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Ⅳ．研究成果の刊行物・別刷

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Evaluation of Transplacental Treatment for Fetal Congenital Bradyarrhythmia

– Nationwide Survey in Japan –

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Background: There are few large studies of fetal congenital bradyarrhythmia. The aim of the present study was to investigate the effects and risks of transplacental treatment for this condition.

Methods and Results: Using questionnaires, 128 cases of fetal bradyarrhythmia were identified at 52 Japanese institutions from 2002 to 2008. Of the 128 fetuses, 90 had structurally normal hearts. Among these 90 fetuses, 61 had complete atrioventricular block (CAVB), 16 had second-degree AVB, 8 had sinus bradycardia, and 5 had other conditions. The 61 CAVB fetuses were divided into those who did (n=38) and those who did not (n=23) receive transplacental medication. Monotherapy with β-sympathomimetics, steroid monotherapy, and combination therapy with these agents was given in 11, 5 and 22 cases, respectively. Beta-sympathomimetics improved bradycardia (P<0.001), but no medication could significantly improve the survival rate. Fetal hydrops was associated with a 14-fold increased risk of perinatal death (P=0.001), and myocardial dysfunction was a significant risk factor for poor prognosis (P=0.034). Many adverse effects were observed with steroid treatment, with fetal growth restriction increasing significantly after >10 weeks on steroids (P=0.043).

Conclusions: Treatment with β-sympathomimetics improved bradycardia, but survival rate did not differ significantly in fetuses with and without transplacental medication. It is recommended that steroid use should be limited to <10 weeks to avoid maternal and fetal adverse effects, especially fetal growth restriction and oligohydramnios. (*Circ J* 2012; **76:** 469–476)

Key Words: Anti-Ro/SSA antibody; Congenital atrioventricular block; Pregnancy; Steroids; Transplacental treatment

Fetal congenital bradyarrhythmia is an uncommon but life-threatening disease, especially in the case of complete atrioventricular block (CAVB), which has a poor prognosis because of fetal hydrops, endocardial fibroelastosis and late-onset dilated cardiomyopathy.[1–9] Predominantly untreated CAVB has a significant mortality rate of 14–34%, while congenital CAVB is irreversible and requires a pacemaker in approximately 66% of cases after birth.[10] The association of CAVB with maternal anti-Ro/Sjögren's syndrome A (SSA) antibodies is well established, but the trigger for the maternal antibody interaction with the fetal Ro particle is unknown in some cases of antibody-exposed babies.[2,7–9,11,12]

There is limited evidence for the clinical efficacy of transplacental treatment of congenital AVB.[13–19] Steroids and i.v. immunoglobulins are given as anti-inflammatory treatment, while β-sympathomimetics are used for fetal pacing.[20] A recent

Received September 8, 2011; revised manuscript received October 27, 2011; accepted November 1, 2011; released online December 23, 2011 Time for primary review: 18 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-11-1020

Table 1. Baseline Characteristics of CAVB Fetuses

	Medication group (n=38)	No medication group (n=23)	P value
Maternal anti-SSA antibodies	29 (76.3)	11 (47.8)	<0.05‡
Gestational age at diagnosis (weeks)	24±3.2	28±5.7	<0.005†
Fetal heart rate at diagnosis (beats/min)	58±7.9	63±14.7	NS†
Fetal hydrops	16 (42.1)	6 (26.1)	NS‡
Fetal myocardial dysfunction	13 (34.2)	7 (30.4)	NS‡
Gestational age at initiation of therapy (weeks)	26±3.6	–	
Fetal heart rate at initiation of therapy (beats/min)	56±8.4	–	
Gestational age at delivery (weeks)	34±4.0	35±4.5	NS†
Birth weight (g)	2,120±620	2,528±653	<0.001†
Delivery mode			
Vaginal	8	7	NS‡
Cesarean section	30	16	NS‡
Permanent pacemaker implantation	14 (46.7)	6 (35.3)	NS‡
Neonatal survival	30 (78.9)	17 (73.9)	NS‡

Data given as mean±SD or n (%). P<0.05, significant difference.
†Student's t-test; ‡chi-square test and Fisher's exact test.
CAVB, complete atrioventricular block; SSA, Sjögren's syndrome A.

cohort study found an improved survival rate of >90% with initiation of maternal high-dose dexamethasone at the time of CAVB detection, and maintenance of this drug during pregnancy with use of β-sympathomimetics to keep fetal heart rates at >55 beats/min.[9,21] It was also suggested that prolonged use of dexamethasone might render fetuses with congenital CAVB less likely to develop the additional manifestations of myocarditis, cardiomyopathy, and hydrops fetalis, thus improving the overall outcome. Use of steroids, however, is controversial because of the potential risks for the fetus, including problems with neurological development, growth retardation, and oligohydramnios.[22–25]

Few large studies of fetal congenital bradyarrhythmia have been performed in Japan. The aims of the present study were to determine the features of fetal congenital bradyarrhythmia in Japan, and to examine the effects and risks of transplacental treatment for this condition.

Methods

Subjects

Data were collected using questionnaires sent to Departments of Perinatology and Pediatric Cardiology at 750 institutions in Japan over 7 years (2002–2008). The response rate was 60.7% (455 institutions). Fetal bradyarrhythmia was defined as ventricular heart rate <100 beats/min at the time of diagnosis.[4] The following perinatal data were also collected: gestational age at diagnosis and delivery, presence or absence of a congenital heart defect (CHD), type of bradyarrhythmia, method of diagnosis, presence or absence of maternal autoantibodies such as anti-Ro/SSA antibodies, presence or absence of fetal hydrops, presence or absence of fetal myocardial dysfunction, fetal ventricular and atrial heart rate at presentation, prenatal treatment, mode of delivery, and outcome. Adverse effects related to prenatal treatment were also evaluated.

Statistical Analysis

Statistical analysis was performed using STATA 11.1 (StataCorp, College Station, TX, USA) and JMP 9 (SAS Institute, Cary, NC, USA). Data are presented as mean±SD or number of patients and were analyzed using Student's t-test. Categorical variables were evaluated on chi-square test and Fisher's exact test. Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody. Time to fetal or neonatal death was analyzed using the Kaplan-Meier method with a log-rank test and a Cox proportional hazard model. P<0.05 was considered significant.

Results

Baseline Characteristics

A total of 128 cases were registered from 52 institutions during 7 years (2002–2008). All cases of fetal bradyarrhythmia were diagnosed during fetal life using echocardiography. In 8 cases, magnetocardiography was performed due to fetal bradyarrhythmia and family history of long QT syndrome (LQTS). Of the 128 fetuses, 38 (29.7%) had CHD, 15 had left atrial isomerism, 1 had right atrial isomerism, 5 had atrioventricular septal defect, 4 had corrected transposition of the great arteries, 4 had pulmonary stenosis, and 9 had other conditions. Patent ductus arteriosus and atrial septal defect were categorized as an absence of CHD. Ninety fetuses (70.3%) had a structurally normal heart, of whom 61 had CAVB, 16 had second-degree AVB, 8 had sinus bradycardia, 3 had sick sinus syndrome. Nine LQTS cases occurred in combination with another condition.

CAVB

Of the 61 fetuses with a structurally normal heart and CAVB (Table 1), 38 received transplacental medication. No fetus showed improvement of heart block. Monotherapy with β-sympathomimetics was given in 11 cases, steroids were given in 5 cases, and combination therapy with these agents was used in 22 cases. No transplacental medication was given in 23 cases. Ritodrine hydrochloride was used as the β-sympathomimetic agent. Steroids tended to be used in fetuses that were positive for maternal anti-Ro/SSA antibody throughout pregnancy, but the chosen steroid differed among institutions. Maternal i.v. immunoglobulin was not used. After birth, a pacemaker was implanted based on the Japanese guidelines of syncope, ventricular heart rate <50 beats/min, decreased cardiac function, LQTS, and a sudden pause longer than 2–3-fold the regular ventricular heart rate.

