 2:1 (occasionally 3:1 or 4:1) AV relation (Fig. 2). Fetal VT has ventricular tachycardia with dissociated atrial contraction (Fig. 4). Fetal MAT shows irregular atrial tachycardia and ventricular contraction. Although tachycardia is sometimes intermittent during prenatal examination, the chance of hemodynamic complications and development of fetal hydrops remain high.

PSVT in most fetuses is caused by atrioventricular reentrant tachycardia (AVRT) due to Wolff–Parkinson–White syndrome.[8,11] Both the atrial and ventricular heart rates range from 200–300 bpm (Fig. 1). Measurement of the time interval from the ventricular contraction to the following atrial contraction (VA interval) by Doppler echocardiography reveals a short VA interval (Fig. 5).[10,11] The measurement of this VA interval is very useful to distinguish AVRT (short VA interval) from other types of fetal tachycardias, such as atrioventricular nodal reentrant tachycardia (AVNRT) and permanent junctional reciprocating tachycardia (PJRT), which demonstrates a long VA interval (Fig. 6).

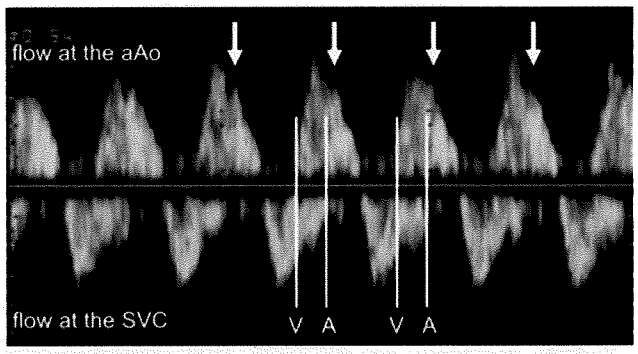

Figure 5 Simultaneous Doppler trace of the ascending aorta (aAo) and the superior vena cava (SVC) in a fetus with supraventricular tachycardia with short ventriculo-atrial interval. Although high-velocity reversal flows of SVC is almost over-wrapped to the flow of aAo, the starting point of the reversal flow can be detected from the interrupted forward flow of SVC.

Perinatal management

Most fetuses with both PSVT and AFL are successfully treated *in utero* by transplacental administration of

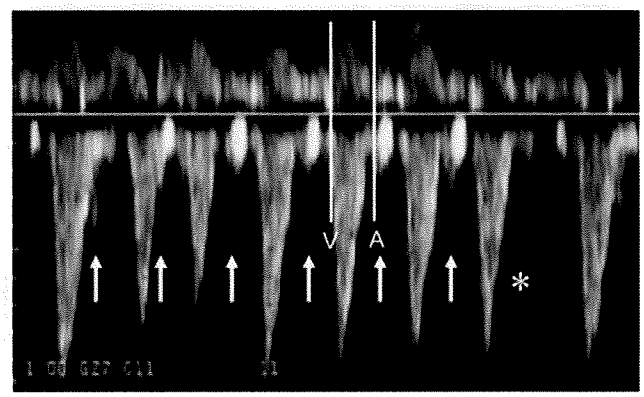

Figure 6 Simultaneous Doppler trace of the ascending aorta and the superior vena cava in a fetus with 1:1 atrioventricular conducted tachycardia with long ventriculo-atrial interval. Tachycardic atrial contraction (A, arrows) disappears after the seventh ventricular contraction (asterisk), and the tachycardia is stopped.

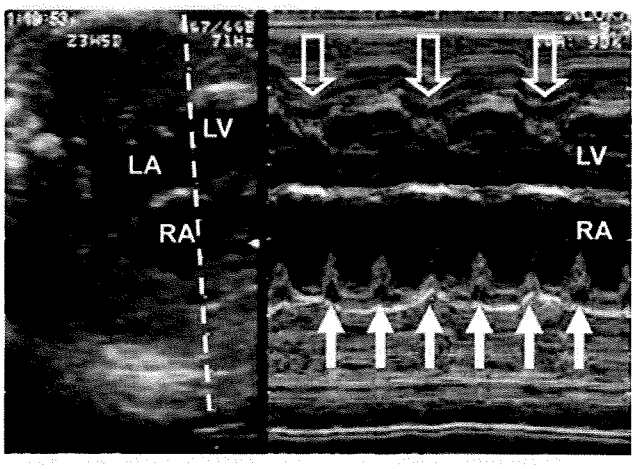

Figure 7 Simultaneous M-mode recording of both ventricles and atria in a fetus with complete atrioventricular block reveals complete dissociation of atrial and ventricular contraction with a ventricular rate of 65 bpm. Large arrows, ventricular contractions; small arrows, atrial contractions; LA, left atrium; LV, left ventricle; RA, right atrium.

antiarrhythmic drugs.[6,9,10,11] Digoxin is widely accepted as a first-line antiarrhythmic drug. Sotalol, flecainide and amiodarone are used as second-line drugs when digoxin fails to achieve conversion to sinus rhythm.[16–21] For fetuses with hydrops and fetal PSVT with long VA interval, digoxin is rarely effective.[11] For fetuses with hydrops, the placental transfer of the digoxin is limited. Hence, sotalol or flecainide, which have good placental transfer ability, should be used from the beginning of fetal treatment for hydrops. Fetal intramuscular administration of digoxin with maternal administration of amiodarone is another effective method.[21]

Although intrauterine treatment is very effective in fetuses with tachycardia, treatment after delivery is also very effective. Hence, decisions for which cases are treated *in utero* or postnatally is often difficult. Management of a premature neonate under hemodynamically unstable conditions with tachycardia and decreased cardiac function is difficult.[22] Hence, it is important not to select postnatal treatment too quickly in premature gestation, even when the fetus has already developed hydrops. Once the tachycardia is converted to sinus rhythm, the hydrops will recover and the fetus can be delivered at term by vaginal birth. However, when the hydrops continues for more than 2 weeks without conversion of tachycardia, postnatal treatment is recommended.

