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Literature Review

Role of inhaled nitric oxides in pregnancy with Eisenmenger syndrome

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ABSTRACT

Eisenmenger Syndrome (ES) is congenital heart disease with pulmonary hypertension and shunting turning from right to left. The resistance of pulmonary vascular more than 7.5 mmHg/L/min. The right ventricle and pulmonary artery always enlarge. During pregnancy, there will be hemodynamic changes that will affect the ES. It can be understood the possible dangers that can occur, like right heart failure; an increase in pulmonary arteries or the aggravation of pulmonary hypertension because there is no decrease in pulmonary resistance; A sudden decrease in venous return in supine hypotension syndrome can cause a relative increase in pulmonary arterial pressure so as to aggravate pulmonary hypertension and reverse shunting. Physiological effects of inhaled nitric oxide (INO) therapy cause selective pulmonary vasodilation: Hypoxia alveoli causes reversible vasoconstriction, thereby increasing pulmonary wedge pressure. INO can lower it. Moderate cardiac output and systematic arterial pressure are not affected; Selective in pulmonary because it is activated by hemoglobin; Selective vasodilation in the ventilated area, local hypoxia alveoli constricts the surrounding vascular tissue and redistributes blood flow to the ventilated lungs better and higher intraalveolar oxygen pressure. INO enhances this mechanism by increasing blood flow through a well-ventilated lung; Bronchodilators; Pulmonary surfactant, The combination of high concentrations of inspired oxygen and high concentrations of INO reduces the minimum surfactant surface tension.

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INTRODUCTION

Research on Nitric Oxide (NO) continues to grow since the identification of this molecule in 1987 has the same effect as the endothelium-derived relaxing factor (EDRF) (Steudel, Hurford, & Zapol, 1999); (Anas & Marlina, 2018). Many views about the mechanism of action of NO were put forward, since the application of inhaled nitric oxide (INO) in the laboratory and patients with primary pulmonary hypertension in 1991. In children and adults who experience severe pain and hypoxemia, INO improves arterial oxygenation and decreases pulmonary arterial hypertension selectively. The combination of INO with a ventilator can reduce the need for extracorporeal membrane oxygenation (ECMO) (Anggard, 1994); (Atz & Wessel, 1997); (Chen, 1997); (Finer & Barrington, 1997); (Steudel et al., 1999); (Barrington, Finer, Pennaforte, & Altit, 2017).

Pregnancy in ES is indicated. However, if the pregnancy continues, it needs special attention. During childbirth and childbirth, it is recommended to be done in the intensive care room with swan Ganz catheter and arterial pathway for serial measurement of arterial blood gas. The preload condition must be maintained by administering fluids, and excessive vasodilation must be avoided. Regional anesthesia should be avoided because it causes enlarged R-L shunting (Gibbs, 1988); (Sullivan & Ramanathan, 1988); (Goodwin, Gherman, Hameed, & Elkayam, 1999); (Brennan & Hatch, 2018).

Inhalation nitric oxidation is a potent and selective pulmonary vasodilator. Relaxation of pulmonary blood vessels that is dependent on endothelium in the Eisenmenger syndrome is impaired. Inhaling NO directly can reduce pulmonary hypertension and increase oxygenation due to the optimization of the ventilation-perfusion relationship. INO also has antithrombotic effects. And it is also used for the preparation of pulmonary heart transplants (Atz & Wessel, 1997); (Chen, 1997); (Cheung, Salas, Schulz, & Radomski, 1997); (Finer & Barrington, 1997); (Goodwin et al., 1999); (Lust, Boots, Dooris, & Wilson, 1999); (Steudel et al., 1999); (Barrington et al., 2017); (Brennan & Hatch, 2018).

PREGNANCY WITH EISENMENGER SYNDROME

Effects of Pregnancy on Eisenmenger Syndrome

In pregnancy, cardiovascular changes and oxygen transport will occur. Oxygen consumption in a state of rest increases in pregnancy. Improvements were apparent from the second trimester and an average increase of 33% above the mean before pregnancy. Oxygen consumption increases during labor. The average increase to the end of the second stage is approximately twice that of oxygen consumption before delivery (Ueland & Ferguson, 1988); (Cheitlin, Sokolow, & Melroy, 1993b); (Biswas & Perloff, 1994); (McAnulty, Metcalfe, & Ueland, 1994); (Cunningham et al., 2014).

Blood volume and its components increase during pregnancy - an average increase of 40% above the average value of nonpregnant women. The increase occurred mainly due to an increase in plasma volume, clearly seen in pregnancies 6-24 weeks and peaks at 30 weeks (Ueland & Ferguson, 1988); (Cheitlin et al., 1993b); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014).

