Asian race, antenatal hospitalization, induction of labor, and epidural anesthesia have been suggested as risk factors for postpartum hemorrhage after vaginal delivery.[23,24] Because many of the patients were delivered by induction under epidural anesthesia, the rate of postpartum hemorrhage might have been increased. Careful management of atonic bleeding is required, especially after vaginal delivery in patients with repaired TOF.

The risk of recurrence of congenital heart disease in women with repaired TOF has been reported to range from 0% to 9.8%.[1–3,25,26] The recurrence rate in our patients was approximately 10%, which is close to the rate of 9.8% in the study by Pedersen et al, in which it was also pointed out that the rate of congenital cardiac disease in the offspring was 4.8%, excluding siblings with chromosome 22q11.2 deletion syndrome.[3] We did not perform genetic tests in our patients and it is possible that some of the patients had a genetic condition. However, all 3 mothers whose children showed congenital heart disease in this study were not TOF with PA and right aortic arch, which suggests the incidence of chromosome 22q11.2 deletion syndrome.

Regarding cardiac size, Uebing et al reported that pregnancy itself was associated with a persistent increase in subpulmonary ventricular size in patients with repaired TOF,[24] using an analysis that did not take the number of deliveries into consideration. Our data suggest that the right heart tends to be more and more dilated after the second and third deliveries, which indicates that pregnancy can affect long-term prognosis in patients with repaired TOF. Clarification of the long-term effects of pregnancy in these patients requires a long-term observational study to compare patients with and without a history of pregnancy. In general, the number of pregnancies complicated with repaired TOF is increasing and further studies are required to establish better management to minimize the risk of pregnancy and give a better long-term prognosis.

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Disclosures

None.

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ORIGINAL ARTICLE
Pulmonary Circulation

Maternal Outcome in Pregnancy Complicated With Pulmonary Arterial Hypertension

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Background: Pulmonary arterial hypertension (PAH), including Eisenmenger syndrome, has a risk of mortality in pregnancy of 10–40%. The aim of this study was to investigate whether pulmonary artery blood pressure (PABP) is a prognostic factor for pregnancy outcome in patients with PAH.

Methods and Results: The subjects were 42 patients with PAH during pregnancy. Severe and mild cases were defined by PABP before and during the first 14 weeks of pregnancy, with severe cases having mean PABP >40 mmHg by catheterization or systolic PABP >50 mmHg on echocardiography. Eighteen women chose termination of pregnancy before 14 weeks, leaving 24 women (10 mild, 14 severe) for analysis. The women with severe PAH delivered earlier (35.4 vs. 31.5 weeks, P<0.05) and had higher rates of small-for-gestational-age infants (0/10 vs. 7/14, P<0.01). Among the women with severe PAH, the New York Heart Association class dropped by 1 in 9 cases, by 2 in 3 cases, and remained the same in 2 cases as pregnancy progressed, whereas among the women with mild PAH, the class dropped by 1 in 1 case and 9 women remained in the same class. Among the severe cases, 1 woman died and there was 1 fetal death; PABP markedly increased in later pregnancy from 54 to 74 mmHg (catheter measurement) and from 78 to 93 mmHg (echocardiography) (P<0.05).

Conclusions: The level of PABP before or in the early stage of pregnancy is an important predictor of pregnancy outcome. (*Circ J* 2012; **76:** 2249–2254)

Key Words: Eisenmenger syndrome; Pregnancy; Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a complex disorder in which pulmonary arterial obstruction leads to elevated pulmonary arterial resistance and right ventricular failure.[1–4] Elevation of the pulmonary arterial pressure correlates with progressive damage to the pulmonary artery.[3,4] Before the development of surgical treatment for ventricular septal defect, atrial septal defect and patent ductus arteriosus, most patients died around the age 40, with right-sided cardiac failure being the main cause of death.[5–7] Treatment with drugs such as epoprostenol, sildenafil, and bosentan causes vasodilatation of the pulmonary vasculature, which reduces pulmonary resistance and allows survival until about 60 years of age, [8–12] and lung transplantation can also increase survival.[13,14]

Pregnancy is strongly associated with life-threatening problems in patients with PAH. The risk of cardiac failure during and after pregnancy increases and sudden cardiac arrest may occur during cesarean section or soon after birth.[15–18] The rate of maternal death in pregnancies complicated by PAH is variouslyreported to be 20–60%.[18–21] Predictors of cardiac failure during pregnancy are elevated pulmonary arterial blood pressure (PABP),[22,23] elevated level of brain natriuretic peptide,[24,25] and increased size of the right ventricle.[26,27] There may also be a genetic predisposition.[28,29] Elliot et al. reported that pregnancy in women with PAH seems to be relatively safe up to a PABP of approximately 40 mmHg.[30] However, Bédard et al found that even patients with mild PAH can develop cardiac failure or die postpartum (within 3 months after delivery) in up to 30% of cases.[31]

Most reports of PAH in pregnancy have only examined PABP pre-pregnancy and do not mention changes in New York Heart

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Table 1. Baseline Demographic and Obstetric Characteristics of Patients With PAH

	Mild PAH (n=14)	Severe PAH (n=28)	P value
Maternal age (years)	29.5±3.5	30.1±4.0	NS
Nulli/multiparous	8/6	15/13	NS
Miscarriage/delivered	4/10	14/14	NS
Week of delivery*	36.4±4.0	31.4±2.8	<0.005
Birth weight (g)*	2543±350	1464±290	<0.005
SGA*	0	8	<0.05
Delivery mode*			<0.05
Vaginal	6	2	
Cesarean section	4	12	
Regional/general anesthesia	0/4	0/12	NS
BMI	21.2±1.5	22.1±1.8	NS
DM	1	3	NS
Hypertension	2	3	NS
Smoking	1	2	NS

*Only for delivery cases: mild group (n=10), severe group (n=14).
P<0.05 indicates a significant difference. Maternal age, week of delivery, birth weight, and BMI are shown as mean± SD and were analyzed by Student's t-test. Other data were analyzed by chi-square test and Fisher exact test.
PAH, pulmonary arterial hypertension; NS, not significant; SGA, small for gestational age; BMI, body mass index; DM, diabetes mellitus.

Table 2. Underlying Diseases in Patients With Mild and Severe PAH

Category	Mild PAH (n=14)		Severe PAH (n=28)	
	Miscarriage (n=4)	Delivered (n=10)	Miscarriage (n=14)	Delivered (n=14)
IPAH	2	–	2	3
Congenital heart disease	2	8	1	6
ASD (pre/post-op)	1 (0/1)	3 (1/2)	1 (0/1)	1 (0/1)
VSD (pre/post-op)	0	3 (1/2)	0	3 (2/1)
PDA (pre/post-op)	1 (0/1)	1 (1/0)	0	2 (0/2)
ECD (pre/post-op)	0	1 (0/1)	0	0
Eisenmenger syndrome	–	–	10*	4*
ASD			3	0
VSD	–	–	5	3
PDA			2	1
Collagen disease	–	2	–	–
Other	–	–	1	1

Data were analyzed by chi-square test and Fisher's exact test. *P<0.05.
PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; ASD, atrial septal defect; pre/post-op, pre/post operation; VSD, ventricular septal defect; PDA, patent ductus arteriosus; ECD, endocardial cushion defect.

