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Pregnant woman with Eisenmenger's syndrome (RCD code: VII-II-1A.4d)

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Abstract

Pregnancy in women with pulmonary arterial hypertension due to congenital heart disease is associated with significant morbidity and mortality both in the mother and fetus. We report a case of a 25-year-old woman with Eisenmenger's syndrome who got pregnant when treated with bosentan. Bosentan was changed to sildenafil. During the course of pregnancy she developed ischemic stroke. She delivered in the 33 week of gestation. We present our treatment approach and review the current literature on pregnany in pulmonary arterial hypertension. JRCD 2013; 1 (3): 113–117

Key words: pulmonary hypertension, congenital heart disease, pregnancy,

Background

Pregnancy in women with pulmonary arterial hypertension (PAH) due to congenital heart disease (CHD-PAH) is associated with significant morbidity and mortality both in the mother and fetus. Data from the years 1978 to 1996 showed a maternal mortality rate of 36% [1]. Historically, neonatal survival was 86% [1]; however, if oxygen saturation was less than 85%, a live birth was unlikely (<12%) [2].

Case presentation

A 25-year-old woman with PAH associated with an aortopulmonary window was admitted to the Centre for Rare Cardiovascular Disease at the John Paul II Hospital in June 2011 because of worsening dyspnea. She worked as a hairdresser. She had a partner but still lived with her parents. On admission, she was classified as class III according to the World Health Organization (WHO) functional classification.

The aortopulmonary window was diagnosed when she was 6-months old. At the age of 3 years, she underwent the first right heart catheterization, which revealed right-to-left flow through the aortopulmonary window.

Prior to admission she was not taking any drugs. A physical examination on admission revealed central cyanosis and clubbing without peripheral edema. Her vital signs were as follows: body temperature of 36.6°C, respiratory rate of 14 breaths/min, heart rate regular of 95 beats/min, blood pressure of 120/80 mm Hg, and oxygen saturation on room air of 88%. Heart auscultation revealed increased accentuation of the second heart sound. Breath sounds were normal. The liver was not enlarged.

Chest radiography revealed thoracic scoliosis and an electrocardiogram showed regular sinus rhythm of 90 beats/min with a high R in lead V_1 (10 mm). The results of pulmonary function tests were normal. A lung ventilation/perfusion scan showed no segmental perfusion defects. Angiographic computed tomography did not reveal signs of pulmonary thromboembolism. In laboratory tests, the N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was 93 pg/mL and the hemoglobin level was 16 g/dL. She walked a distance of 429 m in the 6-minute walking test (6MWT); arterial oxygen saturation decreased from 90% to 79% at the end of the test.

Echocardiography showed normal left heart dimensions and valves, left ventricular ejection fraction of 70%, right ventricular

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hypertrophy, and benign tricuspid valve regurgitation with estimated right ventricular systolic pressure of 110 mm Hg.

In cardiac catheterization, systolic, diastolic, and mean pulmonary artery pressures were 96, 42, and 67 mm Hg, respectively; right atrial pressure was 5 mm Hg, cardiac output was 2.89 L/min, cardiac index was 2.26 L/min/m^2, and pulmonary vascular resistance was 1816 (dyne × s × cm^{-5}). Additionally, there was a decrease in oxygen saturation of 10% between the ascending (98%) and descending aortas (88%). The patient received bosentan at a standard dose.

On routine follow-up in November 2011, the patient was still in WHO class III. In the 6MWT, she walked a distance of 429 m with desaturation from 85% to 70% at the end of the test. During the hospital stay, she experienced the first pulmonary hemorrhage. In bronchoscopy, blood flow to right segmental bronchi 1 and 3 was revealed. The results of the bronchopulmonary lavage were as follows: cultures for bacteria and fungi – negative, cytology – normal, and the test for *Pneumocystis jiroveci* – negative. Owing to low resting oxygen saturation, the patient received home oxygen therapy.

