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ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Cardiopulmonary Variables During Exercise Predict Pregnancy Outcome in Women With Congenital Heart Disease

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Background: Maternal New York Heart Association (NYHA) class is associated with pregnancy outcome in women with congenital heart disease (WCHD), but objective predictive criteria of exercise capacity have not been established.

Methods and Results: A total of 33 WCHD (age, 28±5 years; NYHA class, 1.3±0.6) who had undergone cardiopulmonary exercise testing (CPX) 1.8±2.2 years before their delivery were retrospectively identified. Maternal, cardiac, and neonatal events occurred in 8 (24%), 12 (36%), and 14 (42%), respectively. All CPX parameters correlated with neonatal birth weight (P<0.05–0.001). Exercise time, peak heart rate (HR), peak systolic blood pressure, and peak oxygen uptake ($\dot{V}O_2$) were associated with cardiac events (P<0.05–0.01), and exercise time and peak $\dot{V}O_2$ were also associated with neonatal events (P<0.05). Exercise time, peak HR, and peak $\dot{V}O_2$ were associated with at least 1 of the 3 events (P<0.05–0.01). Receiver operating characteristic analysis showed that peak HR <150 beats/min and/or peak $\dot{V}O_2$ <22.0 ml·kg^{-1}·min^{-1}, peak $\dot{V}O_2$ <26.2 ml·kg^{-1}·min^{-1}, and peak HR <150 beats/min and/or peak $\dot{V}O_2$ <25.3 ml·kg^{-1}·min^{-1} predicted a high probability of maternal cardiac, neonatal, and maternal cardiac and/or neonatal event, respectively.

Conclusions: CPX parameters predict pregnancy outcome and peak HR ≥150 beats/min and/or peak $\dot{V}O_2$ ≥25 ml·kg^{-1}·min^{-1} may be reference value(s) for a safer pregnancy outcome in WCHD. (*Circ J* 2013; **77:** 470–476)

Key Words: Birth weight; Congenital heart disease; Exercise capacity; Exercise test; Pregnancy

More than 90% of patients with congenital heart disease (CHD) survive to adulthood in developed countries, including Japan.[1–5] As a result, pregnancy and delivery-associated complications are assuming major importance in the health care of women with congenital heart disease (WCHD), especially those with severe forms of CHD. Dynamic cardiovascular adaptations as well as neurohormonal changes accompany pregnancy and put significant additional demands on the cardiovascular system. The initial adaptation during the first trimester is a 40–70% decline in total peripheral vascular resistance combined with low vascular resistance in the placenta and uterus, which cause a relatively underfilled vascular status, resulting in 30–50% plasma volume increase until gestational week 34. Furthermore, additional cardiac venous return due to post-delivery uterine contractions together with a decompression of the inferior caval vein causes an additional increase in cardiac output.[6–10] Thus, these dynamic adaptations increase the risk of adverse maternal and neonatal events especially in women with severe CHD. Low functional capacity, that is, higher New York Heart Association (NYHA) class, is a robust predictor of adverse pregnancy outcome.[11] A recent multicenter study demonstrated that impaired heart rate (HR) response during exercise testing was another important predictor.[12] The association of NYHA class and exercise HR response with adverse pregnancy outcome indicates a significant relationship between maternal aerobic exercise capacity and pregnancy outcome. The exact relationship, however, remains unclear, so objective referent exercise-derived values are not able to be used with regard to these expectant women.[12] Accordingly, the aim of the present study was twofold: first to reconfirm a significant association of exercise capacity with pregnancy outcome; and second, to determine objective referent cardiopulmonary variables by cardiopulmonary exercise testing (CPX) for practical use in ensuring safer pregnancy in WCHD.

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Methods

Subjects

We retrospectively reviewed all WCHD at the time of CPX between January 2000 and December 2010 at the exercise laboratory and identified 33 WCHD who had experienced pregnancies and/or deliveries with an interval of ≤6.0 years after the last CPX. Of those, 17 WCHD experienced ≥2 pregnancies, including 3 pregnancies in 1 patient. The clinical characteristics of these 33 patients are listed in Table 1. Fifteen age-matched female volunteers participated in this study to provide normal CPX derived values.

Exercise Protocol

All subjects underwent symptom-limited treadmill exercise using a ramp protocol; endurance time, $\dot{V}O_2$ at anaerobic threshold and peak exercise were measured.[13] A 12-lead electrocardiogram was used to determine HR. Systolic blood pressure was measured by palpation at rest and at peak exercise owing to the difficulty in measuring blood pressure with a mercury sphygmomanometer during exercise. In a preliminary study, systolic blood pressure obtained by this method in 12 children with cardiac disease correlated with measurements taken with a mercury sphygmomanometer ($r=0.98$, $P<0.0001$). Ventilation and gas exchange were measured using a breath-by-breath method. The subjects breathed through a mask connected to a hot-wire anemometer (Riko AS500, Minato Medical Science, Osaka, Japan) to measure inspired and expired volume and a mass spectrometer (MG-300, Perkins Elmer, St Louis, MO, USA) was used to measure oxygen and carbon dioxide partial pressures continuously. Minute ventilation and respiratory rate were measured, and ventilatory equivalents for oxygen and carbon dioxide and respiratory gas exchange ratio were computed in real time and displayed with the HR and $\dot{V}O_2$ on a monitor. Anaerobic threshold was determined by the V-slope method[14] and chronotropic index was also calculated as follows: (peak HR−resting HR)/(220−age−resting HR).