Association (NYHA) classification or PABP during pregnancy or postpartum. Furthermore, there are no reports of the effects of PABP and maternal cardiac performance in pregnant Japanese women, and fetal growth has not been well studied. Therefore, we investigated the relationship of PABP before and during pregnancy to subsequent maternal cardiac function and neonatal outcome.

Methods

To study mortality and morbidity in maternal outcomes following PAH, we examined the charts of 42 pregnant women with PAH from January 1982 to December 2007. Cardiac function was evaluated using right-sided pulmonary catheterization and echocardiography, although in some cases of mild PAH only echocardiography was used. In the middle of the pregnancy, echocardiography was mainly used for the evaluation of PAH. The patients were divided into mild cases (systolic PABP ≥30 and <50 mmHg on echocardiography[32] or mean PABP ≥25 and <40 mmHg by catheterization[33]) and severe cases (systolic PABP ≥50 mmHg on echocardiography or mean PABP ≥40 mmHg by catheterization). Cardiac function was evaluated during pregnancy and after delivery. Some women chose early termination of pregnancy to avoid risk. Vaginal delivery was attempted for women with spontaneous labor, whereas cesarean section was selected for those with a need for early delivery because of an immature cervix. The NYHA classification was used to evaluate cardiac status.[34]

Data Collection

Data were collected for family history (sudden death, PAH), maternal age, height, body weight, parity, presence of hypertension, diabetes mellitus, change in PABP during and after pregnancy, right and left ventricular function, delivery mode (cesarean section or vaginal delivery), time of delivery (gestational week), and birth weight.

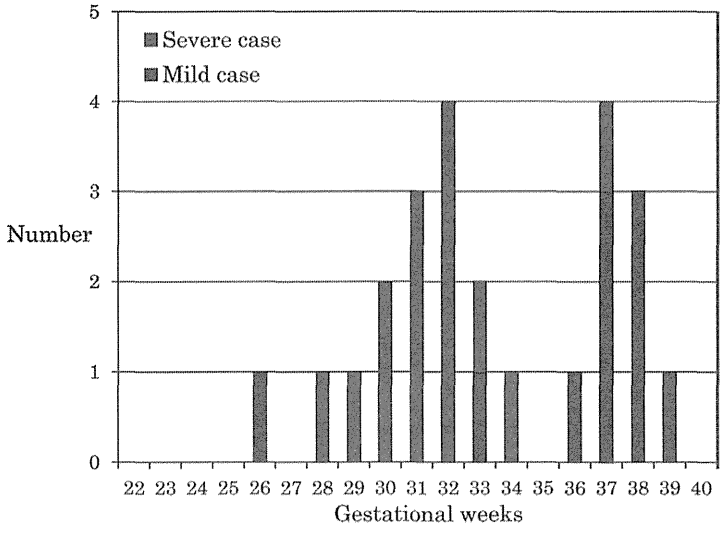

Figure 1. Week of delivery in pregnancies complicated with pulmonary arterial hypertension (PAH). Patients with mild PAH mostly delivered at term, whereas those with severe PAH had earlier deliveries.

Statistical Analysis

For continuous variables, a Student t-test was performed for analysis of normally distributed data, otherwise a Wilcoxon test was used. Chi-square test and Fisher's exact test were performed to compare categorical variables between the mild and severe cases. All statistical analyses were performed using JMP 7 (SAS Institute, Cary, NC, USA). $P<0.05$ was considered statistically significant.

Results

The baseline clinical and obstetrical characteristics of the 42 subjects are shown in Table 1. Overall, 42 cases of pregnancy complicated with PAH were analyzed, including 14 mild cases and 28 severe cases. Of the 42 patients, 18 (mild 4, severe 14) selected termination of pregnancy, and 24 (mild 10, severe 14) selected to continue after counseling. The number of patients in each PAH category is shown in Table 2.

Idiopathic PAH

There were 3 cases of severe idiopathic PAH. The maternal ages were 30, 38, and 20 years. All were referred because of exacerbated exertional fatigue, dyspnea, and pretibial edema at 25–30 weeks gestational age. On admission, the patients' respective PaO_2 level was 75, 66, and 86 mmHg; PABP was 72/30, 61/31, and 82/42 mmHg; and NYHA class was IV, IV, and III. Delivery by cesarean section was performed at 32, 28, and 32 weeks' gestation under general anesthesia with continuous Swan-Ganz catheter and systemic BP (via a radial arterial line) monitoring. Percutaneous cardiopulmonary support (PCPS) was ready in each case for use in an emergency. In the first case (in 1985), the mother died intraoperatively. Emergency cesarean section had been planned because of an abnormal fetal heart rate pattern, but the mother died of hypotension soon after intubation, despite attempts at resuscitation including PCPS. In the other two cases, which occurred in 2000 and 2003, the women survived to leave hospital. We attribute these outcomes to improved management using continuous infusion of epoprostenol. In the 2003 case, postpartum right-sided pulmonary catheterization showed PABP of 68/32. Dobutamine hydrochloride was started at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for severely low cardiac function, after which subjective symptoms such as shortness of breath during walking disappeared. Epoprostenol infusion therapy was then started at 0.5 $ng \cdot kg^{-1} \cdot min^{-1}$ and gradually increased in increments of 0.5 $ng \cdot kg^{-1} \cdot min^{-1}$ twice weekly until reaching a dose of 7 $ng \cdot kg^{-1} \cdot min^{-1}$. During the course the patient felt lower jaw pain as a side effect, but this gradually disappeared. Pretibial pitting edema and PAH evaluated by echocardiography and right-heart catheterization both improved and the patient was discharged from hospital on the 12th postpartum day.

Pregnancy Outcomes for Mild and Severe Cases of PAH

Gestational length at delivery showed a bimodal distribution (Figure 1). Patients with mild PAH mostly delivered at term, whereas those with severe PAH delivered earlier. The indications for delivery in patients with severe PAH were acute dyspnea (3 cases), fatigue and cough (3 cases), elevation of PABP (6 cases), and 2 women went into labor spontaneously. The gestational age at delivery and birth weights were significantly higher in the patients with mild PAH compared with those having severe PAH: 35.4 vs. 31.5 weeks, $P<0.05$; 2,543±350 vs. 1,464±290 g, $P<0.05$; respectively. More cases of fetal restricted growth were observed among the patients with severe PAH than among the mild PAH group: 0/10 vs. 8/15, $P<0.05$. Amniotic volume was adequate in all cases examined in both groups during pregnancy.

