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Multidisciplinary approach for the management of term pregnancy complicated by Eisenmenger syndrome

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Pregnancy in patients with Eisenmenger syndrome (ES) is associated with high maternal mortality rates of 30%–50%, or even up to 65% in the case of a cesarean section (Yuan, 2016). Here, we report a case of term pregnancy complicated with ES and severe pulmonary artery hypertension (PAH), which was managed by a multidisciplinary team (MDT) and resulted in an uncomplicated delivery via elective cesarean section. The goal of this study is to emphasize the importance of multidisciplinary approach in the management of pregnancy with ES, which can profoundly improve maternal and infant outcomes.

A 32-year-old female (gravida 3, para 0) at 36(+6)-week gestation was transferred to our institution (Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China) for further evaluation of hypoxemia and bilateral lower extremity edema. She first received prenatal care at an outside hospital in December 2019, and remained asymptomatic during that time. She was unaware of any cardiac diseases, diabetes, surgery, or trauma. Her obstetric history was significant for a spontaneous miscarriage in 2003 and an induced abortion in 2014. As a result of the corona virus disease 2019 (COVID-19) pandemic, she was lost to follow-up and did not present to the hospital until 36(+6) weeks, when she developed progressive bilateral lower extremity edema. On presentation, she was hypoxic with an oxygen saturation (SpO_2) of 72% on ambient air, and showed digital clubbing. She was transferred to our institution for further evaluation and management.

Upon transfer, her vital signs were as follows: heart rate of 80 beats per minute, blood pressure of 130/70 mmHg (1 mmHg=0.133 kPa), respiratory rate of 21 breaths per minute, and SpO_2 of 77% on ambient air. The cardiac exam revealed a loud P2 and a pansystolic murmur heard over the left sternal border. The lungs were clear to auscultation without rales or crackles. She was noted to have central cyanosis, digital clubbing, and 3+ pitting edema of the bilateral lower extremities. Obstetric exam findings showed a uterine height of 33 cm, maternal abdominal circumference (AC) of 101 cm, responsive non-stress test (NST) without contraction, and a Bishop score of 4 points. Transabdominal ultrasound revealed a biparietal diameter (BPD) of 86 mm, AC of 306 mm, femur length (FL) of 67 mm, and amniotic fluid volume (AFV) of 40 mm.

The arterial blood gas test revealed pH 7.43, partial pressure of oxygen (PaO_2) at 47 mmHg, and SpO_2 at 80%. Significant laboratory findings included elevated B-type natriuretic peptide (BNP) of 278 ng/L and N-terminal pro-BNP (NT-pBNP) of 1192 ng/L. The complete blood count, hepatic and renal function, thyroid function, serum chemistries, and coagulation results were within normal limits. The thrombophilia screening (protein C, protein S, and homocysteine) and autoimmune findings were normal. Computed tomography (CT) of the chest revealed no acute pulmonary embolism or pleural effusion, and a complete

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abdominal ultrasound demonstrated no intraabdominal process or peritoneal effusion. The electrocardiogram discovered a sinus rhythm with right ventricular hypertrophy, and the echocardiogram showed a large arterial septal defect (ASD) measuring 30 mm with bidirectional and mainly right-to-left shunt, severe pulmonary hypertension with a systolic pressure of 135 mmHg, moderate tricuspid regurgitation, and left ventricular ejective fraction (LVEF) of 67%. Given the medical history, physical, laboratory, and imaging findings, she was diagnosed with pregnancy complicated with ES. Her hypoxemia was attributed to a right-to-left shunt secondary to a large ASD and severe pulmonary hypertension.

An MDT was assembled to provide expertise for close hemodynamic and fetal monitoring, with a plan to optimize preoperative hemodynamic status bridging to elective cesarean section. The recommendations from different specialists were described below. (1) Cardiothoracic surgery and cardiology: given the extent of severe pulmonary hypertension, the patient was deemed not a surgical candidate for ASD closure. She was given oxygen therapy to maintain SpO_2> 90%. PAH-specific therapies including sildenafil and treprostinil were initiated. The central line and arterial line were placed under close hemodynamic monitoring. (2) Anesthesiology: the decision was made to perform general anesthesia and endotracheal intubation. Epidural anesthesia was avoided as sympathetic blockade could reduce systemic vascular resistance, leading to worsening right-to-left shunt and hypoxemia. (3) Mechanical circulatory support: extracorporeal membrane oxygenation (ECMO) was planned for rescue in the event of decompensation. Femoral vein and artery were cannulated intraoperatively as needed for ECMO. (4) Obstetrics: as acute blood loss during delivery could pose a high risk for cardiopulmonary decompensation, the decision was made to proceed with judicious use of oxytocin in small and intermittent dose to augment contraction and prevent postpartum hemorrhage. (5) Neonatology: as hypoxemia in maternal circulation could lead to fetal hypoxia, neonatologists were standby in the event of newborn resuscitation. (6) Intensive care: the intensive care unit (ICU) level of care was deemed necessary to provide close monitoring, supportive care, and PAH-specific therapy.

