(Figure 2a). The ductus arteriosus was not occluded, but was constricted. A mural thrombus within the dilated pulmonary artery had adhered to the arterial wall in a part that was already organized, as shown by Masson's trichrome staining (Figure 2b). Excluding the stalk, the thrombus was not fully organized. This strongly suggested that the thrombus originated on the surface of the intima of the main pulmonary artery in the prenatal period. The pulmonary artery itself was structurally normal. However, focal CD34-positive endothelial cells were lacking.

We postulate that thrombus formation in this case was attributable to Virchow's triad. In 1856, Rudolf Virchow proposed that abnormalities in blood flow, hypercoagulability of the blood, and injury to the vessel wall are causally related to thrombus formation[1]. In our case, it is likely that reduced right heart ejection fraction caused by fetal hydrops and premature constriction of the ductus arteriosus after administration of indomethacin led to abnormalities in blood flow[2–6]. Postmortem examination showed a focal defect of the endothelium of the fetal pulmonary artery. The multiple thoracoamniotic shunting procedures performed for fetal chylothorax might have caused hypercoagulability of the blood and injury to the vessel wall. We speculate that surgical stress caused inflammation leading to activation of leukocytes, thrombocytes and coagulation factors. We suggest that indomethacin should be used cautiously when repeated thoracoamniotic shunting is required for fetal chylothorax with hydrops.

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Retrospective Review of Thoracoamniotic Shunting Using a Double-Basket Catheter for Fetal Chylothorax

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Key Words
Chylothorax · Double-basket catheter · Fetal hydrops · Fetal pleural effusions · Fetal therapy · Polyhydramnios · Thoracoamniotic shunting

Abstract
Objective: From a single-center retrospective cohort with fetal chylothorax, we evaluated the factors related to the decision to use shunting, poor prognostic factors, and reported shunting outcomes with a new double basket-catheter device. ***Methods:*** A retrospective single-center study was performed in 35 cases of fetal chylothorax. ***Results:*** There were 35 cases of chylothorax: 23 with hydrops and 12 without hydrops. Twenty-one procedures were performed on 15 fetuses (11 with hydrops) with a single shunt in 11, two shunts in 3 and four shunts in 1. All 12 nonhydropic cases survived. In 23 hydropic cases, overall survival rates with and without thoracoamniotic shunting were 46 and 33%, respectively. The mortality rates of fetal hydropic cases with and without ascites were 93 and 11%, respectively. Fetal ascites, progression of fetal hydrops, and premature delivery at <33 weeks were significant risk factors for a poor prognosis. Progression of polyhydramnios after shunting was also associated with a poor prognosis. Obstruction of the catheter was observed in 38%. There were no direct fetal deaths associated with shunting. ***Conclusion:*** Thoracoamniotic shunting should be considered for pleural effusion before development of fetal hydrops, or at least before the appearance of fetal ascites. A double-basket catheter tends to be obstructive, but may be less invasive for fetuses.

Introduction

Fetal pleural effusion is a rare condition with an incidence of 1/10,000–1/15,000 pregnancies [1]. Primary fetal pleural effusion is most often caused by congenital chylothorax, which is a lymphatic abnormality. The clinical course varies from spontaneous resolution to a progressive increase and development of hydrops and polyhydramnios [2]. If severe and longstanding, fetal pleural effusion has the effect of a space-occupying lesion that impedes normal lung development, with the risk of pulmonary hypoplasia and neonatal death [3]. Compression of the heart and obstruction of venous return subsequently lead to development of fetal hydrops resulting in fetal death, whereas compression of the esophagus leads to polyhydramnios [4–7]. Approximately a quarter of fetal

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deaths are due to circulatory abnormalities that cause tissue hypoxia and acidemia, while most postnatal deaths are due to pulmonary hypoplasia [1, 2, 8].

Nonhydropic fetuses with isolated pleural effusion have a good prognosis; however, when hydrops develops, the outcome without intervention is generally very poor [9]. A meta-analysis by Weber and Philipson [5] was the first to lend support to the idea of prenatal intervention for fetuses with pleural effusion. There is a consensus among fetal medicine specialists that invasive fetal therapy for fetal pleural effusion should be reserved for hydropic fetuses without additional anomalies [10]. However, the clinical course is generally accepted to be difficult to predict and the best timing for the intervention remains uncertain [2]. Most authors would support the decision to shunt a fetal pleural effusion that has rapidly reaccumulated after the initial diagnostic/therapeutic thoracocentesis [1, 2, 5–7]. Deurloo et al. [11] reviewed the perinatal outcome in hydropic fetuses with isolated fetal pleural effusion with any form of prenatal intervention. The treatment options include thoracocentesis, thoracoamniotic shunting, and pleurodesis. Thoracoamniotic shunting is the most common procedure for treatment of fetal chylothorax [10–12]. The vast majority of fetal shunt procedures are performed using a silicone double-pigtail catheter [12]. In Japan, however, only the double-basket catheter is approved as a treatment for fetal chylothorax. There are few reports of this device [13, 14].

In this study, we evaluated the factors related to the decision to shunt the chest, poor prognostic factors, and reported shunting outcomes with a new double-basket catheter device.

Material and Methods

Patient Population

A retrospective single-center study was performed on 35 cases of fetal chylothorax identified at the National Cerebral and Cardiovascular Center from January 2002 to December 2011. Fifteen of these cases underwent thoracoamniotic shunting using a double-basket catheter. The mean maternal age was 32 years (range: 22–44). No patient had a significant medical history or family history.

Clinical Protocol for Fetal Pleural Effusion

Thoracocentesis was performed under local anesthesia as soon as the patients were referred to our center. When polyhydramnios induced uterine contractions and maternal discomfort, amniotic fluid reduction was performed in thoracocentesis or thoracoamniotic shunting. The cell content of the fetal pleural fluid was examined and the fetal karyotype was determined using the fetal pleural fluid or amniotic fluid. Findings exceeding 80% lymphocytes led to the prenatal diagnosis of chylothorax as described by Longaker et al. [1]. Maternal serology was also examined, including maternal blood type, antibody screening, and viral infections such as cytomegalovirus, toxoplasma, parvovirus B19, rubella, and herpesvirus.

Thoracoamniotic shunting was performed for a singleton with fetal chylothorax between 18 and 34 weeks of gestation, based on the following criteria: (1) fetal lateral or bilateral massive pleural effusion caused by isolated fetal chylothorax, with a history of reaccumulation of pleural effusion within 7 days after thoracocentesis; (2) no associated abnormality such as a critical abnormal karyotype, structural anomalies affecting neonatal survival, fetal arrhythmia, viral infections, and blood type incompatibility; (3) no maternal severe complications such as pregnancy-induced hypertension, mirror syndrome, cervical length <10 mm, genital bleeding, and premature rupture of membranes. These exclusion criteria for shunting were also applied for the serial thoracocentesis. Fetal hydrops was diagnosed when factors such as subcutaneous edema in head skin >5 mm, ascites, or pericardial effusion were detected, in addition to fetal pleural effusion.

Thoracoamniotic Shunting Procedure and Prenatal Management

Thoracoamniotic shunting was performed under general anesthesia within 7 days after thoracocentesis. If the effusion pooled bilaterally, the procedure was attempted on both sides. A 16-gauge puncture needle with a trocar (5 Fr, outer diameter 1.6 mm; Hakko Co., Nagano, Japan) was inserted through the abdominal skin and the uterus into the fetal thoracic cavity under ultrasonographic guidance. After removing the inner needle, a silicon double-basket catheter was inserted with a pusher (4.5 Fr, outer diameter 1.5 mm; Hakko Co.) into the trocar. This catheter was the original Japanese device (fig. 1). In Japan, only this type of catheter has been approved for fetal pleural effusion.

Serial thoracocentesis was considered in cases in which thoracoamniotic shunting could not be performed. Tocolysis was provided if necessary. Follow-up was based on daily to weekly ultrasound examinations and a cardiotocogram. Delivery was determined according to obstetrical indications.

Statistical Analysis

Data are presented as means ± SD or number of patients, and were analyzed by a Wilcoxon signed-rank test. Stepwise logistic regression analysis was performed, with results expressed as an odds ratio (OR) with 95% CI. Values of $p < 0.05$ were considered significant in all analyses. All statistical tests were performed using JMP 9 (SAS Institute, Cary, N.C., USA).

The study was approved by the institutional review board at the National Cerebral and Cardiovascular Center.