Echocardiographic and Cardiac Catheter Data

Among the patients with severe PAH, the average PABP increased as pregnancy progressed, based on the mean PABP pre-pregnancy and in the later stage of pregnancy measured by cardiac catheter (53.5±12.3 vs. 72.8±13.3 mmHg, $P<0.05$) and echocardiography (68.2±11.1 vs. 95.8±18.5 mmHg, $P<0.05$) (Figure 2). In the women with mild cases, PABP increased as pregnancy progressed, but did not reach statistical significance (Table 3).

NYHA Class

In 7 of the 10 women with mild PAH, NYHA class I was maintained throughout pregnancy (Figure 3). In these patients, elevation of PABP was not significant during pregnancy. The remaining 3 women were already NYHA class II in the pre-pregnancy period and 2 remained in NYHA class II until the postpartum period and 1 changed to NYHA class III. Of the 14

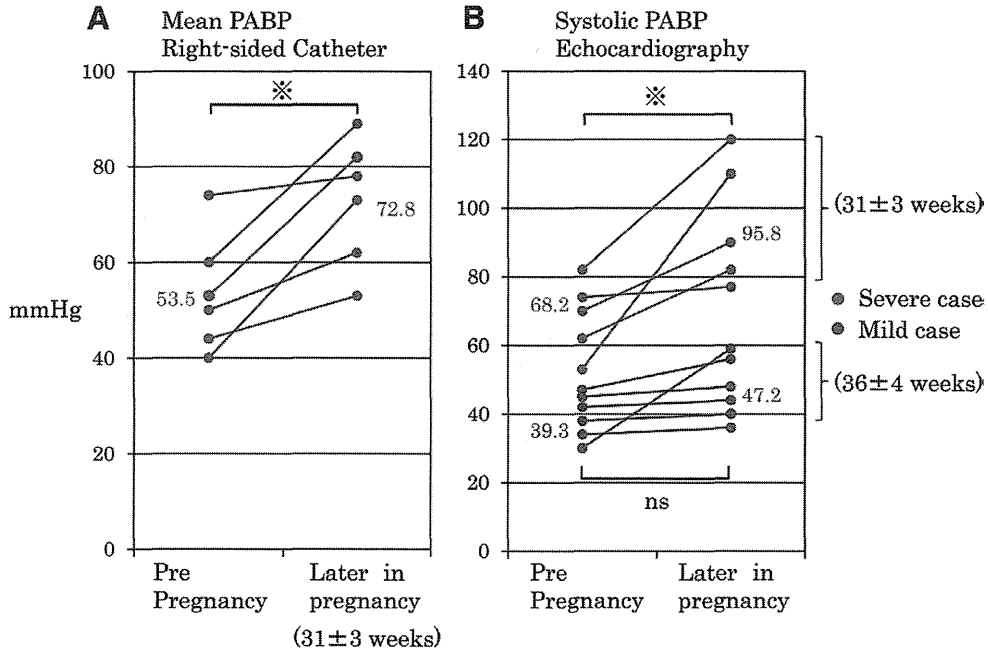

Figure 2. Changes in PABP during pregnancy. (**A**) Change in the mean PABP measured by a pulmonary cardiac catheter. (**B**) Change in the systolic PABP measured by echocardiography. Patients with severe PAH showed a significant increase in PABP later in pregnancy. PABP, pulmonary arterial blood pressure; PAH, pulmonary arterial hypertension.

Table 3. Echocardiographic Findings in Patients With Mild and Severe PAH Measured Early in Pregnancy (Except Systolic PABP)

	Mild PAH (n=14)	Severe PAH (n=28)	P value
Systolic PABP			
Pre-pregnancy	39.3±6.6	68.2±11.1	<0.05
Late-stage pregnancy	47.2±9.2	95.8±18.5	<0.05
Tricuspid valve regurgitation			
None-mild	9	8	<0.05
Moderate-severe	5	20	
LVDs	31.1±4.7	30.1±4.6	NS
Pulmonary artery valve regurgitation	2	3	NS
%FS	36.5±5.6	37.5±4.6	NS
RA cavity enlarged	2	17	<0.05
RV cavity enlarged	2	18	<0.05

LVDd, LVDs, %FS, and systolic PABP were analyzed by Student's t-test and are shown as the mean±SD. Other data were analyzed by chi-square test and Fisher's exact test. P<0.05 indicates a significant difference.
PAH, pulmonary arterial hypertension; PABP, pulmonary arterial hypertension; LVDs, left ventricular end-systolic dimension; NS, not significant; %FS, fractional shortening; RA, right atrium; RV, right ventricle; LVDd, left ventricular end-diastolic dimension.

severe cases, 1 woman was in NYHA class I, 12 women were in class II, and 1 was in class III early in pregnancy. The NYHA class worsened in all but 2 patients as pregnancy progressed. In these women the elevation of PABP was significant during pregnancy. At delivery, 1 patient died soon after intubation in the operation room, 11 were in class III, and 2 were in class IV with severe heart failure.

Discussion

We believe this is the first study in which the change in PABP was monitored during pregnancies complicated by PAH. PABP increased in the later stage of pregnancy in comparison with pre-pregnancy in patients with severe PAH, but not in those with mild PAH. PABP increased in all cases of severe PAH, from a mean of 53.5 mmHg pre-pregnancy to 72.8 mmHg in the later stage of pregnancy. Because pulmonary vascular resistance is elevated in PAH patients, pregnancy continuation may lead to right-heart failure. Circulating blood volume gradually increases by approximately 50% up to around 30 weeks of gestation, and then reaches a plateau.[35] In severe cases, this early rise leads to decompensation and the need for delivery.

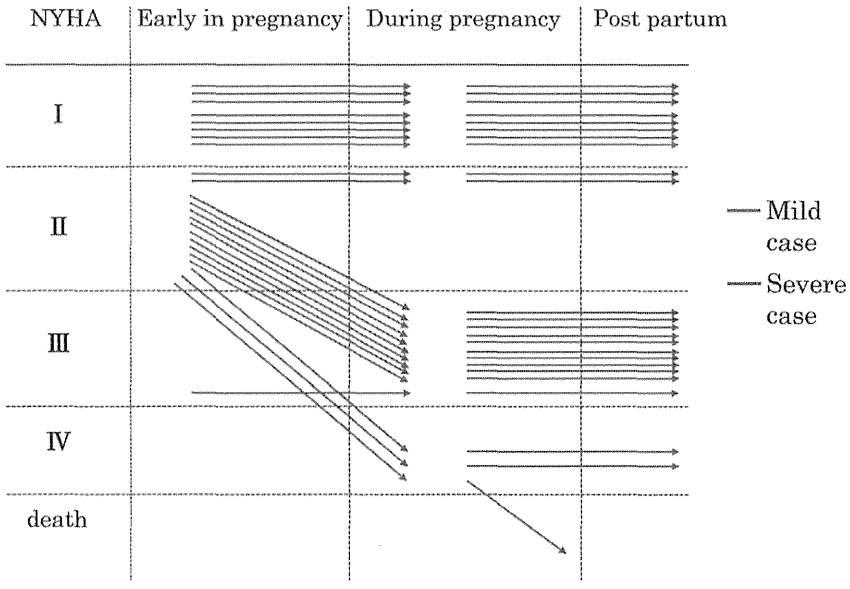

Figure 3. Changes in the New York Heart Association classification over the course of pregnancy.

