measured during 15 pregnancies. Baseline BNP levels did not differ significantly between patients with and without cardiac events. However, peak BNP levels after second trimester were significantly higher in patients with cardiac events, with BNP >100 pg/ml in some of these patients (Figure 3).

Obstetric Events

Two patients were complicated with PIH: 1 had bigeminal premature ventricular contraction, and then BP fall after emergency CS because of PIH, and thus she was also included in the patients with cardiac events (Table 1, patient 1). There were 9 premature deliveries in 8 patients, because of maternal heart failure in 3 cases, premature rupture of membranes in 2, threatened premature labor in 3, and PIH in 1. Therefore, the mean weeks of delivery was shorter in patients with cardiac events than in those without cardiac events, but the difference was not significant. Of the 29 vaginal deliveries, 14 (48.2%) were complicated with postpartum hemorrhage. In contrast, none of the 11 CS deliveries resulted in postpartum hemorrhage. No patient needed a blood transfusion after delivery.

Offspring Events

There were no neonatal deaths. The mean birth weight was 2,665 g and was significantly lower for offspring of patients with cardiac events (Table 2). Two neonates (5.0%) were SGA, including 1 whose mother smoked during pregnancy and 1 whose mother took β-blockers for her history of NSVT; 2 had TOF, 1 had VSD, and 1 had atrial septal defect. Their 3 mothers had TOF without PA or right aortic arch. No patients were tested for genetic conditions.

Changes in Echocardiographic Parameters

Changes in the mean LVDd, LVDs, %FS, and RVDd during the perinatal period are shown in Figure 4. Mean RVDd was 26.7±6.9 mm within 1 year before pregnancy to the first trimester, 27.7±8.9 mm in the second and third trimester, 28.2±10.1 mm after delivery to 1 month postpartum, and 29.6±10.2 mm at 6 months to 1 year after delivery. RVDd at 6 months to 1 year after delivery became significantly greater than that within 1 year before pregnancy to the first trimester. Right ventricular size was able to graded retrospectively in 24 pregnancies and the changes after each pregnancy are shown in Figure 5. Right heart dilatation tended not to recover after pregnancy and to progress with each pregnancy.

Discussion

Our data suggest that most pregnancies in patients with repaired TOF have a favorable outcome, which is compatible with previous reports. Rates of 7–12% have been reported for maternal cardiac events during pregnancy after repaired TOF,[1,2,10–12] and the rate in this study was 17.5%. The reasons of our higher rate of maternal cardiac events may be (1) inclusion of patients with PA and/or MAPCA in the study and (2) the hospital is a referral hospital. Left ventricular dysfunction, severe pulmonary hypertension, decreased subpulmonary ventricular ejection fraction and/or severe PR,[4] use of cardiac medication pre-pregnancy, history of arrhythmia, and prior pulmonary valve replacement[10] have been proposed as predictors of maternal cardiac events during pregnancy. In our study, the predictors of maternal cardiac events were a history of ablation for SVT and large CTR on chest radiograph. This is the first report to show the potential value of chest radiography for predicting maternal cardiac events. Because the number of patients was small, NYHA class ≥II, history of reoperation, use of medication pre-pregnancy, and wider QRS duration on ECG did not reach a significant level as risk factors for cardiac events, we were unable to perform a multivariate analysis of pregnancy-associated risk factors. Moreover, RV dilatation, RVDd, and over-moderate PR on echocardiography were not significantly different between patients with and without cardiac events, whereas CTR reflecting an enlarged right heart was significantly different. We have to consider that the efficacy of echocardiography was not adequate to assess the right heart. A further study is required to investigate these factors.

Management of patients late after repair of TOF has recently focused on the risk of arrhythmia and sudden cardiac death.[13] A Japanese multicenter study of the incidence, manifestation and management of arrhythmia in congenital heart disease during pregnancy found that SVT tended to require antiarrhythmic agents more frequently than ventricular arrhythmia.[14] The current study results clearly show the importance of a prior history of SVT in the evaluation of the risk of pregnancy. PR and progressive dilation of the RV are closely related to SVT and sudden death.[15] Moreover, heart rate variability, which is a significant marker of autonomic nervous function and may predict tachyarrhythmia, may be significantly impaired in pregnant women after repair of congenital heart disease.[16] An arrhythmogenic effect could cause significant hemodynamic compromise in both the mother and fetus in women with repaired TOF with subclinical LV intolerance and RV dilation during pregnancy.[17,18] Therefore, arrhythmia and an enlarged RV should be viewed with particular caution in the pregnancy management of these women.

BNP is useful biomarker for the assessment of congestive heart failure in congenital heart disease, as well as other heart diseases.[19] Tanous et al measured the BNP levels in 66 women with heart disease and found that those with events during pregnancy (n=8) had BNP >100 pg/ml, whereas no women with BNP ≤100 pg/ml had adverse events (negative predictive value: 100%).[20] In our study, in which we followed BNP levels in 15 patients, several of those with cardiac events showed a peak BNP level ≤100 pg/ml. BNP levels at baseline did not predict cardiac events, and the timing of the examination of BNP level after second trimester was similar to the timing for the manifestation of heart failure. Thus, we consider BNP levels not as a predictor of heart failure, but as a useful marker to identify and to manage these obstetric patients.

Ventricular size and function assessed by cardiac magnetic resonance imaging (MRI) are good predictors for major adverse clinical outcomes in patients late after repair of TOF.[21] Because the current study showed that RVDd on routine echocardiographic examination was not an excellent predictor of cardiac events, MRI may be more applicable for screening to assess the risk of pregnancy in severely affected patients.

Japanese guidelines for the indication and management of pregnancy and delivery in women with heart disease recommend the use of antibiotic prophylaxis at the time of delivery for patients with repaired cyanotic heart diseases, including TOF. All patients in our study received antibiotic prophylaxis against endocarditis, and there was no occurrence of endocarditis. The incidence of PIH was 5%, which is similar to that in the Japanese general population (4%).[22] Because one of the patients with PIH had a BP fall from a bigeminal pulse, obstetric events such as PIH may cause fetomaternal morbidity in patients with repaired TOF to a greater extent than in the general population.

In our study population, postpartum hemorrhage occurred in approximately half of the women after vaginal delivery, which is a much higher rate than the 8.8% in a previous report.[11]

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.