Results

Patient Population

There were 11 cases excluded from this study because of secondary effusion due to fetal heart failure with congenital heart defect. A total of 35 cases of fetal chylothorax were managed at the National Cerebral and Cardiovascu-

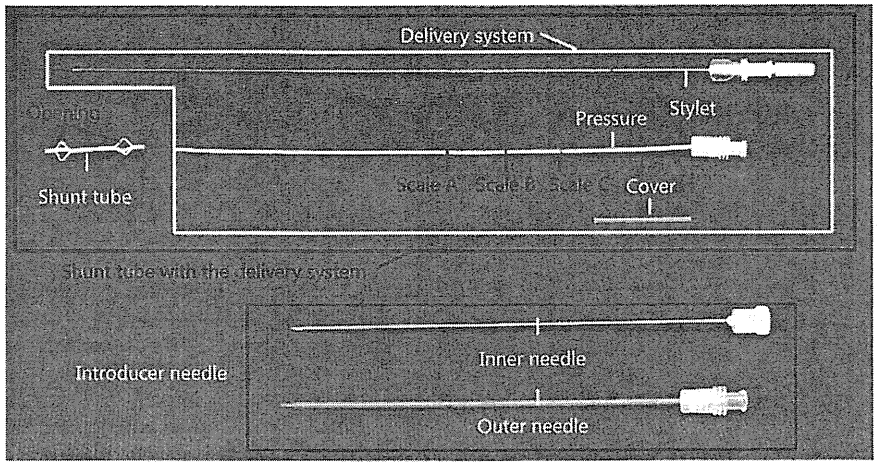

Fig. 1. The double-basket catheter developed by Hakko Co.

lar Center (fig. 2–4). Diagnosis was made at a mean gestation age of 26 weeks (range: 16–37). Thoracocentesis was performed in all cases. All pleural effusions had a lymphocyte proportion exceeding 90%, which was suggestive of chylothorax. No case was found to have secondary effusion after initial thoracocentesis. Of the 35 cases, 9 (26%) had abnormal karyotypes: 5 had trisomy 21 and 4 had 45 XO. No cases had a major malformation such as congenital heart disease. There was no termination, including of abnormal karyotypes.

Nonhydropic Cases

The 12 nonhydropic cases are shown in figure 2. There were no fetal or neonatal deaths. Only 1 case (8%) had bilateral effusions. None of the cases developed hydrops while under surveillance. Four of the 6 cases with rapid reaccumulation of massive fetal pleural effusion underwent thoracoamniotic shunting (fig. 4A). This procedure was not performed in the other 2 cases because their gestation exceeded 34 weeks. Three premature neonates required mechanical ventilation and pleural cavity tube drainage.

Hydropic Cases

The 23 hydropic cases are shown in figure 3. There were 5 fetal deaths and 9 neonatal deaths. Twenty-one cases (91%) had bilateral effusions. All hydropic cases had skin edema at initial presentation. Hydrops was improved while under surveillance in 9 cases (39%). The mortality rate of fetal hydropic cases with and without ascites was 93 and 11%, respectively (fig. 4B, C). Rethoracocentesis was performed just before cesarean section in cases with residual fetal pleural effusion. All premature neonates re-

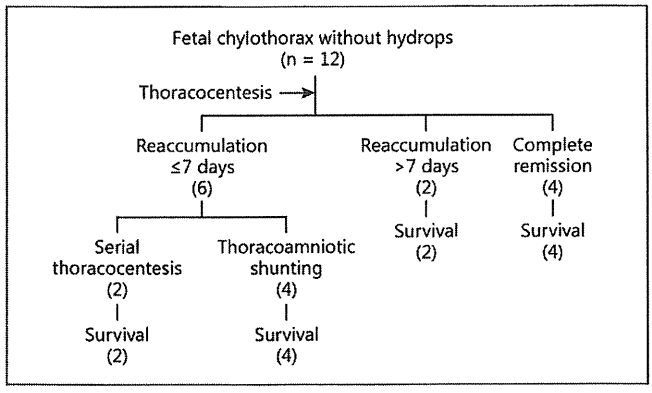

Fig. 2. Disposition of nonhydropic cases of fetal chylothorax (n = 12). Reaccumulation: reaccumulation of fetal chylothorax; complete remission: complete remission of fetal chylothorax.

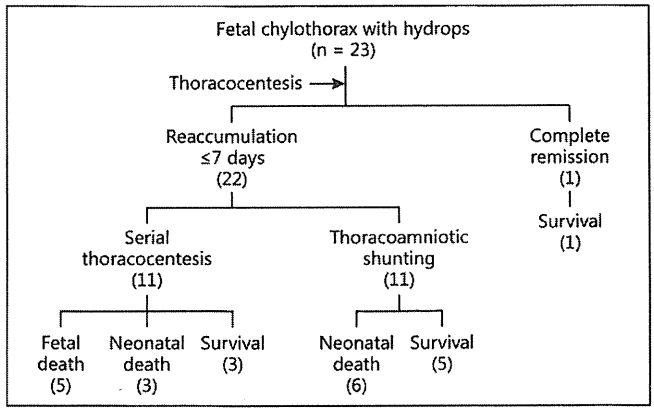

Fig. 3. Disposition of hydropic cases of fetal chylothorax (n = 23). Reaccumulation: reaccumulation of fetal chylothorax; complete remission: complete remission of fetal chylothorax.

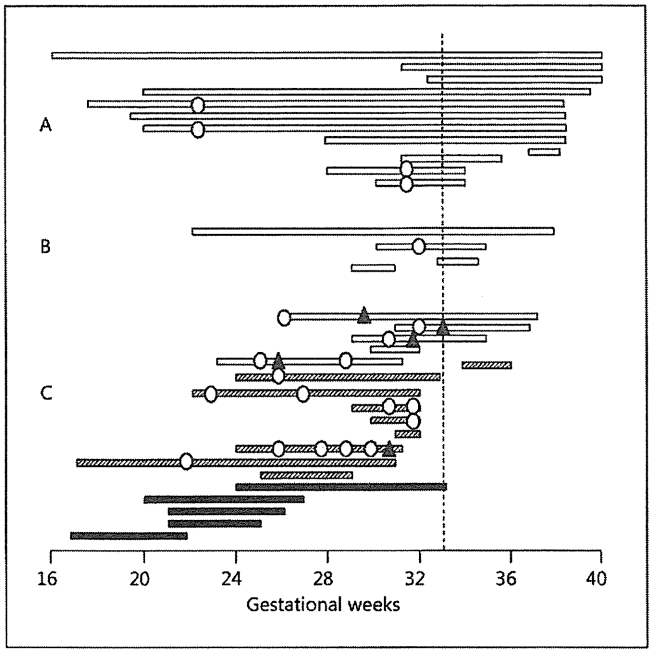

Fig. 4. Interval between diagnosis and delivery (n = 35). The horizontal lines connect the gestation at diagnosis with the gestation at delivery. A: nonhydropic cases (n = 12). B: hydropic cases without ascites at diagnosis (n = 4). C: hydropic cases with ascites at diagnosis (n = 19). White line: neonatal survival; striped line: neonatal death; black line: fetal death; circle: thoracoamniotic shunting; triangle: remission of ascites.

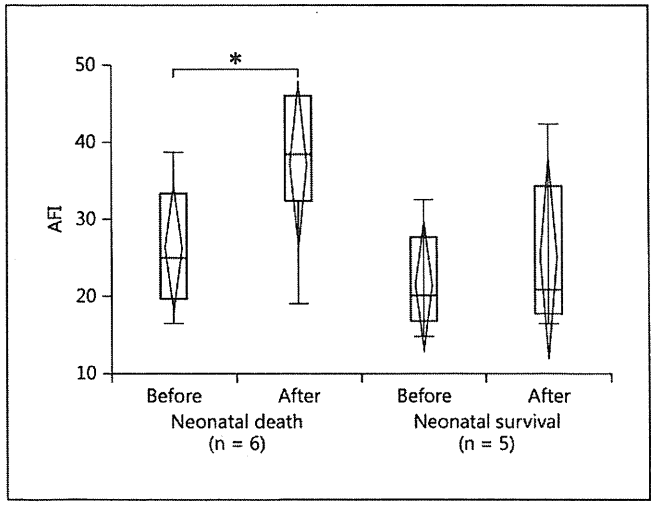

Fig. 5. Box-and-whisker diagram of the maximum AFI before and after thoracoamniotic shunting for hydropic cases of fetal chylothorax. Data were analyzed by Wilcoxon signed-rank test. * p values < 0.05 were considered significant. AFI = Amniotic fluid index.

quired mechanical ventilation and pleural cavity tube drainage. The neonatal survival rates in the 23 hydropic cases were 46 and 33% with and without thoracoamniotic shunting, respectively. The reasons why thoracoamniotic shunting was not performed in the 12 hydropic cases were due to preterm premature rupture of the membrane (n = 3), fetal death before shunting (n = 3), gestational age exceeded 34 weeks (n = 2), cervical length <10 mm (n = 2), placental location (n = 1), and complete remission of pleural effusion after thoracocentesis (n = 1).

