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Original Article

Maternal and fetal outcomes in pregnancy complicated with Eisenmenger syndrome

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ABSTRACT

Objective: The goal of the study was to clarify the risk factors for pregnancy complicated with Eisenmenger syndrome (ES).

Materials and methods: A retrospective study was performed in 15 patients with ES who were managed throughout pregnancy at one institution from 1982 to 2013. Cases associated with congenital heart diseases other than atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA) were excluded.

Results: The congenital heart diseases in ES included ASD (n = 3), VSD (n = 9), and PDA (n = 3). Ten women chose termination and 5 continued with their pregnancies. In the 5 continuation cases (PDA 1, VSD 4), worsening of cyanosis, exertional fatigue and dyspnea appeared between 25 and 30 weeks gestation and cesarean section was performed at 30 (28–33) weeks. LVEF, PaO_2, and SpO_2 decreased and heart rate increased significantly from before pregnancy to 25–30 weeks gestation. From before to during the pregnancy, there were no significant changes in mean PABP or pulmonary vascular resistance (PVR) in four cases with data (582–592, 885 to 868, 1280 to 1291, 1476–1522 dyn × s/cm^2). PVR at conception had a negative relationship with delivery weeks. NYHA classes before, during and 1 year after pregnancy were II, III and II. In one recent case, epoprostenol and tadalafil were administered during pregnancy.

Conclusions: Pregnancy with ES has a high risk due to hypooxygenation, cyanosis, and cardiac failure, which can appear as common complications as early as the 2nd trimester. Early interventions with meticulous care are required for these complications during pregnancy and delivery.

Introduction

Pregnancy is a life-threatening risk in patients with Eisenmenger syndrome (ES) due to thrombosis, sudden death, congestive heart failure, and arrhythmia. These risks of cardiac failure increase during pregnancy and after delivery, and sudden cardiac arrest may occur during Cesarean section or soon after birth [1–4]. The volume load in pregnancy poses an additional burden for the already-compromised right ventricle. The fall in systemic vascular resistance (SVR) during pregnancy can increase right to left shunting and exaggerate cyanosis, which can cause abortion, preterm birth, or intrauterine fetal growth retardation.

While pulmonary vasodilator therapy may improve the outcome for mothers with ES, the condition may still be fatal for many; furthermore, there may be a publication bias as only cases with the best outcomes are reported [5]. Nonetheless, successful outcomes have been reported with both vaginal delivery and Cesarean section. Intravenous prostacyclin (epoprostenol) may be helpful, and sildenafil and tadalafil have also been used. Inhaled nitric oxide may also be useful around the time of delivery. All of

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these therapies are aimed at reducing pulmonary vascular resistance (PVR) and thereby stabilizing right ventricular (RV) function.

Management of ES-complicated pregnancy requires evaluation of cardiac function, oxygenation, cardiac failure, PVR by a right heart catheter, and fetal morbidity and mortality. The PVR reflects the change of occlusive pathophysiology. However, there have been few reports of such data or of the prognosis following pregnancy in patients with ES. Therefore, we investigated the maternal and fetal prognoses in pregnancies complicated with ES, with the aim of finding risk factors for the outcome of pregnancy in patients with this condition.

Patients and methods

Mortality and morbidity in maternal outcomes of pregnancy with ES were studied based on a review of charts for 15 cases managed at the Department of Perinatology and Gynecology at the National Cerebral Cardiovascular Center from January 1982 to December 2013. Our database was limited to institutional medical records. ES is defined as a congenital heart disease characterized by left to right shunt, which induces advanced pulmonary vascular disease and pulmonary arterial hypertension (PAH), and finally results in reversal of the direction of shunting and development of cyanosis [6]. Those who met this definition and those who had right to left or bidirectional shunt through a defect on echocardiography or catheterization were diagnosed with ES. Cases associated with congenital heart diseases other than ASD, VSD, and PDA were excluded. Cardiac function was evaluated by echocardiography before pregnancy, at conception, once every four weeks thereafter, and postpartum. The cardiothoracic ratio (CTR) was measured on chest X-rays taken during each trimester and postpartum. A Holter electrocardiogram was also recorded in each trimester and postpartum. The results and noncardiac complications and morbidity were discussed in a weekly multidisciplinary team conference of obstetricians, pediatric cardiologists, cardiologists, neonatologists, anesthesiologists, and nurses. Cesarean section was selected for maternal indications. The NYHA classification was used to evaluate the cardiac status [7].