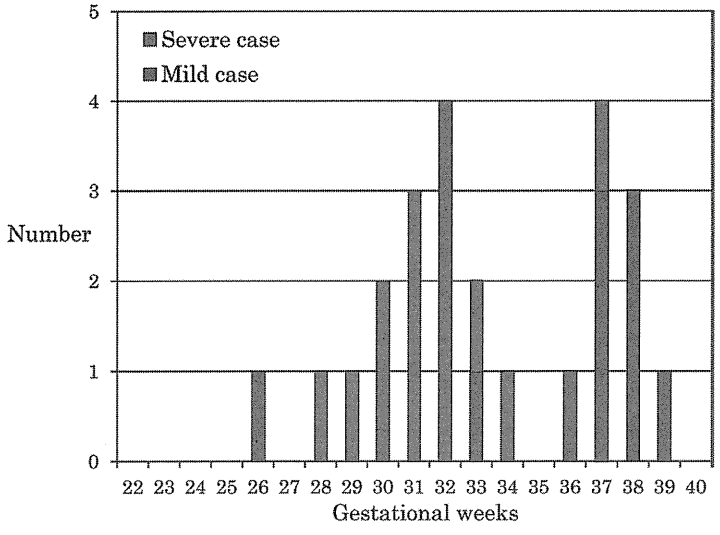

Figure 1. Week of delivery in pregnancies complicated with pulmonary arterial hypertension (PAH). Patients with mild PAH mostly delivered at term, whereas those with severe PAH had earlier deliveries.

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

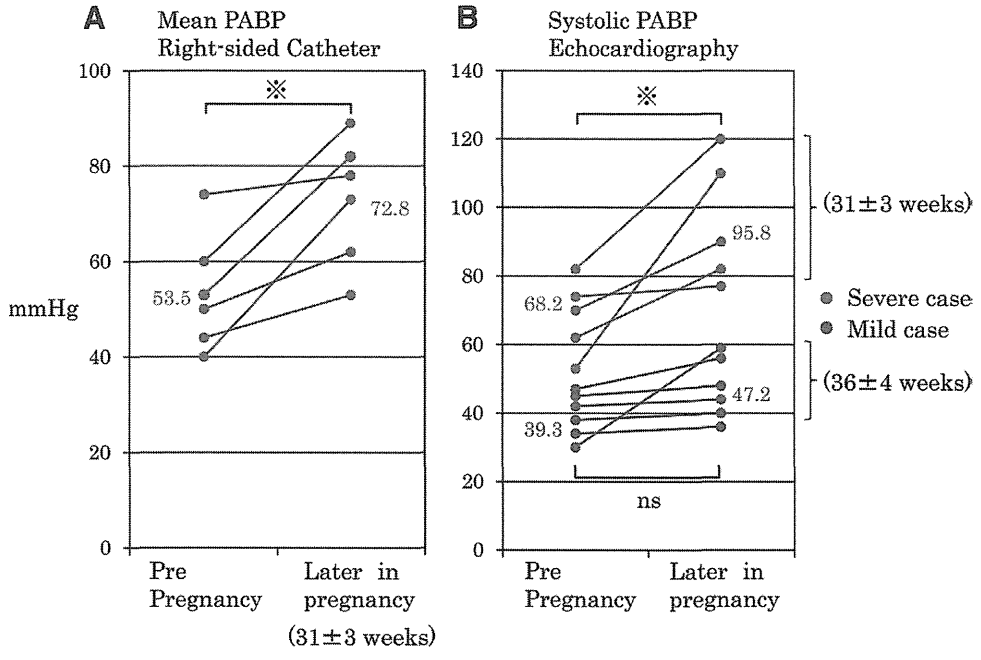

Figure 2. Changes in PABP during pregnancy. (A) Change in the mean PABP measured by a pulmonary cardiac catheter. (B) Change in the systolic PABP measured by echocardiography. Patients with severe PAH showed a significant increase in PABP later in pregnancy. PABP, pulmonary arterial blood pressure; PAH,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

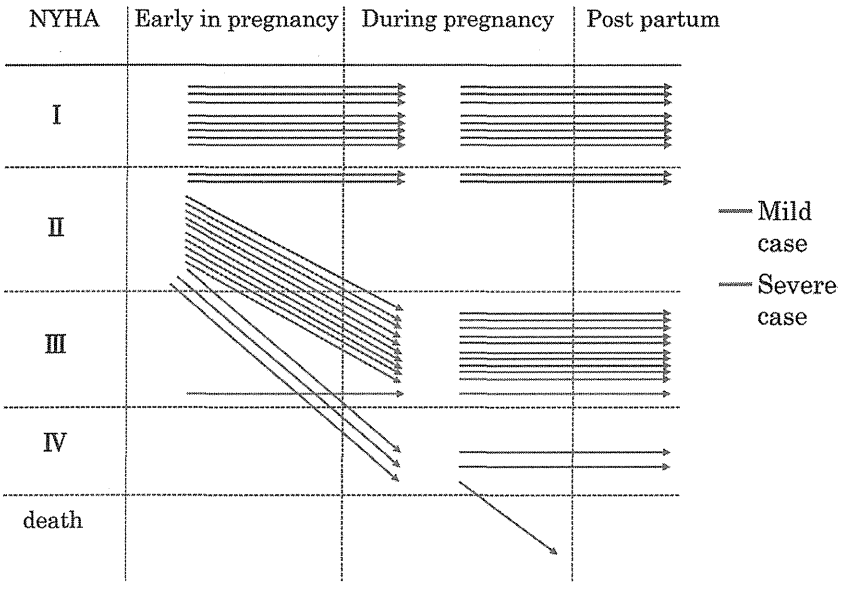

Figure 3. Changes in the New York Heart Association classification over the course of pregnancy.

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.

Acknowledgment

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Disclosure

None of the authors has a conflict of interest to disclose. Financial support was from institutional sources only.

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Case report

Fatal amniotic fluid embolism with typical pathohistological, histochemical and clinical features

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ABSTRACT

Despite the decrease in maternal mortality rate, amniotic fluid embolism (AFE) is still one of the most feared complications of pregnancy due to the high rate of mortality in Japan. The authors present a fatal case of a healthy 39-year-old woman who died during delivery after a normal 40-week second pregnancy. Shortly after the arrival at hospital, an abrupt drop of foetal heart rate was observed, followed by deterioration of consciousness and cardiac arrest of the patient. Prompt cardiopulmonary resuscitation (CPR) was performed but the patient died about an hour and a half after her arrival at hospital. Forensic autopsy confirmed the pathohistological diagnosis of amniotic fluid embolism supported by histochemical analysis results and excluded other possible causes of death. This paper stresses the fundamental importance of autopsy in an unexpected maternal death in conjunction with the significance of data accumulation on maternal death.