Arrhythmias During CPX

Clinically relevant exercise-induced arrhythmias were identified as those including ≥2 forms of premature ventricular contraction, ≥couplets for atrial and/or ventricular arrhythmias, and transient frequent arrhythmias including bigeminy.[15]

Maternal Cardiac, Obstetric, and Neonatal Outcome

Maternal cardiac complications were subdivided into primary and secondary events as described previously.[11] Primary maternal cardiac outcomes included heart failure, which was considered to be present if there were symptoms either at rest or on exercise with objective evidence of cardiac dysfunction and/or a response to treatment. Other maternal cardiac adverse events included sustained tachyarrhythmia or bradyarrhythmia requiring treatment, cardiac arrest, stroke, or death. Secondary maternal cardiac outcomes included decline in NYHA class by 2 classes, need for urgent invasive cardiac intervention during pregnancy or within 6 weeks postpartum, or symptomatic non-sustained tachyarrhythmia or bradyarrhythmia requiring therapy. Maternal obstetric outcomes included non-cardiac death, pre-eclampsia, or postpartum hemorrhage. Neonatal outcomes included miscarriage (≥16 weeks gestation), premature birth (<37 weeks gestation), small for gestational age birth weight (<10th percentile), fetal death (≥16 weeks gestation), neonatal death (<1 month of birth), respiratory distress syndrome, or intraventricular hemorrhage.

Table 1. Maternal Clinical Characteristics

n	33
Age at delivery (years)	28±5
NYHA class (I/II/III)	1.3±0.6 (25/6/2)
Diagnosis	
Biventricular physiology	31
Simple	
Atrial septal defect	7 (3†)
Ventricular septal defect	3
Aortic valve stenosis	2 (1†)
Pulmonary valve stenosis	1
Coarctation of aorta	1
Complex	
Tetralogy of Fallot	6
Tetralogy of Fallot with pulmonary atresia	2
Corrected transposition of the great arteries	3
Transposition of the great arteries	2
Ebstein's anomaly	1
Double outlet right ventricle	1
Total anomalous pulmonary venous connection	1
Pulmonary atresia with intact ventricular septum	1
Single ventricular physiology	2
Transposition of the great arteries (Eisenmenger syndrome)	1
Tricuspid atresia (Fontan circulation)	1
Systemic ventricular function (Preserved/Reduced/Poor)	(29/3/1)
Systemic ventricular AVR ≥moderate	1
Pulmonary ventricular AVR ≥moderate	2
Systemic ventricular outflow stenosis ≥30 mmHg	1
Pulmonary ventricular outflow stenosis ≥30 mmHg	2
Pulmonary valve regurgitation ≥moderate	8
Medications	8 (24)
Diuretics	7 (21)
Anti-coagulant	4 (12)
Angiotensin converting enzyme inhibitor	2 (6)
Anti-arrhythmic	3 (9)
Digoxin	1 (3)

Data given as mean±SD or n (%). †Unoperated patients. AVR, atrioventricular valve regurgitation; NYHA, New York Heart Association.

Statistical Analysis

Descriptive data are expressed as mean±SD. Comparisons between 2 groups were carried out with 2-sided t-tests for continuous variables. We used simple regression analysis to determine correlations between continuous parameters obtained. Logistic regression analysis was used to identify potential risk factors for any cardiac, neonatal, and cardiac and/or neonatal event. When the variables were statistically significant, we used receiver operating characteristic (ROC) curve analysis to determine cut-offs that could meaningfully predict the probability of maternal and/or neonatal events, that is, the values with a maximum area under the curve (AUC). Statistical analysis was performed using JMP 6 (SAS Institute, Cary, NC, USA).

Table 2. Cardiopulmonary Exercise Variables

	WCHD	Volunteers
n	33	15
Age at CPX (years)	26.3±5.9	24.3±6.0
CPX to delivery (years)	1.8±2.2	–
Body height at CPX (cm)	157±5	156±6
Body weight at CPX (kg)	49±7	49±6
Variables		
Exercise time (min)	6.8±1.6††	9.2±0.8
Peak respiratory exchange ratio	1.19±0.07	1.21±0.08
Heart rate (beats/min)		
Rest	77±13	75±10
Peak	163±23**	182±8
Chronotropic index	0.74±0.19**	0.89±0.07
Systolic blood pressure (mmHg)		
Rest	104±12	106±8
Peak	160±17	168±14
Oxygen uptake ($ml \cdot kg^{-1} \cdot min^{-1}$)		
Anaerobic threshold	16.9±3.2**	19.8±2.7
Peak	26.8±5.8††	36.7±4.2
Arrhythmia		
Relevant (multi-form, frequent, couplet≤)	7 (21%)	0

Data given as n or mean±SD. **P<0.01; ††P<0.0001.
CPX, cardiopulmonary exercise testing; WCHD, women with congenital heart disease.

Table 3. Cardiac, Obstetric, and Neonatal Outcome

n	33
Age at delivery (years)	28±5
Gestational weeks	37±4
Birth weight (g)	2,693±534
Maternal cardiac events	8 (24)
Heart failure	4 (12)
Arrhythmia	1 (3)
Heart failure/Arrhythmia	3 (9)
Neonatal events	12 (36)
Pre-term (<37 weeks)	6 (18)
Small for date (<10%tile)	8 (24)
Pre-term/small for date	4 (12)
Fetal distress	1 (3)
Miscarriage	1 (3)
Obstetric events	12 (36)
Postpartum hemorrhage	11 (33)
Pregnancy-related hypertension	0 (0)
Placental abruption	1 (3)
Delivery	
Vaginal	18 (56)
Cesarean section	14 (44)

Data given as mean±SD or n (%).

P<0.05 was considered significant.

Results

Maternal Clinical Characteristics

Clinical characteristics of the study patients are listed in Table 1. Thirty-one had undergone a biventricular repair, 1 had had a Fontan operation and 1 had palliative surgery for Eisenmenger syndrome. Three women with unrepaired atrial septal defect and 2 with aortic valve stenosis were also included. A balloon angioplasty had been applied in 1 woman with aortic valve stenosis before the pregnancy. Medication(s) were prescribed in 8 (24%) and angiotensin-converting enzyme inhibitor had been discontinued at the time of the pregnancy.

CPX Variables During Exercise Testing

Results of CPX before pregnancy are summarized in Table 2. The interval from CPX to delivery (miscarriage in 1) was 1.8±2.2 years and the peak respiratory gas exchange ratio was 1.19±0.07, indicating maximum exercise effort during CPX. When compared with normal volunteers, exercise time, peak HR, $\dot{V}O_2$ at anaerobic threshold and peak exercise were significantly lower (P<0.01–0.001) in the WCHD despite there being no difference in the peak respiratory gas exchange ratio. Clinically relevant exercise-induced arrhythmias were seen in 7 WCHD (21%).