During pregnancy, cardiac output at rest increases by an average of 40% above the value of not getting pregnant. This increase starts from the first trimester of pregnancy. During labor (first stage of labor), cardiac output will

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increase with each uterine contraction, with an increase of approximately 24% above cardiac output before contraction. In vaginal delivery (second stage), the increase ranged from 59 to 80% while in labor with a cesarean section about 25-57% above the resting value. Hemodynamic changes due to uterine contractions depend on the position of the mother. In the supine position, there is an increase in cardiac output by 25%; the heart rate decreases by 15%, causing an increase in stroke volume by 33%, while the slanted position changes as follows 7.6% - 0.7% and + 7.7%. So the degree of hemodynamic stability is in the oblique position (Ueland & Ferguson, 1988); (Cheitlin et al., 1993b); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014); (Brennan & Hatch, 2018); (Karelkina et al., 2019).

Anesthesia has a vital role in modifying cardiovascular responses during childbirth and delivery. Anesthesia does not modify significant changes related to labor (Gibbs, 1988); (Ueland & Ferguson, 1988); (Biswas & Perloff, 1994); (Brennan & Hatch, 2018); (Karelkina et al., 2019).

Estimated bleeding at 500 ccs vaginal delivery while cesarean section 1000 cc. Three days after delivery, the decrease in blood volume was the same in both types of labor (16.2%). The difference is only in vaginal hematocrit increased by 6% while cesarean section decreased by 6% Normal values such as the state before pregnancy, achieved less than two weeks after delivery. As a result of these changes will occur cardiovascular adaptation in the form (Gibbs, 1988); (Ueland & Ferguson, 1988); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014); (Brennan & Hatch, 2018):

1. Ventricular enlargement as a result of hyperdynamic circulation during pregnancy.
2. Decreased systematic or pulmonary vascular resistance due to the influence of pregnancy hormones, and
3. Suppression of inferior vena cava by the gravid uterus (especially in the third trimester of pregnancy), resulting in a decrease in cardiac output.

From these changes, it can be understood the possible dangers that can occur in pregnancy with ES. During pregnancy can occur (Gibbs, 1988); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014):

1. Right heart failure, even if there is no significant increase in pulmonary artery pressure.
2. Increased pulmonary arteries or increased pulmonary hypertension because in patients with Eisenmenger Syndrome, there is no decrease in pulmonary resistance during pregnancy.
3. A sudden decrease in venous return in supine hypotension syndrome can cause a relative increase in pulmonary arterial pressure to aggravate pulmonary hypertension and reverse shunting.

This danger can occur at any time during pregnancy, especially in old pregnancy, childbirth, and postpartum (McAnulty et al., 1994). In ES with secondary pulmonary hypertension or in primary pulmonary hypertension, decreased peripheral resistance when associated with decreased preload induced by changes in position or bleeding during labor. Which causes hypotension so that the right ventricle is unable to maintain blood flow through pulmonary arteriolar tissue with high resistance (Gibbs, 1988); (De Swiet, 1993); (McAnulty et al., 1994); (Cunningham et al., 2014); (Brennan & Hatch, 2018).

In the first stage of labor, there is an increase in pulmonary artery pressure because of his and pain. Aside from that, caution should be given when administering analgesics or anesthetics because the hypotensive effect can relatively

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increase pulmonary arterial pressure (Gibbs, 1988); (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014); (Brennan & Hatch, 2018).

In the second stage, it should be accelerated because of his pain, and straining can increase pulmonary artery pressure to aggravate pulmonary hypertension. Also, in the second and post-partum labor, the occurrence of bleeding or hypovolemia should be prevented because it can suddenly aggravate pulmonary hypertension or cause severe shortcuts. Circumstances that cause extensive thrombosis of small blood vessels in the pulmonary arterial system that occur in the postpartum period also cause increased pulmonary hypertension (Gibbs, 1988); (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014).

Regional anesthesia should be avoided because a decrease in systemic pressure causes the R-L shunting to enlarge. Also avoid hypoxia because it will increase pulmonary vascular resistance and further increase RL shunting (Gibbs, 1988); (Ueland & Ferguson, 1988); (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014); (Brennan & Hatch, 2018).

Effects of Eisenmenger Syndrome on Pregnancy

In cyanotic congenital heart disease that persists into adulthood, decreased blood vessel resistance causes an increase in R-L shunting by increasing cyanosis. Pregnancy in ES is contraindicated, and usually, spontaneous abortion occurs. Decreased oxygenation causes impaired fetal growth (Sullivan & Ramanathan, 1988); (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014).

In the case of pregnancy with cardiac abnormalities, aside from determining the functional effects, it is also essential to know the etiology. Mothers based on congenital heart abnormalities will increase the risk of cardiac malformations in their children, both due to genetic factors or due to impaired blood flow to the uterus. Whittemore et al. reported that 11% of infants with congenital heart abnormalities from 66 pregnancies of 36 mothers with ASD (Atrial Septal Defect) (McAnulty et al., 1994).