Cardiac function was evaluated before pregnancy and after delivery using cardiac catheterization and echocardiography in 13 cases and echocardiography alone in 2 cases. Pulmonary arterial blood pressure (PABP) was measured by right heart catheterization. The systolic pressure gradient of tricuspid valve regurgitation on echocardiography was measured during pregnancy. Diuretics were administered during pregnancy when a patient showed worsening of edema or congestive cardiac failure. Unfractionated heparin (10,000 units per day) was administered during pregnancy and after delivery for prophylaxis of thrombosis. Antiplatelet drugs were not used during pregnancy. In the most recent case, the patient received pulmonary PAH targeted therapy. Echocardiography measurements were based on a report from the ACC/AHA guidelines [8]. Resting heart rate (HR), blood pressure (BP), systemic pulse oximetry (SpO_2), and PaO_2 were measured in a sitting position.

Heart failure is defined as a pathophysiological state in which the heart, due to an abnormality of cardiac function, fails to pump blood at a rate commensurate with the requirements of metabolizing tissues, with symptoms of dyspnea, exertional fatigue, leg swelling, persistent cough, and bloody phlegm [9,10]. All neonates underwent echocardiography to evaluate any associated congenital heart diseases.

Statistical analysis

For continuous variables, a Student t test was performed for analysis of normally distributed data; otherwise a Wilcoxon test was used. Categorical variables were compared using chi-square test and Fisher exact test. All statistical analyses were performed using JMP 10 (SAS Institute, Cary, NC). $P < 0.05$ was considered significant.

Ethics statement

The study was approved by the ethics board of the National Cerebral and Cardiovascular Center, Osaka, Japan, and was conducted according to the principles of the Declaration of Helsinki. Informed consent was not obtained from patients or their families because the study was based on medical records and information that were anonymized prior to analysis.

Results

The characteristics of the 15 patients with ES are shown in Table 1. These cases included 3 with ASD, 9 with VSD, and 3 with PDA. Ten patients (3 ASD, 5 VSD, 2 PDA) selected termination of pregnancy, while 5 (4 VSD, 1 PDA) chose to continue with pregnancy after counseling regarding the maternal and fetal prognoses.

PaO_2 and SpO_2 during pregnancy

Median [interquartile range] PaO_2 in the 5 continuation cases decreased significantly from 63 [57–65] mmHg before or early in

Table 1
Patient characteristics in cases with miscarriage or delivery.

		Miscarriage (n = 10)	Delivery (n = 5)	P value
Shunt location	ASD	3	0	ns
	VSD	5	4	
	PDA	2	1	
Maternal age		29.9 ± 4.7	33.0 ± 4.4	ns
Nulliparous/Multiparous		5/5	5/0	ns
Weeks at termination		10.0 ± 1.2	30.4 ± 1.8	–
Birth weight (g)[a]		–	1218 ± 182	–
Small for gestational age[a]		–	3	–
Vaginal/Cesarean section delivery		10/0	0/5	–
Regional/General anesthesia		2/8	0/5	ns
Body mass index (kg/m^2)		21.2 ± 1.5	22.1 ± 1.8	ns
Diabetes mellitus		0	0	–
Hypertension		0	0	–
Smoking		0	0	–

Maternal age, weeks at termination, birth weight, and body mass index are shown as means ± SD and were analyzed by Student t-test. Other data were analyzed by Chi-square test and Fisher exact test. $P < 0.05$ indicates a significant difference.