Table 2. Factors in Improvement of Bradycardia

	OR	95%CI	P value
β-sympathomimetics	49.02	5.18–464.02	<0.005
Steroids	1.32	0.24–7.20	0.745
β-sympathomimetics+steroids	725,448.8	0	0.996
Fetal heart rate	1	0.93–1.08	0.924
Fetal hydrops	0.41	0.07–2.39	0.319
Fetal myocardial dysfunction	1.14	0.20–6.60	0.883
Maternal anti-Ro/SSA antibodies	0.22	0.04–1.36	0.1 5

P<0.05, significant difference.
Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody.
OR, odds ratio; CI, confidence interval; SSA, Sjögren's syndrome A.

Table 3. Factors in Fetal or Neonatal Death

	HR	95%CI	P value
β-sympathomimetics	1.16	0.37–3.63	0.792
Steroids	0.56	0.20–1.58	0.273
Fetal heart rate	0.98	0.92–1.05	0.546
Fetal hydrops	13.84	3.12–61.44	0.001
Fetal myocardial dysfunction	2.44	0.71–8.40	0.157
Maternal anti-Ro/SSA antibodies	1.07	0.33–3.47	0.906

P<0.05, significant difference.
Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody.
HR, hazard ratio; CI, confidence interval; SSA, Sjögren's syndrome A.

Table 4. Factors in Development of Fetal Hydrops

	OR	95%CI	P value
β-sympathomimetics	2	0.35–11.50	0.439
Steroids	0.27	0.04–1.97	0.198
Fetal heart rate	1.01	0.94–1.08	0.813
Fetal myocardial dysfunction	5.71	1.14–28.62	0.034
Maternal anti-Ro/SSA antibodies	0.71	0.13–3.90	0.698

P<0.05, significant difference.
Logistic regression was used to adjust for baseline variables known to be associated with fetal ventricular heart rate, fetal myocardial dysfunction, and maternal anti-Ro/SSA antibody.
OR, odds ratio; CI, confidence interval; SSA, Sjögren's syndrome A.

The anti-Ro/SSA antibody-positive rate was significantly higher in fetuses treated with transplacental medication compared to those who did not receive this medication (76.3% vs. 47.8%; P=0.031). Gestational age at diagnosis was significantly lower in those receiving transplacental medication (24.0 weeks vs. 28.3 weeks; P=0.003). Fetal ventricular heart rate at diagnosis did not differ between the 2 groups, but the ventricular heart rate was significantly lower in fetuses treated with transplacental medication (56 beats/min vs. 63 beats/min; P=0.034). Birth weight was also significantly lower in fetuses treated with transplacental medication (2,120 g vs. 2,528 g; P=0.006). Gestational age at delivery, neonatal survival rate, and pacemaker implantation rate did not differ between the 2 groups.

Multivariate analysis was performed with adjustment for baseline variables with a known association with fetal ventricular heart rate, fetal hydrops, fetal myocardial dysfunction, and the presence of maternal anti-Ro/SSA antibodies (Tables 2–4). In this analysis, β-sympathomimetic treatment was significantly associated with improved bradycardia (odds ratio [OR], 49.02; 95% confidence interval [CI]: 5.18–464.02; P<0.001), whereas steroids were ineffective, and no evidence of a synergistic effect was obtained. The presence of maternal anti-Ro/SSA antibodies may inhibit improvement of bradycardia, but this effect was not significant (OR, 0.22; 95%CI: 0.04–1.36; P=0.105). Drug therapy had no significant effect on survival. Fetal ventricular heart rate and the presence of maternal anti-Ro/SSA antibodies also had no influence on prognosis, but fetal hydrops was associated with a 14-fold increased risk of perinatal death (hazard ratio [HR], 13.84; 95%CI: 3.12–61.44; P=0.001).

Kaplan-Meier survival curves are shown in Figure. The primary endpoint was intrauterine death or neonatal death. Beta-sympathomimetic treatment was not associated with improved prognosis. Steroid also did not improve the prognosis (HR, 0.56; 95%CI: 0.20–1.58; P=0.273). Fetal myocardial dysfunction was a significant risk factor for fetal hydrops (OR, 5.71; 95%CI: 1.14–28.62; P=0.034). Fetal ventricular heart rate and the presence of maternal anti-Ro/SSA antibodies were not associated with fetal hydrops. Beta-sympathomimetic treatment did not inhibit development of fetal hydrops. Steroids tended to inhibit fetal hydrops, but again this effect was not

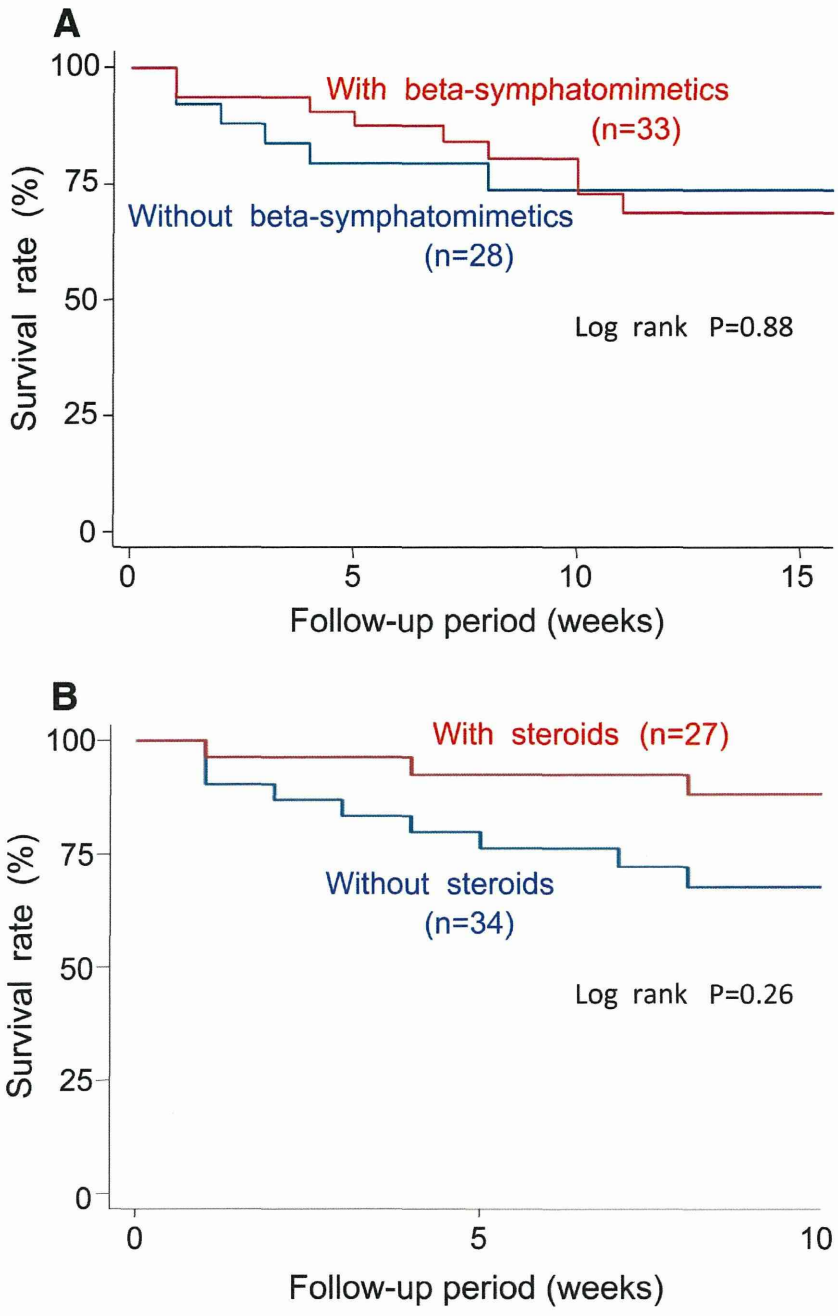

Figure. Kaplan-Meier survival curves (log-rank test and Cox proportional hazard model) for the primary endpoint (fetal death or neonatal death) in fetuses treated (**A**) with and without β-sympathomimetics and (**B**) with and without steroids. Follow-up period, time from diagnosis in utero to fetal or neonatal death. Significant difference defined as P<0.05.

statistically significant (OR, 0.27; 95%CI: 0.04–1.97; P=0.198). Drug therapy had no significant effect on improvement of fetal myocardial dysfunction.