The occurrence of heart functional disorders in the form of heart rhythm disorders, heart failure that occurs pulmonary hypertension is something that needs to be treated more carefully because the prognosis for the mother or fetus is not good. Fetal growth and development are influenced by the severity of circulatory physiology and arterial oxygenation saturation. Reportedly, in pregnant women with pulmonary hypertension, the incidence of preterm birth is 55%, IUGR (intrauterine growth restriction) 30% and perinatal death 28% (Sullivan & Ramanathan, 1988); (De Swiet, 1993); (McAnulty et al., 1994). Maternal mortality with ES or pulmonary hypertension ranges from 30-70% (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014). Karelkina et al. reported outcomes of 13 pregnancy in women ES, 4 cases, a transfer to mechanical ventilation was required. Intensive therapy included a combined use of vasodilators, the use of inotropes, the prevention of thromboembolic complications. Three women died within six months of delivery (9, 14, and 15 days post-delivery). Eleven children were discharged from the hospital in a satisfactory condition (Karelkina et al., 2019).

The danger of maternal death can occur both during pregnancy, especially advanced pregnancy, childbirth, and early postpartum. Regarding the cause of death, it is not known with certainty, suspected (Pitts, Crosby, & Basta, 1977); (Midwall, Jaffin, Herman, & Kupersmith, 1978); (Sullivan & Ramanathan,

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1988); (McAnulty et al., 1994); (Cunningham et al., 2014); (Brennan & Hatch, 2018); (Katsurahgi et al., 2019):

1. Because of a sudden increase in pulmonary arterial pressure, it can cause a "thrombotic occlusion pulmonary artery channel," which is a blockage of the small pulmonary arteries by the thrombus, which had previously been chronically narrowed.
2. Blockage of small pulmonary arteries by embolism
3. Cardiac arrhythmias that can occur due to a sudden decrease in cardiac output resulting in impaired coronary perfusion, and
4. Right ventricular failure due to a sudden increase in pulmonary artery pressure.

Management of Pregnancy with Eisenmenger Syndrome

If found congenital heart abnormalities with Eisenmenger Syndrome, it is advisable to end the pregnancy. According to Gleicher et al., Termination of pregnancy is less dangerous than if the pregnancy is continued. However, during the procedure, strict monitoring of pulmonary artery pressure, cardiac output, rhythm, and heart rate should be monitored. Besides that, an active examination should be carried out to detect congenital abnormalities in the fetus before birth (Sullivan & Ramanathan, 1988); (De Swiet, 1993); (Biswas & Perloff, 1994); (Cunningham et al., 2014).

For a pregnancy that remains desirable, the maternal hemodynamic status and fetal growth are closely monitored. The mother's hemodynamics are kept stable until postpartum. She has been given prophylactic antibiotics. Infectious diseases should be treated quickly and adequately because infections can increase the work of the heart and especially respiratory infections, which can increase pulmonary vascular resistance so that it worsens pulmonary hypertension and its backflow (Sullivan & Ramanathan, 1988); (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014).

They should be hospitalized since the second trimester and remain treated for at least two weeks post-delivery. During childbirth and childbirth, it is recommended to do in an incentive care room with Swan Ganz catheter and arterial pathways for serial measurement of arterial blood gas (Sullivan & Ramanathan, 1988); (De Swiet, 1993); (Biswas & Perloff, 1994); (Cunningham et al., 2014); (Brennan & Hatch, 2018).

At the time of labor, pain needs attention. Analgesics can be given, but still, need to be careful. Preferably with general anesthesia or intra-tidal morphine because analgesic effects are perfect, and there are no motor and autonomic effects (Heytens & Alexander, 1986); (Bistch, Johansen, Wennevold, & Osler, 1988); (Buckshee, Biswas, Mittal, & Agarwal, 1988); (Gibbs, 1988); (Sullivan & Ramanathan, 1988); (Roberts & Keast, 1990); (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014); (Brennan & Hatch, 2018).

If labor induction is needed, intra-cervical prostaglandin administration (for priming and induction of labor) followed by oxytocin drip after 6-12 hours later (Heytens & Alexander, 1986); (Bistch et al., 1988); (Sullivan & Ramanathan, 1988); (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Cunningham et al., 2014).

Labor is carried out by vaginal delivery, fired by cunam or vacuum extraction. However, some have suggested that cesarean section planning is better than vaginal delivery because of maternal stress on labor, and is a planned procedure so that it can be optimally prepared, hemodynamics and ventilation can be well controlled. Also, it was suggested

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that in vaginal delivery, the contents of the stroke, cardiac output, and left ventricular work increase during uterine contractions. There is also a sudden increase in preload and venous return during uterine contractions and placental release. So it is not surprising that the death of two-thirds of mothers occurred at that time. What is important to note in labor is to prevent excessive blood loss. Therefore, uterotonics are given immediately as soon as the placenta is born, and if there is bleeding it is immediately treated, and adequate correction is made (Sullivan & Ramanathan, 1988); (Roberts & Keast, 1990); (De Swiet, 1993); (McAnulty et al., 1994); (Cunningham et al., 2014).

Vasodilators such as tholazolin or others are not routine. Anticoagulant is also not routinely given. Oxygenation or phlebotomy (Pitts et al., 1977); (Jones et al., 1981); (Lieber, Dewilde, Huyghens, Traey, & Gepts, 1985); (Heytens & Alexander, 1986); (Bistch et al., 1988); (Buckshee et al., 1988); (Sullivan & Ramanathan, 1988); (Roberts & Keast, 1990); (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Weiner & Thompson, 1997); (Weiss et al., 2000); (Brennan & Hatch, 2018).