1. Introduction

Despite earlier recognition and aggressive treatment, morbidity and mortality rates of amniotic fluid embolism (AFE) remain high. An estimated 5–15% of all maternal deaths in Western countries are due to AFE [1]. The reported maternal mortality rates for AFE range from 37% to over 80%, with one report stating that 25–50% of deaths occur within the first hour of diagnosis [2–4]. Diagnosis of AFE has historically been based on autopsy, revealing amniotic components in maternal pulmonary vasculature. Some recent studies introduced zinc coproporphyrin I (ZnCP-I) and sialyl-Tn (STN), both characteristic components in meconium, as less invasive, diagnostic markers for AFE [5,6]. Presented in this paper is a fatal AFE case in which the typical features were observed in pathohistological, histochemical and clinical findings.

2. Case history

The patient was a 39-year-old multiparous woman without any medical history or eventful course of pregnancy at 40-week gestation. She had no known allergies and was not taking any medication. Shortly after the membrane rupture at home, she was brought to the labour and delivery unit of the hospital by her husband's car, in active labour. Her cervix was dilated 4 cm and contraction occurred every 1.5 min on admission. Although the foetal heart rate (FHR) was 140–160 bpm, meconium staining was already observed at this stage. About 12 min later the FHR dropped to less than 120 bpm, and it became undetectable by a few minutes after the initial drop. An intravenous infusion of tocolytic agent was started to weaken labour pains, but the patient deteriorated, becoming unconscious, displaying the signs of cardiovascular collapse. Cardiopulmonary resuscitation (CPR) was begun immediately but the patient was pronounced dead about an hour and a half after her arrival at hospital. Because of the abrupt onset of symptoms and intensive CPR, an emergency caesarian section could not be carried out to deliver the foetus. The estimated blood loss was very little.

3. Autopsy findings

Forensic autopsy was performed approximately 18 h postmortem. The decedent was 162 cm in height and weighed 63 kg. No significant findings at external examination of body were present. All organs were congested. The weights of lungs were 442 g left and 535 g right, both strongly oedematous. The heart was of normal size, weighing 336 g, and the coronary arteries were free of atherosclerosis. No clots were found in the heart blood and a number of petechiae were seen in bilateral palpebral conjunctiva and epiglottis. A male foetus without remarkable anomaly was in

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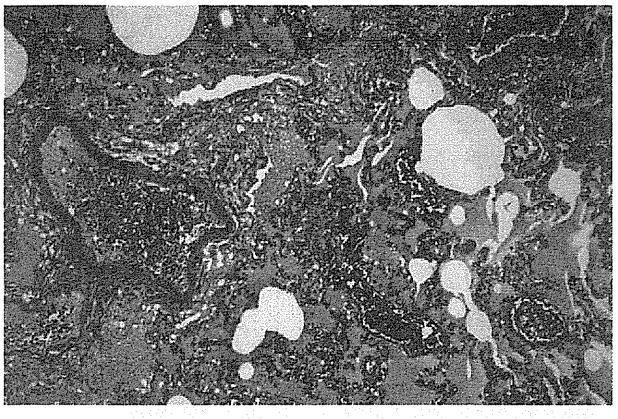

Fig. 1. Pathohistological section of the lung: blood congestion in capillaries (haematoxylin-and-eosin stain, original magnification 100×).

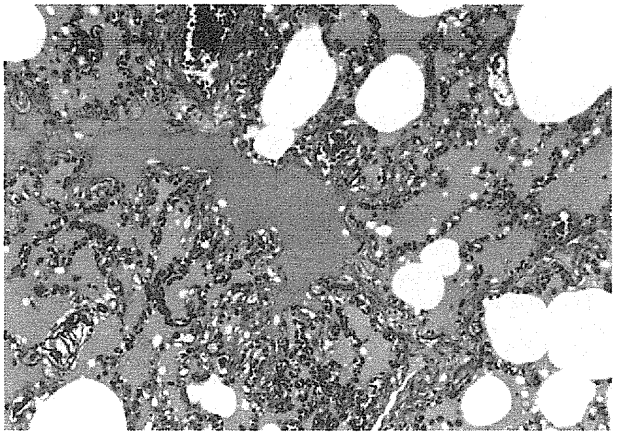

Fig. 3. Pathohistological section of the lung: blood congestion in capillaries (Azan stain, original magnification 100×).

the uterus, weighing 3800 g. The placenta was intact, and the umbilical cord was also normal. A small tear was observed on the posterior wall of cervix. Biological sample from heart blood was reserved but no urine could be obtained for toxicological investigation. Microscopic examination revealed extensive blood congestion in the pulmonary vasculature and microthromboemboli in the uterine microvasculature by haematoxylin-and-eosin and azan staining (Figs. 1–4). Furthermore, amniotic components were also detected inside the pulmonary vessels by alcian blue and ZnCP-I staining (Figs. 5 and 6). Immunohistochemical staining for C5a receptor (C5aR) was positive in stromal cells around the pulmonary capillaries and inflammatory cells in alveolus (Fig. 7). No remarkable pathological changes were observed in placenta. Alcohol and drugs were not detected by routine toxicological analysis. Concentrations of ZnCP-I and STN were 72.5 pmol/mL (normal: <1.6 pmol/mL) and 2630 U/mL (normal: <45 U/mL), respectively. These findings confirmed AFE as cause of death of the patient.

4. Discussion

The Japanese maternal mortality rate (number of maternal deaths per 100,000 live births) has been declining since the 1970s, being stable around 5 for the past decade [7]. Nevertheless, maternal death occurs on occasion, and the most frequently reported causes today include AFE, complications of pregnancy induced hypertension (PIH), pulmonary embolism, haemorrhage and infectious diseases [8–11]. The AFE syndrome was first described by Meyer in 1926 [12] and numerous case reports have been published from various countries to date. Despite its long, worldwide recognition, it is still challenging to save AFE patients due to the fulminant onset of symptoms and rapid clinical course [13].