The primary cause of fetal and neonatal deaths was fetal hydrops and pulmonary hypoplasia, respectively. Postmortem examinations showed the mean lung/body weight ratio was 0.0061 (range: 0.0035–0.0083), which was suggestive of pulmonary hypoplasia. Only 1 case exceeding 33 weeks of gestation died due to disseminated intravascular coagulation. In 1 case, fetal hydrops remarkably improved after four thoracoamniotic shuntings; however, fetal pulmonary thrombosis complicated right heart failure, leading to early neonatal death.

Thoracoamniotic Shunting Cases

The initial thoracoamniotic shunting was performed in 15 cases at a mean gestational age of 27 weeks (fig. 4). The mean time interval between the initial shunting and delivery was 6.5 weeks (range: 0–16). Shunting was bilateral in 8 cases and unilateral in 7 cases. Shunt placement was performed successfully in all except 1 case of placental puncture. In this case, the placenta was widely distributed on the anterior wall of the uterus and the 16-gauge puncture needle caused placental bleeding. Obstruction of the catheter was observed in 8 of 21 shunting procedures (38%). All catheters were obstructed by fibrin deposition. Displacement of the catheter was observed in only 1 case (5%). This catheter was expelled in the amniotic cavity, and shunting had to be repeated. Reshunting was required in 4 cases (27%): 1 had to be shunted four times, and the other 3 had to be shunted twice. Premature rupture of the membrane within 4 weeks after shunting occurred in 3 cases (20%) at a mean interval of 3.3 weeks after shunting (range: 1–6). Preterm delivery occurred in 11 cases (73%). All cases with multiple shunts had polyhydramnios and fetal hydrops with ascites, and delivered at a mean gestational age of 31 weeks (range: 31–32) because of premature rupture of the membrane or onset of labor. Three of them died in the neonatal period. There were no cases of intrauterine infection and fetal death during shunting. There were no cases of difficulty removing the catheter at birth.

When comparing the maximum amniotic fluid index before and after thoracoamniotic shunting, the median

Table 1. Effects of baseline characteristics on fetal or neonatal death in 35 cases with fetal chylothorax

Characteristics	OR	95% CI	p
Ascites	22.1	3.2–152.8	0.0003
Progression of hydrops	34.8	5.0–241.7	0.0029
Gestational age at delivery <33 weeks	22.0	3.8–128.8	0.0043

$p < 0.05$ indicates a significant difference in stepwise logistic regression analysis.

amniotic fluid index significantly increased after shunting in the death cases (24 vs. 39, $p < 0.05$) and did not differ in the survival cases (19 vs. 20, $p = 0.81$; fig. 5). Amniotic fluid reduction was required several times after shunting in 4 of 6 cases of neonatal death.

Risk Factors of Fetal or Neonatal Death

Stepwise logistic regression analysis of factors with a potential association with fetal or neonatal death was performed in all 35 cases (table 1). Fetal ascites, progression of fetal hydrops, and gestational age at delivery <33 weeks had significant effects on fetal or neonatal death ($p < 0.05$). Persistent polyhydramnios tended to be associated with poor prognosis (OR: 4.3, 95% CI: 1.0–18.4, $p = 0.05$). Gestational age at diagnosis, cardiothoracic area ratio and lung thoracic area ratio at diagnosis, and presence of abnormal karyotype were not associated with prognosis. In receiver operating characteristic analysis of the relationship of neonatal survival with gestational age at delivery, the area under the curve was 0.905 and a gestational age at delivery of 33 weeks gave the best sensitivity (1 – specificity). Fourteen infants were delivered before 33 weeks: 9 due to progression of fetal hydrops, 4 due to preterm premature rupture of the membrane, and 1 due to placental bleeding during shunting.

Discussion

This is one of the largest retrospective single-center studies of thoracoamniotic shunting using the double-basket catheter for fetal chylothorax. All nonhydropic fetuses survived, whereas the prognosis of hydropic fetuses was very poor. All fetuses presenting with significant pleural effusion due to chylothorax should be evaluated first by thoracocentesis; in cases with rapid reaccumulation (<7 days), a thoracoamniotic shunt is indicated, even in the absence of fetal hydrops. All hydropic cases had skin edema, and hydropic cases with ascites had high mortality. Fetal ascites, progression of fetal hydrops, and premature delivery at <33 weeks of gestation were significant risk factors for a poor prognosis in cases with fetal chylothorax. Thus, thoracoamniotic shunting for massive pleural effusions should be performed before the development of fetal hydrops, or at least before the appearance of fetal ascites. In our experience, a double-basket catheter tended to be obstructive, but might be less invasive for fetuses. Displacement was less likely to occur with our catheter, and it was not difficult to remove at birth.

The clinical course of a case with fetal chylothorax is generally accepted to be difficult to predict, and development of fetal hydrops makes fetal and neonatal outcomes very poor [2–7]. In this study, all nonhydropic fetuses survived, whereas hydropic fetuses with and without thoracoamniotic shunting had a poor prognosis. All fetuses presenting with significant pleural effusion due to chylothorax should be evaluated first by thoracocentesis; in cases with rapid reaccumulation (<7 days), a thoracoamniotic shunt is indicated, even in the absence of fetal hydrops. All hydropic fetuses had skin edema, and fetal ascites was a significant risk factor for a poor prognosis. We suggest that skin edema is the first step in hydrops caused by fetal pleural effusion, and that this is followed by ascites as the second step. Thus, it is important to make intervention for fetal chylothorax before development of fetal hydrops, or at least before the appearance of fetal ascites.

Serial thoracocentesis is unlikely to be of benefit because it is associated with rapid reaccumulation of the effusion in many reports [1, 2, 5–7]. Therefore, we included 4 cases of nonhydrops. Thoracoamniotic shunting is the most common procedure for treatment of fetal chylothorax [10–12]. Shunting benefits the fetus by allowing the pleural fluid to decompress to the pressure of the amniotic fluid. This allows the lungs to expand, potentially reducing the risk of pulmonary hypoplasia, and also reduces pressure on the venous system, which increases venous return to the heart and improves coexisting heart failure and hydrops [15]. Decompression of the esophagus leads to improvement of polyhydramnios. This is important because progression of polyhydramnios after thoracoamniotic shunting occurred in cases with a poor prognosis. Such progression may have been due to fetal dysphagia since severe hydropic fetuses were not able to recover from fetal dysphagia, or due to the amount of pleural effusion since a large amount of pleural effusion is pro-

duced and transferred into the amniotic cavity through the catheter.

The vast majority of fetal shunt procedures are performed using a silicone double-pigtail catheter (Rocket of London Ltd., Watford, UK), which is inserted under ultrasound guidance through an introducer with an outer diameter of 3 mm [12]. Our device is thinner, with an outer diameter of only 1.6 mm. The most common complication is shunt failure. In this study, obstruction of the catheter was observed in 38% of the cases (n = 8), compared to 6–33% in reports of a double-pigtail catheter [9–12, 16–19]. Obstruction was more likely to occur with our thinner catheter. Displacement of the catheter was observed in 1 case (5%), compared to 4–50% of the cases in reports of a double-pigtail catheter [9–12, 16–19]. Displacement was less likely to occur with our catheter, and there were no cases in which it was difficult to remove at birth despite its fixability in utero. The rate of preterm premature rupture of the membrane within 4 weeks after shunting was 20% in this study, compared to 6–20% in recent large studies of a double-pigtail catheter [9–12, 16–19]. More cases are required to determine if the rate of preterm premature rupture of the membrane is truly comparable to the double-pigtail catheter. The location of the placenta is important for safe performance of thoracoamniotic shunting, with increased difficulty with this procedure caused by a placenta widely distributed on the anterior wall of the uterus. In this study, 1 case required emergency cesarean section because of placental bleeding due to a puncture needle, and thoracoamniotic shunting could not be performed in another case. All 4 cases with multiple shunt procedures delivered before 33 weeks of gestation because of preterm premature rupture of the membrane or onset of labor, and 3 of them died in the neonatal period. However, polyhydramnios before/after thoracoamniotic shunting might be associated with preterm delivery. In 1 case with four shunts, the neonate died 3 h after birth because of pulmonary thrombosis, which is described in detail in our previous report [20]. There was no direct fetal death associated with shunting using our device, whereas a rate of 5–10% has been reported with the double-pigtail catheter [15, 21]. Thus, we suggest that our double-basket catheter may be less invasive for the fetus compared to the double-pigtail catheter.