Postpartum care can be done early mobilization but by using stockings (long socks). This activity is to prevent thromboembolism and a sudden decrease in venous return. Breastfeeding is not recommended for subsequent pregnancies, the best choice is sterile (Lieber et al., 1985); (Sullivan & Ramanathan, 1988); (Cheitlin et al., 1993b); (De Swiet, 1993); (McAnulty et al., 1994); (Cunningham et al., 2014).

USE OF INHALATION NITRIC OXIDES IN EISENMENGER SYNDROME IN LABOR AND POST-LABOR PREGNANCY

Inhalation of nitric oxide in pulmonary hypertension

Robinson et al. (1999) reported that pulmonary hypertension therapy in pregnancy includes diuretics, digoxin, and oxygenation with limited efficacy. INO has demonstrated effectiveness and safety in the acute management of patients with pulmonary hypertension. The continuous use of extended INO affects a selective pulmonary vasodilator and is useful in the management of pulmonary hypertension in pregnancy (Robinson, Banerjee, Landzberg, & Thiet, 1999). The effect of INO's work on pulmonary circulation can be seen in the image

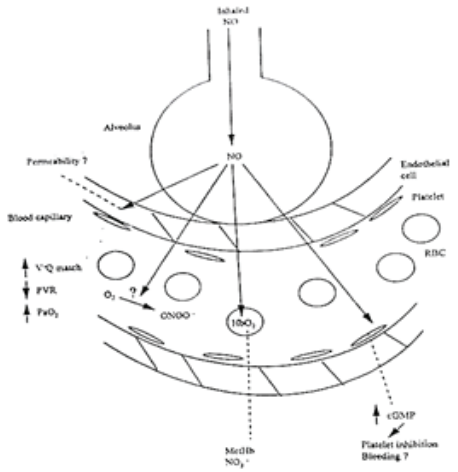

Figure 1. The pharmacological action of inhaled nitric oxide shows the effect on pulmonary veins by improving the accuracy of perfusion (V / Q) ventilation, decreasing PVR, and increasing PaO2. Nitric oxide also affects platelets, by inhibiting platelet function and increasing the tendency for bleeding. Red blood cells that contain oxyhemoglobin activate nitric oxide by converting it to methemoglobin and nitrate. Quoted from (Cheung et al., 1997).

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Experiments on goat-born babies born with ligation of the ductus arteriosus get conditions such as primary pulmonary hypertension. Furthermore, INO is given at various concentrations to see changes in the hemodynamic parameters of the pulmonary circulation. Decreased pulmonary artery wedge pressure and pulmonary vascular resistance so that pulmonary blood flow and systemic oxygen pressure increase. (Steinhorn, Morin, & Fineman, 1997).

Kinsella et al., (1997) reported experiments on rabbits who were very premature with IMV (intermittent mandatory ventilation) found conditions that worsen the progressive gas exchange and increased pulmonary arterial pressure. With immediate and continuous INO administration 20 ppm, a gradual improvement in the condition of gas exchange and hemodynamic circulation of the pulmonary circulation results (Kinsella & Abman, 1997).

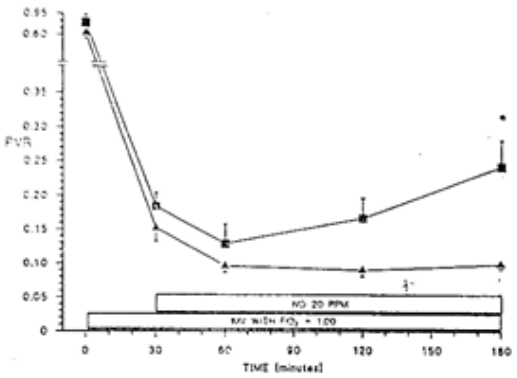

Figure 2. Early and ongoing management with low-dose inhalation nitric oxide prevent an increase in PVR associated with tidal volume ventilation in premature goats in 78% of the term ■ (control) ▲ (inhaled nitric oxide). Quoted from (Kinsella & Abman, 1997).

Fineman et al. (1997) in Chen (1997) found that the continuous release of nitric oxide is essential in the reasonable regulation of pulmonary vessels. Dysfunction of nitric oxide release is one of the causes of primary pulmonary hypertension in neonates. Neonates who get inhaled nitric oxide show a marked increase in oxygenation in the first 20 minutes and then (Chen, 1997). Weiss et al. (2000) found that treatment that immediate and continuous treatment with INO and Prostasklin IV or inhalation can improve pulmonary endothelial cell function, abnormal platelet aggregation, right hemodynamic heart, and life expectancy of patients with primary pulmonary hypertension (Weiss et al., 2000).

Finer et al. (2000) found that in neonates near term or near term with hypoxic respiratory failure given INO showed increased oxygenation, and there was a decrease in the incidence of death and the need for ECMO. Pedersen et al. (1997) say that nitric oxide is a pulmonary vasodilator and can correct inaccurate perfusion ventilation in cases that affect the lung parenchyma (Pederson, Hansen, & Henneberg, 1997).