It is difficult to predict when the fetus will develop hydrops.[23,24] Several Doppler echocardiographic parameters that demonstrate congestive heart failure cannot be used at this extremely high heart rate. Serial measurement of the cardiothoracic ratio may be useful for monitoring the degree of heart failure. The presence of atrioventricular valve regurgitation, especially at the mitral valve, may represent severe congestive heart failure.

The safety of the mother is of great concern when managing fetal tachycardia. Administration of antiarrhythmic drugs for intrauterine treatment may cause pro-arrhythmia and threaten the mother. ECG monitoring, especially of the QT prolongation of the mother is very important when a new drug is started or the dosage is increased.

Bradycardia

Prenatal diagnosis

Fetal bradycardia is diagnosed when the fetal ventricular heart rate is slower than 100 bpm, mainly due to AV block (Fig. 7).[1,11,25] Approximately half of all cases are caused by associated congenital heart disease (CHD), and the remaining cases that have normal cardiac structure are often caused by maternal SS-A antibody.[26–28] The two most common CHD associated with AV block are left atrial isomerism (Fig. 8) and discordant AV connection. Maternal SS-A antibody to AV block is usually that for 52kd SS-A, and many mothers are rarely diagnosed with collagen disease when the fetus develops AV block.[29–32] Although rare, the other important cause of fetal bradycardia is long QT syndrome, which can cause 2:1 AV block or sinus

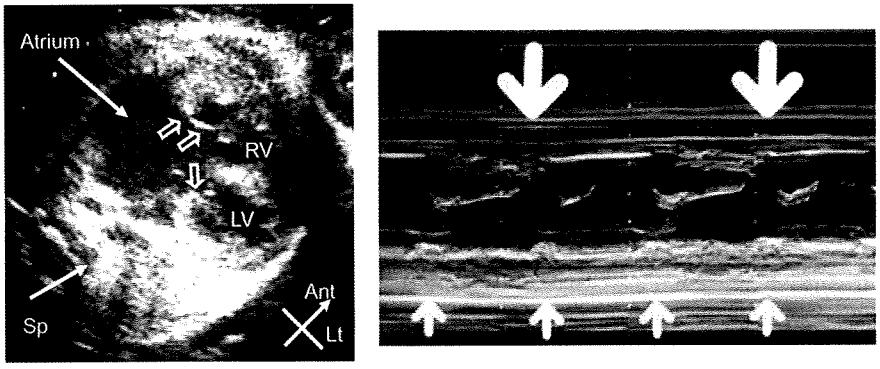

Figure 8 Left panel reveals four-chamber view of polysplenia with the single atrium, the common atrioventricular valve (open arrows) and cardiomegaly. Right panel reveals simultaneous M-mode recording of ventricles (large arrows) and atria (small arrows) in this case, which demonstrates 2:1 atrioventricular block. Ant, anterior; Lt, left; LV, left ventricle; RV, right ventricle; Sp, spine.

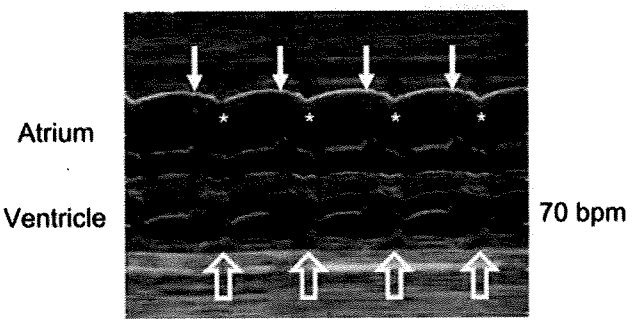

Figure 9 Simultaneous M-mode recording of ventricles and atria in a fetus with blocked paroxysmal atrial contraction (PAC) with bigeminy. The PAC (asterisk) shortly after regular atrial conduction (small arrows) does not conduct to the ventricle causing bradycardia with a ventricular rate of 70 bpm.

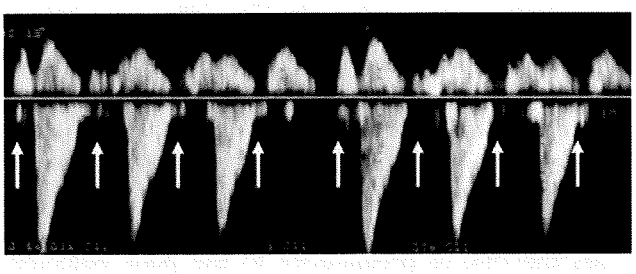

Figure 10 Wenckebach type atrioventricular block. Simultaneous Doppler trace of the ascending aorta and the superior vena cava reveals atrial contraction with regular rhythm (arrows), atrioventricular conducting time of gradual prolongation, and block with pose of ventricular contraction.

bradycardia.[33] Blocked paroxysmal atrial contraction (PAC) with bigeminy also mimics 2:1 AV block and causes fetal bradycardia (Fig. 9).[11]

Doppler echocardiography is useful for diagnosing fetal bradycardia. The relation and interval of atrial and ventricular contractions revealed by SVC and aAo Doppler flow can demonstrate the severity of AV block, not only complete dissociation of AV contraction, but also first-degree and Wenckebach-type second-degree AV block (Fig. 10).[11,34]

Fetal bradycardia with either CHD or fetal hydrops has a significantly worse prognosis.[26,27] Although a heart rate of less than 55 bpm is thought to be the cut-line for congestive heart failure, some recent reports included cases without heart failure even when the fetal heart rate was less than 50 bpm.[27] Cardiac function or presence of CHD affects the severity of congestive heart failure.[35] It is important that transferred maternal IgG can cause pleural, pericardial and peritoneal effusion, in addition to myocarditis and poor cardiac function in the fetus, even if there is no hydrops.[36]

Perinatal management

Efficacy of prenatal treatment for fetal AV block is limited compared with treatment for fetal tachycardia. Beta stimulants and steroids have been reported to be effective transplacental treatments for fetal AV block.[11,37,38] Beta stimulants, such as ritodrine, terbutaline, and salbutamol effectively increase fetal ventricular rate by approximately 10–20% and reverse hydrops in some fetuses with AV block. Several reports have demonstrated that transplacental administration of steroids, such as dexamethasone and betamethasone, are effective for fetuses with AV block caused by anti-SSA antibody.[39–41] Jaeggi *et al.* recently reported that prenatal steroid treatment improves the outcome of fetuses with AV block.[32]

There are two targets for prenatal steroid therapy. The most attractive target is the direct effect of treating AV block. The prompt administration of steroids immediately after the onset of AV block has improved the degree of AV block.[39] However, other studies have shown spontaneous improvement of the degree of AV block without any steroid therapy.[42] Hence, the direct effect of steroids for AV block remains uncertain.