In the series of our cases, all of them had the procedure done under general anesthesia, which is beneficial for a few reasons. First, general anesthesia could achieve full analgesia and sedation of the pregnant women and fetuses which made the procedure easy. Another reason was that the use of sevoflurane enabled tocolysis for the contractions during procedure. Therefore, we believe that general anesthesia helped to prevent direct fetal death during shunt procedure and displacement of the catheter. There were no fetal and maternal complications due to general anesthesia. In the future, however, we will consider regional anesthesia as a less invasive process because serious maternal complications such as aspiration pneumonitis or pneumothorax are known to occur under general anesthesia.

Associated malformations and aneuploidy have been reported in about 25 and 7% of in utero and postnatal cases, respectively, and these conditions clearly worsen the outcome of fetal chylothorax [21, 22]. However, in this study, an abnormal karyotype such as trisomy 21 and 45 XO were not associated with fetal and neonatal outcome, which suggests that the severity of malformation associated with an abnormal karyotype is more important. Thus, thoracoamniotic shunting should be performed in cases without a critical malformation.

There are several limitations in this study. First, we could not statistically verify the efficacy of thoracoamniotic shunting because of a potential retrospective data selection bias and the relatively small sample size. In particular, thoracoamniotic shunting was not performed in half of the hydropic cases for several reasons, and the rate of advanced hydropic cases with ascites was higher in cases with thoracoamniotic shunting. Second, the follow-up period after birth was insufficient to permit analysis of long-term morbidity and mortality, which prevented evaluation of the potential long-term benefits and risks of thoracoamniotic shunting. However, the results provide important information as a single-center study of thoracoamniotic shunting using a double-basket catheter for a rare condition.

In conclusion, all fetuses presenting with significant pleural effusion due to chylothorax should be evaluated first by thoracocentesis, and in cases with rapid reaccumulation (<7 days), a thoracoamniotic shunt is indicated, even in the absence of fetal hydrops. We suggest that skin edema is the first step in hydrops caused by fetal pleural effusion, and that this is followed by ascites as the second step, making the fetal and neonatal outcomes very poor. Thus, thoracoamniotic shunting for massive pleural effusions should be performed before development of fetal hydrops, or at least before the appearance of fetal ascites. A double-basket catheter tends to be obstructive, but may be less invasive for fetuses. Displacement is less likely to occur with our catheter, and there have been no cases in which it was difficult to remove at birth. In the future, there should be a randomized controlled trial comparing

the pigtail catheter and our double-basket catheter to evaluate the efficacy and safety of fetal pleural effusion. Further large prospective studies are needed to establish the most appropriate treatment strategies for fetal chylothorax.

Disclosure Statement

None of the authors have a conflict of interest. This work received only institutional support.

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Safety and Efficacy of Implantable Cardioverter-Defibrillator During Pregnancy and After Delivery

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Background: There are few studies of pregnancy and delivery in patients with an implantable cardioverter-defibrillator (ICD). The purpose of this study was to investigate maternal and fetal outcome in these patients.

Methods and Results: Six pregnant women with an ICD were retrospectively reviewed. All women underwent implantation of an ICD before pregnancy and delivered at the National Cerebral and Cardiovascular Center. The mean age at pregnancy and the mean follow-up period after ICD implantation were 28±3 years old and 5±3 years, respectively. There was no device-related complication during pregnancy. In 4 women, the number of tachyarrhythmias such as non-sustained ventricular tachycardia increased after the end of the second trimester of pregnancy and anti-arrhythmic medications were gradually increased. No patient received discharges or shocks from the ICD during pregnancy, however, and only one required anti-tachycardia pacing at 27 weeks' gestation. Mean gestational age at delivery was 37±2 weeks and all deliveries were by cesarean section, including 5 as emergency deliveries due to a fetal indication. After delivery, 2 mothers had reduced cardiac function and 1 received an ICD shock for the first time.

Conclusions: Pregnancy did not increase the risk of an ICD-related complication under appropriate management. Additional caution might be required in the postpartum period as well as during pregnancy and labor. (*Circ J* 2013; **77:** 1166–1170)

Key Words: Beta-blocker; Delivery; Implantable cardioverter-defibrillator; Pregnancy; Ventricular tachycardia

Cardiac disease complicates approximately 1% of all pregnancies, and women with arrhythmias comprise only a small number of these cases.[1] Although arrhythmias are uncommon during pregnancy, they may jeopardize the health of both mother and fetus. Ventricular tachyarrhythmia may be triggered during pregnancy as a result of hemodynamic changes and autonomic nervous system modification.[2,3] Recurrence of malignant ventricular arrhythmias can be treated by defibrillation and anti-tachycardia pacing (ATP) to prevent sudden cardiac arrest.[4] An implantable cardioverter-defibrillator (ICD) improves survival in patients with life-threatening arrhythmias.[5] The number of women with congenital heart disease continues to increase and the use of an ICD has resulted in an increasing number of these women reaching a reproductive age.[6] Natale et al performed a multicenter retrospective analysis of 44 pregnant women with ICDs and found that the majority completed and tolerated pregnancy without serious complications.[7] There are few studies, however, of pregnancy with an ICD managed at a single center and it remains unclear how to manage pregnant women with ICDs. The aim of this study was to investigate the maternal and fetal outcomes in these patients during pregnancy and after delivery.

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Methods

Study Design

The subjects were all pregnant women with an implanted ICD who delivered at the National Cerebral and Cardiovascular Center. Data were retrospectively collected for age at the time of initial ICD implantation and delivery; heart disease and arrhythmia; New York Heart Association class; anti-arrhythmic medications and other anti-arrhythmic treatment; indication

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Table 1. Baseline Pre-Pregnancy Patient Characteristics

Patient	Heart disease	NYHA class	Age at ICD implantation (years)	LVEF at ICD implantation (%)	No. ICD shocks	Anti-arrhythmic medication	Other treatment
1	DCM, VT	2	25	37.5	0	Metoprolol	Catheter ablation
2	DCM, VF	2	23	21.3	2	Carvedilol, Mexiletine, Aprindine, Digoxin	
3	CHD†, VF	1	30	73.4	0	Mexiletine, Propranolol	
4	SSS, VT, PAF	1	26	62.7	16	Propranolol	PMI (DDD)
5	LQTS type 1	1	14	68.2	3	Atenolol	
6	LQTS type 2	1	26	56.5	0	Propranolol	
Mean±SD			25±6	53±20			

†Repair of coarctation of the aorta and patent ductus arteriosus, and aortic valve replacement for congenital bicuspid aortic valve.
CHD, congenital heart disease; DCM, dilated cardiomyopathy; DDD, dual-chamber inhibits and triggers; ICD, implantable cardioverter-efibrillator; LQTS, long QT syndrome; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; PMI, pacemaker implantation; SSS, sick sinus syndrome; VF, ventricular fibrillation; VT, ventricular tachycardia.

for ICD implantation; device information; device-related complications; number of ICD discharges and shocks; gestational age at delivery; mode of delivery; total blood loss at delivery; device status at time of delivery; and fetal and neonatal complications.

Data for maternal age, gestational age, left ventricular ejection fraction (LVEF), total blood loss during cesarean section, birth weight, and follow-up period are given as mean±SD.

Device Implantation

All ICDs were implanted via transvenous placement of a ventricular lead for defibrillation and pacing using standard techniques under fluoroscopic guidance. Pacing, sensing and defibrillation thresholds were tested during implantation. The devices used were manufactured by Medtronic (Minneapolis, MN, USA), Guidant (St Paul, MN, USA), and Boston Scientific (Natick, MA, USA).

Management of Pregnancy and Delivery

Fetal growth restriction was defined as an estimated fetal body weight <–1.5 SD of the Japanese standard value. Non-reassuring fetal status was diagnosed by cardiotocogram. Induction and augmentation of labor was performed according to obstetric or maternal indications using i.v. oxytocin following mechanical cervical dilation. Epidural anesthesia was electively used to minimize hemodynamic changes arising from pain or bearing down during labor and after cesarean section.

Results

Baseline Characteristics

Six Japanese women with an ICD who delivered between 2006 and 2012 were enrolled in the study. The mean follow-up after ICD implantation was 5±3 years (range, 2–9 years). The baseline pre-pregnancy characteristics of the 6 patients are given in Table 1. The indication for ICD implantation was secondary prevention in all women.