AFE is generally characterized by a rapidly progressive clinical course with dyspnoea, hypoxaemia, hypotension and foetal bradycardia with subsequent and acute cardiorespiratory collapse, disseminated intravascular coagulopathy (DIC), neurological compromise, maternal and foetal death [14,15]. Since not all of these symptoms are evident on presentation, the differential diagnosis for AFE is broad and includes anaphylactic or haemorrhagic shock, eclampsia, cerebrovascular diseases and pulmonary embolism [16,17]. There are no universal diagnostic criteria to confirm AFE but some countries have their own for the national registry, including the United States of America, the United Kingdom and Japan [2,3,18]. A reliable diagnosis can be made only upon pathohistological examination, by the proof of amniotic fluid elements such as epithelial squamous cells, lanugo hair, and fat from vernix or infantile mucin in the pulmonary vascular bed of the mother [19]. These components of amniotic fluid could be identified in routine haematoxylin-and-eosin-stained sections, but the use of immunohistochemistry permits a more reliable assessment of the dimension of AFE. Special stains that have been used to demonstrate amniotic fluid include alcian blue stain to

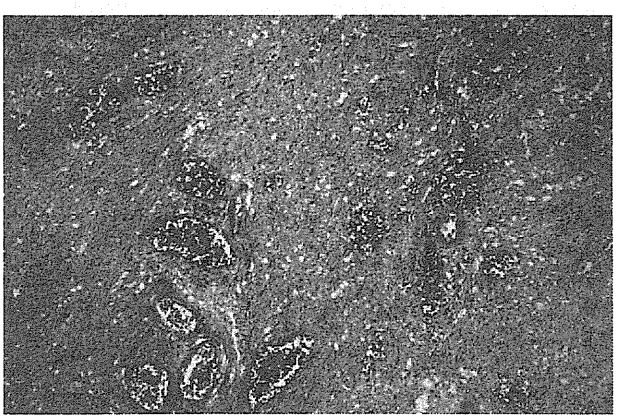

Fig. 2. Pathohistological section of the uterus: emboli in capillaries (haematoxylin-and-eosin stain, original magnification 100×).

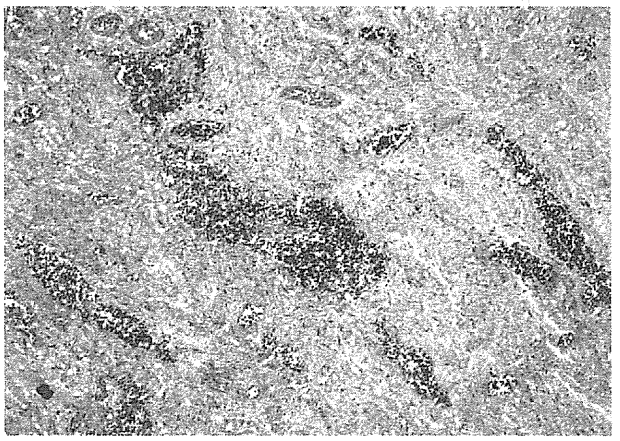

Fig. 4. Pathohistological section of the uterus: emboli in capillaries (Azan stain, original magnification 100×).

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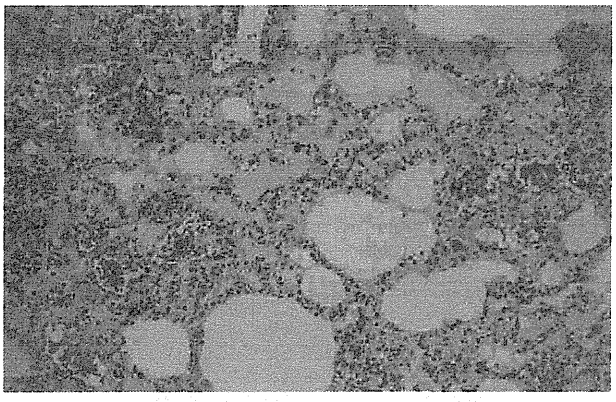

Fig. 5. Pathohistological section of the lung: positive staining in vessels (Alcian blue stain, original magnification 200×).

detect mucin, cytokeratin AE1/AE3 to detect foetal squamous cells, and ZnCP-I stain to detect meconium [20,21]. A recent study by Töro et al. introduced C5aR stain as a helpful technique to prove the complement activation and anaphylatoxin formation [22]. It is suggested that in the presented case that meconium components had entered the maternal circulation, as the interior space of pulmonary vessels and uterine capillaries being positively stained with haematoxylin-and-eosin, alcian blue and ZnCP-I. Additionally, it is likely that an anaphylaxis had been provoked as positive C5aR staining was distinctly observed in the interstitial space between the capillaries of lungs and uterus.

Two main pathophysiological mechanisms have been proposed to be associated with death in AFE. Elements of an embolus may inflict mechanical obstruction of the pulmonary vasculature and cause pulmonary vasospasm, leading to haemodynamic changes [19,23–25]. Moreover, it has been suggested that the amniotic fluid constituents can provoke an anaphylaxis or anaphylactoid reaction which may be fatal depending on the severity [25–27]. The results of histopathological findings in conjunction with immunohistochemical staining suggest that both mechanisms have contributed significantly to the presented case. Furthermore, the marked elevation of AFE diagnostic markers, ZnCP-I and STN, as well as the fulminant clinical course, which had taken only about an hour from the onset of the symptoms until death, support the diagnosis of AFE. The absence of clots in cardiac blood and the presence of petechiae in palpebral conjunctiva and epiglottis are both compatible with the characteristics of sudden death. It could be said that the presented case is typical in pathohistology, histochemistry and symptomatology of AFE.

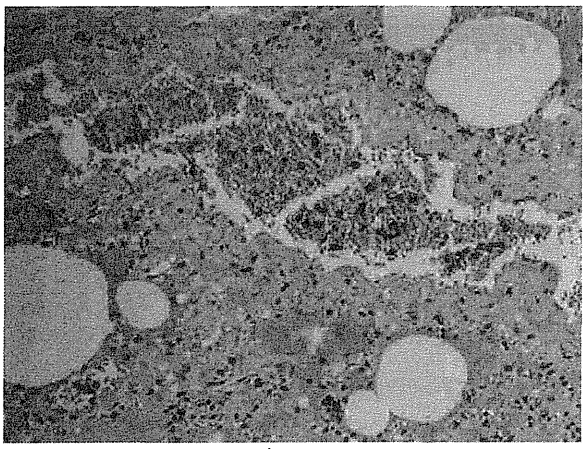

Fig. 6. Pathohistological section of the lung: positive staining in vessels (ZnCP-I stain, original magnification 200×).

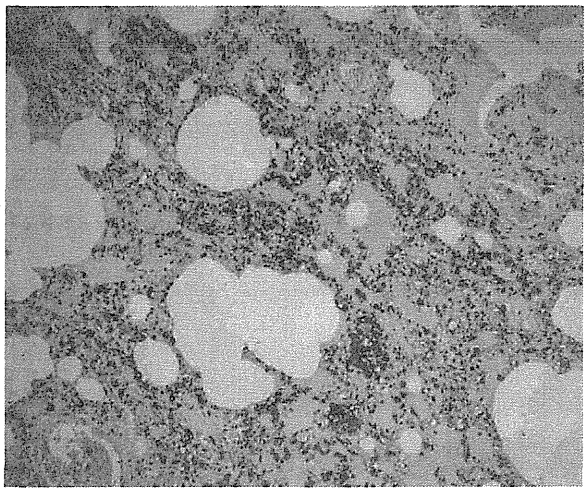

Fig. 7. Pathohistological section of the lung: positive staining in stromal cells around the pulmonary capillaries and inflammatory cells in alveolus (C5a receptor stain, original magnification 200×).