Prevalence of Maternal Cardiac, Obstetric and Neonatal Events

The pregnancy outcomes are given in Table 3. Fourteen deliveries were by cesarean section and for this group the gestational age was shorter (37±4 weeks) and birth weight lower (2,693±534 g) than for normal delivery. Maternal cardiac events occurred in 8 (24%), including heart failure in 4, arrhythmia in 1 and heart failure with arrhythmia in 3. Neonatal events occurred in 12 pregnancies (36%), including fetal distress in a woman with tetralogy of Fallot with pulmonary atresia and miscarriage at 17 weeks gestational age in the Fontan patient. Overall, 14 (42%) of the WCHD experienced either maternal and/or neonatal events. In contrast, postpartum hemorrhage was the main obstetric event, and included 1 placental abruption. No pregnancy-related hypertension was observed.

Impact of Gestational Age and Exercise Variables on Birth Weight

Although the gestational age at the time of delivery was closely associated with the birth weight, there was a trend for lower birth weight for gestational age (Figure 1A). The maternal NYHA class and all CPX variables, especially the exercise time, peak systolic blood pressure and peak $\dot{V}O_2$, had a significant impact on birth weight (P<0.005; Table 4; Figures 1B–D).

Impact of Height, NYHA Class and Medication(s) on Maternal and Neonatal Events

The NYHA class had a significant impact on all the pregnancy outcomes. In addition, the use of medication(s) before pregnancy had a strong impact on the pregnancy outcomes and all the women on medication(s) before pregnancy experienced at least 1 adverse event(s). In contrast, body height had no impact on pregnancy outcome, including birth weight.

Impact of Exercise Variables on Maternal and Neonatal Events

Peak HR and $\dot{V}O_2$ were significantly lower in the WCHD with adverse pregnancy events, except for peak HR between the WCHD with and without neonatal events (Figure 2). The impact of CPX variables is given in Table 4. Maternal cardiac events were significantly associated with exercise time, HR, systolic blood pressure, and $\dot{V}O_2$ at peak exercise, while exer-

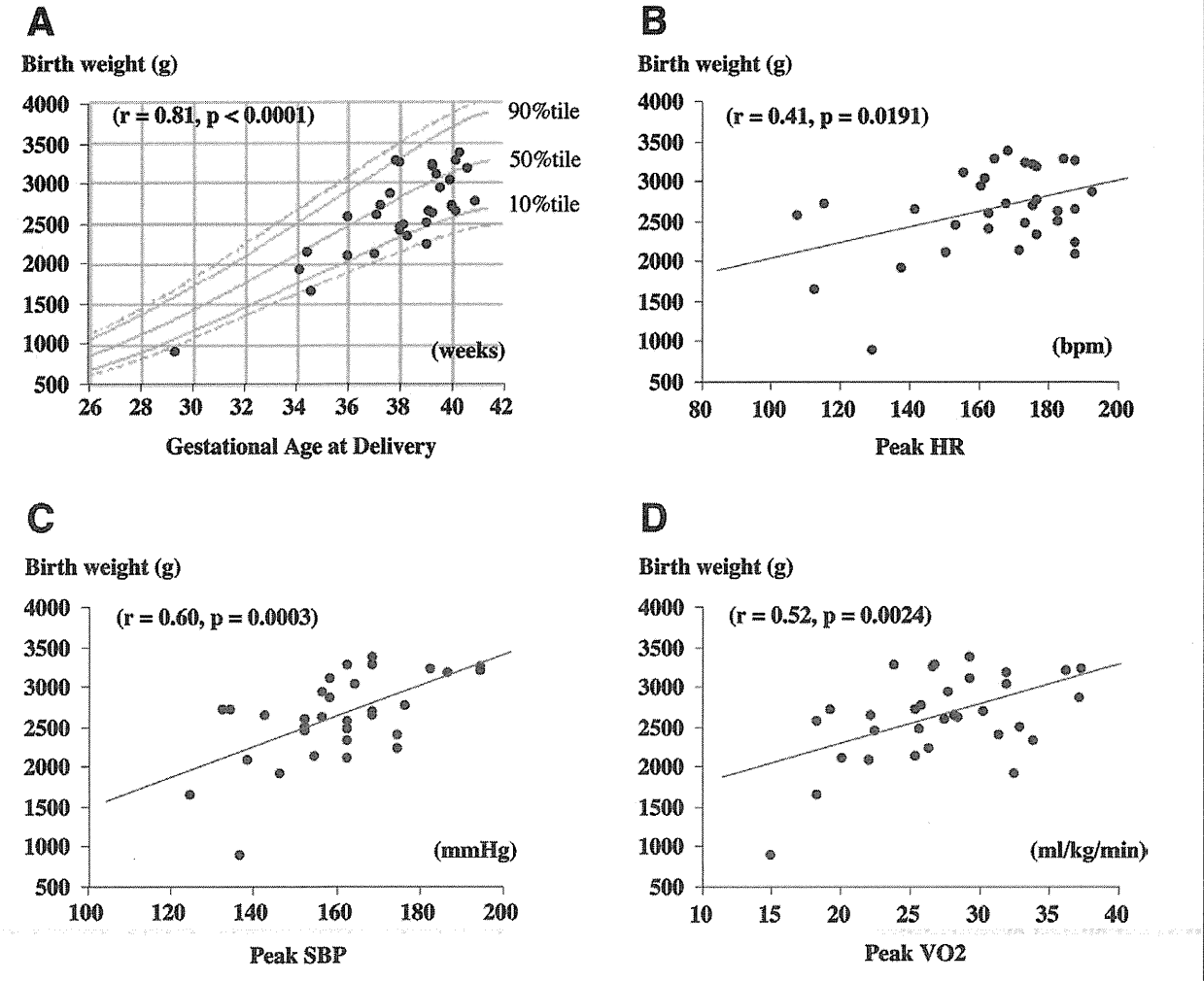

Figure 1. Impact of (A) gestational age at delivery; (B) maternal peak heart rate (HR); (C) peak systolic blood pressure (SBP); and (D) peak oxygen uptake ($\dot{V}O_2$) on birth weight.

cise time, $\dot{V}O_2$ at the anaerobic threshold and peak exercise, and the appearance of clinically relevant arrhythmia(s) were associated with neonatal events. Exercise time, peak HR, and $\dot{V}O_2$ at the anaerobic threshold and that at peak exercise were associated with maternal and/or neonatal events. Neither CPX variables nor NYHA class were associated with obstetric events.