Patient 1 had dilated cardiomyopathy (DCM) with spontaneous ventricular tachycardia (VT) causing hemodynamic instability, for which catheter ablation was not effective. Patient 2 had DCM with chronic heart failure and repeated ventricular fibrillation (VF) that required cardioversion. Patient 3 had congenital heart disease, including coarctation of the aorta and patent ductus arteriosus that had been repaired at 2 years old. Aortic regurgitation progressed gradually because of a congenital bicuspid aortic valve and the patient had cardiopulmonary arrest caused by VF at 30 years of age. ICD implantation was performed following aortic valve replacement with a Carpentier-Edwards perimount valve. Patient 4 had sick sinus syndrome with repeated syncope and underwent permanent pacemaker implantation (dual-chamber inhibits and triggers) at 23 years old. This patient had wide QRS tachycardia, and ICD implantation was performed for spontaneous VT causing hemodynamic instability. This patient had experienced 16 ICD shocks in response to VF following paroxysmal atrial fibrillation (PAF) caused by acute pharyngitis. Patient 5 had repeated syncope once a year since 3 years of age and had been diagnosed with long QT syndrome type 1 on genetic testing at 10 years old. After introduction of atenolol at 18 years old, syncope reduced to once every 3 years. The severe long QT syndrome was linked to a double-point mutation in the potassium voltage-gated channel KQT-like subfamily, member 1 in re-testing at 25 years old. Her corrected QT time was 470–500 ms. Patient 6 had experienced repeated syncope since 25 years of age and had been diagnosed with long QT syndrome type 2 on genetic testing at 26 years old. Her corrected QT time was 430–470 ms.

Patients 1 and 4 had implanted dual-chamber ICDs with DDI pacing. The other 4 patients had implanted single-chamber ICDs with VVI pacing. All devices were programmed for the VF zone and 4 (patients 1–4) were also programmed for the VT zone with ATP such as burst and ramp pacing and cardioversion. Patient 2 had inappropriate ICD shocks due to sinus tachycardia, and the VT zone was used only for sensing before pregnancy. Patient 3 had no inappropriate ICD shocks due to discrimination of supraventricular tachycardia. Patient 4 received propranolol before pregnancy to avoid a recurrence of PAF during pregnancy.

Pregnancy and Labor

Baseline pregnancy and labor patient characteristics are given in Tables 2,3. There were no device-related complications. In 4 women the number of arrhythmias (patients 1–3, non-sustained VT; patient 4, PAF) increased after the end of the second trimester and anti-arrhythmic medications were gradually increased. During pregnancy, no patient received discharges or shocks from the ICD, and only 1 (patient 1) received ATP at 27 weeks' gestation. After ATP in patient 1, the detection zone was changed from 2 zones (VT 180 beats/min with 3 burst ATPs; VF 240 beats/min) to 3 zones (VT-1 160 beats/min with 3 burst and 3 ramp ATPs; VT-2 180 beats/min with 3 burst ATPs; VF 220 beats/min).

Labor was induced as planned in 3 cases: 2 (patients 1, 2)

Table 2. Baseline Pregnancy Patient Characteristics

Patient	Age at conception	LVEF in pregnancy (%)	NYHA class	No. ICD shocks	LVEF at delivery (%)	Anti-arrhythmic medications (mg/day)			
							1st trimester	2nd trimester	3rd trimester
1	26	61.1	2	0 (29 weeks ATP)	48.4	Metoprolol	40	160	200
2	27	47.7	2	0	44.2	Carvedilol/ Mexiletine/ Aprindine/ Digoxin	5/200/ 20/0.125	10/200/ 40/0.125	10/200/ 50/0.125
3	33	76.1	1	0	72.4	None			
4	29	61.8	1	0	68.8	Bisoprolol	2.5	5	5
5	25	54.8	1	0	51.3	Atenolol	50	50	50
6	28	56.2	1	0	57.3	Bisoprolol	5	5	5
Mean±SD	28±3	60±10			57±11				

ATP, anti-tachycardia pacing. Other abbreviations as in Table 1.

Table 3. Baseline Delivery Patient Characteristics

Patient	During delivery						After delivery		
	Weeks at delivery	ICD mode	Labor	Delivery mode	Indication for CS	Blood loss (ml)	Minimum LVEF (%)	No. ICD shocks	Follow-up period (months)
1	37	Off	Induced	Emergency CS	NRFS	1,190	42.1	1 (ATP 6)	12
2	37	Off	Induced	Emergency CS	NRFS	300	32.6	0	47
3	33	Off	None	CS	FGR	840	64.1	0	26
4	40	Off	Spontaneous	Emergency CS	NRFS	210	61.9	0	16
5	35	Off	Induced	Emergency CS	NRFS	340	59.3	0	12
6	38	On	Spontaneous	Emergency CS	NRFS	400	56.9	0	3
Mean±SD	37±2					547±384	53±13		19±15

Bood loss, total blood loss including amnion at cesarean section; CS, cesarean section; FGR, fetal growth restriction; NRFS, non-reassuring fetal status. Other abbreviations as in Tables 1,2.

Table 4. Baseline Fetus and Neonate Characteristics

Patient	Weeks at birth	Birth weight (g)	Apgar score (1 min)	Apgar score (5 min)	UmA pH	Fetal complications	Neonatal complications
1	37	2,684	7	9	7.312	NRFS	
2	37	2,622	8	9	7.283	NRFS	
3	33	1,240	8	9	7.332	FGR	Hypoglycemia, Hyperbilirubinemia
4	40	2,750	8	9	7.344	NRFS	
5	35	1,776	9	10	7.268	FGR, NRFS	Hypoglycemia, yperbilirubinemia, LQTS type1
6	38	2,188	8	10	6.963	FGR, NRFS	Metabolic acidosis, Hypoglycemia, LQTS type2
Mean±SD	37±2	2,210±603					

UmA, umbilical artery. Oher abbreviations as in Tables 1,3.

for maternal indication of increased non-sustained VT and reduction of cardiac function at 37 weeks' gestation, and 1 (patient 5) for fetal indication of fetal growth restriction and growth arrest at 35 weeks' gestation. All patients delivered by cesarean section under spinal and epidural anesthesia due to fetal indications. The ICD was turned off in patients 1–5 and turned on in patient 6 during labor and cesarean section. Electrocautery was not used during cesarean section. During delivery, there were no syncopal or hypotensive episodes and no patients received ICD discharges or shocks.

After Delivery

Baseline post-delivery patient characteristics are listed in Table 3. All but 2 women with DCM (patients 1, 2) breast-fed the neonate. Patient 1 had reduced LVEF before delivery and recovered within 1 month after delivery. She received an appropriate ICD shock after unsuccessful ATP for VT at 6 weeks after delivery. After an increase of β-blockers and construction of 2 more burst ATPs, there were no ICD shocks except for 6 ATP shocks for VT in 1 year after delivery. All ATP shocks were appropriate and successful. Patient 2 had reduced LVEF for 1 week and recovered within 1 month after delivery. In patient 4, PAF increased until 1 week after delivery. In the 2

women (patients 5, 6) with long QT syndrome, the corrected QT time was 505–510 ms and 460–490 ms, respectively; these were almost the same as before pregnancy, and there were no episodes of ventricular arrhythmia after delivery.

Fetus and Neonate Outcome

Baseline characteristics of fetuses and neonates are given in **Table 4**. Five neonates were born by emergency cesarean section due to non-reassuring fetal status. We observed persistent late decelerations in 3 fetuses and prolonged decelerations in 2 fetuses during labor on cardiotocogram. One neonate (patient 6) had metabolic acidosis that required infusion of bicarbonate. Two neonates (patients 3, 5) were born preterm and 3 (patients 3, 5, 6) were small for date. The 2 neonates of mothers with long QT syndrome (patients 5, 6) were also diagnosed with long QT syndrome on genetic testing. No major complications were observed in the observation period.

Discussion

To our knowledge, this is the largest single-center retrospective study to investigate the outcome of pregnancy in women with an ICD. According to the present 6 cases, pregnancy did not increase the risk of an ICD-related complication under appropriate management (eg, increase of β-blockers and change of the ICD setting), even though the number of ventricular arrhythmias increased after the end of the second trimester of pregnancy. Additional caution might be required in the postpartum period, as well as during pregnancy and labor.

Pregnancy and Ventricular Arrhythmia

Pregnancy is associated with reversible increases in blood volume, heart rate and cardiac output.[8,9] In some instances, these changes can trigger maternal cardiac deterioration during pregnancy.[10–13] Some studies have suggested that pregnancy may have an adverse effect on subsequent maternal cardiac outcome, perhaps as a result of the hemodynamic burden on ventricular structure and function during pregnancy.[14–17] Clearly, special caution is required for patients with an ICD with regard to cardiac function and arrhythmias. In this context, pregnancy can be thought of as a physiological stress test, and complications during pregnancy identify women at high risk for late events.[18] We monitored the ICD settings from before pregnancy to prevent inappropriate ICD discharges due to heart rate increases during pregnancy. In 1 case, β-blockers were introduced before pregnancy to avoid a recurrence of PAF during pregnancy. Although the number of tachyarrhythmias increased in all women after the end of the second trimester except in 2 with long QT syndrome, ICD discharges were not precipitated during pregnancy, when anti-arrhythmic medications were gradually increased and the setting of the ICD was changed.

