Usui N, Kitano Y, Okuyama H, Saito M, Masumoto K, Morikawa N, Takayasu H, Nakamura T, Hayashi S, Kawataki M, Ishikawa H, Nose K, Inamura N, Sago H.	Prenatal risk stratification for isolated congenital diaphragmatic hernia: results of a Japanese multicenter study.	J Pediatr Surg	46(10)	1873-1880	2011
Matsuoka K, Hayashi S, Urano F, Zhu J. L, Okita H, Sago H, Nakazawa A.	Squamous metaplasia in the cyst epithelium of type 1 congenital pulmonary airway malformation after thoracoamniotic shunt placement.	Human pathology	Mar 2.	Epub ahead of print	2012
Okada J, Iwata S, Hirose A, Kanda H, Yoshino M, Maeno Y, Matsuishi T, Iwata O	Levothyroxine replacement therapy and refractory hypotension out of transitional period in preterm infants.	Clin Endocrinol	74	354-364	2011
Minakami H, Hiramatsu Y, Koresawa M, Fujii T, Hamada H, Iitsuka Y, Ikeda T, Ishikawa H, Ishimoto H, Itoh H, Kanayama N, Kasuga Y, Kawabata M, Konishi I, Matsubara S, Matsuda H, Murakoshi T, Ohkuchi A, Okai T, Saito S, Sakai M, Satoh S, Sekizawa A, Suzuki M, Takahashi T, Tokunaga A, Tsukahara Y, Yoshikawa H	Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2011 edition.	J Obstet Gynaecol Res	37	1174-1197	2011
Yorifuji T, Naruse H, Kashima S, Ohki S, Murakoshi T, Takao S, Tsuda T, Doi H	Residential proximity to major roads and preterm births.	Epidemiology	22	74-80	2011
桂木真司, 三好剛一, 池田智明	胎児不整脈	産婦人科の実際	60(11)	1702-1713	2011
前野泰樹	胎児不整脈の診断と治療	周産期医学	41(1)	59-64	2011
青木宏明, 林聡, 金子正英, 伊藤裕司, 村島温子, 左合治彦	ベタメタゾンとリトドリンを用いた胎児心ブロック胎内治療の検討	日本周産期・新生児医学会雑誌	47(3)	601-606	2011
左合治彦	胎児治療Up-to-date	日本周産期・新生児医学会雑誌	47(4)	737-739	2011

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
前野泰樹	胎児不整脈	長嶋正實	小児不整脈 改訂第2版	株式会社 治療と診 断社	東京	2011	204-214

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 –

Takekazu Miyoshi, MD; Yasuki Maeno, MD; Haruhiko Sago, MD; Noboru Inamura, MD; Satoshi Yasukohchi, MD; Motoyoshi Kawataki, MD; Hitoshi Horigome, MD; Hitoshi Yoda, MD; Mio Taketazu, MD; Makio Shozu, MD; Motoki Nii, MD; Hitoshi Kato, MD; Satoshi Hayashi, MD; Asako Hagiwara, MD; Akiko Omoto, MD; Wataru Shimizu, MD; Isao Shiraishi, MD; Heima Sakaguchi, MD; Kunihiro Nishimura, MD; Keiko Ueda, MD; Shinji Katsuragi, MD; Tomoaki Ikeda, MD

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

National Cerebral and Cardiovascular Center, Suita (T.M., W.S., I.S., H. Sakaguchi, K.N., K.U., S.K., T.I.); Kurume University School of Medicine, Kurume (Y.M.); National Center for Child Health and Development, Tokyo (H. Sago, H.K., S.H.); Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi (N.I.); Nagano Children's Hospital, Nagano (S.Y.); Kanagawa Children's Medical Center, Yokohama (M.K., A.H.); University of Tsukuba, Tsukuba (H.H.); Toho University Omori Medical Center, Tokyo (H.Y.); Saitama Medical University International Medical Center, Hidaka (M.T.); Chiba University, Chiba (M.S., A.O.); and Shizuoka Children's Hospital, Shizuoka (M.N.), Japan

Mailing address: Takekazu Miyoshi, MD, Department of Perinatology and Gynecology, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: gomiyoshi0327@yahoo.co.jp

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	0.105

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

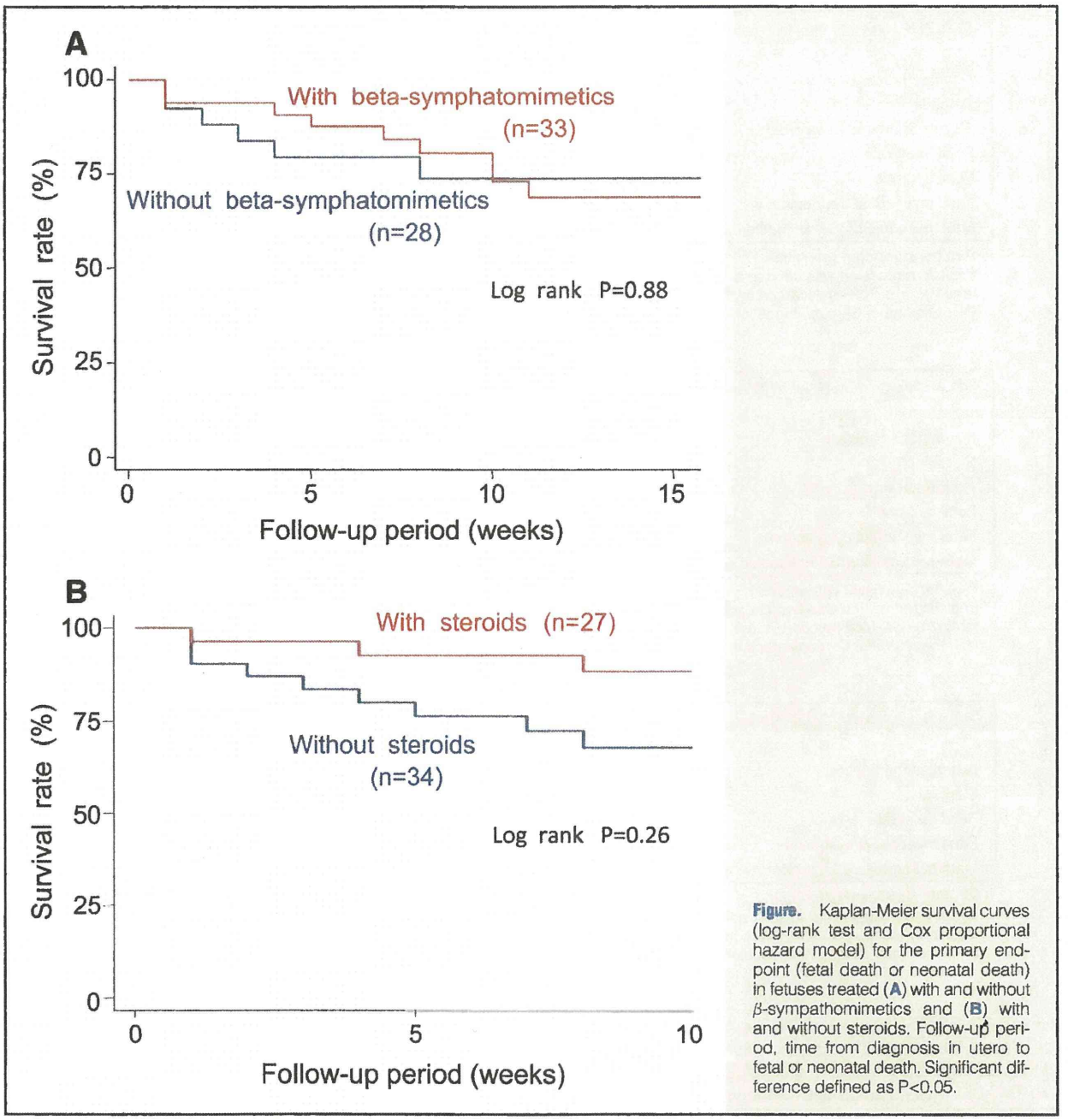

Figure. Kaplan-Meier survival curves (log-rank test and Cox proportional hazard model) for the primary endpoint (fetal death or neonatal death) in fetuses treated (**A**) with and without β-sympathomimetics and (**B**) with and without steroids. Follow-up period, time from diagnosis in utero to fetal 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).[29] 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.