After optimization and finalization of the management plan, we conducted caesarean section under general anesthesia at 37(+2)-week gestation. A floating catheter was inserted to dynamically monitor the pulmonary artery pressure, and the pre-cannulation of the femoral vein and artery were prepared for the availability of standby ECMO. A live baby girl with an Apgar score of 4 points at 1 min, 7 at 5 min, 9 at 10 min, and 10 at 20 min, weighing 2495 g, was delivered and immediately resuscitated by the neonatologist. After delivery, intravenous oxytocin 5 U was given immediately and 10 min after delivery. The ligation of bilateral ascending branches of uterine artery and B-lynch suture was subsequently performed due to the concern of uterine inertia and postpartum hemorrhage. The estimated blood loss was 400 mL. Intraoperatively, vasopressors and inotropes including dopamine and norepinephrine were used and titrated as needed to maintain adequate systemic vascular resistance. Continuous treprostinil infusion was titrated to sustain a low pulmonary vascular resistance in order to prevent an increase in the right-to-left shunt.

The patient was transferred to ICU for close hemodynamic monitoring and postpartum management. She was extubated 6 h postoperatively and placed on high flow oxygen to maintain SpO_2 at 95%–98%. Macitentan was added as a third agent for PAH on postoperative Day 1. Dopamine and norepinephrine were eventually weaned off one weeks and three weeks post partum, respectively. Treprostinil was transitioned from intravenous injection to subcutaneous injection at postpartum Week 4.

Subcutaneous weight-adjusted low-molecular-weight heparin (LMWH) was started within 12−24 h postoperatively for venous thromboembolism (VTE) prophylaxis. To minimize the risk of infection, patient was treated with intravenous antibiotics prophylactically and lines were removed one week postoperatively. In addition, the patient received bromocriptine for lactation suppression to ensure adequate bedrest and sleep. On postoperative Day 37, a repeat echocardiogram showed a pulmonary arterial pressure of 124 mmHg.

She was discharged on postoperative Week 6 on oral sildenafil, macitentan, and subcutaneous treposti-nil, with a plan to follow up with cardiology. Contraception was started to avoid pregnancy. On 12-month follow-up, her overall condition was satisfactory and her daughter was healthy. Fig. 1 demonstrated the outline of postoperative MDT management. Fig. 2

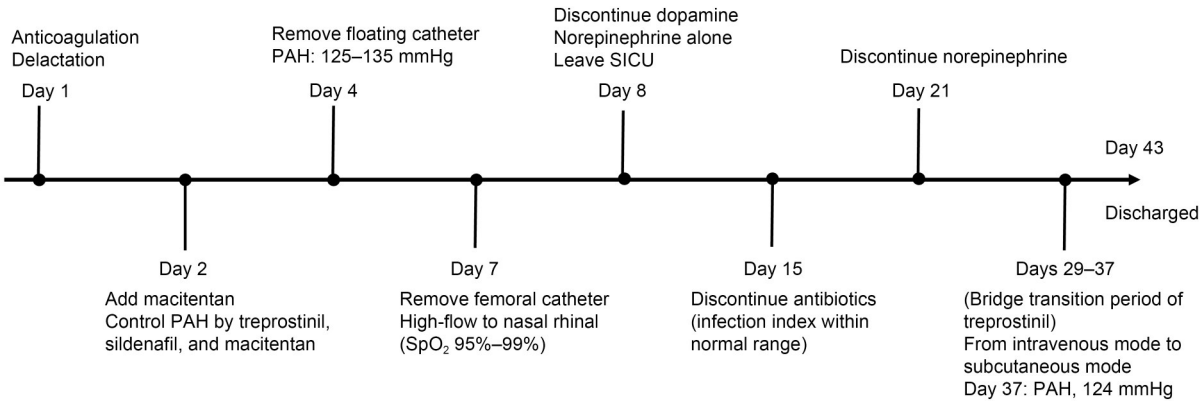

Fig. 1 Outline of postoperative management. PAH: pulmonary artery hypertension; SpO_2: oxygen saturation; SICU: surgical intensive care unit.

