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Journal of Pharmaceuticals Sciences and Drug Discovery

Case Report

Maternal Death with Severe Pulmonary Hypertension

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Abstract

Background: Maternal heart disease occurred approximately 2-4% of pregnancies, which increased the risk to both mother and fetus. Pregnancy complicated with pulmonary hypertension (PH) is a serious problem. The presence of heart failure (HF) due to atrioventricular septal defect (AVSD) with PH in pregnancy results in high rates of preterm labor, stunted fetal growth and chronic intrauterine asphyxia and death in both mother and baby.

Objectives: To report the case and management of pregnancy with pulmonary hypertension.

Case Report: Mrs. AM, 32 years old G5P0A4, 36 weeks' gestation, 50 days premature rupture of membranes (PROM) with recurrent miscarriage and mother with AVSD, severe tricuspid valve regurgitation, moderate mitral and pulmonary valve regurgitation, with pulmonary artery hypertension. Left ventricular ejection fraction (LVEF) 70-71%, modified World Health Organization IV (mWHO IV). 5 days after the section and sterilization, the patient died with a live birth weighing 2000 grams, APGAR score 6-7-9. Echocardiographic examination of the baby showed a secundum atrial septal defect (ASD II), with a diameter of 0.2 cm, mild regurgitation of the tricuspid valve.

Conclusion: Pregnant women with congenital heart defects that result in PH and HF must be monitored closely and need collaboration between cardiologists, obstetrics, pediatrics and anesthesiologists. It is important to educate mothers and families about the risks of pregnancy and perinatal complications. In pregnant women with pulmonary hypertension, if the patient's condition is stable, delivery is planned at 34-36 weeks' gestation. However, if the mother's condition is unstable, the pregnancy must be terminated in an emergency manner.

Keywords: Maternal death, Pulmonary hypertension in pregnancy, Atrioventricular septal defect

INTRODUCTION

Heart disease is one of the leading causes of maternal death from non-obstetric causes. Based on recent studies, the incidence of congenital heart disease (CHD) in the Asian region is 9.3/1000 live births. Thus, it is estimated that no less than 40,000 babies are born with CHD every year in Indonesia. The prevalence of adult CHD is said to be 6/1000 population, increasing by 5% per year, the fastest growth of heart disease patients today. It is estimated that there are 50 million CHD patients worldwide, and probably around 1.5 million of them live in Indonesia [1]. Approximately 2-4% of pregnancies involve maternal heart disease, which can increase the risk for both mother and fetus[1] In Indonesia, the incidence of CHD is 8 per 1,000 live births. It is assumed that there are an additional 32,000 new cases of CHD each year [2]. According to the latest statistics from WHO, maternal mortality in developed countries is approximately 12 per 100,000 live births (0.012%) and 239 per 100,000 live births (0.2%) in developing countries [3].

The intrapartum and postpartum periods are critical periods where most deaths occur in this period [4]. Deaths of pregnant women due to heart disease can result directly (obstetric complications) and indirectly (aggravated disease due to pregnancy). Pregnancy in women with heart disease not only poses a risk of death for the mother, but also serious morbidities such as heart failure, stroke, and cardiac arrhythmias [5]. Perinatal morbidity and mortality are variably increased in pregnant women with heart disease. The presence of heart failure in pregnancy results in high rates of preterm labor, stunted fetal growth and chronic intra-uterine asphyxia [6]. Changes in the cardiovascular and hematological systems during pregnancy can complicate the diagnosis of heart disease and can aggravate heart disease. Thus, impacting mothers who already have abnormalities in anatomy and heart function. The intrapartum and postpartum period is a critical period where most deaths occur in this period. Manifestations that arise in the form of heart function failure increase maternal and fetal morbidity and mortality [7]. Arterial and venous relaxation and increased blood volume begin in the early phases of conception. In the

Received: *April 12, 2022;* ***Revised:*** *April 22, 2023;* ***Accepted:*** *April 25, 2023*

Citation: Wasyanto T, Anggraini N & Yasa A. (2023) Maternal Death with Severe Pulmonary Hypertension. J Pharm Sci Drug Discov, 2(1): 1-10.

embryonic phase of the first 5-8 weeks of pregnancy, systemic vascular resistance decreases and cardiac output increases to 20-30% compared to before pregnancy. Poor prognosis is found in pregnant patients with pulmonary hypertension [8,9].