References

1. Brucato A, Cimaz R, Caporaili R, Ramoni V, Vuyon J. Pregnancy outcome in patients with autoimmune diseases and anti-Ro/SSA antibodies. *Clin Rev Allergy Immunol* 2011; **40:** 27–41.
2. Silverman ED, Buyon J, Laxer RM, Hamilton R, Bini P, Chu JL, et al. Autoantibody response to the Ro/La particle may predict outcome in neonatal lupus erythematosus. *Clin Exp Immunol* 1995; **100:** 499–505.
3. Buyon JP, Ben-Chetrit E, Karp S, Roubey RA, Pompeo L, Reeves WH, et al. Acquired congenital heart block: Pattern of maternal antibody response to biochemically defined antigens of the SSA/Ro-SSB/La system in neonatal lupus. *J Clin Invest* 1989; **84:** 627–634.
4. Schmidt KG, Ulmer HE, Silverman NH, Kleinman CS, Copel JA. Perinatal outcome of fetal complete atrioventricular block: A multicenter experience. *J Am Coll Cardiol* 1991; **17:** 1360–1366.
5. Ichikawa R, Sumitomo N, Komori A, Abe Y, Nakamura T, Fukuhara J, et al. The follow-up evaluation of electrocardiogram and arrhythmias in children with fulminant myocarditis. *Circ J* 2011; **75:** 932–938.
6. Jaeggi ET, Laskin CA, Hamilton RM, Kingdom J, Silverman ED. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus: A prospective study of 186 antibody-exposed fetuses and infants. *J Am Coll Cardiol* 2010; **55:** 2778–2784.
7. Brucato A, Grava C, Bortolati M, Ikeda K, Milanesi O, Cimaz R, et al. Congenital heart block not associated with anti-Ro/La antibodies: Comparison with anti-Ro/La-positive cases. *J Rheumatol* 2009; **36:** 1744–1748.
8. Lopes LM, Tavares GM, Damiano AP, Lopes MA, Aiello VD, Schultz R, et al. Perinatal outcome of fetal atrioventricular block: One-hundred-sixteen cases from a single institution. *Circulation* 2008; **118:** 1268–1275.
9. Jaeggi ET, Fouron JC, Silverman ED, Ryan G, Smallhorn J, Hornberger LK. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. *Circulation* 2004; **110:** 1542–1548.
10. Buyon JP, Hiebert R, Copel J, Craft J, Friedman D, Katholi M, et al. Autoimmune-associated congenital heart block: Demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J Am Coll Cardiol* 1998; **31:** 1658–1666.

11. Lee LA, Bias WB, Arnett FC Jr, Huff JC, Noris DA, Harmon C, et al. Immunogenetics of the neonatal lupus syndrome. *Ann Intern Med* 1983; **99:** 592–596.
12. Watson RM, Lane AT, Barnett NK, Bias WB, Arnett FC, Provost TT. Neonatal lupus erythematosus: A clinical, serological and immunogenetic study with review of the literature. *Medicine* 1984; **63:** 362–378.
13. Bierman FZ, Baxi L, Jaffe I, Driscoll J. Fetal hydrops and congenital complete heart block: Response to maternal steroid therapy. *J Pediatr* 1988; **112:** 646–648.
14. Carreira PE, Gutierrez-Larraya F, Gomez-Reino JJ. Successful intrauterine therapy with dexamethasone for fetal myocarditis and heart block in a woman with systemic lupus erythematosus. *J Rheumatol* 1993; **20:** 1204–1207.
15. Saleeb S, Copel J, Friedman D, Buyon JP. Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody associated congenital heart block. *Arthritis Rheum* 1999; **42:** 2335–2345.
16. Groves AMM, Allan LD, Rosenthal E. Therapeutic trial of sympathomimetics in three cases of complete heart block in the fetus. *Circulation* 1995; **92:** 3394–3396.
17. Harris JP, Alexson CG, Manning JA, Thompson HO. Medical therapy for the hydropic fetus with congenital complete atrioventricular block. *Am J Perinatol* 1993; **10:** 217–219.
18. Copel JA, Buyon JP, Kleinman CS. Successful in utero therapy of fetal heart block. *Am J Obstet Gynecol* 1995; **173:** 1384–1390.
19. Cuneo BF, Zhao H, Strasburger JF, Ovadia M, Huhta JC, Wakai RT. Atrial and ventricular rate response and patterns of heart rate acceleration during maternal-fetal terbutaline treatment of fetal complete heart block. *Am J Cardiol* 2007; **100:** 661–665.
20. Lazzerini PE, Capecchi PL, Laghi Pasini F. Anti-Ro/SSA antibodies and cardiac arrhythmias in the adult: Facts and hypotheses. *Scand J Immunol* 2010; **72:** 213–222.
21. Hutter D, Silverman ED, Jaeggi ET. The benefits of transplacental treatment of Isolated congenital complete heart block associated with maternal anti-Ro/SSA antibodies: A review. *Scand J Immunol* 2010; **72:** 235–241.
22. French NP, Hagan R, Evans SF, Godfrey M, Newnham JP. Repeated antenatal corticosteroids: Size at birth and subsequent development. *Am J Obstet Gynecol* 1999; **180:** 114–121.
23. Abbasi S, Hirsch D, Davis J, Tolosa J, Stouffer N, Debbs R, et al. Effect of single versus multiple courses of antenatal corticosteroids on maternal and neonatal outcome. *Am J Obstet Gynecol* 2000; **182:** 1243–1249.
24. Spinillo A, Viazzo F, Colleoni R, Chiara A, Cerbo RA, Fazzi E, et al. Two-year infant neurodevelopmental outcome after single or multiple antenatal courses of corticosteroids to prevent complications of prematurity. *Am J Obstet Gynecol* 2004; **191:** 217–224.
25. Brucato A, Astori MG, Cimaz R, Villa P, Li Destri M, Chimini L, et al. Normal neuropsychological development in children with congenital complete heart block who may or may not be exposed to high-dose dexamethasone in utero. *Ann Rheum Dis* 2006; **65:** 1422–1426.
26. Franceschini F, Cavazzana I. Anti-Ro/SSA and La/SSB antibodies. *Autoimmunity* 2005; **38:** 55–63.
27. Routsias JG, Tzioufas AG. Sjögren's syndrome: Study of autoantigens and autoantibodies. *Clin Rev Allergy Immunol* 2007; **32:** 238–251.
28. Taylor PV, Taylor KF, Norman A, Griffiths S, Scott JS. Prevalence of maternal Ro (SS-A) and La (SS-B) autoantibodies in relation to congenital heart block. *Br J Rheumatol* 1988; **27:** 128–132.
29. Sonesson SE, Salomonsson S, Jacobsson LA, Bremme K, Wahren-Herlenius M. Signs of first-degree heart block occur in one-third of fetuses of pregnant women with anti-SSA/Ro 52-kd antibodies. *Arthritis Rheum* 2004; **50:** 1253–1261.
30. Jaeggi ET, Hamilton RM, Silverman ED, Zamora SA, Hornberger LK. Outcome of children with fetal, neonatal or childhood diagnosis of isolated congenital atrioventricular block. *J Am Coll Cardiol* 2002; **39:** 130–137.
31. Maeno Y, Himeno W, Saito A, Hiraishi S, Hirose O, Ikuma M, et al. Clinical course of fetal congenital atrioventricular block in the Japanese population: A multicentre experience. *Heart* 2005; **91:** 1075–1079.
32. Rein AJ, Mevorach D, Perles Z, Gavri S, Nadjari M, Nir A, et al. Early diagnosis and treatment of atrioventricular block in the fetus exposed to maternal anti-SSA/Ro -SSB/La antibodies: A prospective, observational, fetal kinetocardiogram-based study. *Circulation* 2009; **119:** 1867–1872.
33. Friedman DM, Kim MY, Copel JA, Davis C, Phoon CK, Glickstein JS, et al. Utility of cardiac monitoring in fetuses at risk for congenital heart block: The PR Interval and Dexamethasone Evaluation (PRIDE) prospective study. *Circulation* 2008; **117:** 485–493.
34. Friedman DM, Llanos C, Izmirly PM, Brock B, Byron J, Copel JA, et al. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. *Arthritis Rheum* 2010; **62:** 1138–1146.
35. Lazzerini PE, Acampa M, Guideri F, Capecchi PL, Campanella V, Morozzi G, et al. Prolongation of the corrected QT interval in adult patients with anti-Ro/SSA-positive connective tissue diseases. *Arthritis Rheum* 2004; **50:** 1248–1252.
36. Ravens U, Cerbai E. Role of potassium currents in cardiac arrhythmias. *Europace* 2008; **10:** 1133–1137.
37. Nakamura K, Katayama Y, Kusano KF, Haraoka K, Tani Y, Nagase S, et al. Anti-KCNH2 antibody-induced long QT syndrome: Novel acquired form of long QT syndrome. *J Am Coll Cardiol* 2007; **50:** 1808–1809.
38. Cuneo BF, Zhao H, Strasburger JF, Ovadia M, Huhta JC, Wakai RT, et al. Atrial and ventricular rate response and patterns of heart rate acceleration during maternal-fetal terbutaline treatment of fetal complete heart block. *Am J Cardiol* 2007; **100:** 661–665.
39. Nishizaki M, Hiraoka M. Gene mutations associated with atrioventricular block complicated by long QT syndrome. *Circ J* 2010; **74:** 2546–2547.
40. Oka Y, Itoh H, Ding WG, Shimizu W, Makiyama T, Ohno S, et al. Atrioventricular block-induced Torsades de Pointes with clinical and molecular backgrounds similar to congenital long QT syndrome. *Circ J* 2010; **74:** 2562–2571.