Anggard (1994) says low concentrations of INO (50-80 ppm) are selective pulmonary vasodilators and increase arterial oxygenation. This effectiveness is demonstrated in changes in pulmonary vasoconstriction due to hypoxia in humans without causing systemic vasodilation (Anggard, 1994). Prostacyclin Analog, Iloprost inhalation is a prostacyclin analog that has a longer half-life of up to 25 minutes after inhalation so that it can be given 6-8 times per day and has minimal systemic side effects, but the efficacy in patients with adult Eisenmenger Syndrome has not been studied (D'Alto, Merola, & Dimopoulos, 2005); (Oechslin et al., 2010).

Inhalational Nitric Oxide in Pregnancy with Eisenmenger Syndrome

Kazue (1995) found that INO, even at low doses, is a potent and selective pulmonary vasodilator in congenital heart disease complicated by pulmonary hypertension. The results of his study found a positive correlation between initial pulmonary artery pressure and

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pulmonary artery vasodilation (Kazue, 1995). Goodwin et al. (1999) reported a case of a 27-year-old woman. Gravida 2 para 1 with 36 weeks of gestational age diagnosed with ASD with SE (Goodwin et al., 1999).

Furthermore, IUGR was obtained, so termination was carried out with drip oxytocin. Patients are given epidural narcotics, ampicillin, and gentamicin. Moreover, oxygen with 100% FiO2, but SaO2 keeps going down so that it adds INO 20 ppm for 5 minutes and baby boy 2640 gr AS 8-9 with low forceps. INO was continued for 45 minutes and obtained SaO2, and pulmonary arterial pressure returned to the baseline, and the hypoxemia was corrected (Goodwin et al., 1999).

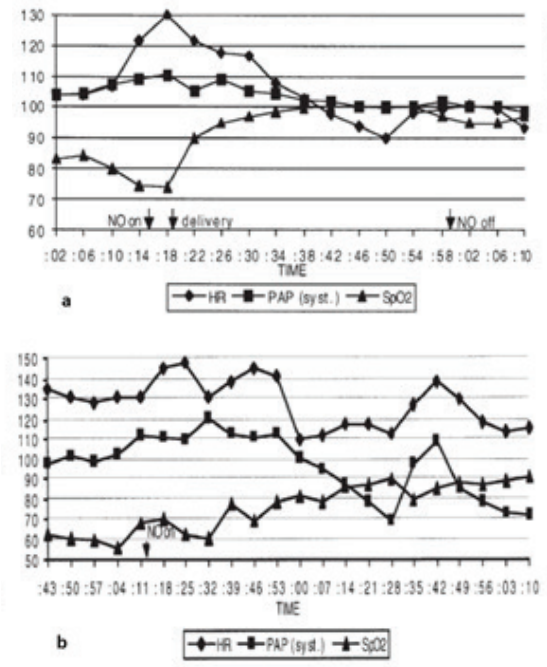

Figure 3. a) Effects of NO on oxygen saturation and hemodynamic parameters during labor and postpartum, b) Effect of nitric oxide on oxygen saturation and hemodynamic parameters postpartum; HR: Heart Rate; PAP: Pulmonary Artery Pressure; SpO2: O2 saturation. It modified from (Goodwin *et al*., 1999).

Until two days postpartum, the condition is stable, then an increase in pulmonary artery pressure. Trying to reduce it with nifedipine and hydralazine did not work because of a decrease in systematic pressure. Day 3 hypoxemia is heavy even with maximal O2. INO is given by titrating up to 80 ppm, and the hemodynamic and SaO2 parameters are improved. Several attempts have been made to reduce INO, but there has been a marked desaturation. Due to the limitations of INO, on the 5th day, INO was stopped after 48 hours of therapy, and a significant reduction in SaO2 was obtained. Prostacyclin is given peripherally. After improving briefly, his hypoxemia worsened and died on the 6th day postpartum. At autopsy, ES was obtained with ASD and a 1 cm diameter thrombus in the pulmonary artery. The goal of therapy is to try to go through a period of maximum stimulation to the deterioration of pulmonary hypertension that is characteristic of the peripartum period. Although death is reported no later than two weeks postpartum, most occur daily (Goodwin et al., 1999).

Differ with the case reported by Katsurahgi et al. (2019). They collect 15 patients with ES that the characteristics 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 the pregnancy after counseling regarding the maternal and fetal prognoses. Of the 5 ES cases, the 5th case, VSD case, was the hardest. Hospitalization has been carried out since the 9th week of SpO2 81%, and its condition worsened at the 26th week of NYHA III so that the termination is done at the 28th week and birth weight is 1027 grams. The description of the case can be seen in figure 4.

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Clinical characteristics of the five delivery cases.