[a] Only delivery cases. ASD: Atrial septal defect, VSD: Ventricular septal defect, PDA: Patent ductus arteriosus; ns, not significant.

Table 2
Vital signs, SpO_2, PaO_2, and echocardiographic findings in cases with miscarriage or delivery after different gestational periods.

Parameter	Miscarriage (n = 10)	Delivery (n = 5)		P value
	10 weeks	10 weeks	30 weeks	
HR (bpm)	76 [69–89]	68 [65–84]	93 [86–102]	<0.05
BP systolic (mmHg)	115 [101–124]	108 [85–119]	116 [98–140]	ns
BP diastolic (mmHg)	61 [47–74]	52 [44–57]	54 [53–67]	ns
SpO_2 (%)	89 [85–90]	90 [88–92]	85 [83–86]	<0.05
PaO_2 (mmHg)	56 [51–59]	63 [57–65]	50 [49–55]	<0.05
Mean PABP (mmHg)	60 [52–68]	63 [58–79]	79 [72–88]	ns
LVDd	39 [33–44]	39 [34–43]	40 [35–44]	ns
LVDs	23 [19–25]	23 [18–24]	27 [23–28]	ns
EF (%)	52 [49–57]	50 [47–54]	42 [38–47]	<0.05
RA enlargement	7	3	3	ns
RV enlargement	7	3	3	ns

HR, heart rate; BP, blood pressure; PABP; pulmonary arterial blood pressure; LV, left ventricle; LVDd, left ventricle diastolic diameter; LVDs, left ventricle systolic diameter; RV, right ventricle.
HR, BP systolic, BP diastolic, SpO_2, PaO_2, Mean PABP, LVDd, LVDs, EF are shown as median [interquartile range] and were analyzed by Wilcoxon test. Other data were analyzed by Chi-square test and Fisher exact test. $P < 0.05$ indicates a significant difference.

pregnancy to 50 [49–55] mmHg around 30 weeks gestation ($p < 0.05$). SpO_2 in the same 5 cases decreased significantly from 90 [88–92] mmHg before or early in pregnancy to 85 [83–86] mmHg at 28–30 weeks gestation ($p < 0.05$) (Table 2).

Left ventricular (LV) function

Echocardiography up to about 10 weeks gestation in all cases revealed an enlarged right atrium and right ventricle with moderate to severe tricuspid valve regurgitation. The median ejection fraction (EF) of the left ventricle decreased from 50 [47–54] % before pregnancy or up to 10 weeks gestation to 42 [38–47] % at 28–30 weeks gestation ($p < 0.05$) (Table 2).

Pulmonary vascular resistance (PVR)

PVR did not change significantly from before conception to 30 weeks (Table 3). PVR before conception was highest in case 5 (1560 dyne × s/cm^2) and lowest in case 1 (582 dyne × s/cm^2), and in the series heart failure developed earliest and latest in these respective cases. Thus, a high PVR at conception may be related to development of heart failure earlier in pregnancy, but this finding was not significant.

NYHA class

NYHA classes before pregnancy were II, III and IV in 4, 5, and 1 termination cases, respectively, and remained in the same class at 1 year after termination. NYHA classes before, during pregnancy, and 1 year after delivery were II, III and II in all 5 delivery cases.

Pregnancy and neonatal outcomes

In the 5 delivery cases, Cesarean section was performed at 30.6 [29.4–31.9] weeks because of heart failure in all cases. Patients had dyspnea, fatigue, persistent cough, bloody phlegm, and decreased LV function. Cesarean section was selected due to an immature cervix. The median birth weight was 1240 [1050–1376] g. In one case, epoprostenol and tadalafil were administered during pregnancy (Fig. 1). In this case, fetal growth was appropriate, whereas 3 of the remaining 4 cases delivered small-for-gestational-age babies (−1.9, −2.2, −3.0 SD). None of the neonates had congenital heart disease. Maternal and neonatal survival was 100%. At two years after delivery, all of the neonates showed normal growth and good neurological development. During pregnancy and postpartum, none of the cases exhibited excessive bleeding, thromboembolism or arrhythmia that required medical therapy.