10.5005/jp-journals-10009-1174

REVIEW ARTICLE

Screening of Fetal Heart for the Congenital Heart Diseases

[1]Yasuki Maeno, [2]Akiko Hirose

Division of Maternal and Perinatal Medical Center, Department of Pediatrics and Child Health
Kurume University, School of Medicine, Kurume, Japan

Correspondence: Yasuki Maeno, Division of Maternal and Perinatal Medical Center, Department of Pediatrics and Child Health Kurume University, School of Medicine, 67 Asahi-mach, Kurume-830-0011, Japan, e-mail: yasukim@med.kurume-u.ac.jp

ABSTRACT

Screening of the congenital heart disease (CHD) is one of the most important techniques in prenatal ultrasonographic examination. Step by step screening methods for taking account for the level of screener, especially in the area with poor detection rate, is needed for starting effective fetal CHD screening. In this review, the fetal cardiac screening is divided into two methods accounting for steps for learning screening technique; the basic screening and the advanced screening. Basic screening is a simple method even for the one who is not familiar to the cardiac anatomy. The goal of this basic screening is to detect most of the ductal dependent lesions including transposition of the great arteries. For the basic screening, 'location' and 'size' of the heart and vessels are checked in standard four-chamber view and three-vessel view. Advanced screening is a screening for detecting all fetal CHDs, including total anomalous pulmonary venous return. For the advanced screening, the side of the heart is defined, and then the 'detail anatomy' and the 'function and blood flow' are assessed in all standard screening views, including one fetal abdominal transverse view and three fetal chest transverse views, such as four-chamber, three-vessel and three-vessel and trachea view.

Keywords: Fetal echocardiography, Fetal screening, Congenital heart disease.

INTRODUCTION

Screening of the congenital heart disease (CHD) is one of the most important techniques in prenatal ultrasonographic examination. Recent conventional ultrasound equipment can visualize cardiac anatomy *in utero* from 16 weeks of gestation even by the transabdominal approach.[1-3] Referral to the tertiary care center after effective screening of fetal CHD can make it possible to diagnose detail anatomical abnormality and to plan appropriate perinatal management. Prenatal diagnosis of CHD can improve the outcome of the fetuses with CHD.[4]

For the screening, detail anatomical assessment of the CHD is not needed. The purpose of the screening is to detect the fetuses with possibility of having CHD, and to refer to the fetal cardiac center. Several methods with simple technique have been proposed for effective screening. However, learning the technique for obtaining the images in sufficient quality still requires certain training, hence, the detection rate of fetal CHD is varied between the areas.[5] Different condition of the region and country, such as medical system and political environment, may be one of the causes of difficulty for establishing effective fetal CHD screening program. An issue for poor detection rate in some regions seems to be caused by the feeling of difficulty for starting fetal cardiac screening for the screeners who are not familiar to the fetal echocardiography. Hence, step by step screening methods for taking account for the level of screener in certain area is needed for increasing the area for starting fetal CHD screening.

In this review, we present the fetal cardiac screening dividing into two methods account for step for learning screening technique; the basic screening and the advanced screening. The basic screening is a very simple method even for the screener who is not familiar to the somewhat complicated cardiac anatomy. The advanced screening is the method of goal for all fetal sonographic screener who is trying to detect all major CHD.

INDICATIONS OF THE SCREENING

Appropriate ultrasonographic screening of fetal CHD is indicated for all pregnant women.[1-3] Unlike in the newborn period, the presence of severe cardiac disease in the fetus, such as heart murmur and cyanosis, cannot be detected by physical examination. Therefore, fetal ultrasonographic screening of a completely healthy mother with an uneventful pregnancy is the only method of identifying the majority of cases of congenital heart disease *in utero*.

The first screening ultrasound should be performed at approximately 20 weeks of gestation, if termination of pregnancy is to be considered as an option in complex cardiac problems, and there is some restriction in gestational age by law for termination. Screening has to be performed sufficiently early to make it possible to refer the case to a fetal cardiac center and to allow the parents to make their decision. The second screening for fetal CHD should be performed at approximately 30 weeks of gestation because some cardiac abnormalities develop more obvious structural abnormality in later gestation.

CONCEPT OF BASIC AND ADVANCED SCREENING

Basic Screening

Basic screening is a simple method even for the one who is not familiar to the cardiac anatomy. This screening method can be

applied when the detection rate of fetal CHD is low in that region. The goal of this basic screening is to detect most of the ductal dependent lesions including transposition of the great arteries (TGA). Although, standard four-chamber view and three-vessel view are used in this basic screening, the check point is only limited to the location and size of the heart and vessels. Checking the detail anatomy of the heart is not required if the purpose of the screening is limited to detect major CHD, except total anomalous pulmonary venous drainage (TAPVR).

Advanced Screening

Advanced screening is a screening for detecting all fetal CHDs as much as possible, including TAPVR. First, the side of the heart is defined. Then, all standard screening views including one fetal abdominal transverse view and three fetal chest transverse views are checked. In all view, detail anatomy and function and blood flow of the heart and vessels, in addition to the location and size, are checked.

FETAL HEART SECTIONS FOR SCREENING CHD

For the fetal heart screening, defining the side of the heart is needed (advanced screening). The other views are four transverse images of the fetus. First one is an abdominal transverse image of the fetus, and remaining is three simple transverse images of the fetal chest, such as the four-chamber, the three-vessel, and the three-vessel and trachea view (Figs 1 and 2). In each view, checking points are divided into location, size, detail anatomy and function and blood flow.