Pregnancies complicated by pulmonary hypertension (PH) are a serious problem for cardiologists, obstetricians, pediatricians and anesthetists because of the high potential for maternal and fetal complications [9]. PH described by an increase in mean PA pressure >20mmHg. The diagnosis of pre-capillary PH or pulmonary arterial hypertension (PAH) is established by an increase in pulmonary vascular resistance (PVR) ≥ 3 Wood Units (WU) [9]. Pregnant women with PH need monitoring with multidisciplinary team collaboration. Although specific treatment modalities are available in the management of PH during pregnancy, most drugs are contraindicated due to their teratogenicity [10]. Reducing maternal mortality is a WHO global health goal. Although maternal deaths due to hemorrhage and infection are decreasing, deaths related to heart disease are increasing and are now the most important cause of death in western countries. Maternal mortality rates due to heart failure (HF) are high in women with heart disease. The highest complication rates occur in pregnant women with PH [11].

Pregnancy in women with heart disease is generally associated with an increased risk of maternal mortality. Pre-pregnancy predictors for mortality and HF are NYHA class >II, mWHO IV, LVEF <40%, signs of HF, and use of anticoagulant medication. Until 2010, maternal mortality with heart failure was increasing [11]. The management of normal and caesarean deliveries under regional or general anesthesia is a dangerous situation for pregnant women with heart disease and their fetuses, so joint collaboration and decisions between cardiologist, obstetrician, and anesthesiologist s are very important [12].

This case report will discuss the management of pregnancy with pulmonary hypertension, which is still a matter of debate.

CASE REPORT

Mrs. AM, a 32 years old female was consulted from the Obsgyn department with multigravida, preterm pregnancy G5P0A4, 28 weeks gestation age not yet in labor, with Atrioventricular Septal Defect (AVSD) with high probability of PH, NYHA II history of first pregnancy abortion at 3 months gestation, second pregnancy abortion at 2 months gestation, third pregnancy abortion at 5 weeks gestation, fourth pregnancy abortion at 2 months gestation. The patient was said to have CHD since birth and last took digoxin in 2017. During pregnancy, the patient did not take medication. Before pregnancy, the patient was recommended for heart surgery but the patient refused. The patient came with complaints leakage amnion fluid from the birth canal for 8 h before entering the hospital, fetal movement (+), regular abdominal contraction has not been felt, blood mucus discharge from the birth canal does not exist. There was no complaint of shortness of breath. Complaints of chest pain, palpitations, fever, and cough were denied. There were no complaints of defecation and urination.

Physical examination revealed blood pressure 120/70 mmHg, heart rate 93x/min, pulse 93x/min, respiration 20x/min, oxygen saturation 94% O_2 space. Jugular venous pressure 5+2 cm H_2O, caudolateral dilated impression heart border, regular I-II heart sound with normal intensity, pansystolic murmur 3/6 at apex-axilla, Pansystolic murmur 3/6 left lower sternal border. Lung examination revealed right and left vesicular breath sounds, fine wet rhonchi were absent. On abdominal examination single fetus was palpated, intra uterine, head presentation, left dorsal, head has not entered the pelvis, his (-), fetal heart rate (+) 153x/min, fundal height 3 fingers above umbilicus. Abdominal ultrasound examination revealed a single fetus, intrauterine, estimated fetal weight is 1068 grams, head presentation. Examination of the extremities, there was no lower extremity edema, clubbing finger (-), cyanosis (-). Electrocardiographic examination revealed AV Block 1st degree HR 100 bpm, Right axis deviation, Right ventricle hypertrophy, Right atrial enlargement **(Figure 1)**.

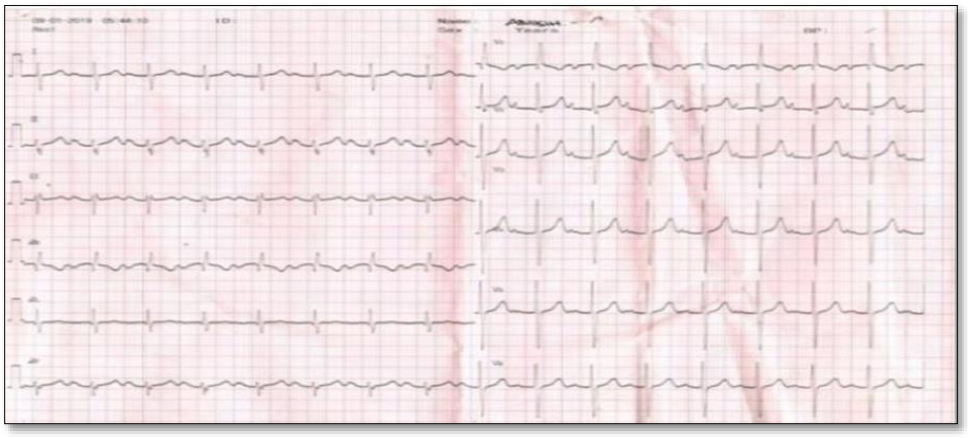

Figure 1. ECG Mrs. AM.