Cardiac failure near delivery and postpartum

Median LVEF decreased from 50 [47–54] % before pregnancy or at 10 weeks gestation to 42 [38–47] % at 28–30 weeks gestation, ($p < 0.05$). Five patients required nasal oxygen therapy during pregnancy and all exhibited exertional fatigue, which was accompanied by elevated HR and decreased SpO_2. In the recent case, in which the patient received therapy targeting the pulmonary artery,

Table 3
Clinical characteristics of the five delivery cases.

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Type of CHD	VSD	VSD	PDA	VSD	VSD
SpO_2 (before, late preg) (%)	90, 86	90, 85	90, 86	94, 85	86, 81
PaO_2 (before, late preg) (mmHg)	63, 50	60, 51	63, 50	68, 59	54, 48
Mean PABP (before, late preg) (mmHg)	63, 75	81, 86	58, 89	55, 79	76, nd
PVR (before, late preg) (dyne × s/cm^2)	582, 592	885, 868	1280, 1291	1476, 1520	1560, nd
NYHA (pre-preg → late preg → 1 year after delivery)	II→III→II	II→III→II	II→III→II	II→III→II	II→III→II
Hospitalization (gestational weeks)	20	22	22	17	9
Worsening of exertional fatigue (gestational weeks)	25	29	30	25	26
Oxygenation, drugs	21 w ~ O_2 5L	23 w ~ O_2 10L	24 w ~ O_2 5L	18 w ~ O_2 5L, HOT	18 w ~ O_2 2L, tadalafil, epo, NO, bosentan
NYHA class, drugs 2 year after delivery,	II, beraprost	II, HOT	II	II, HOT	II, bosentan, tadalafil
Delivery (week-days)	33–0	31–3	30–6	30–5	28–2
Newborn weight (g) (SD)	1490 (−2.2)	1074 (−3.0)	1240 (−1.9)	1562 (−0.1)	1027 (−0.9)

CHD; congenital heart disease; PDA, patent ductus arteriosus; VSD, ventricular septal defect; PABP, pulmonary arterial blood pressure; PVR, pulmonary vascular resistance; preg, pregnancy; NO, nitric oxide; epo, epoprostenol; HOT, home oxygen therapy.

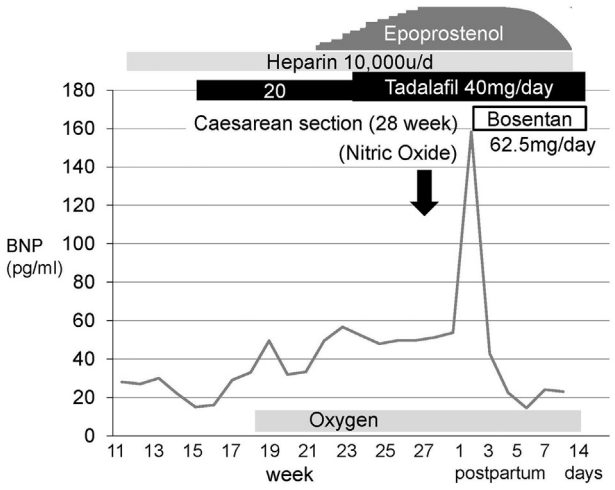

Fig. 1. Clinical course of an ES-complicated pregnancy treated with drugs for PAH (case 5). Heparin, tadalafil, and epoprostenol were administered during pregnancy. Epoprostenol infusion therapy was started at 0.5 ng/kg/min and increased gradually in increments of 0.5 ng/kg/min twice weekly, until a dose of 8 ng/kg/min was reached. Cesarean section was performed at 28 weeks because the NYHA class worsened to Class III. During the operation, inhaled nitric oxide 5 ppm was administered. In the postpartum course, bosentan was initiated and epoprostenol was decreased gradually. After 1 month, the patient was discharged without complications and was NYHA class II.