During a follow-up visit in February 2012, the patient reported to have been pregnant for 8 weeks. She stopped bosentan therapy about 7 weeks before the visit because she suspected to be pregnant. She suffered from more severe dyspnea. In the 6MWT, she walked a distance of 369 m with desaturation from 72% at rest to 62% at the end of the test. The NT-proBNP level was 200 pg/mL and the hemoglobin level was 12.8 g/dL. She was urgently admitted to the hospital. Bosentan was replaced with sildenafil. The patient, her mother, and her partner were informed about the high risk of pregnancy to the mother and the child. However, they refused to stop pregnancy, and they signed a written statement.

During hospital stay, the patient developed the symptoms of stroke. Urgent diffusion magnetic resonance imaging of the brain revealed the area of acute ischemic stroke. She was transported to a stroke unit. Despite the early phase of stroke, thrombolytic therapy was contraindicated because of severe neurological condition. She received 25 points on the National Institute of Health Stroke Scale. The symptoms of stroke resolved during the next 48 hours. Based on an ultrasound examination, deep vein thrombosis was excluded. Acetylsalicylic acid (75 mg) was introduced as secondary prevention of stroke, and the patient was sent back to the cardiac ward. A gynecological examination was normal and ultrasonography revealed normal fetal growth. The case of the patient was consulted by a local multidisciplinary team, including a cardiologist and neurologist, as well as by international experts, including Professor Nazzareno Galiè (Bologna, Italy), Professor Uri Elkayam (Los Angeles, United States), and Professor Adam Torbicki (Otwock, Poland).

Further management plan included:

- hospitalization of the patient in the department of high-risk and pathological pregnancy from the 26th week of gestation
- switch from aspirin to low-molecular-weight heparin with anti-Xa monitoring in the third trimester of pregnancy to prevent premature closure of patent ductus arteriosus in the fetus
- continuation of sildenafil
- treatment with intravenous epoprostenol in case of clinical deterioration
- use of nitric oxide in case of a decrease in arterial oxygen saturation during delivery, combined with milrinone or dobutamine in case of hemodynamic compromise
- slow withdrawal of epoprostenol after delivery with simultaneous introduction of oral therapy of PAH
- supportive management with diuretics during pregnancy, if needed, with higher doses expected in the postpartum period
- digoxin
- iron supplementation for anemia
- embolization of the bronchial arteries after the first trimester in case of recurrent hemoptysis
- planned vaginal delivery in the 34th week of gestation.

The patient was discharged from the hospital 3 weeks after stroke in a relatively good clinical condition (WHO class II). She was prescribed the following drugs: sildenafil, iron supplementation, oxygen, aspirin (75 mg/d), and folic acid. In the 26th week of gestation, she was admitted to the ward, as previously scheduled. Aspirin was switched to enoxaparin at a dose adjusted to the level of anti-Xa activity. The delivery started spontaneously in the 33rd week of gestation and was terminated by a cesarean section with epidural anesthesia. The child was alive (5/6 points in the Apgar scale; weight 1050 g). After delivery, the mother was referred to the intensive care unit for infusion of milrinone owing to low blood pressure. The infusion dose was gradually reduced and stopped after 5 days. She did not require mechanical ventilation and her pressure was maintained at about 110/80 mm Hg. She was then treated in the cardiac ward for the next 4 weeks. Lactation was suppressed pharmacologically and bosentan was added to sildenafil. The patient was discharged from the hospital in stable condition (WHO class II). Currently, after a year from the delivery, both the mother and child are in good condition.

Review of literature

Changes in the cardiovascular system during pregnancy in patients with Eisenmenger's syndrome

In normal pregnancy, the increase in blood volume is accompanied by a reduction in systemic and pulmonary vascular resistance to maintain the systemic and pulmonary artery pressure within the normal limits [3]. The total blood volume rises above the prepregnant level by 10%, 30%, and 45% over the first, second, and third trimester, respectively [4]. During and immediately after the delivery, the uterine contractions and aortocaval decompression lead to an additional increase in the blood volume of up to 1.5 L. In patients with pulmonary hypertension, the increased blood volume in the presence of the reduced total area of the pulmonary vasculature and reduced ability of the pulmonary arteries to dilate results in excessive afterload in the right ventricle and ultimately right ventricular failure [5]. Additionally, in mothers with Eisenmenger's syndrome, a decrease in systemic vascular resistance may increase the right-to-left shunt, which reduces the pulmonary blood flow and worsens hypoxemia [6]. Pulmonary hemorrhage and paradoxical embolism pose an additional risk.