Parameter	Case 5
Type of CHD	VSD
SpO_2 (before, late preg) (%)	86, 81
PaO_2 (before, late preg) (mmHg)	54, 48
Mean PABP (before, late preg) (mmHg)	76, nd
PVR (before, late preg) (dyne × s/cm^2)	1560, nd
NYHA (pre-preg → late preg → 1 year after delivery)	II→III→II
Hospitalization (gestational weeks)	9
Worsening of exertional fatigue (gestational weeks)	26
Oxygenation, drugs	18 w – O_2 2L, tadalafil, epo, NO, bosentan
NYHA class, drugs 2 year after delivery,	II, bosentan, tadalafil
Delivery (week-days)	28–2
Newborn weight (g) (SD)	1027 (–0.9)

CHD; congenital heart disease; PDA, patent ductus arteriosImonary vascular resistance; preg, pregnancy; NO, nitric oxide; epo, epoprostenol; HOT,

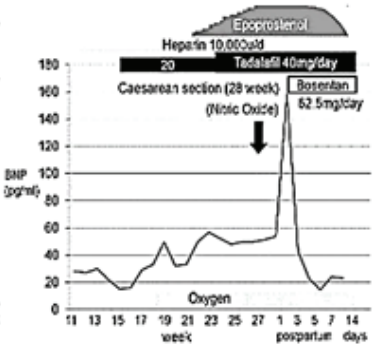

Figure 4. The clinical course of an ES-complicated pregnancy treated with drugs for PAH (case 5). Heparin, tadalafil, and epoprostenol were administered during pregnancy. Epoprostenol infusion therapy was started at 0.5 ng/kg/min and increased gradually in increments of 0.5 ng/kg/min twice weekly until a dose of 8 ng/kg/min was reached. Because the NYHA class worsened to Class III, the cesarean section was performed at 28 weeks. During the operation, inhaled nitric oxide 5 ppm was administered. In the postpartum course, bosentan was initiated, and epoprostenol was decreased gradually. After one month, there are no complications, and NYHA was class II, so the patient discharged. It is modified from (Katsurahgi et al., 2019).

Pregnancy and neonatal outcomes In the five delivery cases, the 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. 4). 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 healthy growth and proper neurological development. During pregnancy and postpartum, none of the cases exhibited excessive bleeding, thromboembolism, or an arrhythmia that required medical therapy (Katsurahgi et al., 2019).

Chronic pulmonary hypertension has two components, fixed and reactive. The remodeling of pulmonary arteries causes the fixed component due to a chronic response to increased pulmonary pressure or pulmonary flow. Pulmonary artery vasoconstriction usually caused by hypoxia, which contributes to the reactive component. Although the fixed component is less responsive to pharmacological manipulation, especially in ES, INO provides a real response in this case with decreased pulmonary arterial pressure and improved arterial oxygenation. What is unfortunate is the creation of INO only at urgent needs, so it is not possible to supply it permanently for definitive purposes (Fishman, 1994); (Kazue, 1995); (Atz & Wessel, 1997); (Pederson et al., 1997); (Robinson et al., 1999); (Steudel et al., 1999).

The effects of NO on chronic constricted pulmonary blood vessels are greatly affected, especially if the smooth muscle of the blood vessels is far from the alveoli, which allows diffusion of sufficient constraints because of the decrease in venous smooth muscle pressure by NO is always inhibited by intra-

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vascular hemoglobin. Changes in endothelial morphology contribute to the limited response to NO. Significant clinical responses appear without any effect on systemic blood vessels (Finer & Barrington, 1997); (Goodwin et al., 1999); (Steudel et al., 1999); (Omer, Rohilla, Rohilla, & Kushnoor, 2012).

At an inhalation dose of less than 100 ppm, methemoglobin formation is reported to be very small. Even so, these patients received episodes of methemoglobin that required a reduction in the INO dose and required the administration of methyl blue. There were no reports of NO tolerance or loss of selectivity in the pulmonary artery during exposure to INO. Back reactions such as vasoconstriction and hypoxemia after INO's sudden release have been explained and precipitated cardiopulmonary collapse (Atz & Wessel, 1997); (Goodwin et al., 1999); (Steudel et al., 1999).

The safety of long-term use of INO has not been established. Continuous use of INO is reported no later than 68 days in primary pulmonary hypertension patients awaiting pulmonary heart transplantation. Side effects of INO use are not significant if the concentration is 50,4±23 ppm (Atz & Wessel, 1997); (Goodwin et al., 1999); (Robinson et al., 1999); (Steudel et al., 1999).

Among ES patients, most deaths occur in the aftermath of early labor and are preceded by refractory hypoxemia. The cause of oxygen desaturation is unclear. Hemodynamic changes immediately before and after labor exacerbated by hypoxemia that initiates death often show a slight but slight association. Small and large pulmonary artery emboli are believed to be contributing factors. In fact, in this patient, there was a hemodynamic disorder, although adequate anticoagulation was given. This shows that there are other mechanisms involved. Significant changes in estrogen levels in the first 2 weeks postpartum contribute to changes in blood vessel reactivity, especially in the pulmonary circulation (Lieber et al., 1985); (Heytens & Alexander, 1986); (Buckshee et al., 1988); (Roberts & Keast, 1990); (Weiner & Thompson, 1997); (Goodwin et al., 1999).