the hemodynamics became unstable from 24 to 72 h after Cesarean section and urine flow was only 10–20 ml/h, leading to use of furosemide 2 mg. This caused urine flow to increase to 200–300 ml/h, which led to hypotension due to hypovolemia. BNP was elevated to135 pg/ml and SpO_2 was 81% with 8 L oxygen/minute via a face mask. From postoperative day (POD) 6, epoprostenol was decreased by 1 ng/day and bosentan was initiated at 62.5 mg/day (Fig. 1). Epoprostenol was stopped on POD 14. After 1 month, the patient was discharged in NYHA class II.

Discussion

During pregnancy, the circulating blood volume gradually increases by about 50% up to about 30 weeks of gestation and then reaches a plateau [11]. In patients with ES, volume overload in pregnancy poses an additional burden for the already-compromised right ventricle. Our data suggest that PVR does not change from before to around 30 weeks in ES-complicated pregnancy. The fall in SVR during pregnancy could increase right to left shunting, leading to exaggerated cyanosis and LV dysfunction, which were observed in the current study. In the 5 cases in which pregnancy was continued, delivery was performed at around 30 weeks because of heart failure with decreased SpO_2 and PaO_2. The decreased oxygen saturation limited physical activity and the NYHA class dropped to III. It is noteworthy that although the 5 cases developed heart failure during pregnancy that led to early delivery, the maternal NYHA class recovered to II one 1 year later. In a series of 73 pregnant patients with ES, Weiss et al. reported a maternal death rate of 36%, with 3 deaths antepartum and 23 deaths postpartum [4]. This high mortality was described as sudden death, therapy-resistant heart failure, or thromboembolism, and was strongly associated with late diagnosis and late hospitalization [4].

We attribute the favorable outcomes in our patients to three factors. The first was early hospitalization. The indication of hospitalization is around 20 weeks of gestation when cyanosis may worsen as circulating volume gradually increases. Also, worsening of O_2 saturation exercise limitation, NYHA functional class and BNP levels possibly important to decide the timing of hospitalization. And in case when the SpO_2 was less below 90 we made the patient hospitalized as soon as the pregnancy was turned out. Nasal mask oxygen therapy helped to maintain a higher PaO_2 and delivery was planned as soon as cardiac failure was diagnosed to avoid possible sudden death and cardiac deterioration postpartum [12]. This decision resulted in a high survival rate of premature infants in the NICU and all infants survived without apparent neurological disorders.

The second factor was the introduction of new drugs for PAH, including bosentan, beraprost, sildenafil, and epoprostenol. Epoprostenol and tadalafil are pregnancy FDA category B drugs that may be used during pregnancy [13]; however, maternal mortality may still be significant, and it should be noted that these drugs have not been proven to be useful during pregnancy.

The third factor was improved anesthetic management. If PABP exceeded systemic BP during Cesarean section, especially after removal of the placenta, reduction of the blood volume was performed through a Swan-Ganz catheter. If SVR was elevated at delivery, the RV outflow tract would lose its escape route due to the fixed pulmonary resistance in ES, which would cause acute heart failure.

Cesarean section is associated with blood loss and increased maternal risks, but was performed in the 5 cases in this study. In a multidisciplinary team conference we decided that it was best to start both maternal and neonatal intensive care in the daytime, when we can offer the best medical care. Anesthesiologists are familiar with management of cardiac function under general anesthesia using transesophageal echocardiography. Furthermore, in Japan, prostaglandin gel to dilate the cervix is not available, so induction of labor was not considered in these cases.