Table 1. Methods of birth control in patients with pulmonary hypertension

Type of contraception	Comment
Combined (estrogen and progesterone) oral contraceptive pills; EVRA®, skin patch; NuvaRing®, vaginal ring	Increased risk of arterious and venous thrombosis posed by the estrogen component. Contraindicated in patients with the right-to-left shunt owing to the risk of stroke
Standard progesterone-only pills	No additional thrombotic risk Less effective than combined; therefore, not advised in patients with Eisenmenger's syndrome where maximum effect is needed. Interaction with warfarin; strict monitoring of the international normalized ratio is advised Bosentan reduces the efficacy of this method; therefore, progesterone-only preparations should not be used in patients on bosentan.
Cerazette® (desogestrel, 75 µg)	A new progesterone-only pill with similar effectiveness to combined oral contraceptives. Can be used in patients with pulmonary hypertension. At increased doses, it can be used in patients taking bosentan
Mirena®, intrauterine system (progestagen – levonorgestrel)	Risk of infection during insertion. The insertion should be covered with antibiotics in patients with Eisenmenger's syndrome Risk of vasovagal reaction during insertion; rare (5%) but hazardous in pulmonary hypertension; therefore, generally contraindicated in patients with pulmonary hypertension but acceptable if no other methods are suitable and risk of pregnancy outweighs risk of insertion As effective as sterilization
Implanon®, subdermal implant (progestagen – etonogestrel)	As effective as sterilization. Safe for patients with pulmonary hypertension. Subdermal implant needs replacing every 3 years
Depo-Provera (progestagen – medroxyprogesterone)	Highly effective. Safe in patients with pulmonary hypertension. Deep intramuscular injection every 12 weeks; risk of hematoma in anticoagulated patients
Barrier methods (condoms, condoms with spermicidal foam)	Safer than other methods but less effective
Tubal ligation	Risk of operation and anesthesia
Levonelle®, emergency contraception (levonorgestrel)	Safe and effective if initiated within 72 hours of sexual exposure. In patients on bosentan, the dose should be increased by 50% to 100%

Adapted from: Thorne S, Nelson-Piercy C, MacGregor A, et al. Pregnancy and contraception in heart disease and pulmonary arterial hypertension. J Fam Plann Reprod Health Care 2006; 32(2): 75–81.

During the past decades, novel advanced therapies have been developed and the management of high-risk pregnancies has improved. In a recent systematic review of the publications from 1997 to 2007, the maternal and fetal/neonatal mortality in CHD-PAH was estimated at 28% and 7%, respectively [7]. A premature delivery occurred in 86% of the women and intrauterine growth retardation was reported in 24% of the newborns. All maternal deaths occurred after delivery (median time postpartum, 6 days), with the majority of cases due to severe right heart failure, followed by pulmonary thromboembolism, sudden cardiac death, pulmonary hypertension crisis, or bacterial endocarditis. A half of the women received advanced PAH therapy and only about 30% received antithrombotic treatment. The main risk factors for unfavorable outcome was general anesthesia as compared with regional anesthesia (odds ratio [OR], 4.37; 95% confidence interval [CI], 1.28–16.5). Additionally, women in their first pregnancies were at a higher mortality risk compared with those with previous pregnancies (OR, 3.7; 95%; CI, 1.15–12.5). In a systemic overview of reports published between 1978 and 1996 [1], the following indications for hospital admission were listed in patients with Eisenmenger's syndrome: worsening of dyspnea and cyanosis, hemoptysis, cerebrovascular incident, syncope, chest pain, atrial fibrillation, or premature uterine contractions. Of 73 women, 3 died during pregnancy, 33 delivered at term, 23 delivered between the 32nd and 36th gestation weeks, and 14 delivered before the 31st gestation week.