Several possible risk factors for AFE have been identified to date, which include maternal age of 35 years or older, multigravida, polyhydramnios, placental abruption, tumultuous labour or delivery with uterine hypercontractility and caesarean section [5,15,28,29]. Of the patients 41% had a medical history of allergy or autopsy [2]. The increased maternal age, multigravida and uterine hypercontractility could have been predisposing factors in the presented case. It is also speculated that a small tear in the posterior cervix during labour caused amniotic fluid to slowly infiltrate the maternal circulation.

In Japan, it is encouraged to report all maternal mortality cases to the Japan Association of Obstetricians and Gynaecologists, but there is no legal responsibility for physicians to do so. The available data and the conclusions that can be drawn depend on the depth and precision of the cases reported voluntary. Nevertheless, it is speculated that there were 60–70 maternal deaths in Japan in 2010, but only about half of the cases had been brought to either forensic or clinical autopsy [30]. Needless to say, thorough postmortem investigation, including autopsy, is essential for the accurate cause of death determination in any case, and it is possible that AFE would be underestimated in Japan, due to the low autopsy rate. Accumulation of cases nationwide would allow the establishment of wide and reliable database and possibly the identification and standardization of treatments for the diseases associated with maternal death. The elevation of autopsy rate, especially in the maternal death cases, is strongly desired not only from the aspects of forensic science but also of obstetrics and preventive medicine. Whilst on the other hand, it is encouraged for both forensic and clinical pathologists to continuously disclose the information derived from postmortem investigation.

5. Conclusion

Postmortem histopathologic and histochemical analyses further support the clinical diagnosis of AFE. The authors emphasize the significance of postmortem examinations in cases of maternal death, including the cases of suspected AFE.

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Successful Living Donor Liver Transplantation for Fulminant Hepatic Failure That Manifested Immediately After Cesarean Delivery

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A 31-year-old pregnant woman was diagnosed as having acute hepatitis of unknown etiology and conservatively treated. An emergency cesarean delivery was performed 5 days later at 33 weeks and 3 days of gestation because of a gradual deterioration in liver function. Two days after the cesarean delivery, she lost consciousness in the evening (Glasgow coma scale [GCS] = 9) because of hepatic encephalopathy and was diagnosed as having fulminant hepatic failure (FHF). Five days after the cesarean delivery, the patient (blood type B) underwent a successful left lobe with caudate lobe (S1+2+3+4) liver transplantation from her father (blood type AB), an ABO-incompatible donor. At 1 year follow-up, she and her baby are in good medical condition. The drastic deterioration in hepatic function, despite intensive plasmapheresis and continuous hemodiafiltration, during the early postpartum period suggested a possible causative association between the termination of pregnancy and progression of FHF from acute hepatitis of unknown etiology. *ASAIO Journal* 2012; 58:174–176.

Fulminant hepatic failure (FHF) has been reported at various points during pregnancy.[1,2] A gold standard for treatment has not yet been established, especially concerning the timing of termination of pregnancy, because the condition can have serious consequences not only for the mother but also for the fetus.[3] There is limited experience in liver transplantation during pregnancy or the early postpartum period.[4] We here report a case of acute hepatitis that progressed to FHF 2 days after cesarean delivery in the third trimester of pregnancy. Intensive plasmapheresis and continuous hemodiafiltration according to Japanese style of artificial liver support (ALS) did not improve her hepatic coma but gave her a greater chance of undergoing successful living donor transplantation at a different clinical institution located in another prefecture.

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Case Report

A 31-year-old gravida 1 and parous 1 woman became pregnant. Neither the patient nor her family had any history of hepatic disease. At 32 weeks and 6 days of gestation, she complained of epigastric pain and consulted a local outpatient clinic. She was transferred to Hamamatsu University Hospital because of elevated liver enzyme levels. On physical examination, she presented with severe jaundice, a mild fever of 37.8°C, and tachycardia of 116 beats/min, although her blood pressure and urinalysis were normal. Mild tenderness was observed in the right hypochondriac area; however, abdominal ultrasonography of the liver was unremarkable. Laboratory evaluation showed alanine transaminase (ALT) 930 unit/L, aspartate aminotransferase (AST) 1553 unit/L, platelet count 299,000/μl, prothrombin time (PT) (international normalized ratio [INR] 1.01, 97%), blood urea nitrogen (BUN) 6.0 mg/dl, negative serologic tests for viral hepatitis A, B, C, and E, as well as Epstein-Barr (EB), herpes, and cytomegaloviruses. Electric fetal heart rate monitoring showed a reassuring fetal status. She was diagnosed as having acute hepatitis of unknown etiology and conservatively treated.

However, her liver function gradually deteriorated as shown in **Figure 1**, and an emergency cesarean delivery was performed 5 days after admission at 33 weeks and 3 days of gestation. An immature, male baby weighing 2,268 g was born with an Apgar score of 6 (1 minute) and subjected to a resuscitation procedure.

Two days after the cesarean delivery, she lost consciousness in the evening (Glasgow coma scale [GCS] = 9) because of hepatic encephalopathy and was diagnosed as having FHF, *i.e.*, PT (INR 1.86, 30%), BUN 2.3 mg/dl, and ammonia (NH_3) 235 μg/dl. Plasmapheresis and continuous hemodiafiltration were immediately performed in accordance with Japanese style of artificial liver support (ALS)[5] (**Figure 1**).

The ALS did not achieve recovery from coma in the patient, but provided more time for us to assess the indications for liver transplantation according to the Liver Transplantation Guideline published by the Acute Liver Failure Study Group of Japan (*i.e.*, 11 days from onset of hepatitis to hepatic coma, low percentage of PT, total bilirubin level more than 10 mg/dl, low ratio of direct to total bilirubin).[6] She was transferred to Kyoto University Hospital by helicopter 5 days after the cesarean delivery. On the same day, the patient (blood type B) underwent a successful left lobe with caudate lobe (S1+2+3+4) liver transplantation from her father (blood type AB), an ABO-incompatible donor. Rituximab 300 mg was administered during surgery. She regained