Sudden death due to thromboembolism and systematic hypotension with backflow causes hypoxemia and induces arrhythmias, or causes right ventricular failure. Transient hypotension is seen in normal labor but also general anesthesia or infiltration. Unfavorably, sudden death in ES is not always consistent after hypotensive episodes. Furthermore, thromboembolism is enough to cause sudden death. The typical scenario of the gradual disorder is multiple small pulmonary artery emboli or recurrent hypoxemia that triggers pulmonary vasoconstriction (Lieber et al., 1985); (Heytens & Alexander, 1986); (Gibbs, 1988); (Roberts & Keast, 1990); (Finer & Barrington, 1997); (Goodwin et al., 1999).

Kopp et al., (1997) in Weiner and Thompson (1997) found that nitric oxide synthesis increases starting in early pregnancy before prostacyclin synthesis increases, this increase is in line with the increase in plasma estradiol. This increase can be blocked with estrogen receptor antagonists such as tamoxifen (Weiner & Thompson, 1997).

Lust et al. (1999) reported a 29-year primigravida case with a 26-week pregnancy diagnosed with ASD with ES. Patients were MRS-treated, bed rest, O2, and heparin. It has bee planned elective vaginal delivery at 34 weeks' gestation. Betamethasone, ampicillin, and gentamicin are given. When induction with PGE2, heparin is stopped. Epidural morphine anesthesia was given and transferred to an intensive care room (Lust et al., 1999).

Inhalation nitric oxidation is given by titrating in 80% FiO2 until a maximum

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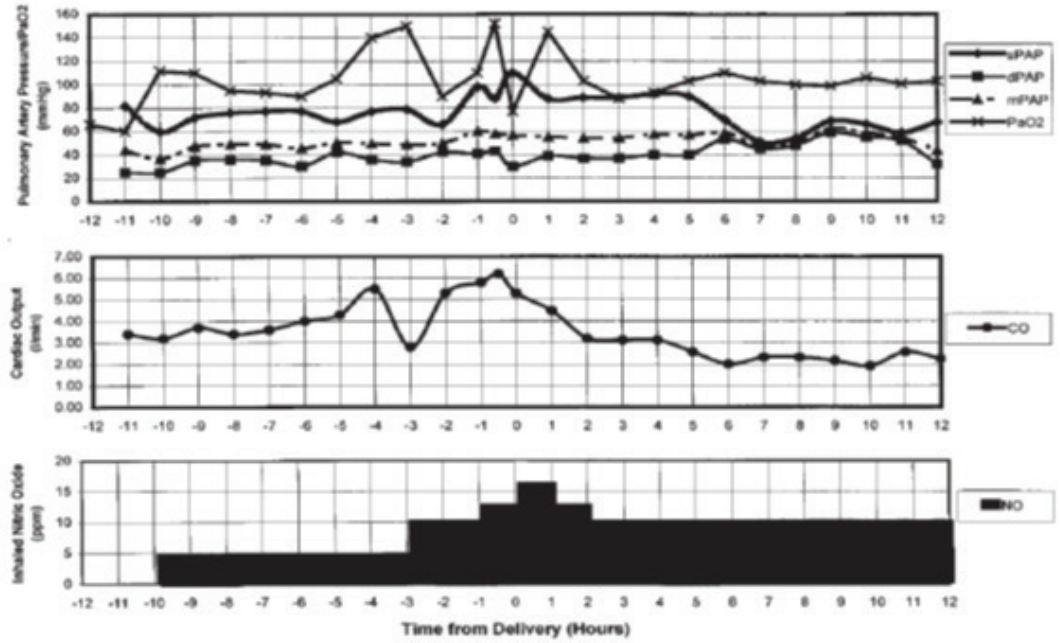

Figure 5. Development during labor. Labor occurs at 0. S, systolic; PAP, pulmonary artery pressure; d, diastolic; m, average value. It quoted from (Lust et al., 1999).

reduction in pulmonary arterial pressure and an increase in gas exchange is achieved. During labor, pulmonary pressure is increased given prostacyclin nebulizer and systematic hypotension and type II deceleration without changes in pulmonary arterial pressure. When maximal dilatation is performed, an amniotomy and birth of a female baby 1823 gr AS 10-10 by vacuum extraction during neonates is not problematic (Lust et al., 1999).

Ten ppm inhalation nitric oxidation is continued with 80% FiO2, and pulmonary arterial pressure decreases gradually. Cardiac output increases within 24 hours after delivery. The second day after childbirth, there is a lot of vaginal bleeding and persistent and supraventricular tachycardia without clinical changes in oxygenation or the incidence of heart failure. Pulmonary arterial pressure increases, and cardiac output increases during supraventricular tachycardia. Bleeding is stopped with steady cardiac output and increased pulmonary diastolic pressure which shows a shift in fluid after delivery (Kazue, 1995); (Finer & Barrington, 1997); (Kinsella & Abman, 1997); (Pederson et al., 1997); (Lust et al., 1999); (Robinson et al., 1999).