Prevention of pregnancy

Any type of pulmonary hypertension belongs to class IV of the modified WHO classification of maternal cardiovascular risk. This means that pulmonary hypertension is associated with an extremely high risk of maternal mortality or severe morbidity and, therefore, pregnancy in pulmonary hypertension is contraindicated (Class I, Level of Evidence C) [8]. Currently, there is no consensus relating to the most appropriate method of birth control in patients with pulmonary hypertension. It is important to educate on and discuss the methods of birth control with the patient [9]. The contraceptive methods recommended by experts and their potential drawbacks are presented in Table 1. Usually, the use of at least two effective forms of birth control are recommended [10], especially in patients treated with bosentan, which may reduce the effectiveness of hormonal birth control. It is our practice to refer every patient with pulmonary hypertension to a gynecologist with experience in the management of such patients. Our patient was advised against pregnancy and after discussing the possible methods of birth control, she declared to use condoms with spermicide. Unfortunately, the risk of pregnancy in this method, even in compliant users, is 3% per year.

Pregnancy outcome

If pregnancy occurs in a patient with pulmonary hypertension, it is recommended to discuss with the patient early termination in the first trimester [10]. However, this procedure is associated with a significant risk [10].

Table 2. Pregnancy categories according to the Food and Drug Administration

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

In patients with Eisenmenger's syndrome, spontaneous abortion occurs in up to 40% of the cases, premature delivery in 50%, and term delivery only in 25% of the pregnancies [11,12].

The optimal mode of delivery is a matter of debate. Vaginal delivery is associated with smaller shifts in blood volume, fewer thrombotic and bleeding complications, and a lower risk of infection [13]. However, a recent review showed a decrease in the number of vaginal deliveries in the last decades [7]. Generally planned elective delivery in a tertiary center conducted by a specialist multidisciplinary team is recommended [10]. A scheduled cesarean section has the advantage over an urgent delivery of occurring during the day and in stable hemodynamic conditions. If the maternal or fetal condition deteriorates, an early cesarean delivery should be planned [2,8].

If vaginal delivery is chosen, low-dose epidural analgesia is recommended because it has no significant deleterious hemodynamic effect by itself [14] and it considerably decreases the adverse hemodynamic effects of labor [15]. General anesthesia is associated with worse outcomes, which is explained by negative inotropic effects of volatile agents and also by increased pulmonary pressure due to positive pressure ventilation [7].

Specific therapies for pulmonary arterial hypertension in pregnancy

Generally, no PAH-specific drugs are currently registered for use in pregnant women because they have not been tested in this population. However, several case reports described a beneficial effect of PAH-specific drugs during pregnancy. Most authors reported positive outcomes with the use of epoprostenol [16-20]. Less data is available for nitric oxide [21], sildenafil [22,23], iloprost [24], and nebulized iloprost combined with epoprostenol [16,25]. A recent study has shown that 52% of pregnant women with CHD-PAH received PAH-specific therapy [7]. The Food and Drug Administration assigned the following risk categories to the currently used PAH-specific drugs:

- Revatio (sildenafil) – category B
- Adcirca (tadalafil) – category B
- Flolan (epoprostenol) – category B
- Remodulin (treprostinil) – category B
- Ventavis (iloprost) – category C
- Tracleer (bosentan) – category X
- Letairis (ambrisentan) – category X.

The definitions of the different pregnancy categories are summarized in Table 2.

Management strategy

In pregnant women with Eisenmenger's syndrome, the risk of complications should be discussed and a termination of pregnancy should be recommended. If the patient decides to continue pregnancy, she should be treated in a specialized (preferably tertiary) unit. The use of PAH-specific drugs should be considered. Supportive treatment should be based on an individual clinical status. The delivery should be planned (not urgent). Regional anesthesia is preferred over general anesthesia. If the maternal and fetal condition deteriorates, an early cesarean section should be scheduled.

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