Defining the Side of the Heart

Since conventional ultrasound image is two-dimensional in nature, the side of the image depends on the probe direction, and cannot be interpreted from the 2D image itself. Hence, the side of the fetal heart has to be defined at the beginning of the examination (Fig. 3).[6] A longitudinal section of the fetal chest or abdomen is imaged with the fetal head positioned at the right side of the screen. Then, a fetal transverse section is imaged by rotating the probe by 90° clockwise. Regardless of fetal position,

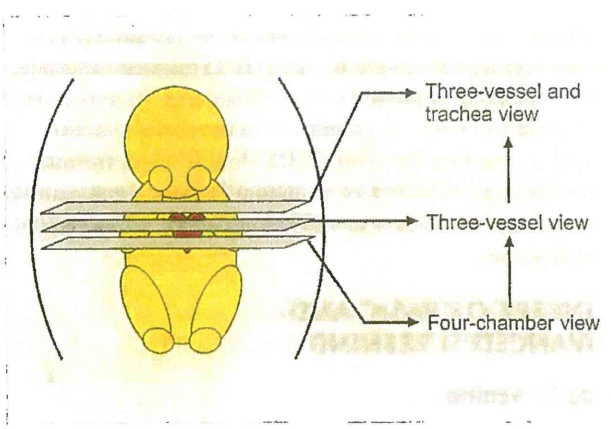

Fig. 1: Three transverse sections of the fetal chest, four-chamber, three-vessel, and three-vessel and trachea view

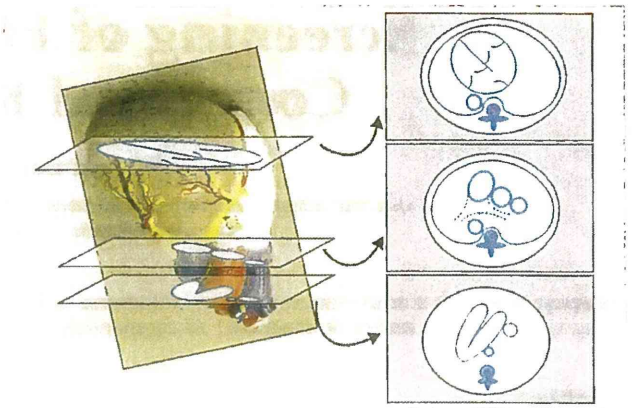

Fig. 2: Location of the each transverse section of the fetal heart

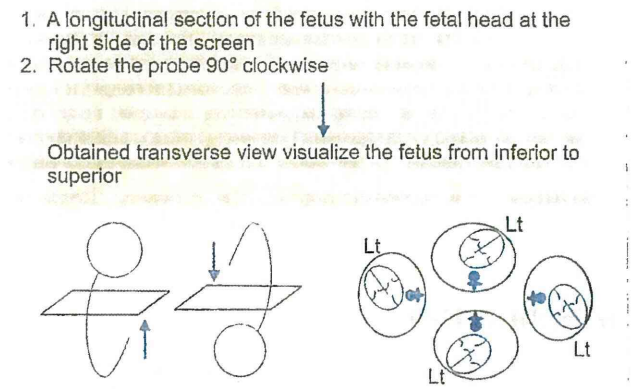

Fig. 3: Step for deciding the side of the fetal heart

the obtained image should be used to visualize the fetus from inferior to superior. In this view, the side of the heart and stomach should be defined whether it is left side (normal) or right side (abnormal). The easy way to interpret the side of the heart is that the heart is rotated clockwise after the probe is rotated clockwise.

Transverse Section of the Fetal Abdomen

Assessment of location is sufficient in this view. The stomach is left side, same as the fetal heart. In front of the fetal spine, the descending aorta (dAo) is positioned left side, and the superior vena cava (SVC) is positioned right and anterior to the dAo.

Four-Chamber View

A four-chamber view of the fetal heart is obtained by a transverse section of the lower part of the fetal chest (Figs 2, 4 and 5). This four-chamber view can detect more than 50% of CHDs, such as single ventricle, hypoplastic left ventricle (Fig. 6) and Ebstein's anomaly (Figs 7 and 8).

The location and size in this four-chamber view should be assessed for basic screening (Figs 4 and 5). There are three check points in each of location and size assessment in four-chamber view. For the location assessment, the fetal heart is positioned at left side of the chest, and the heart axis is about 45%. The dAo is positioned at the left anterior to the spine. For

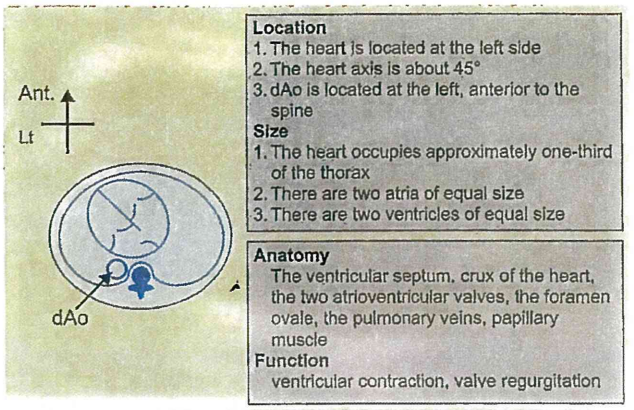

Fig. 4: Check list of four-chamber view

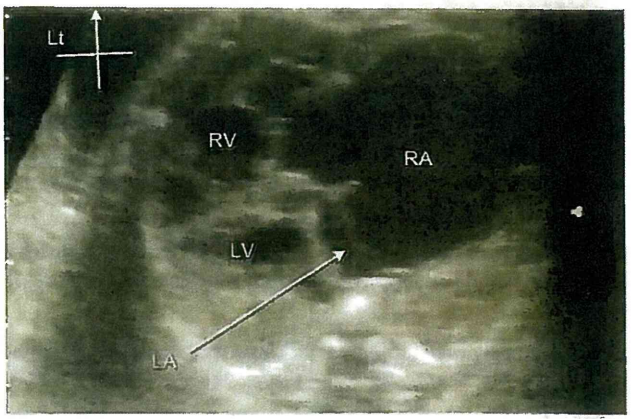

Fig. 7: A four-chamber view of a fetus with Ebstein's anomaly. The heart is quite enlarged and fills almost the entire chest. The right atrium (RA) is enlarged because of severe tricuspid valve regurgitation. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

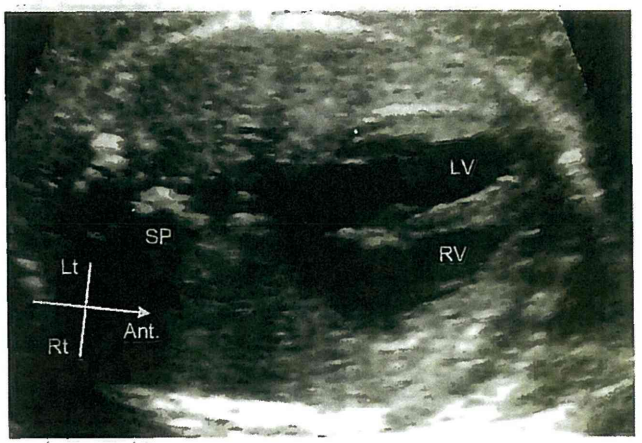

Fig. 5: Fetal echocardiographic image of four-chamber view

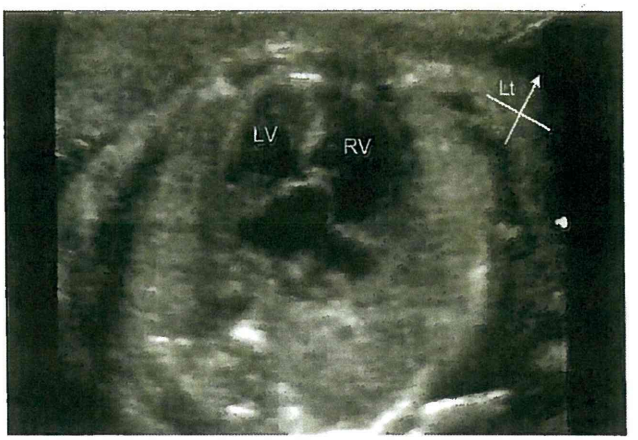

Fig. 8: A four-chamber view of a fetus with atrioventricular septal defect. A large one common atrioventricular valve is revealed, and the crux of the heart is not formed. LV, left ventricle; RV, right ventricle

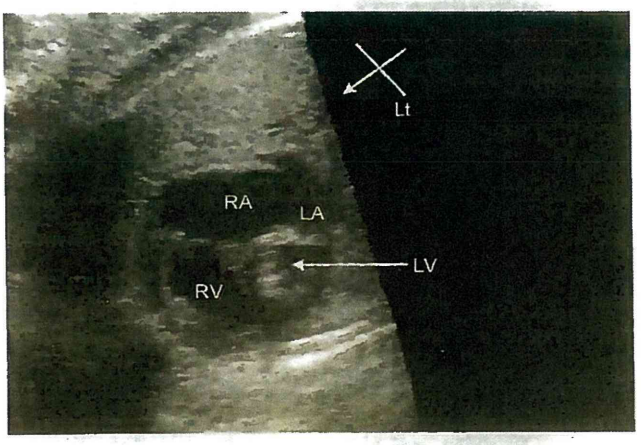

Fig. 6: A four-chamber view of a fetus with hypoplastic left heart syndrome. The left ventricle (LV) is small and endocardium of LV is high echogenic due to endocardial fibroelastosis. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

the size assessment, the fetal heart occupied approximately 1/3rd of the fetal chest. There are two atria of equal size, and two ventricles of equal size.