Many factors are involved in the progression of pulmonary hypertension during the 14 days postpartum, which causes heart failure and death. Including postpartum bleeding causes a decrease in pulmonary blood flow. The patient had never experienced clinical hypotension, and pulmonary diastolic pressure remained high during the postpartum period. He gets an arrhythmia, but it is not related to an increase in cardiac output. Both events are related to the development of in situ pulmonary thrombus and the deterioration of pulmonary hypertension (Buckshee et al., 1988); (Roberts & Keast, 1990); (Lust et al., 1999).

Pregnancy and childbirth add to the burden on patients with fixed pulmonary circulation resistance. Blood volume increases by 50%, stroke volume, and cardiac output increased in the first trimester, second trimester, and during labor. Increased pulmonary artery pressure

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causes enlargement of the right ventricle, arrhythmias, and heart failure. R-L shunting by hypoxemia is worsened by the regular decrease in systemic vascular resistance. During labor, uterine contractions cause autotransfusion and increase cardiac output by 25%. This increase in pulmonary arterial pressure precipitates heart failure or arrhythmias. A decrease in cardiac output may occur during stage II as a result of increased intrathoracic pressure when striking. In stage III, autotransfusion of 500 ccs occurred. Stroke volume and cardiac output return to normal gradually in the two weeks postpartum. These factors contribute to maternal death during childbirth and childbirth (Gibbs, 1988); (Ueland & Ferguson, 1988); (De Swiet, 1993); (Biswas & Perloff, 1994); (McAnulty et al., 1994); (Lust et al., 1999); (Cunningham et al., 2014).

Giving NO through nasal cannula and catheter through the trachea is useful in this patient because it allows him to communicate with family and food and drink needs. The use of catheters through the trachea can prevent sudden hypoxic crises and increased pulmonary arterial pressure associated with terminating the mask release system (Atz & Wessel, 1997); (Lust et al., 1999); (Steudel et al., 1999).

This patient was monitored at the intensive care unit during labor day and 21 days postpartum until he died. During this period, the management of pulmonary heart transplantation remains the potential to be continued. NO is continued with the catheter versus the trachea to maintain oxygenation and additional benefits in decreasing pulmonary artery pressure and the risk of pulmonary arterial thrombosis (Cheung et al., 1997); (Finer & Barrington, 1997); (Kinsella & Abman, 1997); (Lust et al., 1999).

Immediate management of factors known to cause adverse shunting dynamics such as hypoxemia, arrhythmias, fluid balance, and acidosis, should be carried out, as well as prophylactic antibiotics for bacterial endocarditis and careful anticoagulant therapy. The postpartum monitoring period is related to the severity of the underlying cardiovascular disease. This patient is dependent on NO to improve oxygenation and requires intensive care. The contribution of the difficulty of anticoagulant therapy in increasing pulmonary artery pressure is unclear. Cardiopulmonary transplantation in ES due to ASD is essential because these patients will be able to get pregnant with good results (Pitts et al., 1977); (Jones et al., 1981); (Lieber et al., 1985); (Heytens & Alexander, 1986); (Fremes et al., 1990); (McCarthy et al., 1991); (De Swiet, 1993); (Biswas & Perloff, 1994); (Weiner & Thompson, 1997); (Lust et al., 1999).

Inhalation nitric oxidation is useful for improving oxygenation and decreasing pulmonary arterial pressure. Maintaining improved oxygenation during childbirth and the postpartum period and vasodilation and anti-thrombotic effects of NO limit the increase in pulmonary arterial pressure, so expect an increase in cardiac output during childbirth among patients with fixed pulmonary artery disease. Despite prompt treatment by improving oxygenation and anti-coagulants, the prognosis of this patient remains poor. Death is caused by progressive arrhythmia and pulmonary hypertension before a pulmonary heart transplant is carried out. ES remains a life-threatening condition when it comes to pregnancy. Patients with ES abnormalities must explain the risks of pregnancy, contraception, and early termination if contraception fails. Fruitful of labor can be enhanced by improved oxygenation using INO in patients with pulmonary hypertension and hypoxemia (Lieber et al., 1985); (Roberts & Keast, 1990); (Cheitlin, Sokolow, & Melroy, 1993a); (McAnulty et al., 1994); (Kazue, 1995); (Pederson et al., 1997); (Lust et al., 1999); (Robinson et al., 1999); (Steudel et al., 1999); (Weiss et al., 2000).

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CONCLUSION

Pregnancy in ES is a contraindication, but if the pregnancy continues, during the process of giving birth and delivery, it is recommended to be carried out in an intensive care room with a strict monitor. The preload condition must be maintained by administering fluids, and excessive vasodilation must be avoided. Regional anesthesia should be avoided because of the enlarged R-L shunting.

Inhalation nitric oxide is a potent and selective pulmonary vasodilator. In ES, relaxation of the endothelium-dependent pulmonary blood vessels is disturbed. Patients with ES who inhale NO can directly reduce pulmonary hypertension and increase oxygenation due to the optimization of the ventilation-perfusion relationship. Inhalation nitric oxide also has an antithrombotic effect and is also used in preparation for a pulmonary heart transplant.

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