Second-Degree AVB With Bradycardia

Of the 90 fetuses with a structurally normal heart, second-degree AVB was present in 16 cases (**Table 5**). Transplacental medication was given in 8 of these cases: β-sympathomimetic monotherapy in 4, steroids in 3, and a combination of these therapies in 1. In the 8 medication cases, fetal ventricular heart rate at diagnosis was significantly lower than that in the non-medication cases (70 beats/min vs. 79 beats/min; P=0.017). No other clinical characteristics differed significantly between the 2 groups. Of the 8 medicated fetuses, 3 developed CAVB, 3 maintained second-degree AVB, 1 improved to first-degree AVB, and 1 had no AVB at the time of delivery. Of the 8 non-medicated fetuses, 2 developed CAVB, 3 maintained second-degree AVB, and 3 had no AVB at the time of delivery. Survival rate did not differ between the groups (87.5%).

Adverse Effects of Transplacental Treatment

Treatment-related adverse events were examined in the 63 fetuses with a structurally normal heart and no fetal hydrops (**Table 6**). Steroids were given in 23 cases, drugs other than steroids were given in 10 cases, and no treatment was given in 30 cases. Gestational age at delivery did not differ among these 3 groups. In the steroid group, birth weight was significantly lower than in the non-treatment group (2,201 g vs.

Table 5. Second-Degree AVB Fetus Baseline Characteristics vs. Medication

	Medication (n=8)	No medication (n=8)	P value
Maternal anti-Ro/SSA antibodies	4	3	NS‡
Gestational age at diagnosis (weeks)	28±4.3	26±5.0	NS†
Fetal heart rate at diagnosis (beats/min)	70±9.0	79±10.4	<0.05†
Fetal hydrops	2	2	NS‡
Fetal myocardial dysfunction	3	2	NS‡
Gestational age at initiation of therapy (weeks)	29±4.8	–	
Fetal heart rate at initiation of therapy (beats/min)	70±10.0	–	
Gestational age at delivery (weeks)	35±3.8	37±2.1	NS†
Birth weight (g)	2,207±688	2,533±544	NS†
Delivery mode			
Vaginal	2	5	NS‡
Cesarean section	6	3	NS‡
Degree of AVB at delivery			
Complete	3	2	NS‡
Second	3	3	NS‡
First	1	0	NS‡
None	1	3	NS‡
Neonatal survival	7 (87.5)	7 (87.5)	NS‡

Data given as mean±SD or n (%).
P<0.05, significant difference. †Wilcoxon test; ‡chi-square test and Fisher's exact test.
AVB, atrioventricular block; SSA, Sjögren's syndrome A.

Table 6. Baseline Characteristics vs. Treatment Type†

	Steroid treatment (n=23)	Non-steroid treatment (n=10)	No treatment (n=30)
Treatment (weeks)	8.8±4.4	5.6±3.2	–
Gestational age at delivery (weeks)	36±2.6	35.8±2.6	36.8±3.0
Birth weight (g)	2,201±525*	2,413±552	2,713±512*
Fetal arrythmia: CAVB	21	6	23
Fetal arrythmia: Second-degree AVB	1	2	5
Maternal diabetes	1 (4.3)	0	0
Fetal growth restriction	6 (26.1)	0	2 (6.7)
Fetal oligohydramnios	2 (8.7)	0	0
Neonatal adrenal insufficiency	1 (4.3)	0	0

Data given as mean±SD or n (%).
†For fetuses without fetal hydrops and with a structurally normal heart. *P<0.05 (Student's t-test).
CAVB, complete atrioventricular block; AVB, atrioventricular block.

Table 7. Baseline Characteristics vs. Length of Steroid Treatment

	<10 weeks (n=12)	≥10 weeks (n=11)	P value
Treatment (weeks)	5.4±2.7	12.5±2.5	<0.01†
Gestational age at delivery (weeks)	35±3.2	36±1.7	NS†
Birth weight (g)	2,184±569	2,218±503	NS†
Maternal diabetes	0	1 (9.1)	NS‡
Fetal growth restriction	1 (8.3)	5 (45.5)	<0.05‡
Fetal oligohydramnios	0	2 (18.2)	NS‡
Neonatal adrenal insufficiency	0	1 (9.1)	NS‡

Data given as mean±SD or n (%). P<0.05, significant difference.
†Student's t-test; ‡chi-square test and Fisher's exact test.

2,713 g; P=0.001) and fetal growth restriction was close to being significantly higher than in the non-steroid (26.1% vs. 0%; P=0.050) and non-treatment (26.1% vs. 6.7%; P=0.074) groups. Adverse effects that might have been attributable to the use of steroids included development of oligohydramnios in 8.7% of cases, maternal diabetes in 4.3%, and neonatal adrenal insufficiency in 4.3%. All these adverse effects were observed in cases of steroid use >10 weeks (Table 7). In particular, fetal growth restriction increased significantly after steroid use >10 weeks (45.5% vs. 8.3%; P=0.043).

LQTS

Of the 90 fetuses with a structurally normal heart, 9 (10.0%) were diagnosed with LQTS, including 4 diagnosed on electrocardiography after birth and 5 diagnosed on magnetocardiography during fetal life. The background of the LQTS fetuses included a family history of LQTS (n=2), maternal anti-Ro/SSA antibody (n=2), fetal hydrops (n=3), myocardial dysfunction (n=2), CAVB (n=6), second-degree AVB with bradycardia (n=1), and sinus bradycardia (n=2). In 4 of the 9 cases of LQTS, emergency cesarean section was performed because of fetal ventricular tachycardia/torsades de pointes (VT/TdP) at 33–36 weeks of gestation. In 2 of the 9 cases, fetal hydrops caused neonate death.

Discussion

This is the first large-scale study to investigate the effects and risks of transplacental treatment for fetal congenital bradyarrhythmia in Japan. The results indicate that fetal hydrops is associated with a 14-fold increased risk of perinatal death, and that fetal myocardial dysfunction is a significant risk factor for fetal hydrops. Fetal ventricular heart rate and the presence of maternal anti-Ro/SSA antibodies were not associated with neonatal prognosis. Beta-sympathomimetics improved bradycardia, but survival rate did not differ significantly with regard to transplacental medication. Maternal and fetal adverse effects were observed in cases of steroid use. In particular, fetal growth restriction increased significantly after steroid use >10 weeks.

Evaluation of Anti-Ro/SSA Antibodies

Ro/SSA is one of the major immunogenic ribonucleoproteins, and antibodies against these proteins are found in a number of connective diseases, especially in Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE). Anti-Ro/SSA antibodies are detected in 60–90% of SS cases and in 30–50% of SLE cases.[26,27] Interestingly, these antibodies are relatively common and are detected in 1–2% of randomly tested pregnant women.[28] Currently, the outcome of anti-Ro/SSA-positive pregnancies is very good when prospectively followed by multidisciplinary teams with experience in this field.[1] Transplacental passage of anti-Ro/SSA antibodies from mother to fetus, however, is associated with a risk of development of neonatal lupus erythematosus (NLE).[2,11,12] NLE is an uncommon but life-threatening disease of the fetus and neonate, with important cardiac complications of CAVB, sinus bradycardia, QTc interval prolongation, endocardial fibroelastosis, and late-onset dilated cardiomyopathy.[3–5] Congenital CAVB develops in 1–5% of anti-Ro/SSA antibody-positive pregnancies, typically between 18 and 24 weeks of gestational age. Predominantly untreated CAVB has a mortality rate of 14–34%,[1–9] consistent with the untreated CAVB mortality rate of 26% in the current study.

The association of NLE with maternal anti-Ro/SSA antibodies is well established, but the trigger of the maternal antibody interaction with the fetal Ro particle is unclear in some antibody-exposed babies. The percentage of maternal anti-Ro/SSA antibody-positive fetuses with CAVB diagnosed in utero is unknown. Brucato et al and Jaeggi et al found maternal anti-Ro/SSA antibodies in 92% of 37 CAVB cases,[7,9] whereas in the present study maternal anti-Ro/SSA antibodies were detected in only 66% of 61 CAVB fetuses with a structurally normal heart. Jaeggi et al also reported that CAVB occurred in 5% of prospectively screened pregnancies with anti-Ro/SSA ELISA levels >100 U/ml, but did not occur in pregnancies with levels <50 U/ml.[6] Approximately two-thirds of anti-Ro/SSA antibody-positive mothers had low anti-Ro/SSA levels and probably little risk of development of fetal cardiac NLE.[8] It is unclear why the anti-Ro/SSA-positive rate in the present study was lower than in other reports. It is unlikely to be due to the sensitivity of the laboratory methods, but it is possible that other undetectable antibodies associated with congenital AVB are present in the Japanese population. Brucato et al and Lopes et al found similar mortality rates in the anti-Ro/SSA-positive and -negative groups,[7,8] and in the present multivariate analysis anti-Ro/SSA antibodies were not associated with prognosis.