Patients who did not receive PAH-targeted therapy had a greater tendency to deliver small-for-gestational-age babies, which was probably due to reduced cardiac output and increased desaturation [14]. In contrast, the single patient treated with epoprostenol and tadalafil delivered an infant with adequate growth. In this case, although SpO_2 and PaO_2 dropped as in other cases, the pulmonary blood flow may have been increased by these drugs; although this was not confirmed [15]. During pregnancy, there is an increase in all circulating anticoagulant factors, including fibrinogen, and a hypercoagulative state occurs [16]. During pregnancy and postpartum we administered heparin 10,000 U/day as a prophylactic treatment for thromboembolism, while monitoring the levels of markers of thromboembolism (i.e., soluble fibrin and D-dimer).

It is noteworthy that in 5 patients with PVR of 500–1600 dyn $\times$ sec/cm^2 had decreased left cardiac function in pregnancy and their NYHA class dropped from II to III, with a decrease in PaO_2 from around 60 to 50 mmHg, SpO_2 dropped from 90 to 85 mmHg before 30 weeks of pregnancy. But PVR did not change from before to late pregnancy. Furthermore, those with a higher PVR at conception tended to develop heart failure earlier during pregnancy. This indicates the usefulness of PVR for preconceptional counseling in patients with ES.

In patients with ES, bosentan is well tolerated and improves exercise capacity and hemodynamics without compromising peripheral oxygen saturation [17]. In the BREATHE-5 studies, bosentan for 16 weeks was effective in decreasing PABP and PVR without leading to deterioration of SpO_2 in patients with ES in WHO class III [17]. However bosentan cannot be used during pregnancy because of its teratogenicity [18]. To assure maternal safety, further studies are needed to determine whether combined therapy is effective during pregnancy without use of bosentan. Volume overload, hypertension, tachycardia, and hypercoagulability also need to be examined to determine the safety of pregnancy complicated with ES. Multidisciplinary therapy performed at a tertiary center by experienced obstetricians, anesthesiologists, neonatologists,

cardiologists, nurses, and a genetic consultant is necessary to select the best treatment plan to optimize maternal and neonatal prognoses.

There are several limitations in the study. ES is a relatively rare disease, and therefore we were only able to include 15 patients in the study. The small number of subjects prevented correction of the results for the effects of potential confounding factors, such as hypertension and obstetric history, and did not allow multifactorial analysis or analysis of the effects of shunt location (Table 1). Furthermore, PAH targeted therapy was only used in one case, which did not permit evaluation of the effect of this treatment on the pregnancy. To evaluate LV function, the LVEF measurement alone was not sufficient for a large VSD and right ventricle pressure load. Therefore, further study with increased number of patients will be necessary to conclude the recommendation of management of Eisenmenger patients during pregnancy, delivery and postpartum.

However, standardized measurements of the ventricle and atrium and the degree of tricuspid valve regurgitation were performed, compared with other multicenter studies. In future, we plan to investigate a larger cohort of patients to clarify the risk factors for cardiac dysfunction in patients with ES during pregnancy.

Conclusion

In our patients with ES, it was observed that PVR did not increase during pregnancy, but PaO_2 and EF decreased significantly. All cases developed cardiac failure in weeks 25–30 and early delivery was needed. While there were no maternal deaths, postpartum management was difficult because of the limited therapeutic window to control volume, due to the increased circulating blood volume, but limited vascular bed, reduced cardiac function, and hypercoagulability. Bosentan is useful for ES, but is contraindicated during pregnancy. Further studies are needed to assure the maternal safety of targeted therapy in pregnancy complicated with ES. Until further data are available, it should be assumed that maternal cardiac failure could occur in such a pregnancy, even with optimal treatment.

Conflict of interest

The authors declare no conflicts of interest in association with the study. Financial support was from institutional sources only.

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