CPX Cut-Off for Adverse Pregnancy Outcomes

According to ROC analysis, we determined the cut-off values of peak HR and $\dot{V}O_2$ for efficient prediction of the pregnancy outcomes. For peak HR, we determined a cut-off of 150 beats/min for the maternal cardiac events (AUC=0.74) and maternal and/or neonatal events (AUC=0.77). Regarding the cut-offs for peak $\dot{V}O_2$, 22.0 $ml \cdot kg^{-1} \cdot min^{-1}$ (AUC=0.82), 26.2 $ml \cdot kg^{-1} \cdot min^{-1}$ (AUC=0.79) and 25.3 $ml \cdot kg^{-1} \cdot min^{-1}$ (AUC=0.85) were the corresponding values for predicting maternal, neonatal, and maternal and/or neonatal events, respectively. In addition, 16.9 $ml \cdot kg^{-1} \cdot min^{-1}$ (AUC=0.77) was the cut-off value of $\dot{V}O_2$ at the anaerobic threshold for the efficient prediction of the maternal and/or neonatal events.

Discussion

The present study has confirmed the strong association between maternal functional capacity, that is, NYHA class, and pregnancy outcomes in WCHD. Furthermore, to our knowledge, this is the first study to demonstrate a close correlation between objective values of aerobic capacity and pregnancy outcomes in WCHD. Heart failure (NYHA class III–IV, left ventricular ejection fraction [LVEF] <35–40%) has been 1 of several robust risk factors for pregnancy outcomes in WCHD.[16] Considering the weak correlation between LVEF[17] and peak $\dot{V}O_2$ and a significant discrepancy between subjective and objective assessments of postoperative status in adults with CHD,[18] tangible and objective CPX measurements are useful not only for physicians but also for WCHD who are pregnant. In addition, we have also demonstrated for the first time that maternal aerobic exercise capacity is associated with fetal growth. Because abnormal maternal cardiac function and morphology cause reduced placental perfusion and eventually result in fetal growth restriction,[19] limited cardiac reserve (reduced peak $\dot{V}O_2$) may be associated with frequent placental

Table 4. Impact of Body Size, CPX-Derived Variables and Medication(s) on Maternal and Neonatal Outcomes in WCHD

Maternal characteristics	Birth weight (g)		Maternal events		Neonatal events		Maternal/Neonatal events	
	r	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Body height (cm)	0.013	0.9437	0.98 (0.84–1.15)	0.7921	1.00 (0.86–1.15)	0.941	0.96 (0.83–1.11)	0.5681
NYHA class	−0.583	0.0005	7.21 (1.45–35.9)	0.0158	21.0 (2.13–207)	0.0092	13.8 (1.50–127)	0.0205
Exercise variables								
Exercise time (min)	−0.521	0.0022	0.22 (0.07–0.66)	0.007	0.48 (0.26–0.89)	0.0196	0.44 (0.23–0.83)	0.0113
Heart rate								
Rest	−0.039	0.8319	0.98 (0.92–1.04)	0.4474	0.98 (0.93–1.04)	0.4521	0.98 (0.93–1.04)	0.5591
Peak	−0.412	0.0191	0.95 (0.91–0.99)	0.0119	0.97 (0.94–1.00)	0.0774	0.96 (0.93–1.00)	0.044
Chronotropic index (per 0.1)	−0.442	0.0113	0.56 (0.34–0.91)	0.019	0.72 (0.48–1.09)	0.1206	0.67 (0.44–1.03)	0.0678
Systolic blood pressure								
Rest	0.388	0.0284	0.97 (0.90–1.04)	0.3622	1.01 (0.95–1.07)	0.8302	0.99 (0.94–1.05)	0.8277
Peak	0.599	0.0003	0.92 (0.86–0.98)	0.0159	0.96 (0.92–1.01)	0.1183	0.95 (0.91–1.00)	0.061
Oxygen uptake								
Anaerobic threshold	−0.469	0.0068	0.78 (0.60–1.02)	0.0702	0.72 (0.55–0.95)	0.0186	0.74 (0.57–0.97)	0.0273
Peak	−0.519	0.0024	0.77 (0.62–0.94)	0.01	0.81 (0.68–0.96)	0.0139	0.78 (0.64–0.94)	0.008
Arrhythmia								
Relevant	–	0.0809	5.60 (0.94–33.4)	0.0588	6.79 (1.06–43.4)	0.043	4.72 (0.876–29.4)	0.0961
Medication(s)	–	0.0003	80.5 (6.31–1026)	0.0007	28.0 (2.77–283)	0.0048	–	–

CI, confidence interval; CPX, cardiopulmonary exercise testing; NYHA, New York Heart Association; OR, odds ratio; WCHD, women with congenital heart disease.

hypoperfusion during daily life, ultimately causing fetal growth restriction. Nevertheless, according to the present results, in addition to the maternal NYHA class I, peak HR ≥150 beats/min (82% of normal) and/or peak $\dot{V}O_2$ ≥25 ml·kg^{-1}·min^{-1} (68% of normal) during CPX may be referent objective value(s) for a safer pregnancy outcome in WCHD, including appropriate fetal development.