Benefits and Risks of Transplacental Treatment

Congenital AVB is a progressively developing disease that evolves through 2 fundamental phases: an early phase characterized by the occurrence of still reversible AV conduction abnormalities (first- or second-degree AVB) and a final phase in which development of irreversible damage of the conduction system leads to the appearance of CAVB.[29] The specific pathogenetic mechanisms involved in the 2 phases have not been clarified, but there are 2 main theories. The first is based on an inflammatory-driven injury elicited by interaction between anti-Ro/SSA antibodies and specific antigens expressed in the conduction tissue of the fetal heart (inflammatory theory). The second theory involves electrophysiologic interference of anti-Ro/SSA antibodies with heart conduction (electrophysiological theory).[20] Consistent with these respective theories, steroids and i.v. immunoglobulins are used for anti-inflammatory treatment, while β-sympathomimetics are given for fetal pacing.

Several studies have found that a ventricular heart rate <55 beats/min is a risk factor for fetal and neonatal death,[4,14] and have recommended transplacental treatment with β-sympathomimetics to increase the heart rate. Jaeggi et al and Maeno et al, however, found that fetuses with CAVB without CHD and with a ventricular heart rate of <55 beats/min were not at risk.[30,31] In the present study, fetal ventricular heart rate did not influence fetal hydrops and prognosis, but treatment with a β-sympathomimetic agent was significantly associated with improved bradycardia.

To date, evidence of clinical efficacy of transplacental treatment has been limited to cases of congenital AVB.[13–19] Jaeggi et al reported a significant improvement in the outcome of fetal CAVB simultaneously with the introduction of routine perinatal treatment guidelines in 1997.[9] Hutter et al obtained an improved survival rate of >90% by initiation of maternal high-dose dexamethasone at the time of CAVB detection and maintenance of this dose during pregnancy, with addition of β-sympathomimetics to keep the fetal heart rate above 55 beats/min.[21] It was also suggested that prolonged use of dexamethasone might render a fetus with congenital CAVB less likely to develop additional manifestations of cardiac NLE such as myocarditis, cardiomyopathy, and hydrops fetalis, thus improving the overall outcome. The present findings suggest that use of steroids might render the affected fetus less likely to develop fetal hydrops, but that the neonatal survival rate improved only to 79%. The reason for the relatively bad prognosis in the present study may have been the difference in the rate of fetal hydrops compared to the Hutter et al study (42% vs. 10%). Undetectable autoantibodies or virus infection may be related to the increased rate of fetal hydrops in the Japanese population. Furthermore, Hutter et al initiated maternal high-dose dexamethasone at the time of CAVB diagnosis, at a mean gestational age of 24 weeks. The mean age of diagnosis was similar in the present study, but mean gestational age at which steroids were started was 26 weeks. In addition, the percentage of steroids used in transplacental treatment was

lower in the present patients (71% vs. 95%). These findings suggest that sufficient steroid dose at an early stage is very important to prevent fetal hydrops and to improve prognosis.

Use of steroids is controversial because of the potential risks for the fetus and mother, including problems with fetal growth restriction, oligohydramnios, and neurological development. Animal models suggest that repeated antenatal steroid doses can interfere with the growth and development of the immature brain, and human studies suggest that antenatal and postnatal dexamethasone may negatively affect a child's neuropsychological development.[22–24] In contrast, Brucato et al found no negative effects on neuropsychological development and intelligence in a cohort of preschool- and school-age children with CAVB who had been prenatally exposed to maternal anti-Ro antibodies and prolonged dexamethasone treatment.[25] The association of fetal growth restriction and oligohydramnios with antenatal steroids is well established, but the amount and length of steroid treatment that can be used safely is unclear. We note that development of fetal growth restriction and oligohydramnios are dose-related complications of steroids. Consequently, we recommend limiting steroid use to <10 weeks to avoid maternal and fetal adverse effects.

Prevention of Progression to Congenital CAVB

There are many case reports describing prevention of congenital CAVB, and first- or second-degree AVB is also relatively common and often normalizes spontaneously before or soon after delivery.[32] Recent prospective studies suggest that steroids and i.v. immunoglobulins are not beneficial for preventing progression to congenital AVB.[33,34] Similarly, the present study found a lack of superiority of transplacental treatment for second-degree AVB with bradyarrhythmia.

LQTS

Recent evidence has shown that anti-Ro/SSA antibodies are associated with prolongation of the QTc interval.[35] Although the exact arrhythmogenic mechanisms have not been clarified, anti-Ro/SSA antibodies may trigger rhythm disturbances through inhibition of cross-reactions with several cardiac ionic channels, including calcium channels and the hERG potassium channel.[36,37] Beta-sympathomimetics may trigger life-threatening arrhythmia such as VT/TdP in patients with LQTS, and therefore use of these drugs should be avoided in fetuses with QTc interval prolongation.[38,39] In the present study, in 4 of the 9 LQTS cases, emergency cesarean section was performed because of fetal VT/TdP at 33–36 weeks of gestational age. Oka et al also recently described atrioventricular block-induced TdP.[40] With this background, we recommend avoidance of β-sympathomimetics in a fetus with a heart rate >55 beats/min. Furthermore, assessment of QTc interval prolongation on magnetocardiography may be required to evaluate the risk of fetal congenital bradyarrhythmia.

Study Limitations

There were several limitations in the present study due to retrospective data selection bias and the relatively small sample size. The nature of a multicenter retrospective observational study using a questionnaire is such that the clinical data obtained vary among cases, so treatment bias may exist. Only ritodrine hydrochloride was used as β-sympathomimetic treatment, but was given in cases involving fetal heart rate >55 beats/min at some institutions, while dexamethasone, betamethasone and prednisolone were used as steroids at different doses among institutions. The follow-up period after birth was insufficient to permit analysis of long-term morbidity and mortality, and this prevented evaluation of potential long-term benefits and risks of transplacental medication. Finally, the sample size might have been too small to detect the effects of steroids on fetal congenital bradyarrhythmia. The steroid effect may become significant in a study with a higher number of cases.

Guidelines are required for transplacental treatment of fetal congenital bradyarrhythmia and follow-up after birth. We expect to analyze long-term outcome of fetal congenital bradyarrhythmia in a future study. Further large prospective studies are also needed to establish the most appropriate treatment strategies in Japan.

Conclusion

Beta-sympathomimetics improved bradycardia, but survival rate did not differ significantly in fetuses treated with and without transplacental medication. We recommend limiting steroid use to <10 weeks to avoid maternal and fetal adverse effects, with fetal growth restriction and oligohydramnios being of particular concern.

Acknowledgments

This work was supported by a grant from The Ministry of Health, Labor and Welfare of Japan (Health and Labour Science Research Grants for Clinical Research for New Medicine).

Disclosures

Sources of financial support: The Ministry of Health, Labor and Welfare of Japan (Health and Labour Science Research Grants for Clinical Research for New Medicine). None of the authors have a conflict of interest to disclose.

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Journal of Pediatric Surgery (2012) 47, 441–447

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Original articles

Outcomes of prenatally diagnosed sacrococcygeal teratomas: the results of a Japanese nationwide survey

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Received 4 June 2011; revised 28 July 2011; accepted 27 August 2011

Key words:
Prenatal diagnosis;
Sacrococcygeal teratoma;
Tumor component;
Preterm labor;
Multicenter survey;
Mortality

Abstract

Background/Purpose: Few large multicenter surveys have been performed on sacrococcygeal teratomas (SCTs) describing both the prenatal and postnatal courses. The aim of this study was to review and report on the prenatal surveillance and postnatal outcome of a large cohort of fetuses with SCTs in Japan.