The signs of decompensation are dyspnea, exertional fatigue, and pretibial edema. Perhaps surprisingly, signs and symptoms of right-heart failure, arrhythmia or angina (resulting from right ventricular ischemia) did not occur in the study subjects, although they might have done so if the pregnancies had been allowed to continue.

Although 70% of maternal deaths reported in the literature occur postpartum, there were no such deaths in our series and no deterioration of NYHA class postpartum. We attribute these improved results to 3 factors. The first is early termination of pregnancy around 30 weeks gestation in severe cases. Improvement of treatment in the NICU facilitated this decision, because all the preterm infants survived without neurological disorders, despite weighing only 1,000–1,500 g with prematurity of most organs. The second factor is the introduction of new drugs for the treatment of pulmonary hypertension, including beraprost, sildenafil, and epoprostenol; and the third is the improvement in anesthetic management. When PABP became higher than systemic BP during cesarean section, especially after removal of the placenta, the anesthetists were ready to reduce the blood volume by 100 ml in a few minutes from a Swan-Ganz catheter and use neosynesin (0.2 mg IV) to raise BP. The women with severe PAH had a higher rate of small-for-gestational-age babies compared with the women with mild cases, which was probably related to reduced cardiac output. However, some babies born to mothers with severe PAH grew adequately.

Patients with mild PAH mostly delivered at or near term, and tolerated the increased heart rate and circulating blood volume of pregnancy well. They were asymptomatic and showed no significant elevation of PABP. These findings indicate that PAH patients with mildly elevated PABP can be advised that pregnancy is appropriate. However, in 8 of 10 mild cases of PAH, the condition was associated with congenital heart disease. Thus, further studies are required to determine the safety of pregnancy for patients with mild idiopathic PAH, including analysis of the need for continuous treatment with epoprostenol (prostacyclin) or oral sildenafil. This study also indicates the significance of evaluating PAH before or in the early stage of pregnancy.

The NYHA class is used as the general standard for rating exercise tolerance in women with heart disease. One patient with severe PAH went from class I to class III during pregnancy and 15 patients with mild or severe PAH in class II pre-pregnancy went to class III during pregnancy (and 1 died), so special care has to be taken of patients who are already class II pre-pregnancy. In contrast, NYHA class I in a woman with mild PAH predicts continuation of pregnancy until term. The disease severity of the present patients may have been higher than that of general patients with PAH because the National Cerebral and Cardiovascular Center is a referral center for cardiovascular diseases. Many patients with severe PAH are referred for genetic analysis because of a family history of pulmonary hypertension. Because PAH is relatively rare, we were only able to include 42 patients in this study. The small number of subjects prevented correction of the results for the effects of potential confounding factors such as hypertension and previous obstetric history, performance of multifactorial analysis, and analysis of the effects of different etiologies of PAH (Table 2). However, measurements of the ventricles and atria, and the degree of tricuspid valve regurgitation, were better defined in the present study compared with other multicenter studies. In future work, we plan to investigate a larger cohort of patients to clarify the risk factors in female patients with PAH for cardiac dysfunction during pregnancy. The outcomes for these patients are improving because of the introduction of intravenous treatment with epoprostenol and/or oral sildenafil[36] during pregnancy. In some cases of severe PAH, use of this treatment results in PABP not increasing during pregnancy and appropriate birth weights for gestational age.

Study Limitations

The definition of PAH is a mean PABP ≥25 mmHg and diagnosis requires confirmation by right-sided catheterization. In

most cases in our study, right-heart catheterization was performed before pregnancy, but not during pregnancy provided the patient was not symptomatic, because this examination is invasive for both mother and fetus. For this reason, we are unable to show changes in PAH evaluated by right-sided catheterization, only the changes determined by echocardiography. Therefore, PABP may have been overestimated, because the mean pulmonary artery pressure has been shown to be significantly overestimated by echocardiography compared with catheterization.[37]

Conclusions

Among the cases of severe PAH in this study, PABP increased during pregnancy and there was 1 maternal death during cesarean delivery. The NYHA class in most cases of severe PAH was III or worse in later pregnancy. Early delivery was required and the rate of small-for-gestational age babies was significantly higher. Pregnancy may be safe for PAH patients with mildly elevated PABP. However, in 8 of 10 cases of mild PAH, the women had associated congenital heart disease, indicating that further studies are needed to determine the appropriateness of pregnancy in patients with idiopathic PAH, even if the condition is mild.

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Disclosure

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Pregnancy and Delivery in Moyamoya Disease: Results of a Nationwide Survey in Japan

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Abstract

Stroke during pregnancy associated with moyamoya disease (MMD) has been reported sporadically, but no systematic surveys have been undertaken. To reveal the current clinical situation, the authors conducted Japan's first nationwide survey of pregnancy and delivery associated with MMD. A questionnaire was sent to all 270 perinatal medical centers across Japan to survey their experiences with delivery associated with MMD within the preceding 5 years (Survey I); another questionnaire was sent to 554 adult female patients with MMD regarding their experience with childbirth (Survey II). Survey I included 59 deliveries among patients with previously diagnosed MMD. The incidence of perinatal neurological events and morbidity was 5.1% and 1.7%, respectively. In another five cases, newly diagnosed after perinatal attacks, disability was noted in three cases, including one death from intracranial hemorrhage. Survey II included 278 deliveries. The perinatal attack rate was 6.6% in 76 previously diagnosed cases and 2.0% in 202 cases undiagnosed at pregnancy, but neither group reported permanent morbidity. Caesarean section in previously diagnosed cases accounted for 76.3% of deliveries in Survey I and 69.7% in Survey II, but no significant difference in event rate was found between caesarean section and vaginal delivery in either survey. Although the incidence of perinatal neurological events is low when MMD has been diagnosed, careful monitoring is required in light of the potential for stroke. Serious events, especially intracranial hemorrhage, can occur if MMD has not been diagnosed at pregnancy. Further efforts to establish management guidelines are required to ensure safer childbirth in patients with MMD.