Laboratory examination showed Hb: 11.8 g/dl; hematocrit 35%; leucocytes 5.000 /ul; platelets 230,000 /uL; erythrocytes 4.04 million/uL; HbSAg non-reactive, HIV non-reactive; IgG Antirubella positive, IgM Antirubella negative.

Echocardiographic examination revealed partial AVSD (Endocardial Cushion Defect). There was echodrop in the IAS of a large primum ASD with a diameter of 3.3 cm L to R shunt. Echodrops were seen in IVS, VSD inlet extended to subaortic with a diameter of 1.1 cm with Qp:Qs 2.17. The mitral valve and tricuspid valve appeared to be single level. Left ventricular contractility was normal with Ejection Fraction (EF) Teichholz 70% EF Simpson 71%; right ventricular contractility was good with TAPSE 2.2 cm. Severe tricuspid valve regurgitation with peak PG 139.98 mmHg (IVC 16/14; eRAP 5 mmHg); TR Vmax 5.62 m/s. Moderate mitral and pulmonary valve regurgitation. High Probability of PH with PVR 3,165 Wood Units; E/e' 11.76 **(Figures 2 & 3)**.

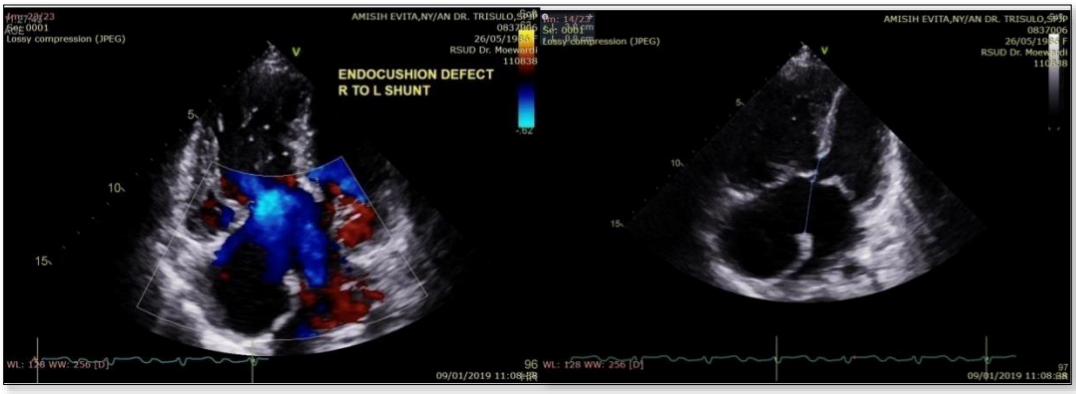

Figure 2. Partial AVSD echocardiography (Endocardial Cushion Defect).