The other target of prenatal steroid therapy is for myocarditis, which is the main aim of the current prenatal treatment. Maternal autoantibodies affect not only the AV node, but also fetal myocardium and can cause myocarditis.[36,43,44] Transplacental administration of steroids is thought to be effective for treating myocarditis, and may improve cardiac function of the fetus. This prenatal treatment of myocarditis is also thought to prevent postnatal cardiac dysfunction, such as endocardial fibroelastosis and late-onset dilated cardiomyopathy.[32]

Early delivery and direct pacing of the ventricle is a reasonable option when the fetal heart rate progressively decreases and fetal hydrops starts to develop in the fetal AV block, with or without CHD.[32] In cases with reduced cardiac function due to myocarditis or severe congestive heart failure, postnatal circulatory management is very difficult, even after pacing. Hence, delivery before the development of reduced cardiac function is important. Nevertheless, too early delivery adds the risk of prematurity to the poor outcome. Further study is required to determine the optimal management strategy.

Prevention of fetal AV block due to maternal SS-A antibody

Steroid therapy to prevent the development of fetal AV block has been one of the most important issues in managing mothers with positive SS-A antibodies. One of the problems of prevention is that most mothers have not been diagnosed with autoimmune disease at the onset of fetal AV block.[25,28,31,32] Another problem is the relatively low (1–7.5%) incidence of fetuses developing AV block in mothers with positive SS-A antibody.[31] As steroid therapy has possible adverse effects for the fetus, preventive maternal steroid therapy for all mothers with SS-A antibody may not be acceptable. Preventive steroid therapy remains controversial, even in high-risk cases in which there is a previous child with AV block. The incidence of AV block in these cases is approximately 15%.[31,41]

Early detection of first-degree AV block and early administration of steroids may be the most accepted of the current methods. However, recent reports have demonstrated the sudden onset of complete AV block in fetuses without any sign of first- or second-degree AV block, even with weekly fetal echocardiography. High echogenesity of the atrial wall and more than moderate tricuspid regurgitation are reported as other early signs of the development of complete AV block.[34] Further study is required to find a better strategy for preventing fetal AV block.

Conclusion

Perinatal management of fetal arrhythmia is important to improve the outcome of affected fetus. Accurate prenatal diagnosis is crucial to the selection of the appropriate prenatal and postnatal treatments. However, there are still many issues regarding the management of both fetal tachycardia and bradycardia, and more useful strategies must be investigated. Perinatal management based on prospective clinical study protocol, rather than on individual conditions is crucial for further improvement of the outcome of affected fetuses.

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Evaluating mortality and disease severity in congenital diaphragmatic hernia using the McGoon and pulmonary artery indices

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Disease severity

Abstract

Purpose: Lung hypoplasia is associated with mortality in congenital diaphragmatic hernia (CDH). However, the association between lung hypoplasia and disease severity is unclear. Early prediction of disease severity would provide parents with more precise information about the anticipated course of treatment, minimize treatment disruption, and maximize the efficient management of patients with CDH. We aimed at identifying the relationship between McGoon index (MGI) and pulmonary artery index (PAI) scores and disease severity among infants with CDH.

Methods: We retrospectively reviewed the medical records of 19 high-risk patients with CDH born between January 2006 and December 2007. McGoon index and PAI scores were determined on admission. We evaluated statistically the relationship between these scores and variables representing severity as follows: number of vasodilators, use of inhaled nitric oxide (iNO), closed method of diaphragm, duration of intubation, duration of hospitalization, and use of home oxygen therapy. Statistical significance was $P < .05$.

Results: Overall median MGI and PAI scores were 1.40 and 108, respectively; scores for nonsurvivors were significantly ($P < .05$ and $P < .01$, respectively) lower than those for survivors. Among survivors, PAI scores were significantly ($P < .05$) lower in infants requiring iNO than in infants not requiring iNO and patch repair. The PAI scores were significantly correlated with the number of vasodilators ($r = -0.789$; $P < .01$) and duration of intubation ($r = -0.610$; $P < .05$).

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Conclusions: McGoon index (cutoff value, 1.31) and PAI (cutoff value, 90) are reliable indices for predicting mortality in CDH. Pulmonary artery index appears to be more useful than MGI for predicting disease severity among survivors.

Congenital diaphragmatic hernia (CDH) has a high mortality rate despite new management techniques, such as high-frequency oxillatory ventilation (HFOV), inhaled nitric oxide (iNO), extracorporeal membrane oxygenation (ECMO), gentle ventilation, and delayed surgery [1-5]. Many indices are used to predict mortality in patients with CDH [6-12]. The McGoon index (MGI) and pulmonary artery index (PAI) have been used to evaluate the pulmonary vascular bed in patients with congenital heart disease since the early 1980s [13,14]. Recently, several studies have suggested that these indices are useful for predicting mortality in infants with CDH [15-17]. However, no study has been published on the usefulness of these indices in predicting disease severity in survivors. The usefulness of these indices in predicting disease severity in survivors would help in the efficient management of patients with CDH. The objective of this retrospective chart review is to evaluate the relationship between these 2 indices and disease severity in infants with CDH.

1. Materials and methods

The medical records of all infants with high-risk CDH admitted between January 2006 and December 2007 to the neonatal intensive care unit (NICU) at the National Center for Child Health and Development in Tokyo, Japan, were retrospectively reviewed and analyzed. We considered the infants to be high risk if CDH had been diagnosed prenatally or if tracheal intubation was performed because of respiratory distress in the first day of life. Patients with associated lethal anomalies and cardiovascular malformations (except patent ductus arteriosus and patent foramen ovale) were excluded.