Key words: delivery, intracranial hemorrhage, moyamoya disease, pregnancy, stroke

Introduction

Moyamoya disease (MMD) is a cerebrovascular disease characterized by progressive bilateral stenoocclusion of the terminal internal carotid arteries accompanied by the extensive formation of collateral vessels (moyamoya vessels) at the base of the brain.[2,13] MMD causes cerebral ischemic attacks as well as intracranial hemorrhage that is supposedly the result of excessive long-term hemodynamic stress to the moyamoya vessels.[8] MMD is more prevalent in females than in males and occurs most frequently during childhood and early adulthood[16]; thus, it is not uncommon for patients to become pregnant and give birth. Pregnancy and delivery are known to significantly affect a woman's physical condition, and the incidence of brain attacks can increase in the perinatal period.[5,17] Since the 1970s, several cases of stroke in pregnant patients with MMD have been reported,[1,12] and these sporadic reports were reviewed in 1998.[6] However, no systematic surveys have ever been conducted, and no guidelines have been established for managing pregnancy and delivery associated with MMD. Even recommendations regarding delivery method (natural labor, painless labor, or caesarean section), for example, seem to differ between hospitals. Consequently, the authors designed and conducted a nationwide survey in Japan on the management of pregnancy and delivery in patients with MMD.

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Methods

This survey comprises two sections: a survey of perinatal medical centers (Survey I) and a survey of

Table 1 List of questions for obstetricians regarding pregnancy, delivery, and moyamoya disease (MMD)

I. Number of deliveries associated with MMD during the preceding 5 years
II. Clinical data for each patient
  1. Age at delivery
  2. Weeks of gestation at delivery
  3. Number of previous deliveries
  4. MMD diagnosed before pregnancy
  5. Had undergone bypass surgery (when diagnosed before pregnancy)
  6. Detailed information on perinatal cerebral events leading to the diagnosis (when not previously diagnosed)
  7. Selection of delivery method
  8. Information on cerebral events during gestation
  9. Information on cerebral events during labor and puerperium
  10. Clinical outcome of patient at discharge (mRS)
  11. Clinical outcome of child at discharge

mRS: modified Rankin scale.

Table 2 Questions for female patients with moyamoya disease (MMD) about their experiences with pregnancy and delivery

I. Age at time of questionnaire
II. Age upon diagnosis of MMD
III. Clinical type of MMD (ischemic, hemorrhagic, hemorrhagic transformation from ischemic type, others)
IV. Occurrence and timing of EC-IC bypass surgery
V. Ongoing medication for MMD
VI. Previous delivery (yes or no)
VII. Detailed information about previous deliveries
  1. Number of deliveries before diagnosis of MMD, method of each delivery, details of any perinatal cerebral events
  2. Number of deliveries after diagnosis of MMD, method of each delivery, details of any perinatal cerebral events
  3. Please describe any problems you experienced during your pregnancy and delivery.

EC-IC: extracranial-intracranial.

adult female patients with MMD (Survey II). The survey was conducted with the approval of the Ethical Committee of the National Cerebral and Cardiovascular Center, and great care was taken to protect all personally identifiable information.

I. Survey I

The survey questionnaires were sent to all 270 centers for maternal, fetal, and neonatal medicine across Japan regarding their experience during the preceding 5 years (January 2003–December 2007). These centers are designated to deal with high-risk pregnancies and deliveries. The questionnaire sought to determine the number of deliveries associated with MMD in each unit, the demographics of these patients, the details of any cerebrovascular events that occurred, and their clinical outcomes. Table 1 shows the questions contained in the questionnaire.

II. Survey II

This survey was conducted in cooperation with the Association of Persons with Moyamoya Disease and Their Families, which is the only Japanese association for patients with MMD, and represents 1,300 patients and their family members. The survey questionnaires regarding experiences with pregnancy and delivery were sent from the association's headquarters to all 554 adult female members. Table 2 lists the questions contained in the questionnaire. All reply forms were collected at the headquarters, and the data were provided to the authors for analysis after all personally identifiable information had been deleted.

III. Statistical analysis

The maternal prognosis was expressed with the modified Rankin scale (mRS)[15] at discharge. The data were presented as frequency or means ± standard deviation. Fisher's exact probability test was applied for categorical data. The analyses were performed with Statcel 3 (OMS Publishing Inc., Tokorozawa, Saitama).

Results of Survey I

Feedback was obtained from 132 medical centers (for a response rate of 48.9%). Among these centers, 33 (25.0%) had experienced a delivery associated with MMD, and 64 cases were recruited. These cases were divided into two groups: 59 cases in which MMD had been diagnosed before pregnancy (Group I-A); and 5 cases in which MMD had been newly diagnosed as a result of neurological incidents during pregnancy, delivery, or puerperium (Group I-B).

I. Group I-A (cases of MMD diagnosed previously)

Table 3 shows the clinical data. The mean age of the patients at delivery was 29.2 ± 4.1 years, with 54.2% being primipara. Thirty-four (57.6%) patients had previously undergone extracranial-intracranial (EC-IC) bypass surgery. Fourteen (23.7%) cases were managed with vaginal delivery (natural labor in 3 cases and painless labor with spinal epidural anesthesia in 11), whereas 45 (76.3%) cases were managed with caesarean section (scheduled in 41 cases, emergent change from vaginal delivery in 2, and others in 2). Although caesarean section tended to be selected more frequently for those who had not

Table 3 Clinical data of the 59 cases in Group I-A

Mean age at delivery, yrs	29.2 ± 4.1
Mean weeks of gestation at delivery	36.9 ± 3.6
Previous deliveries	
none	32 (54.2%)
one	21 (35.6%)
two	4 (6.8%)
three	2 (3.4%)
Previous bypass surgery	
yes	34 (57.6%)
no	24 (40.7%)
unknown	1 (1.7%)
Cerebral events during gestation	
yes	3 (5.1%)
ICH	1
TIA	2
no	56 (94.9%)
Delivery method	
vaginal delivery	14 (23.7%)
natural labor	3
painless labor	11
caesarean section	45 (76.3%)
scheduled	41
emergent	2
others	2
Cerebral events during delivery and puerperium	
yes	0 (0.0%)
no	55 (100%)
ADL at discharge	
unchanged	58 (98.3%)
deteriorated	1 (1.7%)
Prognosis of the child	
alive, no sequela	54 (91.5%)
alive, status unknown	2 (3.4%)
deceased through abortion	2 (3.4%)
deceased (SIDS)	1 (1.7%)

ADL: activities of daily living, ICH: intracerebral hemorrhage, SIDS: sudden infant death syndrome, TIA: transient ischemic attack.

undergone previous bypass surgery, no statistical significance was found ($p = 0.07$).