The other traditional risk factors include pulmonary hypertension (Eisenmenger syndrome), outflow tract stenosis (severe aortic stenosis with a mean pressure gradient >40–50 mmHg), Marfan syndrome (ascending aortic diameter at end-diastole >40 mm), mechanical valves, and cyanotic heart disease (arterial oxygen saturation <85%).[16] In the present study, we had 2 WCHD with NYHA class III (repaired tetralogy of Fallot with pulmonary atresia, patent ductus arteriosus with Eisenmenger syndrome), 1 with corrected transposition of the great arteries after conventional repair with low systemic ventricular ejection fraction <30%, and 1 with aortic valve stenosis (pressure gradient, 40 mmHg). All values of peak $\dot{V}O_2$ for those WCHD were <22.0 ml·kg^{-1}·min^{-1}, except for the woman with aortic valve stenosis (peak $\dot{V}O_2$=29.2 ml·kg^{-1}·min^{-1}, and all the women, except the aortic valve stenosis patient, experienced at least 1 adverse event. In contrast, all 5 WCHD with a peak $\dot{V}O_2$ <20 ml·kg^{-1}·min^{-1} had experienced at least 1 adverse pregnancy outcome, suggesting the importance of peak $\dot{V}O_2$ as a reference measure for safer pregnancy outcome in WCHD.

Prior cardiac events, including arrhythmia, are also important predictors of adverse pregnancy outcomes.[11] The current study has demonstrated that a history of medication(s) prior to pregnancy is strongly associated with obstetric outcomes. This may be due to confounding with prior cardiac history, explaining the higher risk of neonatal/maternal outcomes. Interestingly, clinically relevant arrhythmia(s) were associated with the neonatal events. Although the underlying mechanisms are unclear, frequent hemodynamic fluctuations due to arrhythmia might adversely affect fetal growth.

Study Limitations

The study had several limitations. First, the major limitation was the small number of WCHD included, which prevented multivariate analysis to identify reliable independent predictors for safer pregnancy outcome. In addition, a wide variety of diagnoses in the present patients may have had a significant impact on the associations of CPX-derived variables and pregnancy outcomes. For instance, the clinical meaning of peak HR for repaired patients may be different to that for unrepaired patients because the surgical procedure itself has a significant impact on peak HR.[20] In this respect, peak $\dot{V}O_2$ may be more valuable for predicting safer pregnancy outcome in WCHD with complex pathophysiologies because determinants for peak $\dot{V}O_2$ are multifactorial, including peak HR, respiratory function and working muscle metabolism.[21] Although the present results may not guarantee better fetal development in

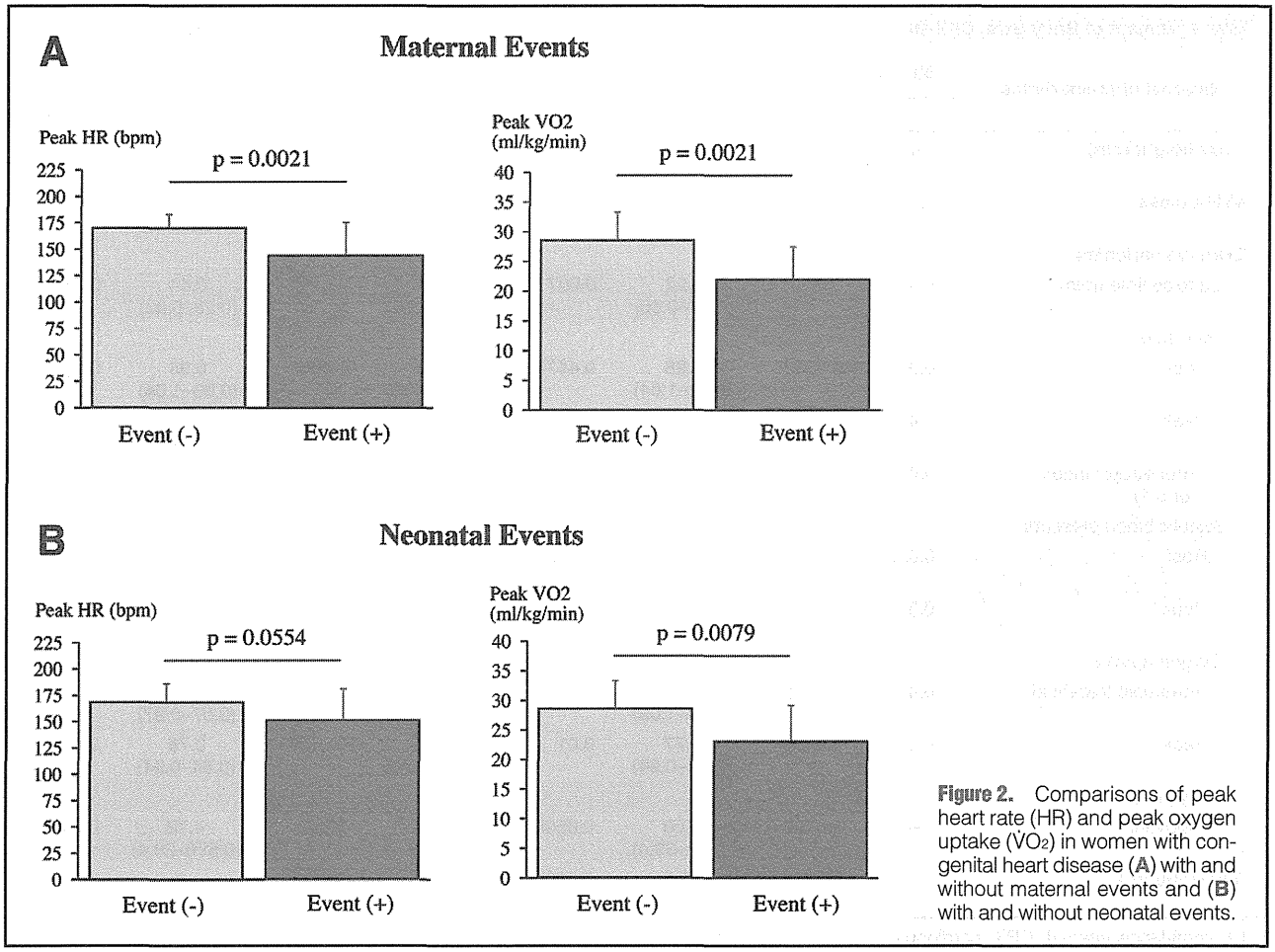

Figure 2. Comparisons of peak heart rate (HR) and peak oxygen uptake ($\dot{V}O_2$) in women with congenital heart disease (A) with and without maternal events and (B) with and without neonatal events.