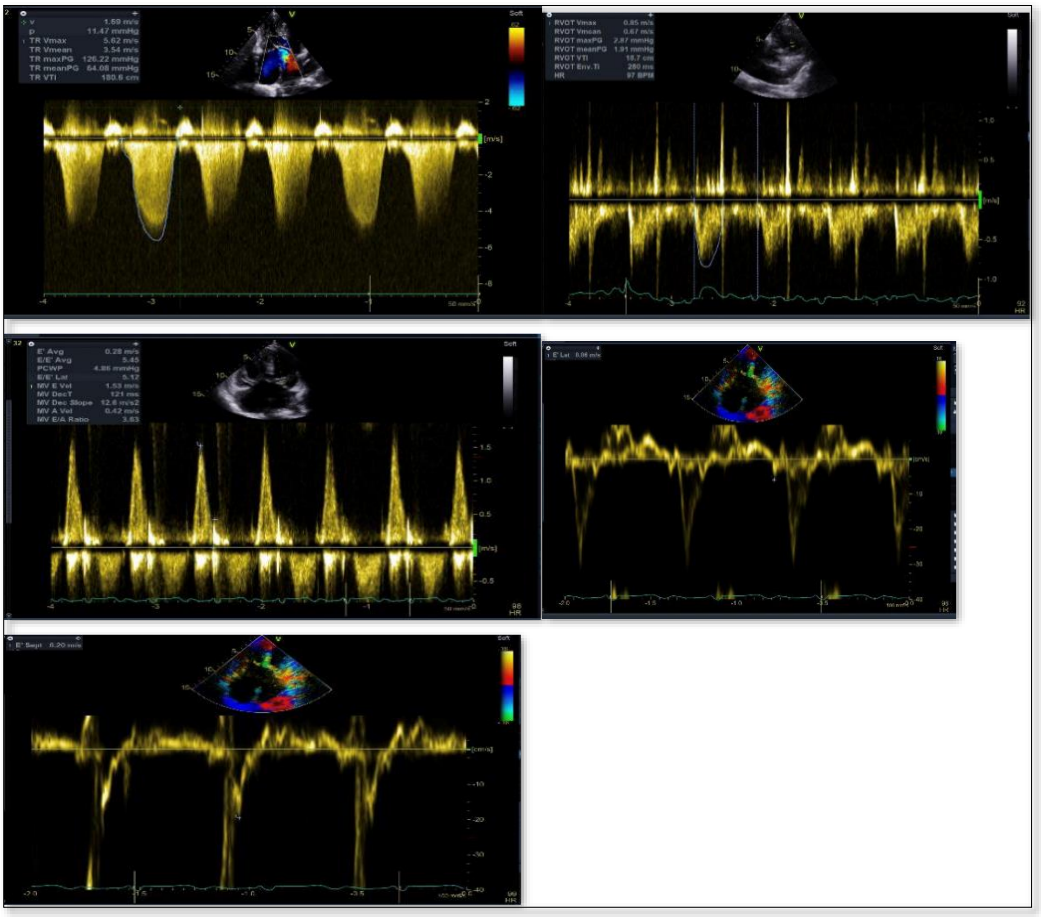

Figure 3. Transthoracic echocardiography High probability of PH with PVR 3.165 Wood Unit, E/e' 11.76.

The patient was diagnosed with G5P0A4 28 weeks gestation age not yet in labor with AVSD Qp: Qs 2.17, EF 70-71% severe tricuspid valve regurgitation, moderate mitral and pulmonary valve regurgitation, pulmonary arterial hypertension, NYHA II. Managed with sildenafil 3x25mg. Therapy from the Obsgyn department Ampicillin injection 1 g/8 h, Dexamethasone injection 5 mg/12 h (for 2 days), observation of Fetal heart rate and fluid balance, vital signs, education about pregnancy risks.

A joint conference was held between the departments of cardiology, obstetrics, anesthesia, perinatology and it was decided to maintain pregnancy and terminate at 32-36 weeks' gestation and recommend sterilization. Family education about surgery with high risk pregnancy for mother and fetus. Re-evaluation at 32 weeks' gestation and initial counseling of preoperative patients to the perinatology department at 32 weeks' gestation, as preparation for the care of premature infants. The patient remains hospitalized until the specified gestational age.

At 36 weeks of gestation, the patient felt regular contractions and complaints of dyspnea, with a diagnosis of G5P0A4 at 36 weeks of gestation with AVSD Qp: Qs 2.17, LVEF 70-71% severe tricuspid valve regurgitation, moderate mitral and pulmonary valve regurgitation, pulmonary arterial hypertension, NYHA IV. An emergency caesarean section was performed and sterilized under general anesthesia. After the procedure the patient was admitted to the ICU and ICVCU. Three days after the caesarean section, the patient experienced a worsening and atrial fibrillation rhythm occurred, CHA2DS2-VASC score 1 HAS-BLED 1, with respiratory failure, anemia (Hb: 8.5). Management therapy at ICVCU O2 12 lpm NRM, injection of ampicillin sulbactam 1.5 g/8 h, NAC 3x200mg, mefenamic acid 3x500mg, vitamin C 2x50mg, bolus injection of amiodarone 300mg IV slowly followed by drip amiodarone 50mg/h for 24 h, sildenafil 3x25mg, PRC transfusion 1 kolf. At 5 days after the caesarean section the patient's condition worsened and died. Live child with a birth weight of 2000 grams APGAR score 6-7-9, ASD II was obtained with a diameter of 0.2 cm, mild regurgitation of the tricuspid valve **(Figure 4)**.