Balint et al recommended that women at high cardiac risk should receive closer surveillance both during pregnancy and late after delivery.[19] Adverse events during pregnancy are associated with higher rates of late events, which makes it important to re-evaluate the cardiac status of women with pregnancy cardiac events more closely after pregnancy.[19] In the present study, 1 woman who had ATP at 27 weeks' gestation received her first ICD shock and several ATP events after delivery despite an increase of anti-arrhythmic medications and a change of the ICD setting. This suggests that additional caution may be required in the postpartum period, as well as during pregnancy and labor.

ICD Mode During Delivery

It remains unclear whether an ICD should be on or off during delivery. In the present study, no arrhythmias or ICD discharges were precipitated during delivery, as also reported by Natale et al.[7] In this respect, the status of the ICD during delivery appears to have no effect on the overall outcome. Recurrence of VT, however, decreases placental perfusion due to maternal hypotension and could be dangerous for the fetus. In contrast, ICD shocks are a concern for the safety of the fetus, although the amount of energy transferred to the uterus is very small and the fetal heart has a high fibrillatory threshold.[7,20] Based on these considerations, we have recently changed our policy to leave the device turned on during vaginal delivery or cesarean section, with the proviso that electrocautery is not used. Because elevated heart rate during labor may cause inappropriate ICD shock, a multidisciplinary approach involving specialists in maternal fetal medicine, cardiology and anesthesiology is needed for total management during labor and delivery for pregnant woman with an ICD. This management needs to be designed specifically to meet these needs at each hospital.

Fetal and Neonatal Complications

Three of the present fetuses (50%) had fetal growth restriction. Gelson et al found a significant reduction in fetal growth rates associated with maternal heart disease, and concluded that the presence of maternal cyanosis and reduced cardiac output are the most significant predictors of this condition.[21] These findings, however, are not necessarily applicable to the present cases.

In the present study, 5 patients (83%) were given β-blockers, and 2 of these experienced fetal growth restriction. Beta-blockers are considered to be reasonably safe for use during pregnancy, but may rarely cause fetal growth restriction, bradycardia, apnea, hypoglycemia, and hyperbilirubinemia of neonates.[22–25] Five patients delivered by emergency cesarean section due to non-reassuring fetal status (ie, hypoxia of the fetus or severe cord compressions in the uterus, which also occurs during labor in those without an ICD). Beta-blockers are thought to have little effect in the unstressed fetus, but adverse effects may become apparent during fetal distress because these drugs impair fetal response to distress.[25] Although the number of cases is small, β-blockers may have been related to fetal and neonatal complications, but these drugs are clearly effective for preventing life-threatening arrhythmias and inappropriate ICD shocks.[26] We consider use of β-blockers permissible during pregnancy on the condition that efficacy surpasses complications. Furthermore, as few drugs as possible and the safest drugs at the lowest effective doses should be chosen for use in pregnancy.

Study Limitations

There are several limitations in the study, including its retrospective design and the relatively small sample size. First, the present 6 patients were relatively low risk: ICD shocks were delivered before pregnancy only in 3 of the 6 patients; clinically documented ventricular arrhythmias were heterogeneous (VT in 2 patients and VF in the other 4 patients); and LVEF was preserved in 4 of the 6 patients. Because risk of recurrence of ventricular arrhythmias would be strongly associated with the clinical and arrhythmia background of pregnant women, further investigation is needed, including in patients with high risk for VT and VF. Second, it may be safe to leave the device turned on during vaginal delivery or cesarean section, but the sample size may have been too small to prove this

point. There were no ICD shocks during pregnancy, and therefore we are unable to determine whether ICD shocks are safe for the fetus. Third, the follow-up period after delivery was insufficient to permit analysis of long-term morbidity and mortality, which prevented evaluation of potential long-term benefits and the risks of use of an ICD after delivery. The present study, however, is worthwhile as a report of a single-center experience of a rare condition that we were able to follow up in 5 patients (83%) more than 1 year after delivery.

Conclusions

In the present 6 patients with an ICD, pregnancy did not increase the risk of an ICD-related complication under appropriate management (ie, increase of β-blockers and changing of the ICD setting). Additional caution may be required in the postpartum period as well as during pregnancy and labor. Guidelines are required for pregnancy and delivery in patients with an ICD. Further large prospective studies are needed to establish the most appropriate treatment strategies.

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Disclosure

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ORIGINAL ARTICLE

Presence of antiphospholipid antibody is a risk factor in thrombotic events in patients with antiphospholipid syndrome or relevant diseases

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Abstract Antiphospholipid antibodies (aPL) including lupus anticoagulant (LA), anticardiolipin antibodies (aCL) IgG and aCL-β2-glycoprotein I (β2GPI) complex IG are causative factors for thrombotic event (THE). We retrospectively investigated relationships between aPLs and THE in 458 patients suspected of having antiphospholipid syndrome. THEs were observed in 232 of 458 patients, including 148 cases of venous thrombosis, 59 of arterial thrombosis, 18 of microthrombosis, and 20 of complications of pregnancy. The frequency of THE was significantly high in patients positive for LA and/or aPL. In patients with autoimmune disease (AID), the frequency of THE was significantly high in patients with any types of aPLs. Additionally, risk of THE was significantly increased in patients with more than two types of aPLs. Prolonged activated partial thromboplastin time indicated a high risk for THE. However, neither thrombocytopenia nor AID was a risk for THE. In conclusion, the presence of aPL is an indicator for high risk of THE in patients in whom THE was suspected. However, the risk of THE in aPL-positive patients varied among patients with different underlying diseases.

Keywords APS · Thrombosis · aPL · LA · β2-Glycoprotein I

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Introduction

The antiphospholipid syndrome (APS) [1, 2] is a systemic thrombotic diathesis associated with antiphospholipid antibodies (aPL). The mechanisms of thrombosis caused by aPL in cerebral thrombosis (CT) [3], venous thromboembolism (VTE) [4], and obstetric morbidity [5] are poorly understood. However, inhibition of natural anticoagulants [6], activation of platelets and endothelial cells [7], blocking of the fibrinolytic system [8], and triggering of the complement cascade [1, 2, 9] have been speculated. aPL from patients with APS preferentially targets the negatively charged phospholipids (PL) and/or their complex with plasma proteins including β2-glycoprotein I (β2GPI) [10]. Clinical laboratory tests for aPL include anticardiolipin antibodies (aCL), lupus anticoagulants (LA), and anti-β2GPI antibodies [11]. These antibodies have different sensitivity and specificity in thrombotic events (THEs). The underlying diseases of APS are autoimmune diseases (AID) including systemic lupus erythematosus (SLE) [12], idiopathic thrombocytopenic purpura (ITP) [13] and related diseases.

This study retrospectively investigated the relationships between aPLs and THEs in 458 patients clinically suspected of having APS.

Materials and methods

Laboratory data were examined in 458 patients with AID, thrombocytopenia (less than 120,000/μl of platelet counts), prolonged activated partial thromboplastin time (pAPTT; more than 37 s of APTT) or THE who consulted the Department of Hematology or the Hemophilia and Thrombophilia Center of Mie University Hospital from January 1, 1994 to March 31, 2012 (Table 1). There were 124 patients with thrombocytopenia, 126 with pAPTT, 146 with AID or 134 thrombotic patients without AID, thrombocytopenia or pAPTT. The patients with thrombocytopenia (with and without VTE) included 81 patients with idiopathic thrombocytopenic purpura (ITP; 7 and 74), 27 with SLE (15 and 12), 3 with Sjögren's syndrome (1 and 2), 3 with hepatitis (0 and 3), 6 with other diseases (4 and 2) and 4 without underlying diseases (2 and 2). The patients with pAPTT include 57 patients without underlying diseases (32 and 25), 20 with SLE (10 and 10), 14 with other AID (10 and 4), 6 with ITP (3 and 3), 7 with solid cancer (6 and 1), 12 with low levels of physiological anticoagulants such as antithrombin, protein C, or protein S (12 and 0) and 10 others (7 and 3). The patients with AID included 53 patients with SLE (21 and 32), 34 with systemic scleroderma (SSc; 5 and 29), 14 with overlap syndrome (2 and 12), 10 with Sjögren's syndrome (2 and 8), 4 with autoimmune hemolytic anemia (AIHA; 2 and 2), one with antineutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis (1 and 0), one with aoritis syndrome (1 and 0), 9 with dermatomyositis (0 and 9), 6 with mixed connective tissue disease (MCTD; 0 and 6), 5 with Hashimoto's disease (0 and 5), 3 with polyarteritis nodosa (0 and 3), 3 with Behçet's disease (0 and 3) and 3 with rheumatoid arthritis (RA; 0 and 3). Thrombotic patients without thrombocytopenia, pAPTT or AID included 111 patients without thrombotic risk factor, 22 with low levels of physiological anticoagulants, 3 with contraceptive drug, 2 with malignant lymphoma, one with hyperthyroidism, one with infection and one with multiple organ failure. Eighty-eight AID patients without thrombocytopenia, prolonged APTT or THE demonstrated some symptoms, such as morning stiffness, numbness, coldness or THE-like symptoms. These patients were suspected to have APS.