The assessment of the detail anatomy and the function and blood flow is included for advanced screening. Sufficient knowledge of cardiac anatomical feature and usage of color Doppler are required for these assessments. For the assessment of the detail anatomy, the crux of the heart, the ventricular septum, flap of the foramen ovale, the atrioventricular valves, the pulmonary veins and the papillary muscles should be checked. Next, function and blood flow should be assessed. Good contraction of each ventricle is carefully checked. By the color Doppler flow, location of the pulmonary venous return can be confirmed. In addition, regurgitant jet at the mitral valve and tricuspid valve can also be detected.

Three-Vessel View

The three-vessel view can be obtained by sweeping superior from the four-chamber view (Figs 2, 9 and 10).[7] This view can detect abnormal connections between the ventricles and the great arteries, such as TGA (Fig. 11) and tetralogy of Fallot.

The location and the size in this three-vessel view should be assessed for basic screening (Fig. 9). There is a just one check point in each of location and size assessment in three-vessel view. For the location assessment, three vessels are straightly aligned from left anterior to the right posterior. In another ward, the most anterior vessel is located at the most

left side. For the size assessment, the vessel size is aligned from the largest to the smallest when the straightly aligned vessels are followed from left anterior to right posterior. The most left anterior side vessel, the main pulmonary artery, is of the largest size. The central vessel, the ascending aorta (aAo), is medium in size. The most right posterior side vessel, the superior vena cava, is the smallest.

In order to assess the location of the three vessels with confidence, sweeping movement of images from the four-chamber view to the three-vessel view is useful. Using this moving image with sweeping, connection from both the ventricle to the vessels is visualized, so that the location of the vessel is clearly assessed. The ascending aorta and the main pulmonary arteries have cross relationship in normal heart (Fig. 12). By this sweeping movement, the connection from the left ventricle to the ascending aorta is first visualized. The ascending aorta is located posteriorly to the right ventricle and running from left to the right side according to the sweeping movement of the images. After this, the connection from the right ventricle to the main pulmonary artery is visualized. The main pulmonary artery is located anteriorly to the aorta just posterior to the chest-wall, and running from right to left side according to the sweeping movement of the images. The most obvious abnormality of this cross relationship of the two vessels is TGA. For the fetus with TGA, two vessels are aligned to parallel and straight rather than cross (Fig. 13), making the most left-side vessel, the main pulmonary artery, located posteriorly to the right sided ascending aorta (Fig. 11).

The assessment of the detail anatomy and the function and blood flow are required for advanced screening. For the detail anatomy assessment, the most left side vessel, the main pulmonary artery, is branching pulmonary arteries. It also connected to descending aorta via the ductus arteriosus at a slightly superior slice of three-vessel view. For the blood flow assessment, color Doppler flow reveals laminar flow in both the main pulmonary artery and the ascending aorta, directed from anterior to the posterior.

Three-Vessel and Trachea View

The last screening view, three-vessel and trachea view (Figs 14 and 15), can be obtained by farther superior sweep from three-vessel view.[8] This view may be included to the advanced

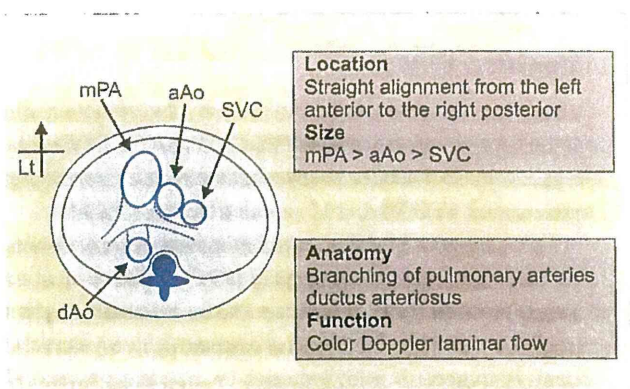

Fig. 9: Check list of three-vessel view

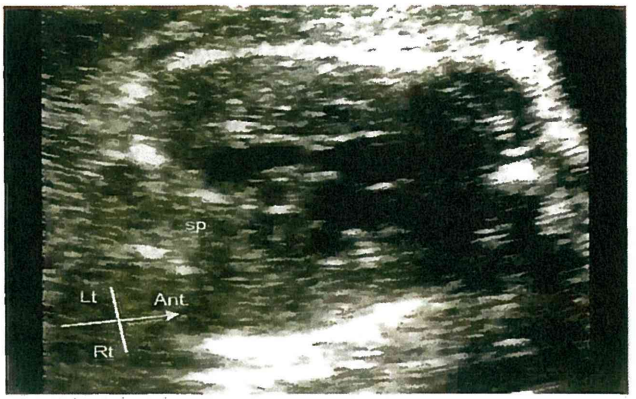

Fig. 10: A fetal echocardiographic image of three-vessel view

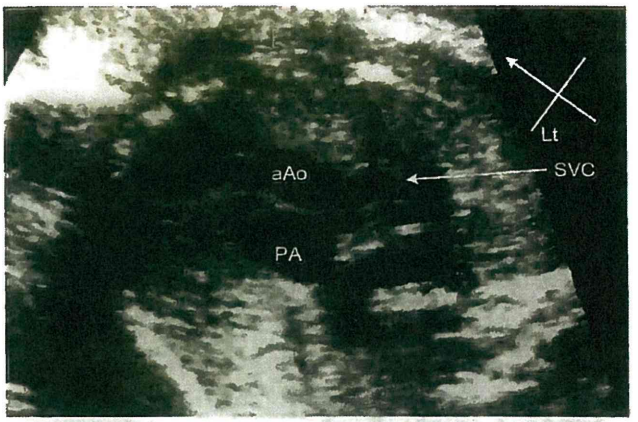

Fig. 11: A three-vessel view reveals a right anterior ascending aorta (aAo) and left posterior main pulmonary artery (PA). ant, anterior; SVC, superior vena cava