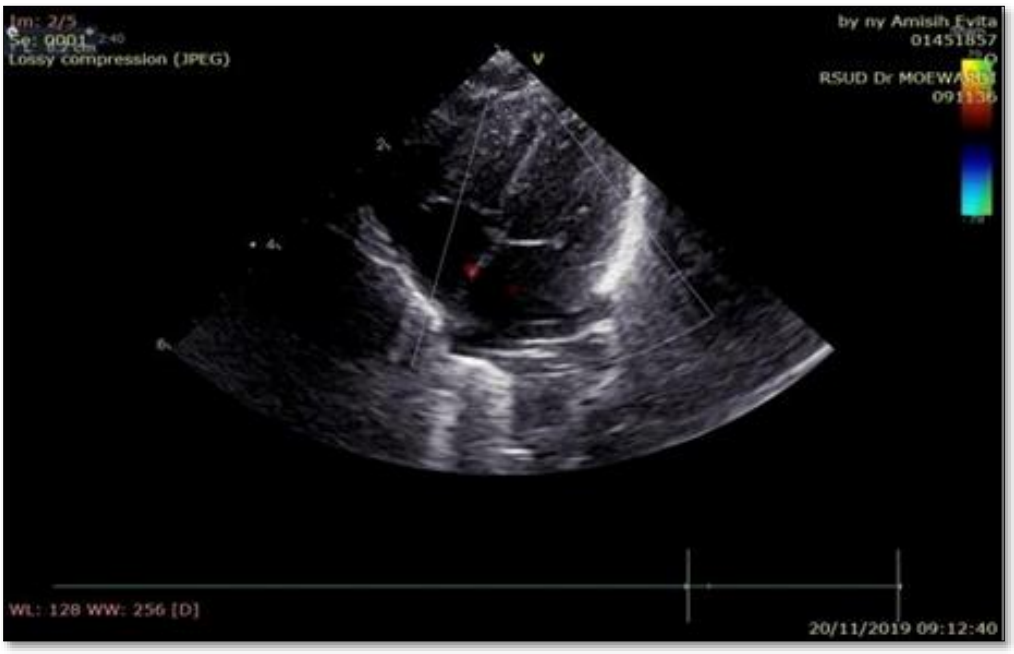

Figure 4. Echocardiography By. Mrs. AM ASD II.

DISCUSSION

The incidence of pregnancy with PH is 1.1/100,000 women. Despite the improvement in survival rates due to treatment and utilization of an effective multidisciplinary approach, high morbidity and mortality complications as high as 56% have been reported due to the adverse circulatory and hematological changes that occur in pregnant women with pulmonary hypertension [13].

The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) in 2015, have classified pulmonary hypertension. PAH was defined as pre-capillary PH with an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest tested by right heart catheterization, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHG and PVR > 3 Wood units (WU) which was not found other causes of pre-capillary PH such as due to lung disease, chronic thromboembolic PH and PH category 5 [14]. The most recent definition of PH is an increase in mean

pressure pulmonary artery (PA) >20mmHg. Diagnosis of pre-capillary PH or pulmonary arterial hypertension (pulmonary arterial hypertension =PAH) is enforced by increasing pulmonary vascular resistance (PVR) ≥ 3 WU [1].

In addition, the risks to the fetus including prematurity, growth retardation and increased perinatal mortality are very high [15]. The prognostic to mother and fetus is poor in pregnant women with pulmonary hypertension, contraception or early termination of pregnancy is recommended. However, the rate of early termination of pregnancy is quite low due to the high demand to continue their pregnancy [9].

High rates of fetal, maternal and intrauterine growth retardation have also been reported. Most of the deaths occurred during labor or in the postpartum period of 30%-56%. Pregnancy with PH carries a high risk for the patient. The normal pulmonary vasculature is adaptable to the hemodynamic and physiologic changes associated with pregnancy. However, with pulmonary vascular remodeling in PH, the capacity to adapt to these changes is impaired. During pregnancy, increased cardiac output due to increased intravascular volume can lead to right heart failure [16]. In this regard, cardiopulmonary function declines in the second and early third trimesters when hemodilution peaks in pregnancy, and the postpartum period is the most critical period for patients with pulmonary hypertension. The postpartum period the mechanical dam by the uterus containing the fetus opens after the baby and placenta were born, uteroplacental blood flow returns to the systemic heart when the baby is born and a process of hemoconcentration occurs as a physiological process after the process of hemodilution during pregnancy [17].

There is an increase in circulating volume that occurs from 6 weeks of gestation until the end of the second trimester of pregnancy by 50-70% higher than in non-pregnant women. Increased blood pressure poses particular problems for women with dilated cardiomyopathy and obstructive lesions such as mitral stenosis or pulmonary hypertension [18]. There is a decreased systemic vascular resistance during pregnancy. This decreased occurs from the fifth week of pregnancy and usually reaches a peak between 20-32 weeks of pregnancy. After 32 weeks, systemic vascular resistance increases again through gestation. The decrease in systemic vascular resistance is due to a combination of an increase in the vasodilator, namely prostacyclin (PGl2) and diversion of blood into the low impedance uteroplacental circulation [17].

By the end of the second trimester, cardiac output increases by about 30-50%. Most of the increase in cardiac output results in an increase in valve content and the heart rate continues to increase in late pregnancy. Pregnant women who are unable to increase cardiac output or require pressure to do so will develop heart failure during pregnancy [19]. An increase in heart rate at the end of the third, second or early trimesters pregnancy usually increases 10 times or 20 times above the heart rate compared to before pregnancy. Oxygen consumption increases by 20-30% as a result of increased cardiac work, increased myocardial oxygen consumption can trigger ischemia in women with coronary heart disease [20,21].