Table 1 Subjects

	With THE	Without THE	Total
All patients	232	226	458
Female:male	135:97	186:40	
Age	45.5	55	
Thrombocytopenia			
Total	29	95	124
With pAPTT	19	12	31
With AID	19	17	36
With pAPTT and AID	13	6	19
Without pAPTT or AID	4	72	76
pAPTT			
Total	80	46	126
With thrombocytopenia	19	12	31
With AID	20	13	33
With pAPTT and AID	13	6	19
Without thrombocytopenia or AID	54	27	81
AID			
Total	34	112	146
With thrombocytopenia	19	17	36
With pAPTT	20	13	33
With pAPTT and AID	13	6	19
Without thrombocytopenia or pAPTT	8	88	96
Without thrombocytopenia, pAPTT or AID	134	0	134

THE thrombotic event, *pAPTT* prolonged activated partial thromboplastin time, *AID* autoimmune disease

DIC was diagnosed by the overt-DIC diagnostic criteria established by the International Society of Thrombosis Haemostasis (ISTH) [17]. Thrombotic microangiopathy (TMA), which results in thrombocytopenia and hemolytic anemia due to the microangiopathy, was identified by the laboratory data and clinical symptoms including neurological dysfunction, renal failure, or fever [18].

The study protocol was approved by the Human Ethics Review Committee of Mie University School of Medicine and an informed consent form was obtained.

Lupus anticoagulant (LA) was measured by diluted Russell's viper venom time using a LA test "Guradipore" (Medical and Biological Laboratories CO., LTD; MBL, Nagoya). Anticardiolipin IgG antibody (aCL-IgG) and anticardiolipin β2-GPI complex antibody were measured by enzyme-linked immunosorbent assay (ELISA) using a MESACUP cardiolipin IgG test (MBL) and anti-CL β2GPI kit Yamasa EIA (Yamasa Shoyu Co, Tyoushi) [14].

Statistical analysis

The data are expressed as the medians (25th–75th percentile). The differences between the groups were examined for statistical significance using the Mann–Whitney U test. A p value < 0.05 denoted the presence of a statistically significant difference. The significance of frequency was examined by a Chi-square analysis.

Results

Thrombotic events were observed in 232 patients including 148 venous thrombosis, 59 arterial thrombosis,

18 microthrombosis and 20 pregnancy complications (Table 2). Venous thrombosis included 117 patients with deep vein thrombosis (DVT), 10 patients with cerebral venous sinus thrombosis. Most arterial thromboses were cerebral thrombosis, and skin ulcers due to microthrombi were observed. The analysis of all patients showed that the frequency of THE was significantly higher in patients positive for LA than in those negative for LA ($p < 0.05$). A patient positive for LA, aCL-IgG or aCL-β2GPI complex antibody was defined as a patient positive for aPL. The frequency of THE was significantly higher in patients positive for aPL than in those negative for aPL ($p < 0.01$; Table 3). An analysis of patients with thrombocytopenia (Table 4) showed that the frequency of THE was significantly higher in patients positive for LA or aPL than in those negative for LA ($p < 0.001$) or aPL ($p < 0.001$). An analysis of patients with pAPTT showed that there were no significant differences in the frequency of thrombosis between patients with each aPL and those without each aPL. An analysis of patients with AID showed that the frequency of THE was significantly higher in patients positive for each aPL than in those negative for each aPL ($p < 0.001$, respectively). The frequency of THE was significantly higher in patients positive for more than 2 aPL than in those positive for less than one aPL (Table 5; $p < 0.05$). Table 6 shows that pAPTT was associated with a high risk for THE, but thrombocytopenia or AID was not.

The LA values were significantly higher in the patients with thrombosis than those without thrombosis, although there were no significant difference in aCL-IgG and aCL-β2GPI complex IgG values between the patients with and without thrombosis (Fig. 1). A ROC analysis showed that the AUC for diagnosis of THE was 0.83 in LA, 0.70 in aCL-IgG and 0.69 in aCL-β2GPI complex IgG (Fig. 2).

Table 2 Thrombotic events

Venous thrombosis	148	117	DVT
		13	DVT and cerebral thrombosis
		10	Cerebral venous sinus thrombosis
		6	Central retinal vein occlusion
		2	Budd–Chiari syndrome
Arterial thrombosis	59	43	Cerebral thrombosis
		13	Cerebral thrombosis and DVT
		2	Infarction (spinal cord or medulla)
		1	Myocardial infarction
Microthrombus	18	9	Skin ulcer
		7	Transient ischemic attack
		2	Disseminated intravascular coagulation
Pregnancy complication	20	17	Miscarriage
		2	Intrauterine growth retardation
		1	Pregnancy hypertension

DVT deep vein thrombosis

Table 3 Chi-square analysis of aPL for thrombotic events in all patients

	With THE	Without THE	Odds ratio
LA			
Positive	40 (63.5 %)	23	1.87 ($p = 0.039$)
Negative	129 (48.1 %)	139	
aCL-IgG			
Positive	20 (62.5 %)	12	1.99 (NS)
Negative	81 (45.5 %)	97	
aCL-β2GPI IgG			
Positive	52 (56.5 %)	40	1.28 (NS)
Negative	160 (45.5 %)	157	
Number of positive aPL			
≧ 1	94 (61.0 %)	60	1.88 ($p = 0.002$)
0	138 (45.4 %)	166	

THE thrombotic event, *aCL-IgG* anticardiolipin IgG antibody, *NS* not significant, *aCL-β2GPI IgG* anticardiolipin β2-GPI complex antibody

Discussion

The frequency of THE was significantly higher in patients positive for aPL, suggesting that aPL is risk factor for thrombosis. aPL was previously reported to be associated with a high risk for thrombosis [15]. An analysis of all patients showed that THE was related to LA but not to aCL-β2GPI complex IgG or aCL-IgG, suggesting that the LA test is useful for prediction of thrombosis. The LA test includes DRVVT and PTT-LA [16] and the results are different in various assays [19]. LA reflects abnormalities in various aPLs except anti-β2GPI antibody or anti-prothrombin antibody [20]. The frequency of THE was significantly higher in the patients with LA than those without LA, especially in patients with thrombocytopenia. About 20–40 % of ITP patients have aPL, and the frequency of thrombosis is high in patients with ITP positive for LA [21]. In patients with pAPTT, no significant differences in LA, aCL or aCL-β2GPI complex IgG were identified between patients with and without thrombosis. The frequency of thrombosis was significantly high in the patients with pAPTT. pAPTT is a high risk factor for thrombosis compared with AID or thrombocytopenia. In patients with AID, presence of any type of aPLs was significantly related to THE. AID includes various diseases, and presence of aPLis a useful marker for risk of THE.