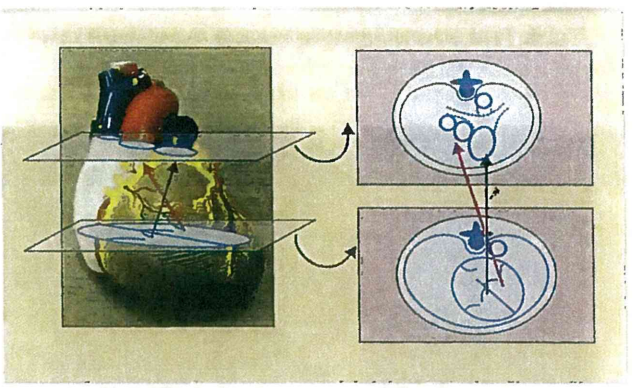

Fig. 12: Normal cross connection of the ventricles and the great vessels

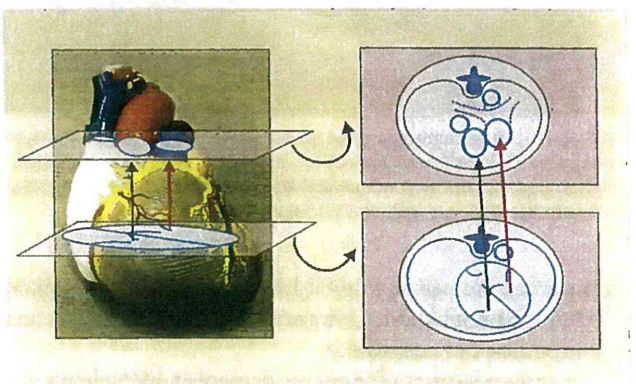

Fig. 13: Abnormal parallel connection of the ventricles and the great vessels

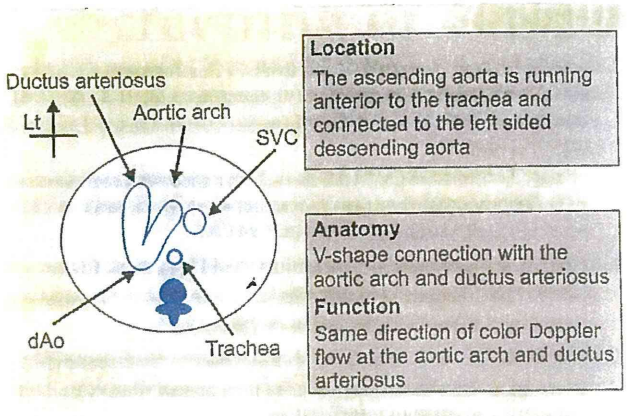

Fig. 14: Check list of the three-vessel and trachea view

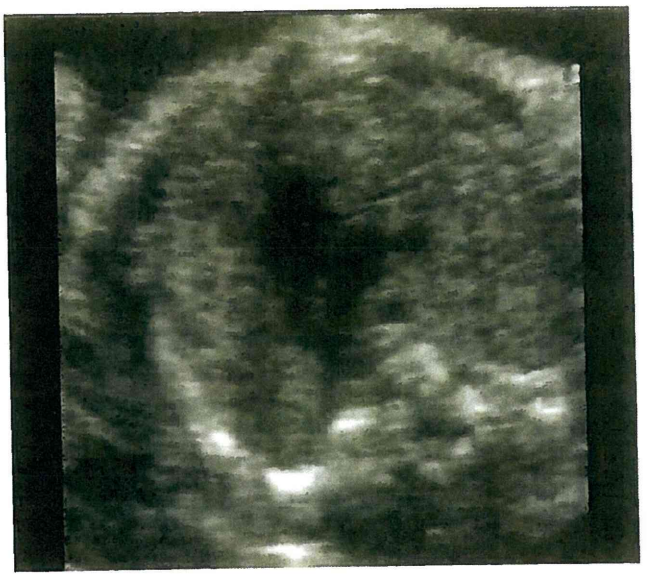

Fig. 15: A fetal echocardiographic image of three-vessel and trachea view

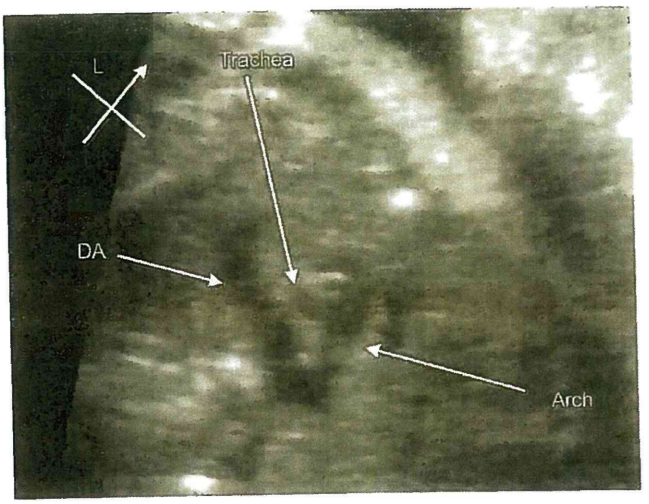

Fig. 16: A three-vessel and trachea view of the fetus with vascular ring caused by right sided aortic arch. The aortic arch is running right side of the trachea, and the ductus arteriosus (DA) is running left side of the trachea which making vascular ring

screening. This three-vessel and trachea view is useful for detecting variable vascular rings, which sometimes cause marked airway problems postnatally (Fig. 16).

For the location assessment, the aortic arch crosses anterior side of the trachea from right anterior to the left posterior, and connected to the descending aorta. There is no 'size' assessment in this view. For the detail anatomy assessment, the ascending aorta is connected to the descending aorta via the aortic arch and isthmus, and the aortic arch and the ductus arteriosus makes V shape at the left side of the trachea. For the function and blood flow assessment, the color Doppler flow reveals the flow to the same direction at both the ascending aorta and the ductus arteriosus.

ROLE OF THREE-DIMENSIONAL ECHOCARDIOGRAPHY TO THE SCREENING

Three-dimensional (3D) echocardiography may have important role for the both the basic and advanced screening of abnormal fetal heart.[9,10] The information of the side of the heart is already included to the 3D data, and the four simple transverse views for screening can be obtained from the 3D data set (Fig. 17). For the conventional two-dimensional echocardiography, fetal movement and limited window due to the fetal position often makes it difficult to do fetal heart screening. Whereas in the 3D echocardiography, any optimal screening image can be obtained without fetal movement once the 3D data set of the fetal heart is acquired and saved into the hard disk.

For only the basic screening, still 3D data set is sufficient to assess the location and the size using the four-chamber view and the three-vessel view (Fig. 18). For the advanced screening, STIC method is needed to assess the detail anatomy and the function and blood flow. The STIC method, 3D images with heart beat, can be created by automatic calculation of fetal heart rate from the acquired data set.

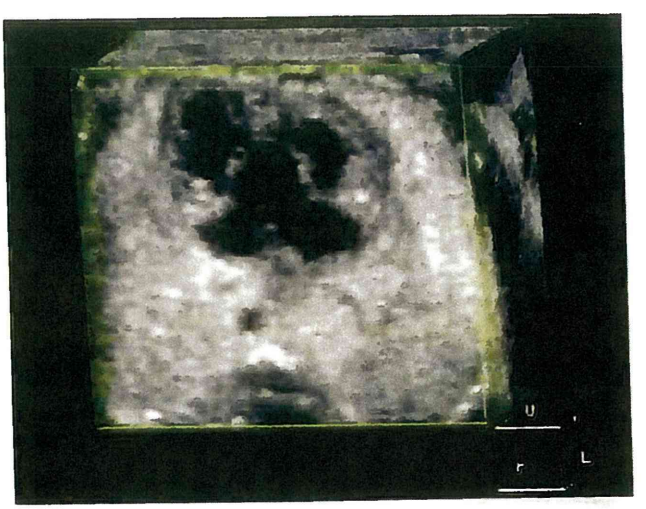

Fig. 17: Three-dimensional echocardiography in a case with common atrioventricular valve (asplenic syndrome). Optimal 2D cutting plane can be created from the 3D data set and demonstrated from optimal angle

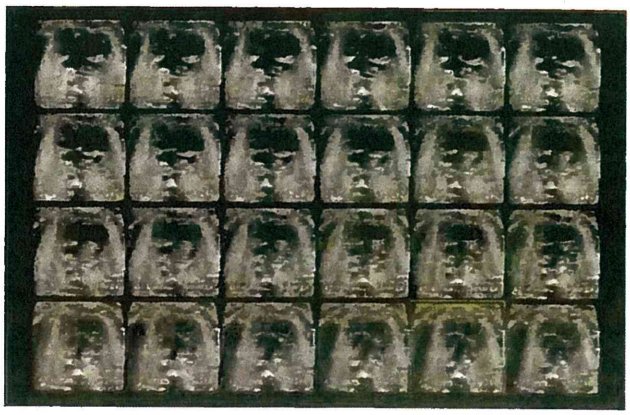

Fig. 18: Three-dimensional echocardiography in a case with common atrioventricular valve. Multiple parallel cutting planes obtained from 3D data set demonstrate the connection from the cardiac chambers to the vessels

CONCLUSIONS

Since the recent development of the fetal echocardiography and development of the perinatal management, the issue of the prenatal diagnosis of the fetal CHD is the screening system. In order to start fetal cardiac screening system in certain region, where the screeners are not familiar to the screening of CHD, step by step screening methods for taking account for the level of screener in certain area is needed. We present the fetal cardiac screening divided into two methods accounting for steps for learning screening technique; the basic screening and the advanced screening. The basic screening using only four-chamber view and three-vessel view with the assessment of location and size does not require complex knowledge of cardiac structures. Using this basic screening method, we believe more region start the systematic fetal screening program, and more fetuses have benefit for recent advanced perinatal management of CHD.