Infants with prenatal diagnosis of CDH were generally delivered vaginally. Resuscitations were performed by neonatologists in the delivery room or in the operating room. All infants were intubated immediately after birth and ventilated by manual bagging (inspiratory pressure, <20 cm H_2O; fraction of inspired oxygen, 1.0) and then administered morphine hydrochloride and pancuronium intravenously. If the elevation in saturation of peripheral oxygen (SpO_2) was unsatisfactory (<85%), HFOV was used first. If a satisfactory preductal SpO_2 value (>85%) was not achieved by HFOV, iNO was considered. After admission to the NICU, all infants were subjected to HFOV (initial settings: fraction of inspired oxygen, 1.0; mean airway pressure, 12 cm H_2O; stroke volume, 10 mL). Hypercapnea and preductal saturation as low as 85% were acceptable. When deterioration of oxygenation (SpO_2, <85%) caused by severe pulmonary hypertension occurred or differential cyanosis was present (preductal SpO_2–postductal SpO_2 > 10%), iNO was administered as first-line therapy (initial dose, 10 ppm; maximum dose, 40 ppm). If a satisfactory effect was not achieved with iNO, several other vasodilators (phosphodiesterase inhibitor, prostaglandin I2, prostaglandin E1, PDE5 inhibitor, and endothelin receptor antagonist) were administered. The PDE3 inhibitor was used if cardiac contraction was impaired. If cardiac contraction was not impaired, PGI2 was used. In addition, when the shunt flow in ductus arteriosus was right-to-left dominant, PGE1 was administered to prevent right-side heart failure and low cardiac output caused by closure of the ductus arteriosus. The PDE5 inhibitor and endothelin receptor antagonist were used when chronic pulmonary hypertension was present after surgical repair because these drugs were orally administered. However, the decision to initiate the use of these vasodilators, except for iNO, depended primarily on the subjective judgment of the physician. All infants were administered morphine hydrochloride and pancuronium continuously until CDH was repaired surgically. Extracorporeal membrane oxygenation was indicated only when infants had temporary diseases such as pneumothorax or pneumonia. Congenital diaphragmatic hernia was surgically repaired when the preductal SpO_2 was stable (SpO_2, >85%), and no flip-flop phenomenon was present at 48 hours after birth or later. We defined the criteria for extubation as a crying vital capacity more than 15 mL/kg and static compliance of more than 0.6 mL/cm H_2O per kilogram [18,19].

Echocardiographic assessment was performed immediately after admission to the NICU. The diameters of the left pulmonary artery and right pulmonary artery were measured at the bifurcation in systole. The diameter of the descending aorta (DAO) was measured at the level of the diaphragm. The body surface area (BSA) used to obtain PAI was calculated using the Dubois formula. The MGI and PAI were calculated as follows [13-16]:

MGI = (RPA diameter + LPA diameter)/DAO diameter and PAI = (RPA area + LPA area)/BSA.

The relationship between these 2 indices and mortality was assessed in all infants with CDH. In survivors, the relationship between these 2 indices and the variables representing disease severity was assessed. The following variables were evaluated to determine the severity of disease: number of vasodilators, use of iNO, closed method of diaphragm, duration of intubation, duration of hospitaliza-

tion, and use of home oxygen therapy (HOT). In addition, we assessed the relationship between DAO and BSA or PAI to determine whether the diameter of the DAO used to calculate the MGI was the appropriate variable to normalize the size of the pulmonary artery.

All data were analyzed using statistical software (Stat Flex for Windows version 5.0; Artec, Osaka, Japan). The Mann-Whitney *U* test was used to compare the median values between groups as follows: including survivors vs nonsurvivors, the iNO group vs the no iNO group, and the patch repair group vs the primary repair group. Correlations (using Spearman's rank correlation coefficient) were assessed between the MGI and PAI and the following variables: the number of vasodilators, the duration of intubation, and the duration of hospitalization. The best cutoff values for mortality and use of iNO in the MGI and PAI were calculated from their respective receiver operating characteristic (ROC) curves. The relationship between HOT and the 2 indices was not analyzed statistically because only one infant required HOT. The correlations between DAO and BSA or PAI were assessed using Pearson's correlation coefficient. *Mortality* was defined as death before discharge from the hospital. Statistical significance was defined as $P < .05$.

2. Results

A total of 19 infants with CDH were admitted during the period selected for the study. The median MGI was 1.40 (range, 0.85-1.89), and the median PAI was 108 (range, 43-202) (Table 1). Of the 19 infants, 4 (21%) died before discharge from the hospital; all of the decedents died before surgery. Two died within 24 hours of life, one of whom was an outborn patient. His preductal SpO_2 was approximately 60% on arrival. The other 2 patients died at 2 days and 6 days of life, respectively. They had no severe complications other than lung hypoplasia. Of the 15 survivors, the median number of vasodilators administered was 1 (range, 0-4); 10 infants (67%) were administered iNO. Four infants (27%) required patch repair. The median intubation time in survivors was 21 days (range, 7-46 days); the median hospitalization length of stay was 46 days (range, 25-72 days). Only one survivor required HOT (Table 2).

Table 1 Patient characteristics

	n = 19
Gestational age at delivery (wk)	39.3 (range, 37.3-40.3)
Birth weight (g)	2908 (range, 2420-3816)
Apgar score at 5 min	4 (range, 2-9)
Cesarean delivery	3/19 (16%)
Inborn	18/19 (95%)
Prenatal diagnosis	17/19 (89%)
CDH right	2/19 (11%)
Liver up	8/19 (42%)
Survived to surgery	15/19 (79%)
Survivors at discharge	15/19 (79%)
MGI	1.40 (range, 0.85-1.89)
PAI	108 (range, 43-202)

Table 2 Clinical presentation of survivors

	Survivors (n = 15)
No. of vasodilators	1 (range, 0-4)
Use of iNO	10/15 (67%)
Use of ECMO	0/15 (0%)
Patch repair	4/15 (27%)
Duration of intubation (d)	21 (range, 7-46)
Duration of hospitalization (d)	46 (range, 25-72)
Home oxygen therapy	1/15 (7%)

The MGI and PAI scores were significantly lower ($P < .05$ and $P < .01$, respectively) in the nonsurvivors (MGI, 1.05 [range, 0.85-1.25]; PAI, 67 [range, 43-86]) than in the survivors (MGI, 1.48 [range, 1.06-1.89]; PAI, 130 [range, 77-202]). The best cutoff values on the ROC curves for MGI and PAI were 1.31 (sensitivity, 100%; specificity, 73%) and 90 (sensitivity, 100%; specificity, 74%), respectively (Fig. 1).