Methods: A nationwide retrospective cohort study was conducted on 97 fetuses prenatally diagnosed with SCTs between 2000 and 2009. The prenatal course, perinatal data, and postnatal outcome were reviewed.

Results: Eleven pregnancies were terminated before 22 weeks of gestation. Of the 86 remaining fetuses, 3 died in utero, and 83 were delivered. Three infants died before surgery, and 8 infants died after excisional surgery. The overall mortality was 26%, with a mortality excluding terminations of 16%. The gestational age at delivery was younger than 28 weeks in 5, 28 to 31 weeks in 13, 32 to 36 weeks in 27, and 37 weeks or more in 37 cases, with mortality rates of 60%, 38%, 11%, and 0%, respectively. The tumor component was predominantly cystic in 54 and predominantly solid in 32 cases, with mortality rates of 2% and 33%, respectively.

Conclusions: The overall mortality of prenatally diagnosed SCTs excluding terminations was 16%. Early delivery and predominantly solid component tumors were associated with an increased risk of mortality.

Sacrococcygeal teratoma (SCT), which originates from the 3 germinal layers, is the most common congenital tumor, with a birth prevalence of 1 in 27,000 live births [1]. Sacrococcygeal teratomas diagnosed postnatally have been associated with an excellent prognosis after surgical excision [2-5]. In contrast, it has been reported that fetuses with a prenatally diagnosed SCTs still have a high risk of death even if the prenatal diagnosis may have made a contribution to improvement of the outcome [6]. The main reason for the

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doi:10.1016/j.jpedsurg.2011.08.020

poor prognosis in fetal SCTs is high-output cardiac failure caused by increased blood flow according to the amount of solid component present in the tumor [7,8] and rupture of the tumor during delivery with a massive hemorrhage [9,10]. However, the reported mortality rate excluding terminations in the fetuses with SCTs varied widely from 18% to 63% in different series [6-16]. Most of these studies were conducted in a single institution with a small number of patients, and there may have been selection bias [8] because some of the institutions were specialized centers for fetal treatment. The natural history of fetal SCTs has not been fully characterized because few large multicenter surveys have been performed describing both the prenatal and postnatal courses. The aim of this study was to review and report on the prenatal surveillance and postnatal outcome of a large cohort of fetuses with SCTs in Japan based on a nationwide survey.

1. Materials and methods

A nationwide retrospective cohort study was conducted on fetuses prenatally diagnosed with SCTs at major Japanese perinatal centers. We initially sent a preliminary questionnaire requesting the number of fetuses prenatally diagnosed with SCTs between January 2000 and December 2009 to 325 major perinatal centers in Japan and asked them to participate in our detailed survey. One-hundred ninety centers (58.5%) responded to the preliminary survey and reported that there were 138 cases with SCTs diagnosed prenatally during the past 10 years. We then sent a second form requesting further details about the fetuses from the centers that had corresponding cases and had accepted our offer to participate in a detailed survey. Forty-eight centers that had 101 cases of fetal SCTs consented to participate in our survey and returned the forms with further details. Four fetuses that had not been followed up until fetal demise or live birth owing to maternal transfer were excluded from the study, so 97 fetuses prenatally diagnosed with SCTs between January 2000 and December 2009 at 46 Japanese perinatal centers were included in the study and analyzed. The patient demographics, including the year of prenatal diagnosis, gestational age at diagnosis, occurrence of polyhydramnios, signs of hydrops fetalis, fetal interventions, prenatal outcome, mode of delivery, gestational age at delivery, sex of the fetus, and birth weight were reviewed. The type of the tumor component, tumor location, histology of the tumor, maximum diameter of the tumor, and postnatal outcome were also reviewed.

Polyhydramnios was regarded as positive if there was a finding of polyhydramnios either in the initial or final fetal ultrasonography. The presence of signs for hydrops fetalis was defined as positive if there was a finding of ascites, pleural effusion, or skin edema either in the initial or final fetal ultrasonography. The type of the tumor component was defined as 1 of 4 categories, such as cystic type (>90% of the tumor is cystic), predominantly cystic mixed type (50%-90% of the tumor is cystic), predominantly solid mixed type (50%-90% of the tumor is solid), and solid type (>90% of the tumor is solid), and the cases were classified according to the schema described in the questionnaire (Fig. 1). The type of the tumor component was determined by pathologic findings in surgical cases and by prenatal or postnatal diagnostic imaging in nonsurgical cases. The tumor location was categorized according to Altman's classification [2] determined by operative findings or diagnostic imaging. The maximum diameter of the tumor was defined as the maximum value of the maximum diameter of the resected tumor, the maximum diameter of the computed tomography performed after birth, and the maximum diameter of the magnetic resonance imaging performed after birth in the cases of live births and as the maximum value on fetal ultrasonography in cases of fetal demise.

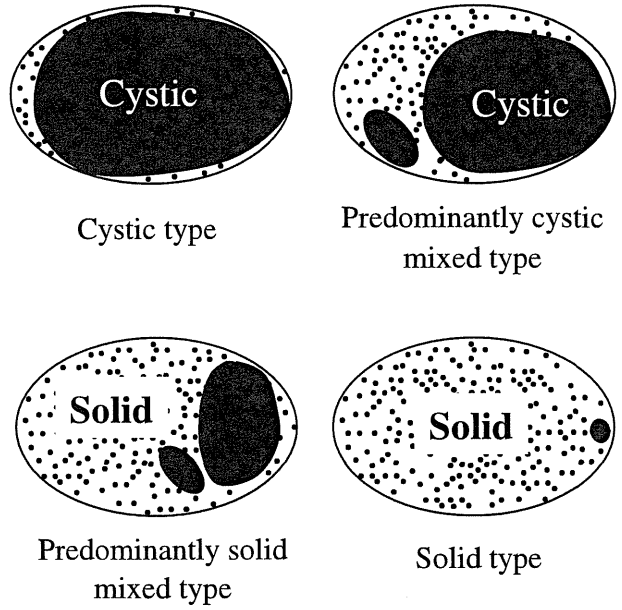

Fig. 1 A schematic diagram of the types of tumor components. Cystic type, more than 90% of the tumor is cystic; predominantly cystic mixed type, 50% to 90% of the tumor is cystic; predominantly solid mixed type, 50% to 90% of the tumor is solid; solid type, more than 90% of the tumor is solid.

The data were expressed as the medians (range). The frequencies and percentages were used to describe categorical data. The χ^2 test was used for the analysis of categorical data. $P < .05$ was considered to indicate statistical significance. Statistical analyses were performed with the JMP software program (version 8.02; SAS Institute, Inc, Cary, NC). This retrospective survey was approved by the institutional review boards of the 5 participating institutions (institutional review board approval no. 09392, National Center for Child Health and Development).

2. Results

The annual number of the fetuses with SCTs was less than 7 before 2005 but increased thereafter and exceeded 14 cases

per year after 2007 (Fig. 2). The median maternal age was 30 years (range, 18-41 years), and median gestational age at diagnosis was 25 weeks of gestation (range, 15-36 weeks). Twenty-four cases (24.7%) were diagnosed before 22 weeks of gestation, the period in which a termination of pregnancy is legally permitted in Japan [17]. Eleven pregnancies were terminated before 22 weeks of gestation, and 86 cases intended to deliver (Fig. 3). Of the 24 cases diagnosed before 22 weeks of gestation, there were no significant differences in the size of the tumor, type of the tumor component, or incidence of the signs for hydrops fetalis between the cases that were terminated and the cases that were intended to be delivered (data are not shown).

The outcomes of the infants with prenatally diagnosed SCTs are shown in Fig. 4. Of the 86 nonterminated fetuses, 3 resulted in intrauterine fetal deaths, and 83 survived to be born. Of these survivors, 4 cases underwent fetal intervention, including radiofrequency ablation (n = 1), abdominal paracentesis (n = 1), and cyst aspiration (n = 2). All 4 of these cases underwent tumor resection, and 3 survived after the surgery. The patient who underwent paracentesis died of a massive hemorrhage during the surgery. Amnioreduction had been performed in 11 pregnancies to prevent preterm labor and maternal discomfort owing to polyhydramnios. After the live birth, 3 infants died before surgery on the day of birth, and 80 infants underwent excisional surgery at a median of 74 hours (range, 1-1581 hours). Twenty-five infants underwent surgery in the first 24 hours of life, and 6 of them (24%) died, whereas 55 cases underwent surgery after 24 hours, and only 2 (4%) of them died. Four infants died after surgery during the early neonatal period, 2 died during the later neonatal period, and 2 died later in infancy. Of the 9 neonatal deaths, 7 were related to massive hemorrhage from the tumors. Bleeding from the tumors was already recognized in 6 neonates at the time of cesarean section delivery, and 4 of them, including 2 neonates with a tumor that ruptured during the delivery, died on the day of birth. The median follow-up of survivors was 23 months (range, 0-113 months). The overall mortality was 26% (25/97), with a mortality excluding terminations of 16% (14/86).