REFERENCES

1. Copel JA, Pilu G, Green J, Hobbins JC, Kleinman CS. Fetal echocardiographic screening for congenital heart disease: The importance of the four-chamber view. Am J Obstet Gynecol 1987;157:648-55.
2. Allan LD, Sharland GK, Milburn A, et al. Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. J Am Coll Cardiol 1994;23:1452-58.
3. Buskens E, Grobbee DE, Frohn-Mulder IME, et al. Efficacy of routine fetal ultrasound screening for congenital heart disease in normal pregnancy. Circulation 1996;94:67-72.
4. Bonnet D, Coltri A, Butera G, et al. Detection of transposition of the great arteries in fetuses reduces neonatal morbidity and mortality. Circulation 1999;99:916-18.
5. Carvalho JS, Mavrides E, Shinebourne EA, Campbell S, Thilaganathan B. Improving the effectiveness of routine prenatal screening for major congenital heart defects. Heart 2002;88: 387-91.
6. Cordes TM. Distinguishing right from left: A standardized technique for fetal echocardiography. J Am Soc Echo 1994;7:47.
7. Yoo S, Lee Y, Kim E, et al. Three-vessel view of the fetal upper mediastinum: An easy means of detecting abnormalities of the ventricular outow tracts and great arteries during obstetric screening. Ultrasound Obstet Gynecol 1997;9:173-82.
8. Yagel S, Arbel R, Anteby EY, Raveh D, Achiron R. The three vessels and trachea view (3VT) in fetal cardiac scanning. Ultrasound Obstet Gynecol 2002;20:340-45.
9. Devore GR, Polanco B, Sklansky MS, Platt LD. The 'spin' technique: A new method for examinination of the fetal outflow tracts using three-dimensional ultrasound. Ultrasound Obstet Gynecol 2004;24:72-82.
10. Herberg U, Steinweg B, Berg C, Breuer J. Echocardiography in the fetus: A systematic comparative analysis of standard cardiac views with 2D, 3D reconstructive and 3D real-time echocardiography. Ultrasound Obstet Gynecol 2010 (Epub ahead).

Original Paper

Fetal Diagnosis and Therapy

Fetal Diagn Ther 2011;30:189–193
DOI: 10.1159/000328456

Received: October 8, 2010
Accepted: April 12, 2011
Published online: July 16, 2011

Decrease in High Human Chorionic Gonadotropin in Twin-Twin Transfusion Syndrome following Fetoscopic Laser Surgery

Masachi Hanaoka[a, c] Satoshi Hayashi[a] Mari Saito[b] Mineto Morita[c]
Haruhiko Sago[a]

[a]Department of Maternal-Fetal and Neonatal Medicine, [b]Clinical Research Center, National Center for Child Health and Development, and [c]Department of Obstetrics and Gynecology, School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan

Key Words
Twin-twin transfusion syndrome · Human chorionic gonadotropin · Fetoscopic laser surgery · Monochorionic twins · Placental anastomoses

Abstract
Introduction: The purpose of this study was to investigate the concentration of maternal serum human chorionic gonadotropin (hCG) in twin-twin transfusion syndrome (TTTS) before and after fetoscopic laser surgery and to clarify the association between TTTS and hCG. ***Material and Methods:*** The concentration of maternal serum hCG was measured before fetoscopic laser surgery and 2 and 4 weeks after laser surgery in 120 patients diagnosed with TTTS. ***Results:*** The preoperative serum concentration of hCG was 6.34 multiples of the median (MoM; interquartile range 3.52–9.86). The concentration of hCG was higher in TTTS of Quintero stage III or IV (7.17 MoM, range 4.21–11.0) compared to stage I or II (3.37 MoM, range 2.35–7.74). When laser surgery for TTTS was effective, hCG gradually decreased to less than half the preoperative concentration 2 weeks after laser surgery, and the concentration was further reduced to within the normal range at 4 weeks. However, the concentration of hCG in 3 cases with TTTS recurrence did not decrease. ***Discussion:*** A close association was observed between the concentration of hCG and the condition of TTTS. A change in the concentration of hCG after laser surgery could be a useful marker to judge the effectiveness of laser surgery in TTTS.

Introduction

Twin-twin transfusion syndrome (TTTS) is a severe complication of monochorionic twin pregnancies, with high perinatal loss and significant morbidity. The pathogenesis of this syndrome remains unclear, but it is known that unbalanced placental intertwin vascular anastomoses play a key role in the pathophysiology of TTTS, wherein one twin becomes hypovolemic (the donor) and the other hypervolemic (the recipient). Laser ablation of placental anastomoses has gained widespread acceptance as the definitive treatment for severe TTTS between 16 and 26 weeks of gestation [1–3]. One randomized trial demonstrated that laser surgery is a more effective first-line treatment than serial amnioreduction for TTTS [4]. Recently, a metaanalysis of comparative studies found that compared with fetuses undergoing serial amnioreduction, fetuses undergoing laser ablation were twice as likely to survive and had an 80% reduction in neurologic morbidity [5].

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–3837/11/0303–0189$38.00/0

Accessible online at:
www.karger.com/fdt

Haruhiko Sago, MD, PhD
Department of Maternal-Fetal and Neonatal Medicine
National Center for Child Health and Development
2-10-1 Okura, Setagaya-ku, Tokyo 157-8535 (Japan)
Tel. +81 3 3416 0181, E-Mail sagou-h@ncchd.go.jp

It has been reported that hCG in monochorionic twin pregnancies complicated by severe TTTS was significantly increased compared to uncomplicated twin pregnancies [6]. It has also been reported that the pathophysiology of TTTS is closely related to hCG [7, 8]. However, the changes in the concentration of hCG after laser surgery have not been studied sufficiently. Therefore, in the present study, the concentration of maternal serum hCG before and after fetoscopic laser surgery for TTTS was measured. The purpose of this study was to investigate the concentration of maternal serum hCG before and after fetoscopic laser surgery and to clarify the association between TTTS and the concentration of hCG.

Material and Methods

A total of 120 pregnant women diagnosed with TTTS who underwent fetoscopic laser surgery from March 2005 to October 2009 were studied. Inclusion criteria were that the pregnant woman was diagnosed with TTTS between 16 and 26 weeks of gestation and had undergone laser surgery at our institute. The diagnosis of TTTS was based upon ultrasonographic evidence of a single monochorionic placenta that was complicated by polyhydramnios with a maximum vertical pocket ≥8.0 cm (with a distended bladder) in the recipient twin and oligohydramnios with a maximum vertical pocket ≤2.0 cm (with a nondistended bladder) in the donor twin.

The exclusion criterion was the occurrence of fetal death after laser surgery, regardless of whether the fetal death was a single death or a double death. Further, recurrence was diagnosed when polyhydramnios/oligohydramnios reappeared after laser surgery.

The concentration of maternal serum human chorionic gonadotropin (hCG) was measured before laser surgery and 2 and 4 weeks after laser surgery. Maternal serum hCG was measured by a chemiluminescent enzyme immunoassay. Changes in the concentration of hCG in uneventful cases were compared with those in 3 recurrent cases. The concentration of hCG was shown as the multiple of the median (MoM). The median was derived from singleton pregnancies.

In our institute, laser surgery was performed for TTTS of Quintero stage [9] I–IV between 16 and 26 weeks of gestation. The laser surgery was performed as described in a previous report [10]. Prophylactic tocolytics and antibiotics were administered perioperatively. Antenatal care with weekly ultrasound surveillance was performed for 1 month at our institute and later at referral centers. All patients provided written consent to undergo fetoscopic laser surgery and to participate in this study, which was approved by the ethics committee of our institution.