Three cerebral events (5.1%) occurred during gestation (intracerebral hemorrhage in 1 case and transient ischemia in 2). A 30-year-old primipara who had been treated with EC-IC bypass developed intracerebral hemorrhage requiring emergent brain surgery. Although the child was delivered successfully by scheduled caesarean section at 32 weeks of gestation, this patient remained severely disabled (mRS 4). No sequelae were noted in the other two cases. No attacks occurred during delivery or during the puerperal period, and the neonates exhibited no problems associated with their mothers' MMD. Two stillbirths were delivered by intentional abortion, and one death during the infantile period was diagnosed as sudden infant death syndrome unrelated to MMD.

II. Group I-B (cases of MMD newly diagnosed)

Perinatal cerebrovascular attacks occurred in 5 patients with undiagnosed MMD. Figure 1 shows the demographics and clinical course of these patients. The mean age at delivery was 30.0 ± 4.9 years. Three patients presented with intracranial hemorrhage, and 2 suffered cerebral ischemia. Case 1 had previously delivered twice developed intracranial hemorrhage during pregnancy and was newly diagnosed with MMD. After emergent brain surgery, her gestation continued and she delivered a baby by scheduled caesarean section at 37 weeks. The maternal outcome was good (mRS 0) and the child survived (although no reply was received regarding any deficits in the child). Case 2 was a primipara who experienced serious intracerebral hemorrhage during pregnancy (no data was provided regarding weeks of gestation). Although an emergency craniotomy and caesarean section were performed, the mother eventually died; the child exhibited no deficit. Case 3 primipara developed intracranial hemorrhage during natural vaginal labor at 39 weeks of gestation. The child was delivered by emergent caesarean section without deficits, but the mother was rendered disabled (mRS 2). Case 4 suffered an ischemic attack during pregnancy and MMD was diagnosed. An elective caesarean section was performed at 37 weeks of gestation and no deficit remained in either mother or child. Case 5 developed severe pregnancy-induced hypertension accompanied by fetal distress syndrome, which required a caesarean section at 31 weeks of gestation. The delivery was uneventful, but the patient developed a cerebral infarction 3 days after delivery, resulting in mild neurological deficits (mRS 1). The infant also exhibited a sequela caused by the fetal distress.

Results of Survey II

Feedback was obtained from 338 female patients (for a response rate of 61.0%). Among these, 146 patients (43.2%) had undergone 278 deliveries. Forty-seven patients had already been diagnosed with MMD before their first pregnancy, whereas 97 patients were diagnosed after delivering all their children. Another two patients were diagnosed with MMD after their first or second deliveries and subsequently gave birth to other infants. Thus, all deliveries could be divided into two groups: 76 deliveries by 49 patients with previously diagnosed MMD (Group II-A), and 202 deliveries by 99 patients unaware of their MMD at childbirth and diagnosed later in life (Group II-B).

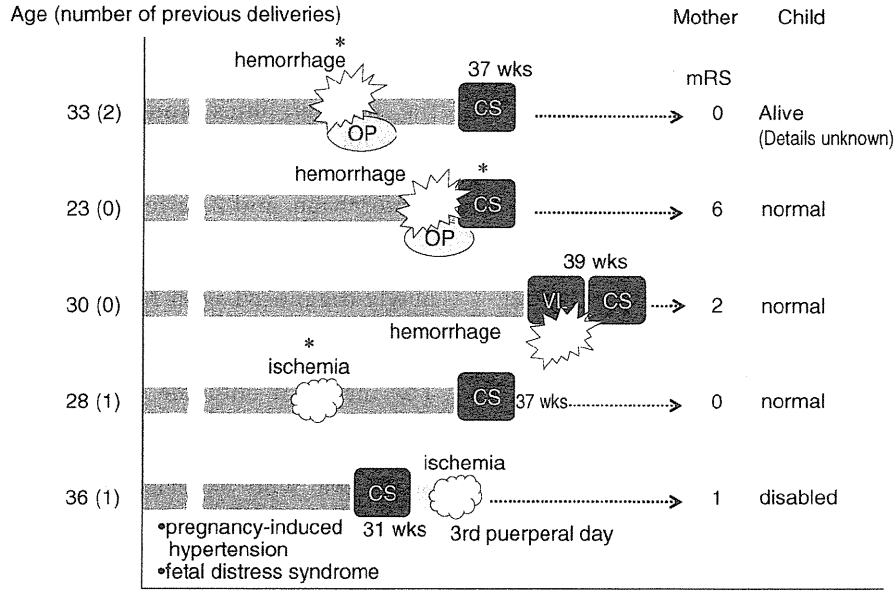

Fig. 1 Clinical course of the five cases in Group I-B. CS: caesarean section, mRS: modified Rankin scale, OP: neurosurgical operation, VL: vaginal labor. *Weeks of gestation unknown.

I. Group II-A (cases of MMD diagnosed previously)

Table 4 shows the clinical data. The mean age of diagnosis with MMD was 13.2 ± 8.2 years (1 to 34 years), and 71.4% of the patients were diagnosed before the age of 20 years. EC-IC bypass was performed in 44 (89.8%) patients and 63 (82.9%) deliveries occurred after surgical treatment. Among all 76 deliveries, 23 (30.3%) were vaginal deliveries, and 53 (69.7%) underwent caesarean section. The occurrence of previous bypass surgery had no significant effect on the selection of delivery methods ($p = 0.37$).

Neurological events were detected in 5 (6.6%) deliveries. Although all these patients had undergone bypass surgery previously, the incidence of the event in surgically-operated cases was not significantly different from non-operated cases ($p = 0.38$). Two events occurred during delivery and three occurred during the puerperal periods, and all were transient, leaving no deficit. The incidence of neurological events did not differ between vaginal delivery and caesarean section ($p = 0.51$). No neurological events were reported during these pregnancies.

II. Group II-B (cases of MMD undiagnosed at childbirth)

Table 5 shows detailed data. The mean age at diagnosis of MMD was 43.1 ± 10.7 years (23 to 69 years), and it is difficult to clarify whether the patients in this group had already contracted MMD or the level of severity. Among all 202 deliveries, 183 (90.6%) were vaginal deliveries, while caesarean section was employed in 19 (9.4%) cases. Transient neurological events were noted in four (2.0%) cases, all related to vaginal delivery. No serious events occurred leading to deficits, and no adverse events during pregnancy were reported.