The increase in plasma volume during pregnancy is greater than the increase in the number of red blood cells resulting in hemodilution which explains the physiological anemia of pregnancy. During pregnancy there is an increase left ventricular end diastolic volume (from echocardiographic examination) from 10 weeks of gestation to the third trimester of pregnancy. Preload influenced by the position of the pregnant woman, when sleeping on her back there is compression of the inferior vena cava which causes obstruction of venous return and reduces cardiac output. The uterus also presses on the abdominal aorta and iliac arteries. This compression can be corrected by the left lateral decubitus position. Another mechanism for hemodilution during pregnancy is that estrogen increases renin levels resulting in sodium retention and an increase in the amount of fluid in the body. Other hormones such as prolactin, placental lactogen, prostaglandins and growth hormone increase during pregnancy which contributes to fluid retention. Women with dilated cardiomyopathy, valvular abnormalities such as mitral valve stenosis and PH cannot adapt to increased fluid volume [22].

Hemodynamic changes in pregnancies with PH increase. This causes an increase in myocardial oxygen demand, right ventricular ischemia caused by reduced right coronary artery flow, decreased left ventricular function, decreased cardiac output, and finally develops into cardiogenic shock [23]. In one study, Katsurahgi and colleagues reported data from 42 Japanese pregnant patients with PH (1982-2007). Eighteen patients terminated before term and 24 patients continued to term. In this study the authors divided patient data according to Pulmonary Arterial Pressure (PAP) and demonstrated that patients with mild PH tolerated pregnancy better than patients with severe PH (severe PH was defined as pulmonary artery systolic pressure (PASP) > 50 mm Hg by echocardiography or mean PAP > 40 mm Hg by cardiac catheterization). They reported one maternal and one fetal death in a patient with severe PH (overall mortality 4%) [24].

In a prospective study of 13 participating centers in France, Jais and colleagues reported data from 26 pregnancies over 3 years. A total of 16 pregnancies were clinically well to term and the babies were healthy, 6 pregnancies underwent abortion and 2 pregnancies had spontaneous abortion. Two women died in the early postpartum period due to right heart failure. The authors reported that pregnancy outcomes were better in patients with lower pulmonary vascular resistance (PVR 500±352 dyn/s/cm5) whereas patients with very high PVR (1667±209 dyn/s/cm5) died. Although the numbers

were small, 62% of all pregnancies were successful in this study [25].

In mothers with CHD, poor prognostic signs are hematocrit values > 60%, oxygen saturation < 80%, right heart failure and a history of syncope attacks [26]. In general, the prediction of death or risk of maternal conditions is related to the functional classification according to the reference from New York Heart Association (NYHA) or WHO for patients with PH. Data shows that 44% of pregnant patients show changes in functional class status during pregnancy [27].

A high risk of mortality has been reported (17-33%) in patients with severe PH and Eisenmenger syndrome. Maternal mortality is most common in the late trimester of pregnancy and first month postpartum due to pulmonary hypertensive crisis, pulmonary thromboembolism, right HF. Risk factors for maternal mortality are severe pulmonary hypertension, late hospitalization, general anesthesia. Pulmonary vascular disease may worsen during pregnancy as a result of decreased systemic vascular resistance and right ventricular overload [10].

In this case Mrs. AM when admitted at 28 weeks gestation was found to be WHO class IV NYHA II, found an unoperated AVSD with PH, based on PH echocardiography with high probability, E/e' 11.76, PVR 3,165 Wood Unit.

Management in this case as high risk pregnancy due to the mother with PH and fetus with recurrent pregnancy loss. The degree of PH significantly increases the risk of pregnancy. Permanent sterilization should be considered because pregnancy increases the risk and degree of PH. Otherwise double contraception is advised to minimize the chance of pregnancy [28].

Termination of pregnancy in this case by caesarean section operation because obstetric indication due to transverse lie in labor and the mother had a dyspneu. An emergency delivery should be taken into consideration in the event of RV dysfunction and hemodynamic instability. According to the guideline, termination of pregnancy is individual depending on the clinical condition of the mother with CHD, Bishop's score, fetal well-being and fetal lung maturity. In general, elective delivery is advised between 34 and 36 weeks of pregnancy [10]. The mode of delivery must be chosen carefully in patients with pulmonary hypertension. In this regard, caesarean delivery is the preferred mode of delivery but requires a multidisciplinary approach as outlined below [29]. Caesarean delivery should be considered for obstetric indications or for patients with ascending aortic dilatation >45 mm, severe aortic stenosis, preterm delivery w/ oral anticoagulants, Eisenmenger syndrome, or severe HF (Recommendation IIa-C). In this case obstetrician placing tourniquet on the lower limbs, to avoid imbalance cause by uterine reflux, and also early ambulation to reduce the risk of thromboembolism was done. Close hemodynamic monitoring continued for 3x24 h after delivery [8]. After maintenance and close monitoring, the patient died day5 after surgery. in Accordance with Research by Sliwa [30] pregnant patients with pulmonary hypertension, divided into 3 RVSP 30- 50 mmHg (n=90, 59.6%), RVSP 50-70 mmHg (n=43 mmHg, 28.5%), RVSP > 70 mmHg (n=18, 11.9%). Patients were also assigned to subgroups: iPAH, CHD-PAH, or oPAH and LHD-PH. More than 75% of patients are diagnosed with pulmonary hypertension before pregnancy. Maternal death occurred 1 week after delivery in 5 patients (3.3%), maternal death occurred 6 months after delivery in 2 patients (2.6%). The highest mortality was found in iPAH patients (3/7, 43%). During pregnancy heart failure occurs as much as 27%. Caesarean section was performed in 63.4% (23% emergency). Abortion was performed in 4% of patients fetal mortalit 2%, premature birth 21.7%, low birth weight babies 19%, neonatal mortality 0.7% [30].