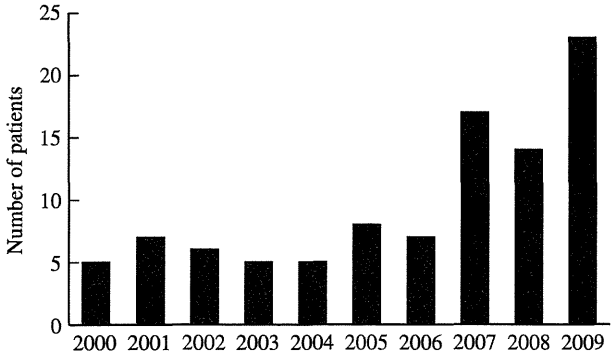

Fig. 2 The number of the fetuses with a prenatal diagnosis of SCT.

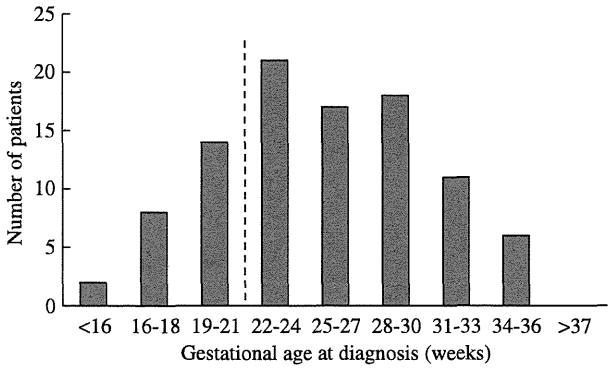

Fig. 3 The distribution of the gestational age at diagnosis. A termination of pregnancy is legally permitted in Japan before 22 weeks of gestation (broken line).

Table 1 reviews the demographics and mortality of the fetuses with SCTs that were intended to be delivered. The fetuses that had been diagnosed before 28 weeks of gestation had a significantly higher mortality rate compared with those diagnosed after 28 weeks of gestation. They were delivered at a median gestational age of 36.4 weeks (range, 26-41 weeks). Forty-five fetuses (55%) were born prematurely, and

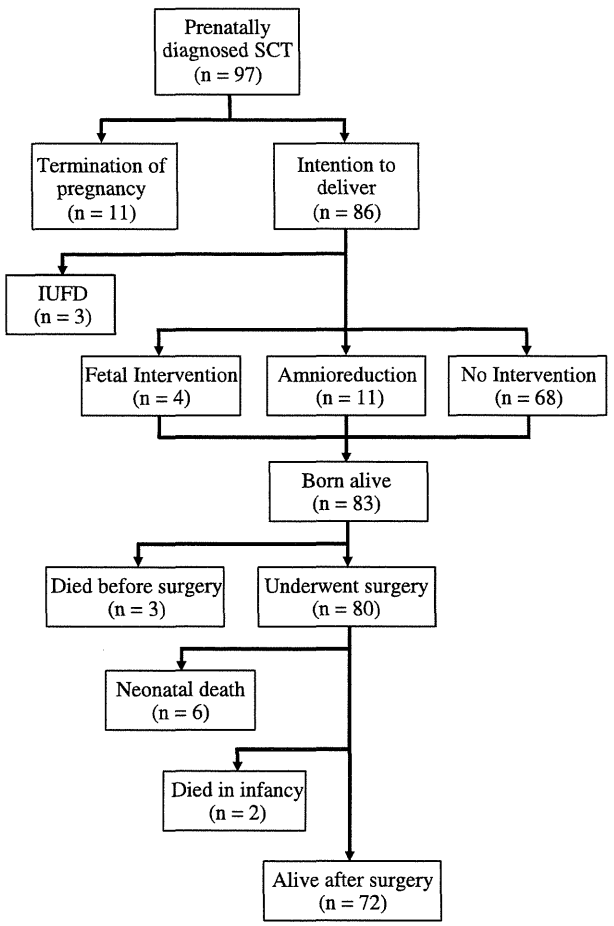

Fig. 4 The outcomes of prenatally diagnosed SCT (2000-2009). IUFD indicates intrauterine fetal death.

Table 1 Demographics and mortality of the fetuses that were intended to be delivered after a prenatally diagnosis of SCT

Characteristics	Distribution of patients (%)	Mortality (%) and *P* value
Gestational age at diagnosis (wk)	n = 86	*P* = .020
<22	13 (15.1)	3 (23.1)
22-27	38 (44.2)	10 (26.3)
≥28	35 (44.2)	1 (2.9)
Gestational age at delivery (wk)	n = 82	*P* < .001
<28	5 (6.1)	3 (60.0)
28-31	13 (15.9)	5 (38.5)
32-36	27 (32.9)	3 (11.1)
≥37	37 (45.1)	0 (0.0)
Sex	n = 85	*P* = .303
Male	23 (27.1)	2 (8.7)
Female	62 (72.9)	11 (17.7)
Birth weight (g)	n = 82	*P* = .404
<2000	7 (8.5)	1 (14.3)
2000-2999	42 (51.2)	8 (19.0)
3000-3999	27 (32.9)	2 (7.4)
≥4000	6 (7.3)	0 (0.0)
Mode of delivery	n = 82	*P* = .036
Vaginal delivery	12 (14.6)	1 (8.3)
Planned cesarean section delivery	39 (47.6)	2 (5.1)
Emergency cesarean section delivery	31 (37.8)	8 (25.8)

37 fetuses (45%) were delivered at full term. The mortality rates based on age at delivery were significantly different, and the younger infants demonstrated a higher mortality rate. The male-to-female ratio was 1:2.6. The median birth weight was 2893 g (range, 1020-5014 g). There was no significant difference in the mortality among the infants with different

Table 2 Characteristics of fetal ultrasonography and the tumor findings of the fetuses that were intended to be delivered along with their mortality

Characteristics	Distribution of patients (%)	Mortality (%) and *P* value
Polyhydramnios	n = 86	*P* = .078
Yes	26 (30.2)	7 (26.9)
No	60 (69.8)	7 (11.7)
Sign of hydrops fetalis	n = 86	*P* < .001
Yes	14 (16.3)	8 (57.1)
No	72 (83.7)	6 (8.3)
Altman's classification	n = 84	*P* = .734
I	48 (57.1)	10 (20.8)
II	26 (31.0)	3 (11.5)
III	5 (5.9)	0 (0.0)
IV	5 (5.9)	1 (20.0)
Type of tumor component	n = 86	*P* < .001
Cystic type	23 (26.7)	0 (0.0)
Predominantly cystic mixed type	31 (36.0)	2 (6.4)
Predominantly solid mixed type	25 (29.1)	8 (32.0)
Solid type	7 (8.1)	4 (57.1)
Maximum diameter of the tumor (cm)	n = 86	*P* = .213
<5.0	4 (4.7)	0 (0.0)
5.0-9.9	26 (30.2)	0 (0.0)
10.0-14.9	28 (32.6)	7 (25.0)
15.0-19.9	22 (25.6)	5 (22.7)
≥20.0	6 (7.0)	2 (33.0)

birth weights. Twelve fetuses (15%), including 2 cases who had undergone cyst aspiration for decompression before delivery, were born by vaginal delivery, whereas 70 fetuses (85%) were born via cesarean delivery: 31 because of the tumor size, 10 because of fetal cardiac failure, 9 because of the repetitive cesarean section, 5 because of the fetal distress, and 15 for other reasons. None of the fetuses delivered by cesarean section underwent ex utero intrapartum therapy (EXIT). The fetuses delivered by emergency cesarean section demonstrated a significantly higher mortality rate. Associated anomalies were detected in 10 (12%) of 83 infants and included congenital heart disease (n = 5), undescended testes (n = 2), an anorectal anomaly (n = 1), an ectopic ureter (n = 1), hydrocephalus (n = 1), and intestinal duplication (n = 1).