Discussion

This is the first nationwide survey of pregnancy and delivery associated with MMD in Japan. The authors designed a survey for all the perinatal medical centers intended to reveal the current clinical situation regarding pregnancy and delivery associated with MMD (Survey I). While this design has the advantage of providing accurate medical information on each delivery, it also has the potential disadvantages of limiting each observation period to only a single perinatal period while failing to extract information about the medical history of each patient. This information is important, especially when a patient has given birth repeatedly. Another survey, therefore, was designed as Survey II. A major limitation must be noted, that patients who responded to the questionnaire were likely to be those in relatively good condition, as any fatalities or severely-disabled patients would have dropped out (inclusion bias). Furthermore, there might be some recall bias in this type of survey. Accordingly, the results must be

Table 4 Clinical data of the 76 deliveries in Group II-A (49 patients)

Mean age at present (range), yrs	34.6 ± 6.6 (20 to 49)
Mean age upon diagnosis of MMD (range), yrs	13.2 ± 8.2 (1 to 34)
Clinical type of MMD	
ischemic	31 (63.3%)
hemorrhagic	7 (14.3%)
ischemic to hemorrhagic transformation	2 (4.1%)
others or unknown	9 (18.4%)
Number of deliveries by each patient	
one	27 (55.1%)
two	17 (34.7%)
three	5 (10.2%)
Previous bypass surgery	
yes	63 (82.9%)
no	10 (13.2%)
unknown	3 (3.9%)
Delivery method	
vaginal delivery	23 (30.3%)
natural labor	21
painless labor	2
caesarean section	53 (69.7%)
scheduled	47
emergent	4
others	2
Neurological events during delivery and puerperium	
yes	5 (6.6%)
vaginal delivery	
TIA during delivery	1
TIA during puerperium	1
caesarean section	
seizure during delivery	1
unknown during delivery	1
TIA during puerperium	1
no	67 (88.1%)
unknown	4 (5.3%)

MMD: moyamoya disease, TIA: transient ischemic attack.

Table 5 Clinical data on the 202 deliveries in Group II-B (99 patients)

Mean age at present (range), yrs	50.8 ± 10.9 (28 to 73)
Mean age upon diagnosis of MMD (range), yrs	43.1 ± 10.7 (23 to 69)
Clinical type of MMD	
ischemic	32 (32.3%)
hemorrhagic	26 (26.3%)
ischemic to hemorrhagic transformation	5 (5.1%)
others or unknown	36 (36.4%)
Number of deliveries by each patient	
one	23 (23.2%)
two	54 (54.5%)
three	18 (18.2%)
more	4 (4.0%)
Delivery method	
vaginal delivery	183 (90.6%)
natural labor	182
painless labor	1
caesarean section	19 (9.4%)
scheduled	9
emergent	10
Cerebral events during delivery and puerperium	
yes	4 (2.0%)
vaginal delivery	
syncope during delivery	1
syncope during puerperium	1
TIA during puerperium	2
no	188 (93.1%)
unknown	10 (5.0%)
Bypass surgery after childbirth	
yes	58 (58.6%)
no	37 (37.4%)
unknown	4 (4.0%)

MMD: moyamoya disease, TIA: transient ischemic attack.

viewed with careful consideration for these biases.

This survey revealed that the incidence of the serious perinatal neurological complications is low when MMD has been diagnosed and treated previously. The one case of intracerebral hemorrhage during the gestational period, however, indicates that this group still has a risk of devastating perinatal stroke. In general, pregnancy induces various physiological changes including hypercoagulability, pregnancy-induced hypertension, and eclampsia.[4,14] Accordingly, intracranial ischemic and hemorrhagic attacks are believed to increase in pregnancy.[5,17]

In MMD, an EC-IC bypass has been reported to apparently improve hemodynamic ischemia,[10,11] so it is possible that previous surgical treatments serve to protect against perinatal ischemic stroke to some extent. However, neither positive nor negative effect of EC-IC bypass on the pregnancy and delivery with MMD was proved in this survey. As for intracranial hemorrhage, the preventive effect of an EC-IC bypass remains totally unproven[3,18] and is now under examination in the Japan Adult Moyamoya Trial, which is a randomized controlled trial to study the effect of EC-IC bypass surgery on hemorrhagic MMD.[9]

Scheduled caesarean section was employed in over two-thirds of the patients already diagnosed with MMD, and no serious events were noted during delivery. This selection could be the result of an obstetrician's decision to avoid hyperventilation and excessive elevation of blood pressure during natural labor. However, the present study detected no serious stroke during vaginal delivery. Therefore, there seems to be no evidence that vaginal delivery should be avoided in cases of MMD. It is notable that painless labor with epidural anesthesia was successfully undertaken in many of the recent cases of vaginal delivery with MMD in Survey I.

At present, there is no definite evidence for the

management of pregnancy with already diagnosed MMD. However, in terms of the perinatal physiological changes and the susceptibility to both ischemic and hemorrhagic stroke in MMD, it is desirable that the cerebral hemodynamic state should be well evaluated before pregnancy, and treated if severely impaired. In addition, extreme hypertension should be corrected during the perinatal period. Caesarean section is a good choice, but painless vaginal delivery can be also considered.

The present study revealed that fatal stroke can occur if a patient with undiagnosed MMD becomes pregnant. Severe disability or death resulted from hemorrhage rather than ischemia, which is the same result as seen in previous reports.[6] This study also identified a case of intracranial hemorrhage just during vaginal delivery. The relationship between perinatal hypertension and hemorrhagic event is unclear, as detailed data on patient blood pressure were not requested in the questionnaire. In addition, the frequency of perinatal stroke cannot be estimated because it is impossible to determine the number of pregnant women with occult, asymptomatic MMD. Realistically, it appears quite difficult to prevent catastrophic perinatal hemorrhagic stroke from moyamoya vessels if MMD remains undiagnosed. The low prevalence of MMD (6.03 per 100,000 Japanese[7]) and much lower in Western countries) does not justify the screening of all young women with magnetic resonance angiography. At present, the course of action seems limited to taking precautions for pregnancy-induced hypertension and making an accurate diagnosis immediately after the onset of stroke, which enables effective treatment in the acute period.

In Survey II, while some minor events occurred with low frequency, no serious event was detected with pregnancy and delivery in patients with undiagnosed MMD. Although this appears curious at first glance, some reasons can be given for this result. In all but two patients, diagnosis of MMD was made after all births had taken place, and it is unclear whether the onset of MMD predated the births and how severely it affected the patients. In addition, Survey II has the above-mentioned inclusion bias that could be caused by the dropping out of catastrophic cases. Therefore, the risk of undiagnosed MMD-associated pregnancy should not be underestimated.

For any pediatric and young-adult female MMD patient, expected pregnancy is a serious issue. The present study has revealed the current situation, but further research is needed regarding selection of the delivery method, the effect of previous bypass surgery on perinatal stroke prevention, and early diagnosis and clinical management following cerebrovascular events in undiagnosed cases. Furthermore, it should be emphasized that greater coordination among obstetricians, neurologists, and neurosurgeons could help female patients with MMD give birth with greater success. The authors strongly hope that practical guidelines for managing MMD-associated pregnancy are established in the near future.