A vaginal delivery should be avoided in patients with PH as it has many disadvantages like valsalva maneuver can reduce venous return. Pain during delivery can cause stimulation of the sympathetic nervous system and increase heart rate and systemic and pulmonary vascular resistance which can produce hemodynamic instability. With uterine contractions, approximately 500 ml of blood is diverted from the uterine circulation into the maternal circulation (autotransfusion), which causes an increase in circulating blood volume. Induction of labor like prostaglandin E produces pulmonary vasodilation while prostaglandin F2a induces pulmonary vasoconstriction [31]. In well-controlled patients with functional class I or II, vaginal delivery can also be considered. If a vaginal delivery is planned, assisted vaginal delivery may be considered to shorten the delivery time and reduce the risks of a lengthy delivery [32].

Caesarean section (C-section) is the preferred mode of delivery. C-sections prevent complications related to childbirth and autotransfusion associated with contractions. However, C- section can cause increased displacement of fluid from the abdomen, as well as increased pulmonary vascular resistance and increased right ventricular afterload exerted by positive pressure ventilation in the mechanical ventilation setting [33].

General anesthetics are known to suppress cardiac contractility (volatile agents), increase pulmonary vascular resistance (positive pressure ventilation), and increase PAP during laryngoscopy and intubation. General and epidural anesthesia should be administered early in labor to minimize the increase in cardiac output that occurs with contractions and pain. In addition, positive pressure ventilation can reduce venous return, causing patients with right heart failure [34,35]. Epidural anesthesia with additional doses is considered the best approach for regional anesthesia in patients with PH. Combined spinal-epidural anesthesia provides better sensory block than epidural anesthesia alone and without the added risk of hypotension when very low

doses are used [35]. Spinal anesthesia consisting of a single injection of an analgesic agent produces a short anesthetic duration (2 h) and may result in worsening rebound PAH. Therefore, it should be avoided in these patients. In addition, spinal anesthesia can cause systemic hypotension [35]. In this case Mrs. AM performed caesarean section under general anesthesia because it is easier to control the patient's hemodynamics during the procedure.

In this case we do close monitoring, the patient stayed at hospital until 36 weeks' gestational age. accordance to the guidelined pregnancies with high-risk PH should be followed up every 4 weeks until the third trimester and weekly evaluations are strongly recommended in the third trimester. An echocardiogram is recommended every 4 weeks and in the third trimester an echocardiogram is recommended to monitor cardiac status and adjust PH therapy [36]. A multidisciplinary approach provides good maternal and fetal outcomes in women delivering with PH. Therefore, close communication between obstetricians, anesthesiologists and pulmonary vascular clinicians who assist in the timely and appropriate management of these high-risk obstetric patients is highly recommended [8].

In this case Non-pharmacological therapy such as sodium restriction/salt restriction, limiting daily fluids given to an amount of 1.5-2 L/day and administering loop diuretics can reduce right ventricular overdistention and avoid cardiac decompensation [36]. However, diuretic administration must also be given carefully with close monitoring to avoid hemoconcentration and intravascular volume depletion [37].

The most critical period for acute decompensation is the postpartum. Therefore, the patient observed in the intensive care unit for postpartum [38]. The vulnerable period is during labor and postpartum, it may take up to 6 months for these patients to return to their previous baseline state. However, it is important to note that not all patients with PH return to their initial cardiopulmonary state after delivery [23].

After delivery, an increase in maternal volume occurs due to autotransfusion of blood from the contracting uterus and shifting peripheral edema from the extravascular compartment to the systemic vascular system. In addition, there is increased venous return from the inferior vena cava because it is not obstructed by the uterus containing the fetus. In this patient presenting with signs and symptoms of right heart failure, standard therapy including diuretics, oxygen therapy, vasodilators were already done [36,39].