Results

During this study of 120 cases, the twin survival rates at 1 month after laser surgery were as follows: 2 survivors in 97 cases (80.8%), 1 survivor in 21 cases (17.5%) and double death in 2 cases (1.7%). Among the cases with 2 survivors (n = 97), recurrence of TTTS with polyhydramnios/oligohydramnios occurred in 3 cases after laser surgery.

The median preoperative concentration of hCG was 6.34 MoM (interquartile range 3.52–9.86). There was no clear correlation between the concentration of hCG and gestational age (R = 0.039). The concentration of hCG was significantly higher in Quintero stage III or IV TTTS than in stage I or II disease (Wilcoxon test: p = 0.002; fig. 1). When laser surgery for TTTS was effective, the concentration of hCG gradually decreased to less than half the preoperative concentration 2 weeks after laser surgery (2.85 MoM, range 1.78–4.68; fig. 2). At 4 weeks after laser surgery, the concentration of hCG was further reduced to 1.67 MoM (range 1.12–2.32).

Polyhydramnios/oligohydramnios reappeared after laser surgery in 3 cases (cases 1, 2, 3; fig. 3). The concentration of hCG in these recurrent cases either remained elevated 2 weeks after laser surgery or increased to more than the preoperative concentration.

Case 2 underwent a second laser surgery (stage III TTTS before surgery). The concentration of hCG decreased and the condition improved in the 2 weeks following the second laser surgery. In contrast, in case 1, who had stage IV TTTS before surgery, polyhydramnios reappeared and an abnormal Doppler was observed after laser surgery. In this case, a cesarean section was performed 40 days after laser surgery (at 31 + 3 weeks of gestation). In case 3, who had stage I TTTS before surgery, polyhydramnios associated with maternal discomfort and an abnormal Doppler was observed after laser surgery. Because amniotic membrane detachment was seen after laser surgery, a second laser surgery was not performed. Placental examination of cases 1 and 3, but not case 2, showed residual anastomoses caused by incomplete coagulation of communicating vessels.

Discussion

In the present study, the concentration of maternal serum hCG before and after fetoscopic laser surgery for TTTS was measured. The preoperative concentration of hCG was significantly high. Two weeks after successful laser surgery, the concentration of hCG decreased to less than half the preoperative concentration, and 4 weeks after laser surgery, the concentration was further reduced. However, in recurrent cases of TTTS with polyhydramnios/oligohydramnios, hCG remained elevated or even

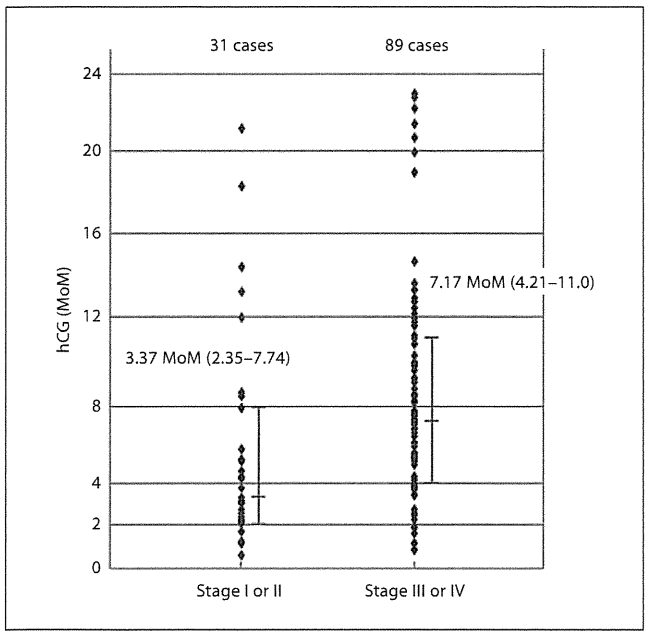

Fig. 1. Preoperative hCG concentration in TTTS according to Quintero stage (120 cases). Medians and interquartile ranges are shown. Preoperative hCG in stage III or IV TTTS (89 cases) was significantly higher than in stage I or II TTTS (31 cases) ($p = 0.0020$, Wilcoxon test).

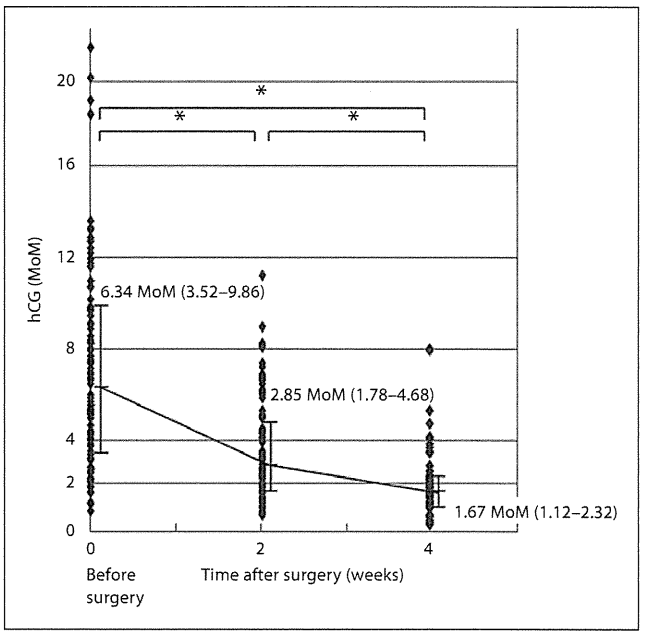

Fig. 2. Changes in hCG concentration after laser surgery (94 cases). Medians and interquartile ranges of the hCG concentrations before surgery and 2 and 4 weeks after surgery are shown. The concentration of hCG decreased to less than half the preoperative concentration 2 weeks after laser surgery, and the concentration of hCG was further reduced to within the normal range 4 weeks after laser surgery. * $p < 0.0001$ (Wilcoxon test).

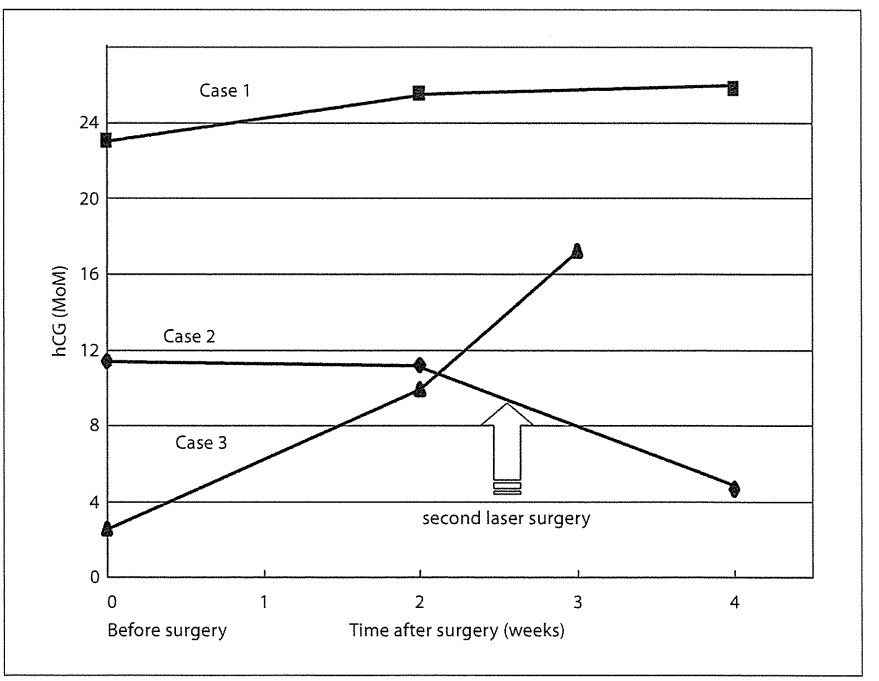

Fig. 3. Changes in hCG concentration after laser surgery in recurrent cases. TTTS recurred in 3 cases after laser surgery (cases 1, 2, 3). The concentration of hCG in recurrent cases either remained elevated 2 weeks after laser surgery or increased to more than the preoperative concentration. The hCG concentration decreased after the second laser surgery in 1 case (case 2).