Table 2 reviews the characteristics of the fetal ultrasonography and the tumor findings in the fetuses that were intended to be delivered along with their mortality. Polyhydramnios was recognized in 30% of the patients, and some signs for hydrops fetalis were seen in 16% of the cases. The mortality of the fetuses with 1 sign of hydrops fetalis was higher than that of the fetuses without any sign of hydrops fetalis. Type I Altman's classification was the most common tumor location, and type II was the second most common. There were no statistically significant differences in the mortality rates among the infants with different Altman's classifications. The type of the tumor component was predominantly cystic (>50% cystic) in 54 cases (63%) and predominantly solid (>50% solid) in 32 cases (37%). There were significant differences in the mortality among the patients with different types of the tumor components, and the predominantly solid type was associated with higher mortality. Although there was no statistically significant difference in the mortality among the patients with different maximum diameters of the tumor, no fetuses that had a tumor with a maximum diameter less than 10 cm by any measurements died.

3. Discussion

We reviewed the prenatal course, perinatal data, and postnatal outcome in this Japanese nationwide retrospective cohort study conducted on 97 fetuses prenatally diagnosed with SCTs between 2000 and 2009. Of the 97 fetuses, 11 pregnancies were terminated, 3 died in utero, and 11 infants died after live births. The overall mortality including the termination of pregnancy was 26% (25/97), and the mortality excluding such terminations was 16% (14/86). The perinatal mortality and the neonatal mortality of this cohort were 12% (10/86) and 11% (9/83), respectively. Table 3 includes data from published series of fetal SCTs involving 10 or more cases, including our present results, which are the largest retrospective cohort study conducted for fetuses with a prenatal diagnosis of SCT [6-16]. Although the mortality among fetuses with SCT varied widely in different series, the outcome of the present study was better than that reported previously [6-11,14-16]. One of the reasons for this discrepancy is the advances that have been made in maternal or fetal management and perinatal care in recent years, as cases from more 10 years ago were included in some series. The other reason may be the effects of selection bias in some institutions, as some of them were highly specialized centers for fetal intervention and may be more likely to receive referrals of more serious cases associated with higher mortality.

Another possibility is that there was an increased population with a prenatal diagnosis of SCTs in our country likely owing to the advent of improved antenatal imaging techniques and screening. The Japanese Society of Pediatric Surgeons reported in their neonatal surgical survey performed every 5 years that the ratio of prenatal diagnosis in neonates with SCTs was 44% in 2003 [18] and 82% in 2008 [19]. The number of registered cases has increased rapidly in the past few years along with the increase in the ratio of prenatal diagnosis during the 5-year period from 2003 to 2008 (Fig. 2). Improvements in prenatal diagnosis may have

Table 3 The number of the patients and the outcomes reported in previous studies

Author	Study period	Study design	No. of cases	No. of TOP	IUFD	Postnatal death	Mortality excluding TOP (%)
Bond et al [7]	1990	M	45	11	11	6	17/34 (50%)
Sheth et al [11]	NA	M	15	2	5	2	7/13 (54%)
Holterman et al [10]	1980-1997	S	24	3	4	5	9/21 (43%)
Brace et al [9]	1992-1998	S	10	2	2	3	5/8 (63%)
Westerburg et al [8]	1986-1998	S	17	2	0	6	6/15 (40%)
Kamata et al [12]	1979-1999	S	14	0	1	2	3/14 (21%)
Hedrick et al [6]	1995-2002	S	30	4	5	7	12/26 (46%)
Benachi et al [13]	1983-2003	M	44	4	2	5	7/40 (18%)
Makin et al [14]	1993-2004	S	35	6	3	4	7/29 (24%)
Sy et al [15]	1991-2005	S	27	3	5	3	8/24 (33%)
Wilson et al [16]	2003-2006	S	23	4	3	4	7/19 (37%)
Present study	2000-2009	M	97	11	3	11	14/86 (16%)

NA indicates not available; S, single-institutional study; M, multicenter study; TOP, termination of pregnancy; IUFD, intrauterine fetal death.

contributed to the increased detection of milder cases that would not have been diagnosed previously. Although there were no significant differences in the prognostic factors between the 11 terminated cases and the 13 continued pregnancies for fetuses that were diagnosed before 22 weeks of gestation, termination of pregnancy may have contributed to the improvement of the mortality because the cases with earlier presentation demonstrated poorer prognosis, probably because of the larger tumor growth, compared with the cases with later presentation [8,16] (Table 1).

This is the first Japanese multicenter survey conducted for fetuses with a prenatal diagnosis of SCT. Our preliminary survey revealed that there were at least 138 fetuses with SCT during the past 10 years in Japan, and 70% of them were surveyed in detail. The population survey report of the Ministry of Health, Labour and Welfare of Japan reported that there were 11,155,608 live births and 329,757 stillbirths during the period between January 2000 and December 2009. Judging from the birth prevalence of SCT, the number of patients with SCT predicted for this period was estimated to be approximately 400 cases including postneonatally presented cases, and the patient number in our survey therefore corresponded to approximately one fourth of the estimated cases for that period. The Japanese Society of Pediatric Surgeons reported that 16 neonates with prenatally diagnosed SCTs were treated in 2003 [18], and 23 neonates with prenatally diagnosed SCTs were treated in 2008 [19]. Together with this demographic information, it is estimated that about half of the prenatally diagnosed cases of SCT in our country have been collected and surveyed from the 46 perinatal centers participated in the present study. In consequence, the results of this study accurately describe the current status of both the prenatal and postnatal courses of these infants and characterize the natural history of fetal SCTs in our country. This study will therefore provide useful information for prenatal counseling of parents.

The gestational age of the fetus at delivery had a major impact on the perinatal and postnatal mortality, as has been previously reported [6,9,10,16]. The mortality rates based on age at delivery were significantly different, and the younger infants demonstrated a higher mortality. This was presumably because of the synergistic effects of several factors, including the high mortality owing to prematurity, the high risk of preterm labor owing to the high-output cardiac failure and polyhydramnios, and the large tumor size that required early delivery. With regard to the mode of delivery, our data showed that emergency cesarean section was likely to be selected in the high-risk patients. The well-known Altman's classification into 4 types, depending on the relationship of the extrapelvic and intrapelvic parts, demonstrated no correlation with the outcome. In contrast, the type of the tumor component was well correlated with the outcome, which is consistent with the previous reports [6,8,10,13]. The solid component of the SCT is generally very vascular and has the potential for rapid growth, resulting in an increased risk of high-output cardiac failure and massive hemorrhage [6,13,15].

Although there were no statistically significant differences in the mortality rates among the cases with different maximum diameters of the tumors, no fetuses whose maximum diameter was less than 10 cm died. A recent study, which proposed a prognostic classification for the fetuses prenatally diagnosed to have SCT [13], defined 3 risk groups as follows: group A with tumor diameters less than 10 cm, absent or mild vascularity, and slow growth; group B with tumor diameter of 10 cm or greater, pronounced vascularity or high-output cardiac failure, and rapid growth; and group C with a tumor diameter of 10 cm or greater, predominantly cystic lesions with absent or mild vascularity, and slow growth. According to their prognostic classification, our cases were classified into 30 cases of group A, 28 cases of group B and 28 cases of group C, with mortality rates of 0%, 39%, and 11% respectively.

There have been some report of fetal interventions, such as maternal-fetal surgery to resect the tumors [6,14], radiofrequency ablation [20], major vessel laser ablation [14], and vessel alcohol sclerosis [14], to prevent the high-output cardiac failure. In some cases, there were indications for prenatal intervention, such as amniodrainage, to prevent preterm labor [6,14,16] and cyst decompression before delivery to prevent tumor rupture [6,9,14,16]. There were 4 cases of fetal intervention and 11 cases of amniodrainage in the present study, and all of the cases survived to be born, and 3 cases of fetal intervention and 7 cases of amniodrainage survived to discharge. However, detailed validation may be necessary to evaluate and definitively conclude the efficacy of these prenatal interventions. Of the 9 neonatal deaths, 6 infants had already developed hemorrhage from the tumor at the time of cesarean section, including 2 cases of tumor rupture during the cesarean delivery. Most of them were premature infants who had huge and predominantly solid tumors. An early delivery with an EXIT-to-resection strategy [21] or emergency preoperative tumor embolization [22] may have some benefits for such critical cases.