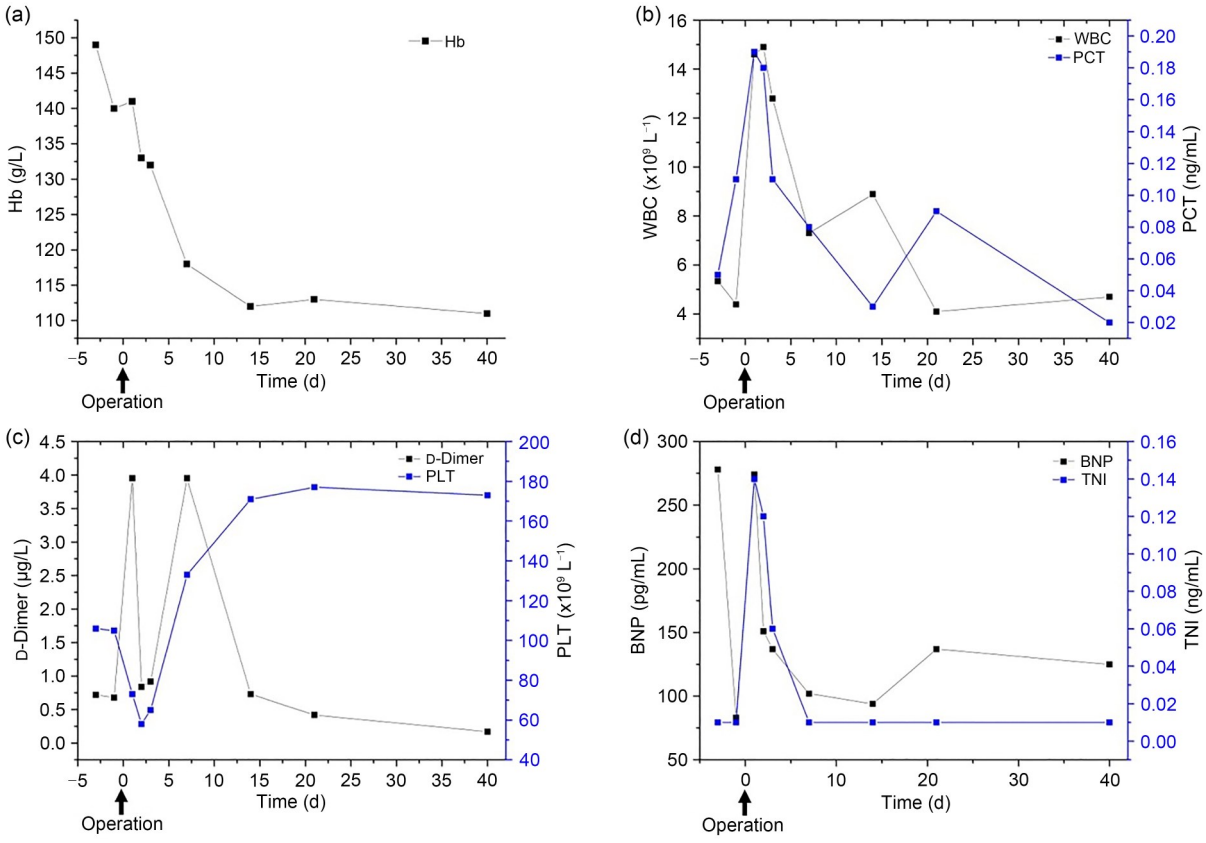

Fig. 2 Alteration of relevant clinical indicators in the perioperative period and puerperium. Haemoglobin (Hb) (a), infection indices such as white blood cell (WBC) and procalcitonin (PCT) (b), blood coagulation states such as D-dimer and platelet (PLT) (c), and cardiac function indices such as B-natriuretic peptide (BNP) and troponin (TNI) (d) were maintained within acceptable fluctuation during the perioperative and puerperal periods.

demonstrated the trend of relevant laboratory indicators during the perioperative and puerperal periods.

Term pregnancy complicated with ES and severe PAH is a rare and potentially life-threatening condition. According to the 2018 European Society of Cardiology (ESC) Guidelines, pregnancy is contraindicated in patients with ES, as PAH has the highest risk level (modified World Health Organization classification of maternal cardiovascular risk level IV (mWHO IV)) (Regitz-Zagrosek et al., 2018). Women who become pregnant should receive counseling and early pregnancy termination should be discussed. For patients

who opt to continue with the pregnancy, referral to a tertiary center with expertise in PAH should be made as soon as possible.