The MGI scores were significantly correlated only with the number of vasodilators; however, PAI scores were significantly correlated with both the number of vasodilators and the duration of intubation. Duration of hospitalization was not significantly correlated with either MGI or PAI (Fig. 2).

The PAI scores were significantly lower ($P < .05$) in the infants requiring iNO (106; range, 77-156) than in the infants not requiring iNO (158; range, 130-202); however, MGI scores did not differ significantly between the infants requiring iNO (1.37; range, 1.06-1.61) and the infants not requiring iNO (1.54; range, 1.45-1.89) (Fig. 3). The best cutoff values on the ROC curves for MGI and PAI for detecting severe pulmonary hypertension requiring iNO were 1.52 (sensitivity, 80%; specificity, 80%) and 150 (sensitivity, 90%; specificity, 80%), respectively. The PAI scores were significantly lower ($P < .01$) in infants requiring patch repair (77; range, 77-103) than in infants who required primary repair (144; range, 79-202). However, MGI scores did not differ significantly between the patch repair (1.31; range, 1.06-1.48) and the primary repair (1.52; range, 1.20-1.89) groups (Fig. 3). The infant who received HOT had the lowest PAI among the survivors. On the other hand, the MGI of the patient who received HOT (1.48) was nearly the same as the median MGI of the infants who did not receive HOT (1.45) (Fig. 3).

The diameter of the DAO was not significantly correlated with BSA ($r = -0.126$) but was significantly correlated with PAI ($r = 0.483$; $P < .05$) (Fig. 4).

3. Discussion

The present retrospective chart review showed that MGI and PAI scores were good predictors of mortality in infants with CDH. In addition, our results suggest that PAI is a useful predictor of disease severity in survivors.

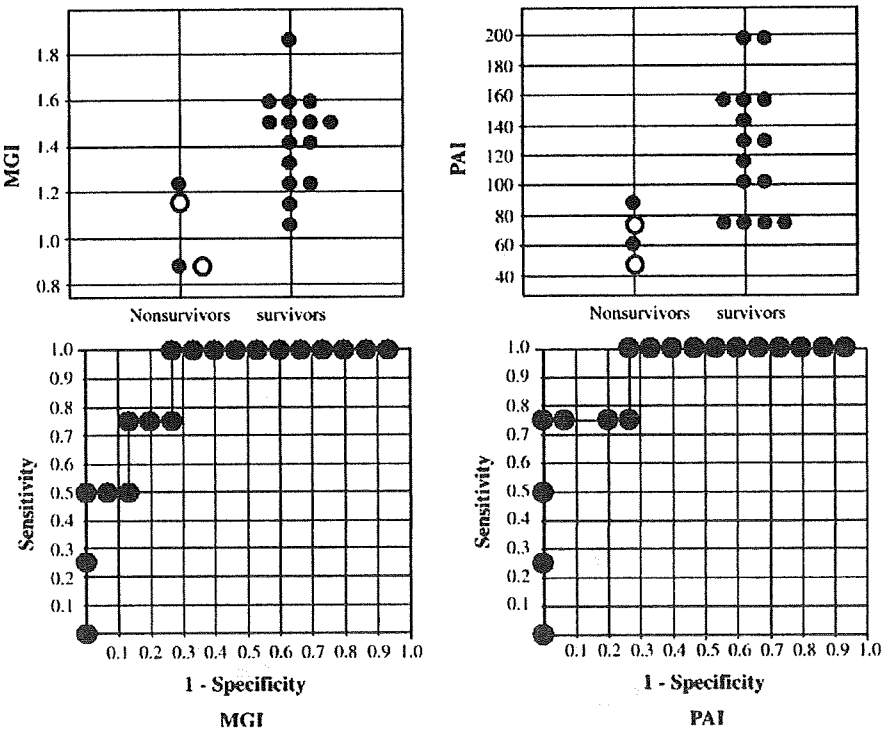

Fig. 1 Upper panels, Scatter plots showing MGI and PAI scores of nonsurvivors and survivors. Nonsurvivors had significantly lower MGI and PAI scores than did survivors. ● indicates left-side CDH; ○, right-side CDH. Lower panels, Receiver operating characteristic curves for MGI and PAI. The best cutoff values for predicting mortality with MGI and PAI were 1.31 (sensitivity, 100%; specificity, 73%) and 90 (sensitivity, 100%; specificity, 74%), respectively.

The degree of lung hypoplasia has been strongly associated with prognosis among infants with CDH [20]. Suda et al [16] and Casaccia et al [15] reported that MGI is a useful predictor of mortality among infants with CDH. The cutoff values reported by these 2 studies are 1.3 and 1.25, respectively, which are similar to the cutoffs in the present study. On the other hand, Yao et al [17] reported that the nonsurvivors had significantly lower PAI scores than did the survivors, whereas there were no significant differences in MGI scores between the survivors and nonsurvivors. Our study found that both PAI and MGI were useful predictors of mortality among infants with CDH. This study used prospective measurements of the pulmonary artery and DAO to calculate MGI and PAI. The measurements in the study by Yao et al [17] were obtained retrospectively by using video recordings, which may have accounted for the differences in results.