WCHD with preserved HR response and/or peak $\dot{V}O_2$, rather, we may have to emphasize a close association of impaired cardiopulmonary response during exercise with adverse pregnancy outcomes. Second, the retrospective nature could not clarify causal associations, especially for the relationships between CPX variables and birth weight because the timing of deliveries was sometimes decided based on obstetric reasons. In addition to hemodynamic issues, traditional risk factors for fetal growth need to be considered. Maternal genes, especially maternal height, which mainly determines uterine size, and nutrient intake are determinants of fetal development.[22–24] Although we did not check maternal nutritional issues, especially iron deficiency,[25] maternal height had no impact on fetal development, implying greater impact of impaired hemodynamics on fetal growth in WCHD. Third, objective CPX values may not be equivalent with regard to different types of CPX data, for instance, those obtained using bicycle exercise. Finally, the interval between CPX and the nearest pregnancy outcome varied significantly, indicating that the CPX values did not reflect the corresponding cardiopulmonary function at the time of pregnancy. A previous serial assessment of exercise capacity in adults with tetralogy of Fallot (mean age, 29±7 years), however, demonstrated no significant serial change in peak $\dot{V}O_2$ with a mean follow-up of 6.7 years.[15] Therefore, we speculate that the CPX values obtained 1.8±2.2 years before the following nearest delivery, to some extent, reflect the cardiopulmonary function at the time of pregnancy. Nevertheless, prospective large-scale studies, including comprehensive maternal environmental assessment, to confirm the present data are warranted.

Conclusions

CPX parameters of peak HR ≥150 beats/min and/or peak $\dot{V}O_2$ ≥25 ml·kg^{-1}·min^{-1} were found to be associated with pregnancy outcome in this study. Larger prospective studies are needed to determine whether these cut-offs for HR and peak $\dot{V}O_2$ may be reference values for safer pregnancy outcomes in WCHD.

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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

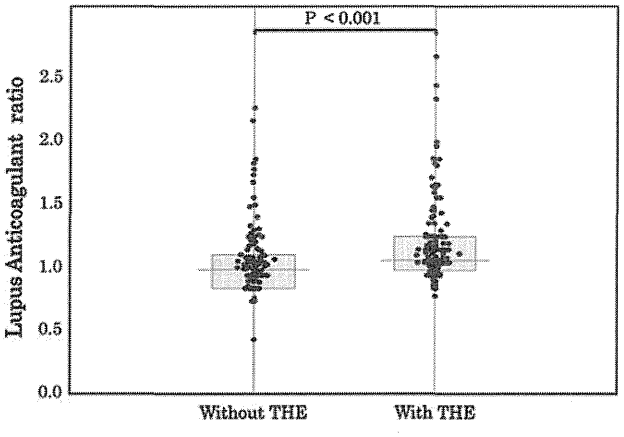

Fig. 1 Lupus anticoagulant in the patients with and without THE

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.

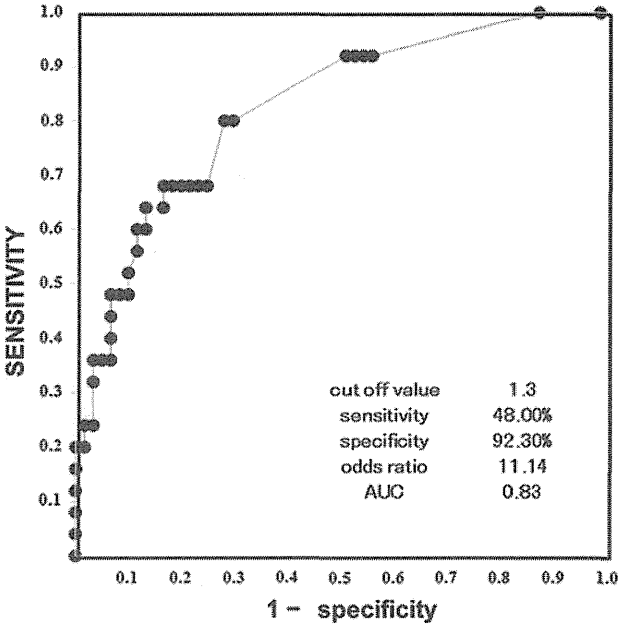

Fig. 2 An ROC analysis of LA for THE

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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Table 1 Summary of patient characteristics

Case No.	Age (yrs)	Parity	AVM grade*	Lesion	Presentation	Gestation at time of presentation
1	27	G1P1	pial AVF	rt parietal	hemorrhage	21st week
2	34	G1P1	I	rt insula	hemorrhage	16th week
3	27	G1P1	II	lt parietal	hemorrhage	25th week
4	30	G0P0	II	multiple	hemorrhage	25th week
5	31	G2P2	II	lt occipital	hemorrhage	5th week
6	22	G0P0	III	rt midbrain	hemorrhage	15th week
7	31	G1P1	II	rt frontal	incidental	pre-pregnancy
8	30	G0P0	II	lt parietal	headache	pre-pregnancy
9	28	G1P1	V	rt parietal	headache	pre-pregnancy

*According to Spetzler-Martin grading scale. AVF: arteriovenous fistula, AVM: arteriovenous malformation, G: gravida, lt: left, P: para, rt: right.

Subjects and Methods

Nine patients with AVM in pregnancy aged 22 to 34 years (mean 28.9 ± 3.4 years) were treated in the National Cerebral and Cardiovascular Research Center between April 2005 and April 2011 (Table 1). Six patients presented with their first episode of intracerebral hemorrhage (ICH) during pregnancy, 2 with headache, and one with incidental finding of AVM. In the 3 patients with unruptured AVM, the diagnosis was made before pregnancy. The Spetzler-Martin grade was I in one patient, II in five, III in one, and V in one. One patient was diagnosed with pial arteriovenous fistula (AVF). In each of these cases, we examined the results of pregnancy and delivery management, and the maternal and fetal outcome with ruptured and unruptured AVMs.