When this patient was emergently transferred to our institution at 36(+6)-week gestation for the further evaluation of severe hypoxemia, the differential diagnosis of pulmonary embolism due to the hypercoagulable state of pregnancy was excluded by CT scan. Using any of the present techniques, the fetal dose is well below the dose levels above that proposed for a significantly increased risk for congenital abnormality (Schaefer-Prokop and Prokop, 2008). Once the diagnosis of pregnancy complicated with PAH and ES is established, treatment strategy is further discussed by MDT: based on the guidance for assessing operability in PAH associated with congenital heart disease (Simonneau et al., 2019), patients with severe residual PAH after the closure of shunts may have more rapid progression of disease and worse outcome. Our patient was not suitable for the management of ASD, and PAH-specific therapy was planned, as recommended in pregnancy with PAH. There are four major classes of PAH-specific therapy: prostaglandins (e.g., treprostinil), phosphodiesterase-5 (PDE-5) inhibitors (e.g., sildenafil), endothelin receptor antagonists (e.g., macitentan), and soluble guanylate cyclase stimulators (Ballard et al., 2021). Sildenafil and treprostinil are associated with risk category B in pregnancy by the United States Food and Drug Administration, while macitentan has been shown to have teratogenic effects and thus is contraindicated during pregnancy (Yang et al., 2021). Of note, sildenafil is an oral medication that has been shown to exert beneficial effects on symptoms and exercise tolerance in patients with ES (Lopez et al., 2020); early initiation or continuation of PDE-5 inhibitors in women with PAH who choose to continue pregnancy is recommended (Yuan, 2016).

Both cesarean and vaginal delivery in women with ES are associated with high cardiovascular risk. Compared to cesarean section, vaginal delivery is linked to reduced blood loss, lower risk of infection, VTE, and sudden hemodynamic changes (Lopez et al., 2020). However, the prolonged delivery course and pain can lead to increased pulmonary arterial pressure (Yang et al., 2021).

As for caesarean section, the placement of a pulmonary artery catheter in delivery may be helpful to assess hemodynamic status and adjust medication (Zhang et al., 2018). The selection of the method and timing of delivery remains debatable and should be individualized (Slaibi et al., 2021).

Postpartum monitoring and management are vital in the first 10 d post partum, which is associated with the highest mortality due to hypovolemia, VTE, and preeclampsia (Maciejewski et al., 2019).

PAH patients complicated with right-to-left shunt are at high risk of VTE, and therapeutic anticoagulation is recommended in pregnancy with ES (Karsenty et al., 2021). In our case, weight-based LMWH at full anticoagulation dose was started within 12–24 h post partum after the risk of postpartum hemorrhage was deemed to be low. According to the recommendation, vasopressors and inotropes should be used with caution. In our case, vasopressors were continued postpartum but eventually weaned off. A third agent (macitentan) was added for PAH and intravenous treprostinil was transitioned to subcutaneous injection at postoperative Weeks 4 and 5. Lastly, psychological support, lactation suppression, and postpartum contraception were all important measures for comprehensive care during the postpartum period. All the above measures resulted in an uneventful delivery under precise management by a coordinated and experienced MDT.

Early screening for heart disease during pregnancy and appropriate referral have crucial importance. Pregnant patients with ES should be treated carefully by an experienced MDT. PAH-specific therapy should be initiated or continued during pregnancy. In our case, precise and standardized management by MDT profoundly improved maternal and fetal outcomes.

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Author contributions

Shibin HONG contributed to data analysis, writing and editing of the manuscript. Xin KANG contributed to data analysis. Ka U. LIO contributed to writing and editing of the manuscript. Yiping LE and Chuan WANG collected materials in the study. Jianhua LIN and Ning ZHANG conceived and designed the study, and revised the manuscript. The scientific guarantor of this publication is Ning ZHANG. All authors have read and approved the final manuscript, and therefore,

have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Shibin HONG, Xin KANG, Ka U. LIO, Yiping LE, Chuan WANG, Jianhua LIN, and Ning ZHANG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the Ethics Committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine and with the Helsinki Declaration of 1975, as revised in 2008 (5). Ethical approval document was not required for the single case report in accordance with the Renji Hospital's requirement. Informed consent was obtained from the patient for being included in the study. Additional informed consent was obtained from the patient for which identifying information is included in this article.

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