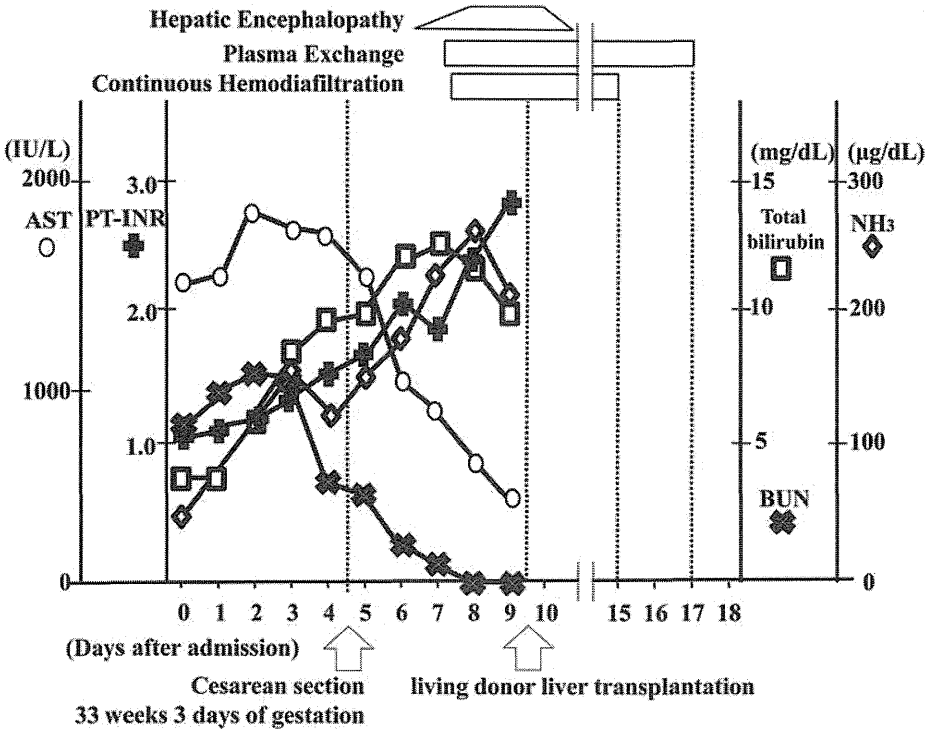

Figure 1. Longitudinal changes of the parameters associated with liver function. AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio.

consciousness 1 day after the operation (**Figure 1**). Plasmapheresis and hemodiafiltration were continued until 8 and 6 days after the operation, respectively (**Figure 1**). Histology showed massive hepatic necrosis. She was discharged 64 days after transplantation. One year on, she and her baby are in good medical condition, although she demonstrated transient ascites 4 months after delivery because of acute cellular rejection.

Discussion

Some cases of FHF during pregnancy are based on diseases unique to pregnancy, such as hemolytic anemia, elevated liver enzymes and low platelet count (HELLP) syndrome, acute fatty liver of pregnancy, and preeclampsia, in which the hepatic dysfunction begins to resolve postpartum.[7,8] Other cases are usually regarded as similar to those seen in nonpregnant women.[9] However, it has been suggested that hepatitis B virus (HBV)-related FHF in pregnancy sometimes improves with delivery to a point suitable for surgical treatment[1,4,10] on modification of the biohumoral substrate[1,4] or stabilization of the viral parameters of hepatic function.[10]

In this case, however, acute hepatitis progressed to FHF 2 days after cesarean delivery (**Figure 1**). The ALS could not improve her coma but effectively reduced total bilirubin levels with a tendency to decrease NH_3 levels (**Figure 1**), which contributed to sustenance of the patient until living donor liver transplantation became available. We cannot deny the possibility that ALS could not remove some toxins.

As far as we know, there have been five case reports, including ours, of FHF rescued by liver transplantation early postpartum during the third trimester of pregnancy (**Figure 1**, **Table 1**).[11–14] These reports suggest that early termination of pregnancy may not always improve FHF. In view of the fact that a better prognosis for newborns is expected in the third trimester of pregnancy than in the second trimester, termination of pregnancy would be one of the therapeutic choices in cases of acute severe deterioration of maternal hepatic function especially in the third trimester. In such situations, it would be worth

Table 1. Reports of Liver Transplantation Soon After Delivery in the Third Trimester of Pregnancy

Reference (year)	Etiology	ALS	Mode of Delivery (w.g.)	Onset of FHF (d.a.d.)	LT (d.a.d.)	Maternal (Fetal) Outcome
Bourliere *et al.*[11]	Drug-induced	NS	CS (30)	1	1	Survived (survived)
Remiszewski *et al.*[12]	AFLP	BT	VD (33)	10	10	Survived (survived)
Gill *et al.*[13]	Drug-induced AFLP	BT	VD (33)	3	3	Survived (fetal death)
Ockner *et al.*[14]	AFLP	BT	CS (37)	1	3	Survived (survived)
This case	FH of unknown etiology	BT and AT	CS (32)	2	5	Survived (survived)

AFLP, acute fatty liver of pregnancy; CS, cesarean section, VD, vaginal delivery; FH, fulminant hepatitis; FHF, fulminant hepatic failure; LT, liver transplantation; w.g., weeks of gestation; d.a.d., days after delivery; ALS, artificial liver support; NS, no statement; BT, before transplantation (no statement after transplantation); and BT and AT, before and after transplantation.

considering a possible manifestation of FHF immediately after delivery, although the exact causative relationship between the onset of FHF and termination of pregnancy is unclear.

The early postpartum period is characterized by a dramatic withdrawal of placental steroid hormones, being associated with enormous changes in almost all maternal physiologic processes, such as cardiovascular, endocrine, immune, nutrient, and energy-metabolic functions.[15] It is plausible that these drastic physiologic changes after delivery might be associated with, at least partly, the acute deterioration of FHF in this case.

Conclusion

In conclusion, we successfully carried out living donor liver transplantation for a patient developing FHF 2 days after cesarean delivery in the third trimester of pregnancy. The drastic deterioration of hepatic function during the early postpartum period suggested that early termination of pregnancy may not always lead to the resolution of FHF.

Author Contributions

YH, HI, AM, and NK contributed toward writing the manuscript; YH, HI, SK, TU, and NK were responsible for the obstetric care of the patient; KS contributed toward image interpretation; and AM and SU performed the liver transplantation.

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Letter to the Editors-in-Chief

The first report of uncontrollable subchorionic and retroplacental haemorrhage inducing preterm labour in complete PAI-1 deficiency in a human

Dear Editors,

Fig. 1

Plasminogen activator inhibitor-1 (PAI-1) is a member of the serine protease inhibitor (SERPIN) superfamily and is the primary physiological regulator of urokinase-type plasminogen activator and tissue-type plasminogen activator [1]. Although a number of studies have indicated that elevated levels of PAI-1 are associated with several pathological states such as arterial thrombotic events [2] and poor prognosis in cancer patients [3], our knowledge of the consequences of PAI-1 deficiency is still limited due to the rarity of this condition. We recently reported a case of genetically identified complete PAI-1 deficiency in a human [4]. The patient showed a tendency for massive bleeding, which was also observed in a PAI-1-deficient patient in a previous report [5].