A major limitation of this study is that this survey was conducted in a retrospective manner by using a questionnaire requesting details about the patients. Many of the centers had a small number of cases, and the maternal and fetal management, including the criteria for fetal intervention, were determined according to the clinical decisions of each institution. Moreover, prognostic factors were analyzed only by a descriptive study. A more detailed analysis of the data and a prospective study will therefore be needed to establish a comprehensive treatment strategy, including preoperative tumor embolization, EXIT procedures, and fetal interventions.

Acknowledgments

This work was supported by a grant from The Ministry of Health, Labour and Welfare of Japan (H22-Nanchi-Ippan-158, Health and Labour Sciences Research Grants for

Research on intractable diseases). The perinatal centers that participated in this survey were Akita University Hospital (Akita), Chiba University Hospital (Chiba), Dokkyo Medical University Hospital (Mibu), Fuji City General Hospital (Fuji), Fujita Health University Hospital (Toyoake), Fukuoka University Hospital (Fukuoka), Gunma Children's Medical Center (Shibukawa), Hiroshima City Hospital (Hiroshima), Hiroshima University Hospital (Hiroshima), Hyogo Prefectural Kobe Children's Hospital (Kobe), Japanese Red Cross Medical Center (Tokyo), Jichi Medical University Hospital (Shimotsuke), Kagoshima City Hospital (Kagoshima), Kameda Medical Center (Kamogawa), Keio University Hospital (Tokyo), Kimitsu Chuo Hospital (Kisarazu), Kitasato University Hospital (Sagamihara), Kobe University Hospital (Kobe), Kochi Health Sciences Center (Kochi), Kumamoto City Hospital (Kumamoto), Kumamoto University Hospital (Kumamoto), Kyorin University Hospital (Mitaka), Kyushu University Hospital (Fukuoka), Matsue Red Cross Hospital (Matsue), Mie University Hospital (Tsu), Miyagi Children's Hospital (Sendai), Nagara Medical Center (Gifu), Nagasaki University Hospital (Nagasaki), Nara Medical University Hospital (Kashihara), National Center for Child Health and Development (Tokyo), National Kyushu Medical Center (Fukuoka), Niigata University Medical and Dental Hospital (Niigata), Ohtawara Red Cross Hospital (Ohtawara), Okayama Medical Center (Okayama), Oita Prefectural Hospital (Oita), Okinawa Prefectural Chubu Hospital (Uruma), Osaka Medical Center and Research Institute for Maternal and Child Health (Izumi), Osaka University Hospital (Suita), Saga University Hospital (Saga), Shizuoka Children's Hospital (Shizuoka), Showa University Hospital (Tokyo), St Marianna University School of Medicine Hospital (Kawasaki), The University of Tokyo Hospital (Tokyo), Toho University Omori Medical Center (Tokyo), Tokyo Womens Medical University Yachiyo Medical Center (Yachiyo), Yamagata University Hospital (Yamagata), Yamanashi Prefectural Central Hospital (Kofu), and Wakayama Medical University Hospital (Wakayama). The authors thank Ms Seimiya of National Center for Child Health and Development and Ms Masumoto, Mr Tamura, and Mr Kurimoto of Japan Clinical Support Unit for their help in processing the data.

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THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/j.1447-0756.2012.01940.x J. Obstet. Gynaecol. Res. 2012

Letter to the Editor

Adverse outcome in monochorionic twins with selective intrauterine fetal growth restriction in the presence of abnormal umbilical artery Doppler and severe oligohydramnios

Dear Editor,

Monochorionic twin pregnancies complicated with selective intrauterine growth restriction (sIUGR) are associated with adverse perinatal outcome, including perinatal death or neurological morbidity for both twins.[1,2] This pathological condition seems to be caused by uneven placental sharing and placental vascular communications.[1,3] In particular, severe oligohydramnios (defined by less than 1 cm of deepest vertical pocket) as well as absent or reversed diastolic flow in umbilical artery Doppler wave form in sIUGR twins were recognized as predictors of death for sIUGR twins.[1,2] Both of these prenatal factors were present via ultrasound evaluation in 11 cases (11%) of 101 sIUGR twins at less than 26 weeks of gestational age, described in our previous study.[2] They were closely followed via expectant management; selective feticide was not applied in our clinical setting. Indications and timing for delivery were at the discretion of the attending obstetrician. There were no cases developing severe twin–twin transfusion syndrome. In four cases, both fetuses expired between 18 and 26 weeks of gestational age. In five cases, one twin exhibited a non-reassuring fetal status by abnormal fetal heart rate or low biophysical profiling score. Of the 11 cases, 10 sIUGR twins suffered fetal or neonatal death; moreover, one surviving sIUGR twin suffered cystic periventricular leukomalacia. The mortality rate for the larger twins was seven of 11; however, four twins survived without major complications at 28 days of age. Based on presence of severe anemia in the surviving twin (if one twin was alive at birth) or the appearance of stillborn infants (if it was both fetal demise), six cases were suspected to have suffered from feto-fetal hemorrhage via vascular communications subsequent to the demise of the co-twin.[4] Because of the unfavorable prognosis in the majority of the larger twins as well as almost all sIUGR twins, prenatal intervention as laser coagulation of communicating vessels should be considered for this condition to prevent severe effects of acute hemodynamic change resulting from the death of the co-twin,[3] especially in Japan where selective feticide is not allowed ethically. We will plan a multicenter study to elucidate the effectiveness of prenatal intervention as laser coagulation of communicating vessels for monochorionic twin pregnancies complicated with sIUGR at less than 26 weeks of gestation, in whom severe oligohydramnios as well as absent or reversed diastolic flow in umbilical artery Doppler wave form are observed.

Disclosure

None of the authors has anything to disclose.

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Human Pathology (2012) 43, 1413–1417

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Original contribution

Squamous metaplasia in the cyst epithelium of type 1 congenital pulmonary airway malformation after thoracoamniotic shunt placement

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Received 25 June 2011; revised 6 October 2011; accepted 20 October 2011

Keywords:
Congenital pulmonary airway malformation;
Thoracoamniotic shunting;
Cyst epithelium;
Squamous metaplasia

Summary Thoracoamniotic shunting is the treatment of choice for management of the fetus with type 1 congenital pulmonary airway malformation. Thoracoamniotic shunting has been performed to reduce life-threatening risks such as fetal hydrops. However, caution is needed because of possible complications. Here, we report that thoracoamniotic shunting can cause histologic changes in the cyst epithelia. In 5 of 8 patients treated prenatally with thoracoamniotic shunting, squamous metaplasia in the cyst epithelia was seen; whereas squamous metaplasia was not found in 6 patients who were not treated with this procedure. Our results reveal that long-term exposure to the intrauterine environment could possibly lead to the change in the nature of cyst epithelium and consequent squamous metaplasia.

1. Introduction

Congenital pulmonary airway malformation (CPAM), formerly known as *cystic adenomatoid malformation*, of the lung is a rare lung disorder characterized by an increased proliferation and cystic dilation of terminal respiratory bronchioles [1-3]. Although the etiology of CPAM is not clear, it has been suggested that it may be caused by a maturation defect in bronchopulmonary development [4,5]. It has been also shown that the presence of bronchial atresia is strongly associated with CPAM, which supports this concept [6].

Congenital pulmonary airway malformation (ie, cystic adenomatoid malformation) was originally classified into 3 groups based on the relative size of the cysts [3]. Currently, CPAM is classified into 5 types based on the presumed site of development of the malformation. Among these 5 types, type 1 CPAM is the most prevalent one, accounting for approximately 60% to 70% of all CPAM lesions [2,3]. Type 1 CPAM consists of 1 or more air- or air/fluid-filled large cysts. The cyst sizes range from 1 to 10 cm. These cysts are often surrounded by underdeveloped alveolar parenchyma and varying number of smaller cysts. Microscopically, the

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0046-8177/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.humpath.2011.10.017