Results

I. Maternal management with ruptured AVMs

Six patients presented with their first episode of ICH during pregnancy; their AVMs were previously undetected. In 3 patients (Cases 1, 2, and 3), removal of the AVM was performed prior to delivery. The ICHs occurred in the 21st week, 16th week, and 25th week of gestation, and the surgery for AVM was performed in the 21st week, 18th week, and 30th week of gestation, respectively. The interval between onset and the surgery was 0 days, 14 days, and 33 days, respectively. Emergency surgery was performed for Case 1 with severe consciousness disturbance due to the mass effect of the hematoma. In another 2 patients with Spetzler-Martin grade I and II AVM, the symptoms were mild and elective surgery for AVM was performed for the prevention of rebleeding because we expected safe resection of the AVM located in superficial lesion. The management of pregnancy after removal of the AVM was similar to a normal pregnancy, with vaginal delivery in one case and cesarean section in two cases. In Case 4, cesarean section was carried out prior to AVM treatment in the 28th week of gestation because the mother suffered from hypoxia, hemoptysis, and transient ischemic attack due to paradoxical cerebral embolism from a pulmonary AVF. The interval from the cerebral hemorrhage onset to delivery was 24 days. In this patient, the AVM lesions were small and multiple, and gamma knife surgery was conducted 4 weeks after delivery. In Case 5, the patient presented with ICH in the fifth week of pregnancy and had a miscarriage on the 11th day after ICH. Endovascular embolization and resection for AVM were performed subsequently. In Case 6, the patient presented with ICH in the 15th week of gestation, and artificial abortion was performed 18 days after onset based on the concerns of her family. Gamma knife treatment was performed subsequently. There was no rebleeding in any patient, including the puerperal period (Table 2).

II. Maternal management with unruptured AVMs

The diagnosis in 3 patients with unruptured AVMs was made before pregnancy. In Cases 7 and 8, gamma knife surgery had been performed previously, and pregnancy occurred before confirmation of the obstruction of the AVM. In Case 9 with Spetzler-Martin grade V AVM, there was no surgical indication for AVM. The vaginal delivery had been performed previously under epidural anesthesia in this patient. Case 7 had severe pregnancy-induced hypertension, and an urgent cesarean section was performed on admission to the hospital in the 28th week of gestation because her blood pressure was difficult to control. In another two cases, blood pressure management was successfully performed during pregnancy, and the patients delivered at full

Table 2 Results of arteriovenous malformation (AVM) treatment, delivery management, and mother and infant clinical outcomes

Case No.	Timing of AVM treatment	AVM treatment	Delivery (week of pregnancy)	Reasons for CS	Outcome for the mother (mRS)	Outcome for the infant
1	21st week of pregnancy	removal (emergency)	CS (36)	hemiparesis	3	infant well
2	18th week of pregnancy	removal (elective)	CS (40)	macrosomia, previous CS	0	infant well
3	30th week of pregnancy	removal (elective)	VD (40)	—	0	infant well
4	post-delivery	RS	CS (28)	pulmonary AVF	0	infant well (temporarily intubated)
5	post-abortion	EE + removal	AB (7)	—	0	—
6	post-abortion	RS	AB (18)	—	3	—
7	pre-pregnancy	RS	CS (37)	previous CS	0	infant well
8	pre-pregnancy	RS	CS (32)	severe PIH	0	infant well (temporarily intubated)
9	pre-pregnancy	conservative	VD (39)	—	0	infant well

AB: abortion, AVF: arteriovenous fistula, CS: cesarean section, EE: endovascular embolization, mRS: modified Rankin scale, PIH: pregnancy-induced hypertension, RS: radiosurgery, VD: vaginal delivery.

term. There were no bleeding complications in any of the patients over the course of the pregnancy, including the puerperal period (Table 2).

III. Method of delivery

Vaginal delivery was performed in two cases, and cesarean section in five cases. Spontaneous vaginal delivery occurred in the 40th week of gestation after removal of the AVM in Case 3, and vaginal delivery under epidural anesthesia occurred in Case 9 with Spetzler-Martin grade V AVM in the 39th week of gestation. Among the 5 patients with cesarean section, 3 had coexistent AVM. Cesarean section was performed due to the existence of the AVM in Case 7 with severe uncontrollable pregnancy-induced hypertension, in Case 4 with pulmonary AVF, and in Case 8 who had previously undergone cesarean section. Two patients underwent cesarean section after AVM resection due to maternal factors; Case 1 with limitation of abduction of the lower limbs because of hemiplegia and twin pregnancy, and Case 3 with previous cesarean section and macrosomia. Mothers and babies suffered no complications during labor (Table 2).

IV. Maternal outcome

The 6 patients with ruptured AVMs had modified Rankin scale (mRS) score of 0 in 4 cases and 3 in 2 cases. The latter resulted from initial cerebral hemorrhage. The 3 patients with unruptured AVMs had mRS score 0. There were no new maternal complications due to cerebral AVM, including bleeding complications, in all patients throughout the pregnancy, delivery, and puerperal periods after the diagnosis of AVM (Table 2).

V. Fetal outcome

One patient suffered spontaneous abortion in the 7th week of gestation (2 weeks after onset), and one patient underwent induced abortion in the 18th week of gestation (third week after onset). Two premature infants delivered by cesarean section in the 28th week and 32nd week of gestation required temporary respirator management, but their subsequent growth and development was good. In the remaining infants, the growth development was excellent (Table 2).

Discussion

I. Epidemiology of AVMs during pregnancy

The prevalence of cerebral AVMs is estimated at 0.01–0.50% of the population. AVM is generally present in patients aged between 20 and 40 years, and is more common in those over 30 years, the childbearing age for women.[3] A previous study reported 21 ischemic strokes and 11 hemorrhagic strokes among 58,429 deliveries, and 4 of 11 hemorrhagic cases resulted from AVM rupture.[18] Although the influence of pregnancy on AVM rupture is controversial among investigators,[2,7,15] in a recent report, the annual hemorrhage rate during pregnancy was 10.8%; the hemorrhage rate per pregnancy was 8.1%; and the hazard ratio for ICH during pregnancy was 7.91.[4] The frequency of rebleeding during the same pregnancy period could be as high as

27%, which is 4 times higher than for the natural course of a ruptured AVM in the first year.[15] However, conservative treatment was done in 20 of 24 cases, and surgical removal was performed during pregnancy in only 4 cases. Similarly, rebleeding of AVM occurred in one of 11 cases, and surgical treatment during pregnancy was only performed in 7 cases after delivery.[16] After AVM rupture during pregnancy, maternal mortality was 28% and fetal mortality was 14%.[2] These risks can be eliminated only by excision of the AVM. The prognosis for the mother and fetus would improve if surgical resection of the AVM is safely performed. In our ruptured cases, AVM resection was performed in 3 of 6 cases (50%) before delivery, and the rebleeding rate in the peri-pregnancy period was 0%. In view of these results, AVM in pregnant women should be treated with great care.