An international multicenter study reported that the anti-β2GPI-dependent lupus anticoagulant (LAC) assay correlates with thrombosis better than the classic LAC assay [22, 23]. However, aCL-β2GPI complex IgG was not suggested

Table 4 Chi-square analysis of aPL for THE in thrombocytopenia, pAPTT and AID

	With THE	Without THE	Odds ratio
Thrombocytopenia			
LA			
Positive	18 (66.7 %)	9	11.8 (4.53–30.71) ($p < 0.001$)
Negative	10 (14.5 %)	59	
aCL-IgG			
Positive	3 (42.6 %)	4	1.22 (0.21–6.91) (NS)
Negative	8 (38.1 %)	13	
aCL-β2GPI IgG			
Positive	13 (31.0 %)	29	1.79 (0.74–4.35) (NS)
Negative	13 (20.0 %)	52	
Number of positive aPL			
From 1 to 3	22 (40.0 %)	33	5.9 (2.42–14.41) ($p < 0.001$)
0	7 (10.1 %)	62	
pAPTT			
LA			
Positive	31 (63.3 %)	18	1.04 (0.48–2.27)
Negative	38 (62.3 %)	23	(NS)
aCL-IgG			
Positive	9 (69.2 %)	4	0.55 (0.14–2.16)
Negative	37 (80.4 %)	9	(NS)
aCL-β2GPI IgG			
Positive	19 (57.6 %)	14	0.54 (0.23–1.26)
Negative	55 (71.4 %)	22	(NS)
Number of positive aPL			
From 1 to 3	45 (63.4 %)	26	0.99 (0.48–2.06)
0	35 (63.6 %)	20	(NS)
AID			
LA			
Positive	16 (66.7 %)	8	9.86 (3.86–25.17)
Negative	14 (16.9 %)	69	($p < 0.001$)
aCL-IgG			
Positive	10 (55.6 %)	8	8.13 (2.96–22.34)
Negative	12 (13.3 %)	78	($p < 0.001$)
aCL-β2GPI IgG			
Positive	15 (48.4 %)	16	4.85 (2.11–11.17)
Negative	17 (16.2 %)	88	($p < 0.001$)
Number of positive aPL			
From 1 to 3	27 (50.0 %)	27	12.14 (5.26–28.07)
0	7 (7.6 %)	85	($p < 0.001$)

Data are shown as the median (95 % CI)

THE thrombotic event, *pAPTT* prolonged activated partial thromboplastin time, *AID* autoimmune disease, *aCL-IgG* anticardiolipin IgG antibody, *aCL-β2GPI IgG* anticardiolipin β2-GPI complex antibody, *NS* not significant

advantages in prediction of THE than aCL, in which "aCL-β2GPI complex IgG was measured instead of "anti-β2GPI antibody". The underlying diseases in the present study are heterogeneous, which might have influenced the sensitivity of the study. However, the frequency of THE in patients with AID was significantly higher in any of aPL-positive patients than negative subjects. The value of prediction of thrombosis, aCL is reported to be higher than anti-β2GPI antibody [24]. Value of presence of aPL in prediction of thrombosis might differ among underlying diseases.

The frequency of THE was significantly high in patients positive for more than 2 of aPLs, which implicates that multiple aPLs might have additional effects in formation of thrombosis. Indeed, LA, anti-β2GPI antibody and aCL, triple-positive case is strongly associated with thrombosis and pregnancy morbidity [25, 26]. A predominance of arterial thrombosis was reported in Japanese patients with primary APS, including 50.4 % of patients with SLE [27], while our study showed that venous thrombosis is predominant. The number of SLE patients was significantly

Table 5 Chi-square analysis of number of positive aPL for THE in all patients

Number of positive aPL	With THE	Without THE	Odds ratio
3	4	2	1.82 (0.33–10.05) (NS)
From 0 to 2	65	59	
2 or 3	11	2	5.59 (1.37–22.80)
0 or 1	58	59	($p = 0.035$)
From 1 to 3	24	12	2.18 (0.98–4.82) (NS)
0	45	49	

This analysis was carried out in the patients who were measured all of three aPLs. Data are shown as the median (95 % CI)

THE thrombotic event, *NS* not significant

Table 6 Chi-square analysis of thrombocytopenia, pAPTT or AID for THE

	With THE	Without THE	Odds ratio
With thrombocytopenia	29	95	0.54 (0.33–0.90)
Without thrombocytopenia	69	122	($p = 0.024$)
With pAPTT	80	46	16.52 (9.61–28.42)
Without pAPTT	18	171	($p < 0.001$)
With AID	34	112	0.50 (0.31–0.81)
Without AID	64	105	($p = 0.008$)

Data are shown as the median (95 % CI)

THE thrombotic event, *pAPTT* prolonged activated partial thromboplastin time, *AID* autoimmune disease

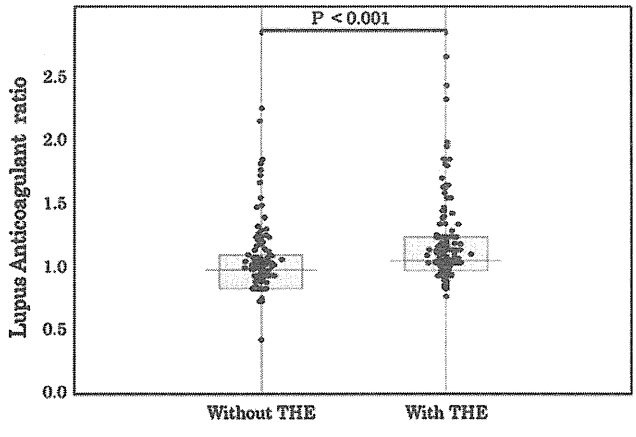

Fig. 1 Lupus anticoagulant in the patients with and without THE

higher in the previous report than in our study, and many patients with venous thrombosis, including thrombophilia, come to the Department of Cardiology or Hematology for evaluation.

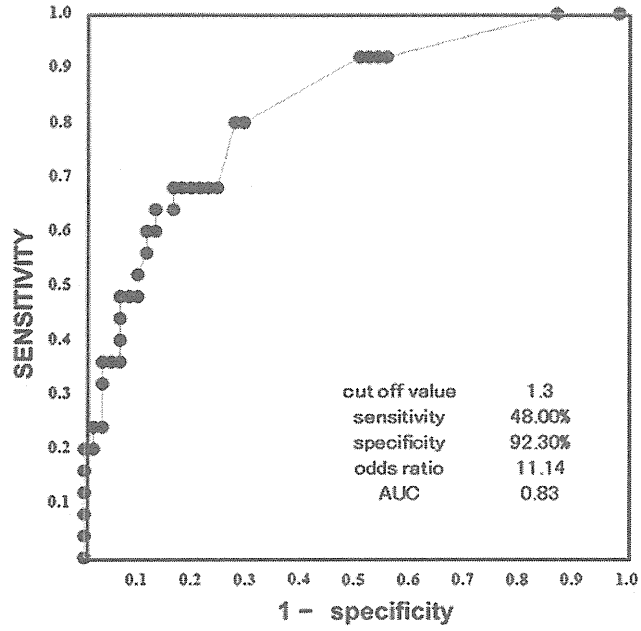

Fig. 2 An ROC analysis of LA for THE

The complication of aPL and a low level of physiological anticoagulant may therefore cause an increase in the risk of thrombosis.

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Special Theme Topic:
Stroke During Pregnancy or Delivery

Pregnancy and Delivery Management in Patients With Cerebral Arteriovenous Malformation: A Single-Center Experience

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Abstract

We described pregnancy and delivery management in 9 patients with cerebral arteriovenous malformation (AVM). Six patients presented with intracerebral hemorrhage (ICH) during pregnancy (first hemorrhagic episode); 2 patients presented with headache; and 1 patient with incidental detection of AVM. In the 3 patients with unruptured AVM, the diagnosis was made before pregnancy. In 3 of 6 patients who presented with ICH, AVM removal was performed during pregnancy. One patient required emergency surgery for the mass effect of the hematoma, and 2 patients with Spetzler-Martin grade I and II AVMs underwent elective surgery for the prevention of rebleeding. Radiosurgery for multiple AVMs was performed after delivery in one patient. Surgical resection and radiosurgery were performed after abortion in two patients. Of 3 patients with unruptured AVM, 2 patients became pregnant after radiosurgery and conservative treatment was initiated in 1 patient for Spetzler-Martin grade V AVM. Cesarean section was performed in 5 patients (one with severe uncontrollable pregnancy-induced hypertension) and vaginal delivery in 2 patients (one with grade V AVM). Delivery by obstetrical indication was possible in patients who underwent AVM resection during pregnancy. No rebleeding during pregnancy occurred. The maternal outcome was good except for the 2 patients with consequences of the initial ICH. The fetal outcome was good except for 2 cases of abortion. Pregnancy and delivery management in patients with AVM was successful in our institution. Early surgical intervention for AVM presenting as ICH during pregnancy could prevent rebleeding and improve the maternal and fetal prognosis.

Key words: arteriovenous malformation, pregnancy, delivery, surgery

Introduction

Cerebral arteriovenous malformations (AVMs) may affect the prognosis for both mother and fetus because they may result in fatal intracranial bleeding during pregnancy.[2,4,7,15,16,18,22] The natural history of AVMs is poorly understood, and even less understood in pregnant patients, because the frequency is rare and changes in the maternal body are complicated during pregnancy. No definitive guidelines for the treatment of AVMs during pregnancy exist and the management of cerebrovascular disease in pregnancy is under discussion.[4,10,20,24] We examined the results of pregnancy and delivery management in patients with AVMs in a single institution.

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