Genetic alterations that lead to a predisposition for bleeding are associated with clinical complications during pregnancy. The most vivid example of this association is congenital afibrinogenemia and congenital coagulation factor XIII (FXIII) deficiency, which result in genital bleeding and spontaneous miscarriage in the first 6–8 weeks of gestation if left untreated [6,7].

The patient with complete PAI-1 deficiency we described recently [4] fell pregnant 3 times, at the age of 26, 27, and 29 years. Although we were unable to identify the reason for her increased bleeding tendency at the time, we attempted to manage her pregnancies. In this report, we describe the clinical course of these pregnancies. This is the first report describing the clinical course of pregnancies in a completely PAI-1-deficient human.

Case report

The patient was a 47-year-old woman who had experienced multiple episodes of major bleeding, as described previously [4]. The first pregnancy occurred at the age of 26 years. The pregnancy course was uneventful and foetal growth was normal until 16 weeks' gestation. At the end of 16 weeks' gestation, a small amount of genital bleeding was observed, and she was hospitalised. Her prothrombin time, activated partial thromboplastin time, and plasma fibrinogen levels were within the normal limits (13.0s, 34.9s, and 165 mg/dL, respectively); however, plasma D-dimer levels were slightly elevated (2.4 μg/mL, a normal range is<0.5 μg/mL). Fresh frozen plasma (FFP) was injected twice a week to control the genital bleeding and maintain her pregnancy. Plasma D-dimer levels were suddenly elevated at the end of 18 weeks' gestation, and massive genital bleeding was observed at 19 weeks' gestation. Although a retro-placental echo-free space was not observed, the foetal heart beat had stopped and the cervix of the patient's uterus was found to be fully opened. Plasma D-dimer levels were decreased and genital bleeding had stopped 1 week after removal of the foetus (220 g). The aborted foetus was male and his appearance was normal.

The second pregnancy occurred at the age of 27 years. Immediately after the confirmation of pregnancy at 7 weeks' gestation, she was admitted to our hospital. Although a small amount of genital bleeding was observed at 8 weeks' gestation, this pregnancy was uneventful until 11 weeks' gestation. A continuous but small amount of genital bleeding was observed after the end of the 11th week of gestation; therefore, FFP administration 2–3 times per week was initiated. Although the genital bleeding had stopped at 20 weeks' gestation, FFP administration was continued to stabilise the pregnancy. Because plasma D-dimer levels were slightly elevated at 28 weeks' gestation, the frequency of FFP administration was changed from 2–3 times per week to once a day. However, plasma D-dimer levels continued to be elevated, reaching 128 μg/mL at 32 weeks' gestation, accompanied by uncontrollable uterine contractions with grade 2 placental abruption diagnosed by ultrasonography. Hence, an emergency caesarean section was carried out; the patient delivered a live 1736-g female infant. Perioperative blood loss amounted to 4500 mL, which was controlled by the administration of 42 U FFP.

The third pregnancy occurred at the age of 29 years. Based on the successful management of the previous pregnancy, the patient was hospitalised at 8 weeks' gestation and continuous FFP administration was initiated. FFP was administered twice a week until 16 weeks' gestation, which was gradually increased until 19 weeks' gestation. After 20 weeks' gestation, FFP administration was performed every day. Although the pregnancy was stabilised until 24 weeks' gestation, plasma D-dimer levels were continuously elevated from 25 weeks' gestation, reaching 57.9 μg/mL at 27 weeks' gestation, accompanied by uncontrollable uterine contractions with placental abruption. An emergency caesarean section was again carried out; the patient delivered a live 978-g female infant. Perioperative blood loss amounted to 1037 mL. In both cases, the blood loss was calculated to measure the weight of the blood absorbed by gauze and/or sanitary napkins. These daughters were healthy and did not have any symptoms.

Discussion

We have intensively investigated the relationship between coagulation disorders and spontaneous miscarriage. Indeed, we have previously reported that fibrinogen and FXIII are critical factors for stabilising placental attachment to the uterus [6,8]. Pregnancies in patients with both afibrinogenemia and congenital FXIII deficiency result in spontaneous miscarriage at around 7–8 weeks of gestation in humans [6,8]. We have successfully managed such pregnancies with suitable supplemental therapies [9,10].

Coagulation factor deficiencies are very rare, and thus, it is difficult to investigate the mechanisms underlying the associated increased bleeding tendency during pregnancy. In order to overcome this difficulty, fibrinogen-deficient mice [11,12] and FXIII-deficient mice [13] were generated by gene manipulation methods. Afibrinogenemia in

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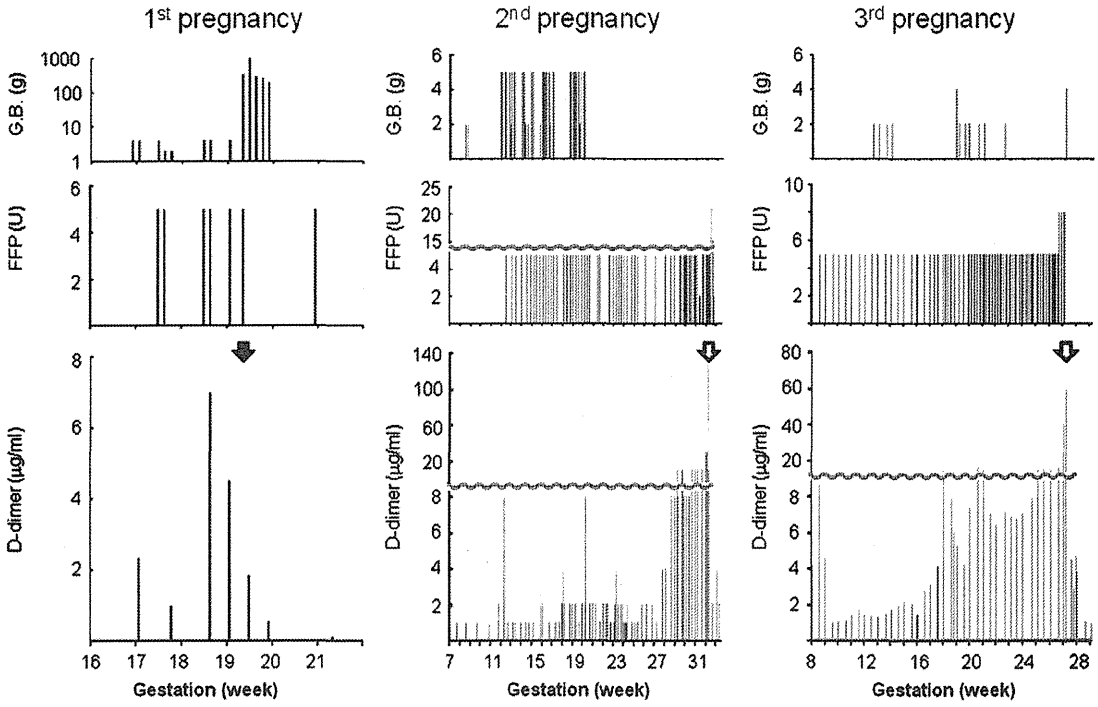