Table 3 Management decision chart for patients with intracerebral hemorrhage from arteriovenous malformation (AVM) during pregnancy

	Operative risk	
	Low	High
Fetus immature/ Early pregnancy	removal of AVM →delivery based on obstetrical indications	conservative maternal management →modified vaginal delivery/ cesarean section once fetus was mature →AVM treatment based on neurosurgical indications
Fetus mature/ Advanced pregnancy	modified vaginal delivery/ cesarean section →removal of AVM	modified vaginal delivery/ cesarean section →AVM treatment based on neurosurgical indications

II. Maternal management with AVMs in pregnancy

Maternal management of patients with ruptured AVMs should be based mainly on neurosurgical indications rather than on obstetrical indications.[2] When neurological deterioration occurs due to AVM rupture, emergency surgery is necessary. If the fetus is sufficiently mature, simultaneous cesarean section is possible. When there is no indication for emergency surgery for AVM, blood pressure management is important.[9] However, this is not necessarily effective for the prevention of rebleeding because patients with ruptured AVM do not always have a history of hypertension. Although radical treatment tended to be performed after delivery in many case reports and case series, some authors suggested that early surgical intervention for AVM before delivery led to improved maternal and fetal prognosis.[15,22] We agree, and try to perform AVM resection during pregnancy with an immature fetus if the surgical risk is low after considering the high risk of rebleeding (Table 3). Indeed, we performed elective AVM resection with pregnancy continuation in 2 patients, with good postoperative maternal and fetal outcomes. The average period between onset and AVM resection was 23.5 days, and no rebleeding occurred during the waiting period. In addition to the maternal and neurosurgical treatment priorities, consideration of the fetus is also necessary and cooperation between obstetricians and anesthesiologists is essential during surgery. We routinely use intraoperative fetal heart rate monitoring. If the fetus has reached the minimum age for extra-uterine life, obstetricians prepare for emergency cesarean section in case of fetal distress.

Surgery for AVM is determined primarily by the Spetzler-Martin grading scale.[19] A potential complication of surgery for AVM during pregnancy is the risk of intraoperative bleeding leading to deterioration of the uterine and placental circulation. Although preoperative embolization is possible for cases with a high risk of intraoperative bleeding, such as deep-seated AVMs, the endovascular treatment itself carries the risk of ischemic and hemorrhagic complications.[5,12,21] In addition, there is not enough evidence to presume the safety of iodinated contrast agents which cross the human placenta and enter the fetus. The potential radiation risk and the potential added risks of contrast medium should be considered in the preoperative study.[23] Previous reports of endovascular treatment for AVM during pregnancy are limited.[17] There would be wider surgical indications by discussing the efficacy and risk more about endovascular treatment for AVMs during pregnancy.

Radical treatment for ruptured AVMs in patients with a mature fetus tends to be performed in the early postpartum period.[22] It is desirable for patients with unruptured AVMs to undergo radical treatment before pregnancy due to the increasing risk of AVM rupture during pregnancy. Prior to pregnancy, multimodal therapies such as direct surgery, endovascular embolization, and radiosurgery can be performed. In patients with unruptured AVMs diagnosed during pregnancy, conservative treatment is performed based on the risk of surgical treatment.

III. Delivery management

If the AVM is completely resected during pregnancy, the method of delivery can be determined based on the obstetrical indications. Our three patients who underwent AVM surgery during pregnancy could deliver at a mature gestational age. In

patients with AVM during pregnancy, problems during labor are related to the excessive cerebral hemodynamic changes, and cesarean section tends to be performed in these circumstances.[8] Cesarean section can be provided relatively safely, and is becoming more common. Recently, the rate of cesarean section has increased with the increase in high-risk pregnancies, such as with older maternal delivery age, and complicated pregnancies, which have increased up to 15% in a recent report from the Japanese Ministry of Health, Labour and Welfare. On the other hand, the maternal risks of cesarean section were reported to be 7 times higher than those of vaginal delivery and included maternal death, massive bleeding, infection, thrombosis, and injury to organs such as the bladder, although the frequency was very low.[1,11,14] If a patient's previous delivery was performed by cesarean section, repeated cesarean section tends to be performed to prevent uterine rupture. There is no definitive evidence that cesarean section prevents the hemorrhagic complications of AVM.[2,7,13] However, it is desirable to use epidural anesthesia or to shorten the second stage of labor with forceps/vacuum delivery techniques during labor.[6] When determining the parturient method, we should understand these points and inform the patient and her family to obtain consent.

We conducted painless vaginal delivery with epidural anesthesia combination in patients with AVM. In one patient with inoperative high-grade AVM, it was possible to perform vaginal delivery safely with this method. However, cesarean section allows easy control of blood pressure during labor, and is more desirable for patients with severe pregnancy-induced hypertension syndrome, as in our Case 7. Cesarean section is also indicated in patients with consciousness disturbance or hemiplegia preventing a dorsosacral position due to the consequences of ICH.

IV. Conclusion

We achieved good maternal and fetal outcomes in our cases, excluding 2 patients with mRS 3 due to the initial ICH. Surgical intervention for ruptured AVM during pregnancy could prevent rebleeding, and allow for determination of the delivery method based on the obstetrical indications. Cooperation between neurosurgeons, obstetricians, and anesthesiologists, and sufficient information about the treatment strategy given to the patients are essential. Finally, for better maternal and fetal prognosis, guidelines for female patients with cerebral AVMs should be established.

Conflicts of Interest Disclosure

The authors declare that they have no conflicts of interest. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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