In the present study, PAI was more significantly correlated with variables indicating severity than was MGI, which suggests that PAI allows the clinician to assess disease severity more precisely than does MGI. The duration of hospitalization was the only variable not correlated with PAI in the present study. This study found 3 outliers in the scatter plot. One of these 2 patients had a PAI of 77 and a prolonged duration of hospitalization (72 days) because of the need for HOT. The other patient had a PAI of 155 and a prolonged duration of hospitalization (65 days) because he had chylous pleural effusion at the affected side for 1 month after surgery. The lack of correlation between PAI and the duration of hospitalization might have been because of these 2 patients.

The cross-sectional area of the pulmonary artery used to calculate PAI reflects the size of the pulmonary artery more than the diameter used to calculate MGI. In addition, PAI has less measurement deviation than MGI because, for MGI, the measurement of the DAO needs to be obtained by echocardiography [21]. We speculated that these were the reasons why PAI was a more useful predictor than was MGI for estimating disease severity in survivors. In addition, the present study showed that the diameter of the DAO in infants with CDH was not significantly correlated with BSA (Fig. 4); therefore, we suggest that the diameter of the DAO among infants with CDH is not an appropriate variable for standardizing the size of the pulmonary artery. In general, the diameter of the DAO depends on the physical size of the infant [22]; however, the present study suggests that the diameter of the DAO in infants with CDH does not correlate with physical size but instead depends on the degree of lung hypoplasia. The ascending aorta and the aortic arch of the infants with CDH are underdeveloped because of the restriction of blood flow to the left ventricle induced by severe pulmonary hypertension [23]; however, VanderWall et al [24] reported that both the right and left ventricles were smaller in the infants with CDH than in the infants without CDH. The patients with CDH with severe pulmonary hypertension may have a significant deviation of the heart

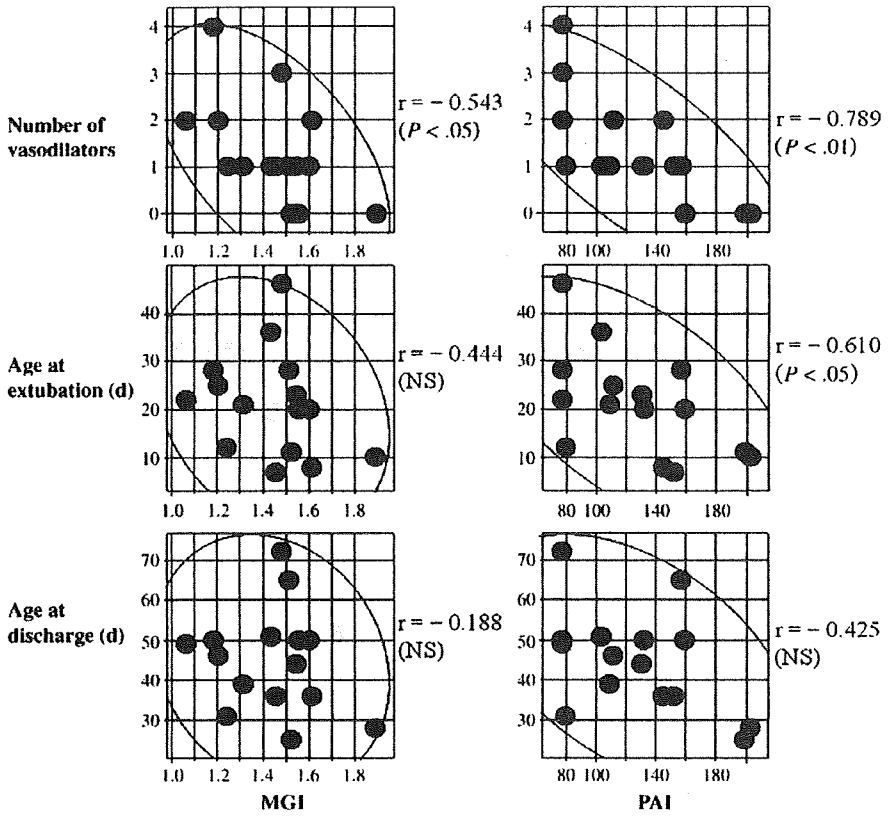

Fig. 2 Scatter plots showing the correlation between 2 indices and 3 variables representing disease severity in survivors. Pulmonary artery index was significantly correlated with the number of vasodilators and duration of intubation. McGoon index was significantly correlated only with the number of vasodilators. NS indicates not significant.

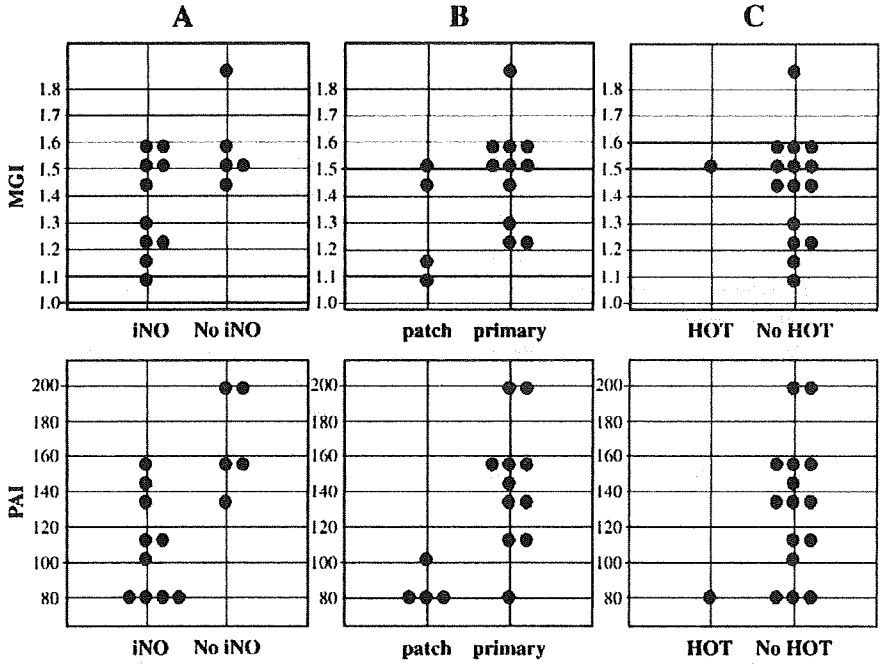

Fig. 3 A, Distribution of MGI and PAI scores of infants treated and not treated with iNO. B, Distribution of MGI and PAI scores of infants requiring patch repair and those requiring primary repair. C, Distribution of MGI and PAI scores of infants who required and those who did not require HOT.