Fig. 1. The amount of genital bleeding (GB) (g), fresh frozen plasma (FFP) administered (U: 1 U = plasma separated from 200 mL blood), and plasma D-dimmer levels (μg/mL) observed during the course of the patient's 3 pregnancies. The black arrow indicates the day of the miscarriage. The white arrows indicate when the emergency caesarean sections were performed.

mice was found always to result in spontaneous miscarriage [11], but supplemental fibrinogen could rescue these pregnancies [14]. Spontaneous miscarriages were also observed in FXIII-deficient mice [13]. It must be emphasised, however, that not all of the latter mice showed spontaneous miscarriage, and some normal deliveries were observed. These results suggest that further stabilisation of the fibrin matrix in the fibrinoid layer through crosslinking is preferable, but not essential, for a successful pregnancy in mice. These mice are reliable tools for mimicking human diseases; however, it should be noted that some phenotypical discrepancies do exist between humans and mice even when the same genes are deficient.

In the case of complete PAI-1 deficiency, such discrepancies must be further emphasised. Several reports have described that PAI-1 deficiency leads to bleeding diathesis in humans [15]. However, *Serpine1*$^{-/-}$ mice do not show an increase in bleeding tendency [16], and pregnancies in *Serpine1*-deficient mice were found to be completely uneventful. Indeed, deficient male and female mice are being successfully crossbred to maintain *Serpine1*-deficient colonies. On the other hand, the PAI-1-deficient patient reported herein experienced a spontaneous miscarriage due to massive genital bleeding in the 19th week of her first pregnancy. The genital bleeding began in the 16th week of gestation in the absence of supplemental therapies. When comparing PAI-1 deficiency to congenital afibrinogenemia or FXIII deficiency, it becomes clear that genital bleeding begins much later in complete PAI-1 deficiency. In this case, the patient was given 5 U FFP twice a week after genital bleeding was observed. Each administration could theoretically restore approximately 20% of plasma coagulation factors. Indeed, the concentration of PAI-1 in FFP is almost equivalent to that in fresh plasma [17]. However, the half-life of active PAI-1 in vivo is extremely short (about 6 min) [18]. Therefore, the supplementation of PAI-1 via FFP administration did not appear to fulfil the demand for this factor in this pregnancy, resulting in further genital bleeding and miscarriage. The next 2 pregnancies were successfully maintained by the administration of large amounts of FFP; however, despite this increased treatment, it was very difficult to maintain the pregnancies in the 2nd trimester. The demand for PAI-1 during pregnancy appears to continuously increase, but the amount of PAI-1 that can be delivered via FFP administration is limited. Thus, the fragile supply and demand balance was broken midway through the last 2 pregnancies. Indeed, uncontrollable uterine contractions with elevated plasma D-dimer levels, which indicate massive genital bleeding in the uterus, especially the foeto-maternal surface, triggered preterm labour, resulting in the need for caesarean section for safe delivery. These findings indicate that PAI-1 plays an important role in the maintenance of pregnancy in humans. It may therefore be assumed that low levels of PAI-1 may be a risk factor for spontaneous miscarriage and/or preterm labour in humans.

In summary, our findings show the following: (1) FFP administration is not sufficient for rescuing PAI-1-deficient patients from massive bleeding after 25 weeks' gestation, and purified and/or recombinant PAI-1 is therefore necessary. (2) Such interventions are not required in mice, because of a lack of such a bleeding tendency. Based on studies in *Serpine1*$^{-/-}$ mice, several PAI-1 inhibitors have been synthesised for use in clinical trials to treat thrombotic events such as stroke and coronary ischaemia. However, the phenotypical manifestations of PAI-1 deficiency in humans are quite different to those in mice. Thus, care must be taken when translating research findings from the mouse to the human in this field.

Authors' roles

Contributions: T.I., K.N., and K.U. analysed results and made the figure; T.K., N.K., and T.T. took clinical care of the proband and her family; T.I. and N.K. designed the research and wrote the paper.

Conflict of Interest Statement

The authors declare no competing financial interests.

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特集 知っておきたい重症産褥合併症

8. 周産期心筋症(産褥心筋症)

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要旨

周産期心筋症(産褥心筋症)は，心疾患の既往がない女性が，妊娠末期から産褥期に突然原因不明の心不全をきたし，心エコーにて拡張型心筋症様の心拡大および左室収縮能の著しい低下所見を認める疾患であり，母体死亡の原因疾患の一つである．これまで，わが国において発生状況や経過などの把握がなされていなかったため，2007年1月から2008年12月の2年間に発症した周産期心筋症についての全国調査が行われた．本稿では，この全国調査結果をもとに，周産期心筋症について解説する．

KeyWords 心筋症，妊娠，心不全

診断基準

周産期心筋症の診断基準はいまだ確立されてはいないが，下記の基準が用いられることが多い[1)2)]．

①分娩前1カ月から分娩後5カ月に発症した心不全
②心不全の基礎疾患がない
③分娩前1カ月以前に心疾患の既往がない
④心エコーにて，左室機能低下所見を認める
左室駆出率(LVEF：left ventricular ejection fraction)＜45-55％
左室短縮率(％FS：percent fractioning shortening)＜30％

ただし，妊娠初期に発症した症例と末期に発症した症例の臨床所見に差がないことが報告された[3)]ため，①の発症時期については，妊娠初期から分娩後5カ月とされることもある．

原因

周産期心筋症の原因は，現在のところ明らかでないが，ウイルス感染，自己免疫機序，ホルモン異常，遺伝子異常，中毒などが原因である可能性が指摘されている[4)]．最近，酸化ストレスによって生じる異型プロラクチンが，心筋を障害し，心筋症を発生させると報告され[5)]周産期心筋症の原因として注目されている．

治療

一般的な急性心不全に準じて行う．重症例では大動脈バルーンパンピングや経皮的心肺補助

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