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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-

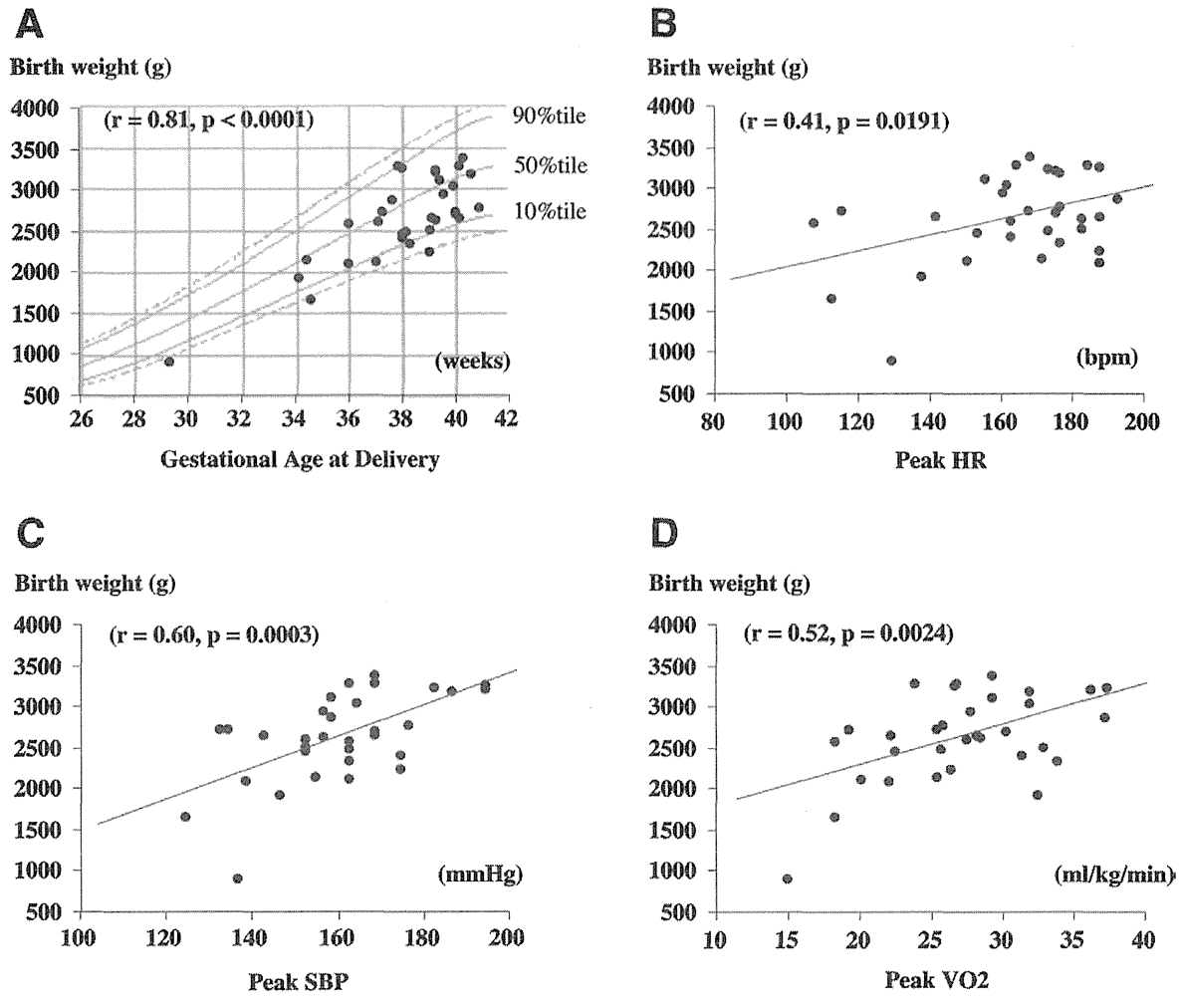

Figure 1. Impact of (**A**) gestational age at delivery; (**B**) maternal peak heart rate (HR); (**C**) peak systolic blood pressure (SBP); and (**D**) peak oxygen uptake ($\dot{V}O_2$) on birth weight.

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

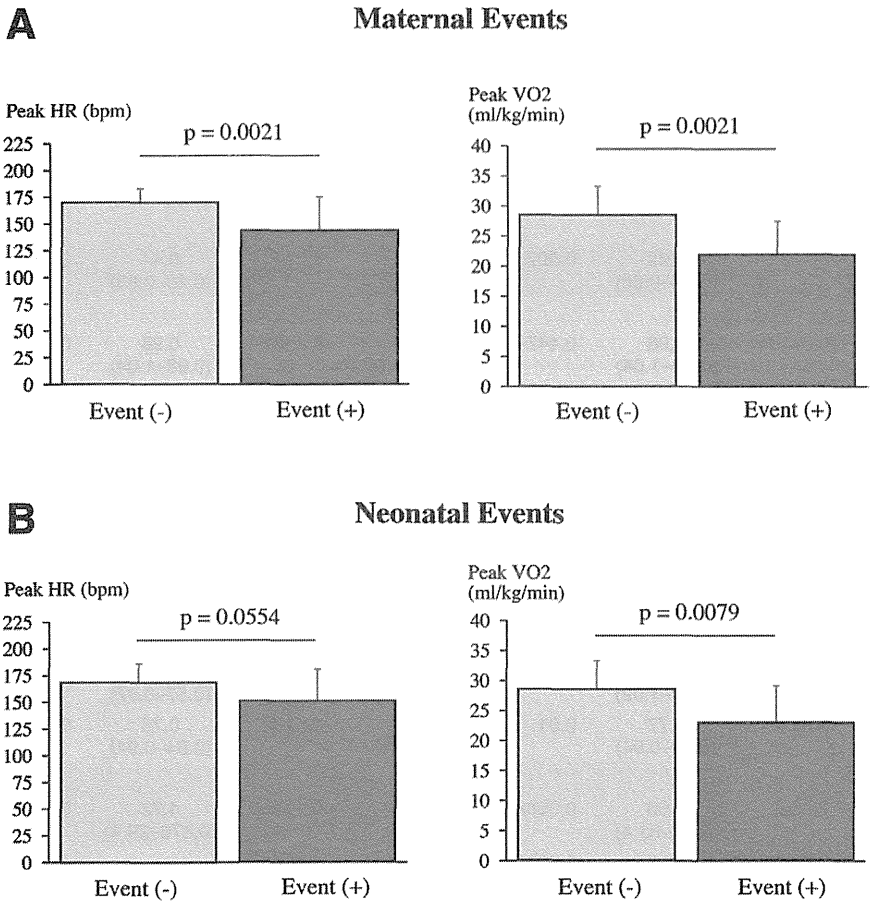

Figure 2. Comparisons of peak heart rate (HR) and peak oxygen uptake ($\dot{V}O_2$) in women with congenital heart disease (A) with and without maternal events and (B) with and without neonatal events.

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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