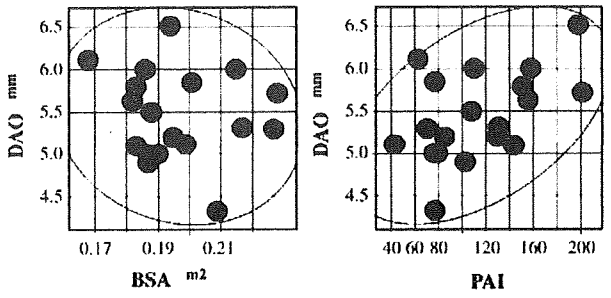

Fig. 4 Scatter plots showing correlations between DAO and BSA and DAO and PAI. The descending aorta was not significantly correlated with BSA ($r = -0.126$) but was significantly correlated with PAI ($r = 0.483$; $P < .05$).

induced by herniation of the abdominal viscera; therefore, the stroke volume from both the right and left sides of the heart may decrease. This factor may constrict the growth of the DAO. Therefore, the diameter of the DAO used to calculate MGI may be an inappropriate variable for standardizing the size of the pulmonary artery.

Although the results of our study are only suggestive, they included limitations such as a small sample size and a single-center trial. None of the survivors in our study had right-side CDH because of the small sample; therefore, the association between 2 indices and disease severity in survivors is applicable only to left-side CDH. In addition, we used muscle relaxants in our patients and did not use ECMO aggressively unless the patients with CDH also had pneumothorax or pneumonia because infants with CDH who were treated with ECMO in our hospital in the past had poor outcomes. These managements could alter the outcome and affect the interpretation of our results. If these indices could predict the need for ECMO, we would be able to decide whether to transfer patient to a facility where ECMO is available.

The results of the present study suggest that PAI is a more useful index for predicting disease severity in survivors as well as mortality in infants with CDH. These findings are important because the determination of disease severity in survivors soon after birth provides parents with more precise information about the anticipated course of treatment, minimizes treatment disruption, and maximizes the efficient management of patients with CDH.

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ワークショップ18「胎児治療」

双胎間輸血症候群に対するレーザー手術の治療効果

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Key words
twin-twin transfusion syndrome
monochorionic diamnionic twin
fetoscopic laser photocoagulation
laser surgery
fetal therapy

はじめに

双胎間輸血症候群（TTTS）は，一絨毛膜二羊膜双胎（MD双胎）において両児間の血流不均衡が顕著となった病態で，胎盤吻合血管に起因する極めて予後不良な疾患である．治療法として胎児鏡下に胎盤吻合血管をレーザー凝固・遮断するレーザー手術（FLP）が導入され，欧米の専門施設ではTTTSの第一選択治療法となっている[1]．2004年Eurofoetusによるランダム化比較対照試験で，羊水吸引術に比べFLPが有効であることが示された[1]が，2007年米国の臨床試験ではFLPの成績が不良で有効性を示すことができず[2]，手術習熟度の重要性が指摘された．

本邦においてもFLPは2002年に導入され[3]，現在までに300例以上施行されている．そこで日本におけるFLPの治療成績を明らかにし，FLPの有効性について評価するためにレーザー手術施行例の予後調査解析を行った．またFLP術後の予後に関連する因子の検索を行った．

対象と方法

2002年7月1日より2006年12月31日までの間に，4施設（国立成育医療センター，聖隷浜松病院，山口大附属病院，国立病院機構長良医療センター）においてFLPを施行したTTTS 181例を対象とした．FLPの適応は妊娠16週以降26週未満のTTTS stage ⅠからⅣで，FLPは各施設の倫理委員会承認後，患者夫婦の同意を得て施行した．胎児鏡を母体経皮的に受血児の羊水腔内に挿入し，胎盤吻合血管をNd：YAGレーザーにてすべて凝固した[4]．調査研究プロトコールと調査票を作成し，各施設の倫理委員会の承認を得た後，診療情報記録をもとに調査を実施し[5]，データ収集・固定後に解析を行った[6]．主な調査項目は，児の生存（生後28日，生後6カ月），児の神経学的後遺症（生後6カ月），術前超音波所見などで，予後に関連する因子の統計解析は単変量解析の後，多変量解析を行った．この研究は，平成19-20年度厚生科学研究費補助金：医療技術実用化総合研究事業「科学的根拠に基づく胎児治療法の臨床応用に関する研究」（左合班）の一部として行われた[5][6]．

結果

181例の臨床背景を表1に示す．手術を施行した妊娠週数の平均は妊娠21週であった．胎盤の位置は，前壁，後壁が約半数であった．Quintero分類のstage Ⅲ，Ⅳが75％を占めた．妊娠帰結を表2に示す．術後28

表1 対象の背景 N＝181

年齢	31.0 ± 4.5
初産婦 - no.（%）	100 (55%)
手術妊娠週数 - wk	21.0 ± 2.4
胎盤位置 - no.（%）	
前壁	89 (49%)
後壁	92 (51%)
Quintero stage - no.（%）	
Stage 1	14 (8%)
Stage 2	30 (17%)
Stage 3	113 (62%)
Stage 4	24 (13%)

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表2 妊娠帰結 N = 181

妊娠合併症		
	術後7日以内流産	4 (2.2%)
	前期破水 (術後7日以内)	7 (3.9%)
	前期破水 (術後28日以内)	14 (7.7%)
分娩週数 - wk		
	中間値	32.9
分娩週数 - no.		
	< 24wk	13 (7.2%)
	24 to < 28wk	20 (11.1%)
	28 to < 32wk	40 (22.1%)
	32 to < 34wk	36 (19.9%)
	34 to < 36wk	19 (10.5%)
	≧ 36wk	53 (29.3%)

