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. Elevation of the pulmonary arterial pressure correlates with progressive damage to the pulmonary artery. 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. Treatment with drugs such as epoprostenol, sildenafil, and bosentan causes vasodilation of the pulmonary vasculature, which reduces pulmonary resistance and allows survival until about 60 years of age, and lung transplantation can also increase survival.

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. The rate of maternal death in pregnancies complicated by PAH is variously reported to be 20–60%. Predictors of cardiac failure during pregnancy are elevated pulmonary arterial blood pressure (PABP), elevated level of brain natriuretic peptide, and increased size of the right ventricle. There may also be a genetic predisposition.

Most reports of PAH in pregnancy have only examined PABP pre-pregnancy and do not mention changes in New York Heart Score.
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) or mean PABP ≥25 and <40 mmHg by catheterization 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.

**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.
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 PaO2 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 μg · kg–1 · 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 · kg–1 · min–1 and gradually increased in increments of 0.5 ng · kg–1 · min–1 twice weekly until reaching a dose of 7 ng · kg–1 · 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
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. In severe cases, this early rise leads to decompensation and the need for delivery.
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 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, PAPB may have been overestimated, because the mean pulmonary artery pressure has been shown to be significantly overestimated by echocardiography compared with catheterization.38

Conclusions
Among the cases of severe PAH in this study, PAPB 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 PAPB. 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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