In patients with severe heart problems, it is necessary to consider bottle feeding [40,41]. There are not enough data showing the excretion of pulmonary vasodilator drugs in breast milk [42]. In this case breastfeeds using a bottle while hospitalized.

Some literature shows the role of specific pharmacotherapy in PH pregnancy. Prostacyclin is a potent endogenous vasodilator and inhibitor of platelet function that is produced from arachidonic acid in endothelial cells by prostacyclin synthetase. There is a deficiency of prostaticin synthetase in PH patients. Currently there are parenteral prostaglandin preparations such as epoprostenol and iloprost [43].

Epoprostenol is preferred because of its better safety profile in the fetus (category B) compared to iloprost (category C). These drugs should be continued during pregnancy and postpartum [43,44]. In general, parenteral prostacyclin analogues are recommended in pregnant and pulmonary hypertensive patients with WHO functional class IV or in whom there is evidence of impaired right ventricular function. The recommended initial dose of epoprostenol is 2-4 ng/kg/min, which is increased slowly and monitored for signs of side effects such as headache, diarrhea, leg pain and flushing. The optimal dose of epoprostenol varies widely between 20-40 ng/kg/min [45].

In one case report, Geohas and McLaughlin successfully treated a pregnant woman with Eisenmenger syndrome with intravenous epoprostenol given during the last trimester (34 weeks and 3 days of gestation). This patient improved clinically with intravenous epoprostenol infusion which was rapidly titrated over 24 h to 9 ng/kg/min and then the patient was terminated by caesarean section for live births [46]. In several small case studies, the dose of epoprostenol was titrated from 0.5 ng/kg/min and gradually titrated to 0.5 ng/kg/min twice a week until it reached a dose of 8 ng/kg/min [24].

The third generation of prostacyclin analogues is iloprost (ventavis), available in IV, oral and aerosol forms. As it has category C iloprost is administered in the form of an inhalation aerosol. Inhalation therapy delivers the drug to the alveoli. Where vasodilation of the pulmonary arterioles occurs. This promotes good hemodynamic effects and increased exercise capacity. This drug has a relatively short duration [47]. Side effects include hypotension, headache, trismus, cough, flu-like symptoms and flushing. The recommended dose is 2.5-5μg/inhalation which can be repeated up to 6-9 times daily or every 2 h with an average maximum dose of 30 μg/day [14]. Sildenafil and tadalafil belong to a class of Phosphodiesterase-5 inhibitors with safety category B. The recommended dose according to ESC/ERS is 20 mg/8 h, with monitoring of side effects such as headache, epistaxis and flushing [14]. While the use of sildenafil monotherapy 25 mg/8 h which was titrated to 50 mg/8 h, showed a good and stable clinical effect on the mother [48]. There are several case reports on the use of sildenafil in pregnant patients with pulmonary hypertension. Tadalafil, a long-acting phosphodiesterase-5 inhibitor, is FDA-approved to treat patients with pulmonary hypertension, but no studies have reported the use of tadalafil in parturition patients with PH [8]. In this case Mrs. AM received sildenafil therapy 25 mg/8 h and Mrs. AP received sildenafil therapy 50 mg/8 h.

Bosentan is a non-selective endothelin receptor antagonist. It acts by blocking the action of endothelin-1 (ET-1), a potent vasoconstrictor and smooth muscle mitogen, on endothelin A and B receptor subtypes (ETA and ETB). Its therapeutic effect is by reducing pulmonary vascular hypertrophy and vasoconstriction caused by increased plasma ET-1 levels in patients with PH. However, its use in pregnant patients is contraindicated because it is included in the teratogenic (X) category [49].

SUMMARY

A case of a pregnant woman with pulmonary arterial hypertension and heart failure due to AVSD has been reported. Patient 32 years old, G5P0A4 36 weeks pregnant, 50 days PROM, recurrent miscarriage, with LVEF 70-71%, World Health Organization Modification IV (mWHO IV), ECG new atrial fibrillation, CHA2DS2-VASC score 1, HAS-BLED score 1, Hospital-acquired pneumonia with respiratory failure and anemia. 5 days after cesarean section the patient died with a live child, birth weight 2000 grams with ASD II.

Pulmonary hypertension in pregnant women is a complex disease with a high risk of maternal mortality. Pregnancy is contraindicated in women with severe pulmonary hypertension. According to current guidelines, pregnancy with severe PH should be avoided or terminated. Women with severe PH and refusing to terminate their pregnancy should be closely monitored and should work closely with cardiologists, obstetricians, pediatricians and anesthetists. It is necessary to educate about the risks of pregnancy to the mother and fetus. In pregnant women with PH, if the patient's condition is stable, delivery is planned at 34-36 weeks' gestation. However, if the mother's condition is unstable, the patient must immediately terminate the pregnancy.

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