表3 生存率

生後28日生存	
0児生存	16 (8.8%)
1児生存	48 (26.5%)
2児生存	117 (64.6%)
少なくとも1児生存	165 (91.2%)
生後6カ月生存	
0児生存	18 (9.9%)
1児生存	51 (28.2%)
2児生存	112 (61.9%)
少なくとも1児生存	163 (90.1%)

表4 FLPの治療成績比較

年	発表者	少なくとも1児生存
1999	Hecher	58/73 (79%)
2000	Quintero	70/89 (78%)
2004	Senat (Ville)	55/72 (76%)
2005	Lopriore	70/85 (82%)
2006	Gray	27/31 (87%)
2007	Middeldrop	81/100 (81%)
2009	本研究	165/181 (91%)

日以内の前期破水は7.7%で，分娩週数の中間値は妊娠33週であった．24週未満の分娩は，7.2%で，34週以降に分娩となったのは39.8%であった．

生存率を表3に示す．生後28日の2児生存率は64.6%で，1児生存率は26.5%で，91.2%で少なくとも1児の生存を得た．同様に生後6カ月の2児生存率は61.9%で，1児生存率は28.2%で，90.1%で少なくとも1児の生存を得た．生後6カ月生存例で重篤な脳神経障害を認めたのは4.7%であった．治療成績の比較を表4に示す[7]．日本の治療成績は欧米の専門施設の治療成績に比較して優るとも劣らぬものであった．

術前所見と生後28日の児の死亡との関連について単変量解析を行ったところ，供血児の死亡に関連する因子として有意であったのは，推定児体重と臍帯動脈拡張期血流の逆流・途絶であった．受血児の死亡に関連する因子として有意であったのは，静脈管血流の逆流と胎児水腫であった．これら単変量解析で有意であった因子を用いた多変量解析では，供血児の死亡に関連する有意な因子は，臍帯動脈拡張期血流逆流 (OR 7.98 (95% CI；2.38-26.68) p = 0.0001)，臍帯動脈拡張期血流途絶 (OR 3.56 (95% CI；1.64-7.95) p = 0.0001) であった．受血児の死亡に関連する有意な因子は，静脈管血流逆流 (OR 2.35 (95% CI；0.98-5.63) p = 0.058) であった．

結論

FLP施行後の児生存率は高く，神経後遺症は少なく，妊娠26週未満のTTTSに対してFLPは有効な治療法である．日本の治療成績は欧米の成績に比較して優るとも劣らぬものであり，日本においてもTTTSに対してFLPは第一選択治療法と考えられる．術前超音波所見では，供血児の臍帯動脈拡張期血流逆流・途絶と受血児の静脈管血流逆流が術後の児の死亡と関連性が高く，FLP治療後の予後予測因子と考えられる．

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ワークショップ19「倫理問題」

胎児治療の倫理と胎児治療法の臨床的評価

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佐々木愛子　大井 理恵　種元 智洋　北川 道弘　名取 道也

Key words
fetal therapy
fetal surgery
clinical assessment
twin-twin transfusion syndrome
laser surgery

はじめに

胎児治療は，子宮内の疾患を有する胎児に対して母体を介して治療行為を行うものである．種々の胎児治療法が試みられているが，治療効果の科学的根拠は乏しく，実験的治療の域を脱していない治療法も少なくない．胎児治療においては，治療対象となる胎児のみならず，胎児のために治療行為を受ける母体にも少なからず侵襲が及ぶ．実験的治療の側面と母体への不利益の観点から，胎児治療の実施においては倫理的検討が必要となる．そこで倫理的検討の基礎として胎児治療法の臨床的評価を試みた．

胎児治療法の評価の考え方

胎児治療を行う条件として次に挙げる2つの条件を満たす必要がある．1）胎児治療を行わないと予後が不良である，2）胎児治療を行うと予後が良好である，どちらか一方では不十分である．1）は自然歴で予後が不良であることであり，2）は治療成績が良好であることである．また実施にあたっては，治療法による母体への侵襲度を考慮する必要がある[1]（図1）．したがって，胎児治療法の評価は，疾患の自然歴に対して，治療によってもたらされる胎児の利益（治療成績）と，治療によってこうむる母体の不利益（母体安全性）を考慮して総合的に判断することとなる[2]（図2）．

胎児治療法の臨床的評価

疾患の自然歴は明らかでない場合も少なくなく，また治療成績もエビデンスとしての精度が低い場合が多く，胎児治療法を正確に評価することは難しい．しかし，現在行なわれている胎児治療法の臨床的位置付けを明

図1　胎児治療法と母体侵襲度

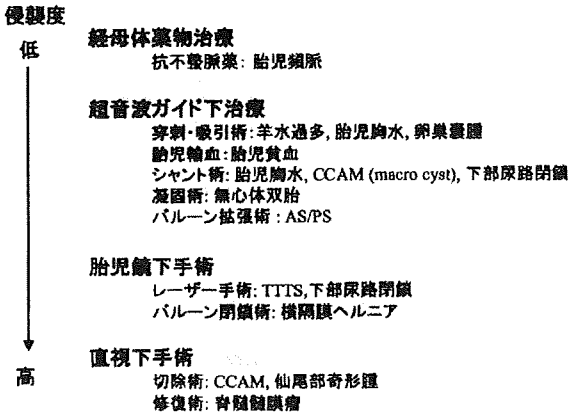
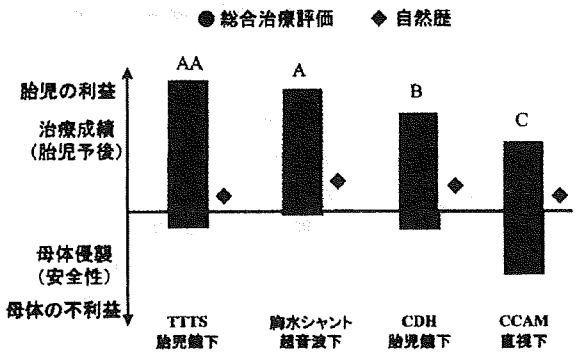


図2　胎児治療法の臨床的評価の考え方



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