Acta Cardiologia Indonesiana
pISSN:2460-5700
eISSN:2579-4345
Web page: jurnal.ugm.ac.id/v3/jaci

Drugs for Pulmonary Hypertension in Pregnancy: What Should We Consider?

Lucia Kris Dinarti*
Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Sardjito General Hospital Yogyakarta, Indonesia

ARTICLE INFO

*Corresponding author
Email:
kris_dinarti@ugm.ac.id

Address:
Jalan Kesehatan No. 1, Sekip, Sinduadi, Mlati, Sleman, Yogyakarta 55284

Keywords:
Pregnancy, Pulmonary Arterial Hypertension, Drugs for PAH

Manuscript submitted: December 10, 2021
Revised and accepted: March 15, 2022

ABSTRACT

Pulmonary Arterial Hypertension (PAH) is a disease characterized by narrowing of the pulmonary arteries and increased vascular resistance cause to increase morbidity and mortality. Women with PAH should avoid becoming pregnant because changes in physiological, cardiovascular dan pulmonary can affect the condition. If these women decide to continue their pregnancy, they have several treatment options: inhaled nitric oxide, calcium channel blocker, and sildenafil. Endothelin receptor antagonists like bosentan, macitentan, ambrisentan are contraindicated. Sildenafil is categorized as a B drug in pregnant patients with PAH. Sildenafil causes vasodilatation in the pulmonary vascular beds and systemic circulation. Iloprost is a pregnancy category C but has beneficial in treating pregnant patients with PAH with no congenital abnormality and increased mortality in mother and infant. Epoprostenol, a potent pulmonary vasodilator categorized as a B drug but unfortunately not available in Indonesia.

INTISARI

Hipertensi Arteri Pulmonal (HAP) merupakan suatu kelainan yang ditandai dengan penyempitan arteri pulmonal dan peningkatan resistensi vaskular yang menyebabkan peningkatan angka morbiditas dan kematian. Perempuan yang didiagnosis HAP seharusnya tidak hamil karena perubahan fisiologis, kardiovaskular dan pulmonal akan memperberat HAP. Jika proses kehamilan tetap ingin dilanjutkan, pilihan terapi yang tersedia adalah nitric oxide inhalasi, penyekat kanal kalsium, dan sildenafil. Penggunaan antagonis reseptor endothelin seperti bosentan, macitentan dan ambrisentan merupakan kontraindikasi. Sildenafil masuk dalam kategori obat B untuk kehamilan. Obat ini menyebabkan vasodilatasi pada pembuluh darah vaskular paru dan sirkulasi sistemik. Iloprost digolongkan dalam kategori obat C, akan tetapi memiliki efek baik bagi pasien hamil dengan PAH, tidak menyebabkan kelainan kongenital dan tidak meningkatkan angka kematian pada ibu dan bayi. Epoprostenol, sebuah vasodilator pulmonal yang kuat, digolongkan dalam kategori B namun sayangnya tidak tersedia di Indonesia.

Introduction

Pulmonary hypertension (PH) and pregnancy are considered a fatal combination, and mortality can occur regardless of the severity of the condition.[1] Pulmonary Hypertension is an uncommon condition in which the mean pulmonary artery pressure (PAP) rises over 20 mmHg. There are five different types of PH. Pulmonary Arterial Hypertension (PAH) is the first group, followed by PH due to Left Heart Disease, PH due to Lung disease, Chronic Thromboembolic PH (CTEPH), and PH due to multifactorial condition.[2] Pulmonary Arterial Hypertension is a progressive condition that leads to right heart failure and death. It is characterized as mean PAP over 20 mmHg, Pulmonary Capillary Wedge Pressure (PCWP) less than 15 mmHg, and Pulmonary Vascular Resistance (PVR) more than 3 Woods unit as measured by right heart catheterizatio.[3] PH is a condition that can affect women of reproductive age and is linked to increased morbidity and death throughout gestation.[4] Based on WHO classification of maternal cardiovascular risk during pregnancy, PAH is categorized as group IV which suggests that pregnancy is not advisable. In some women, PH is newly diagnosed during her pregnancy.[5]

Discussion

If a woman suffering PAH falls pregnant, she should be educated, and a therapeutic termination considered carefully. Patients should be informed that PAH might worsen after childbirth. If a therapeutic termination is approved, it is suggested that it take place before the 22nd week of pregnancy.[6] When a woman with PAH becomes pregnant, she should be referred to a PAH specialist center. Furthermore, from the start of the pregnancy, an antenatal care plan should be detailed, including the schedule and method of delivery for the woman with PAH.[6]

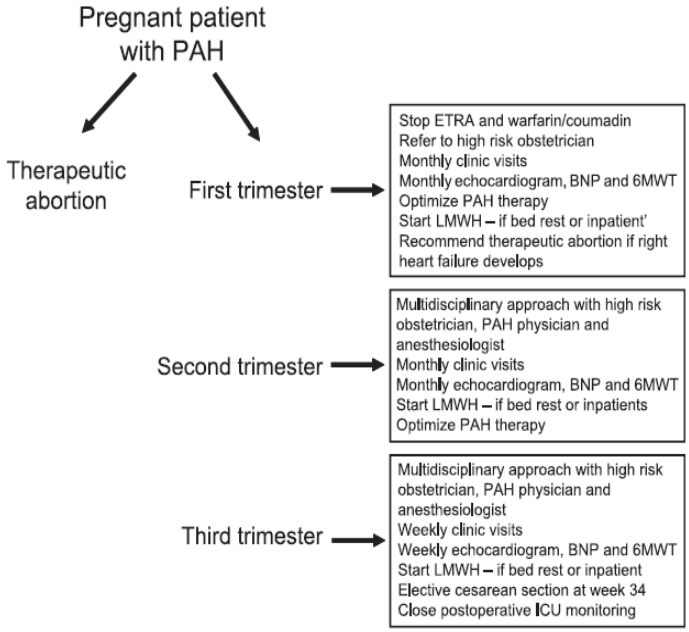

Figure 1. A parturient with pulmonary arterial hypertension should be evaluated and followed upon.

Regular attentive follow-up at a PAH center is indicated for women with PAH who wish to continue their pregnancy, and in certain situations, elective hospitalization for medication optimization before birth could be indicated.[6] Regular echocardiographic testing and monitoring of the fetus for developmental defects should be included in regular follow-up, in addition to a comprehensive clinical examination. The severity of PH and reduce Right Ventricular Function are a predictor of maternal mortality in pregnant women with PAH.[7] Another studies have also identified characteristics linked to a reduced risk of pregnancy in women with PAH. Well-controlled PAH with PAH-specific medication, a low pulmonary vascular resistance (PVR), and a positive response to calcium channel blockers are among them.6 Uncontrolled PAH, first pregnancy, and a high PVR, on the other hand, are linked to an increased risk of pregnancy in women with PAH. Figure 1 shows the assessment and follow-up recommendations for a pregnant woman with PAH.[8]

PAH-specific therapy overview

Nebulized nitric oxide (a broad vasodilator used in the antepartum period), CCB, specific pulmonary vasodilator medication (epoprostenol, iloprost), and sildenafil are among the potential therapeutic choices for pulmonary arterial hypertension. In Figure 2, three primary paths are illustrated.[9]

There are three basic mechanisms implicated in aberrant proliferation and contraction of smooth muscle cells in the pulmonary artery (PA) in individuals with pulmonary arterial hypertension (PAH). Intimal proliferation and considerable medial hypertrophy may be seen in a transverse segment of a small PA (500 mm in diameter) from a patient with severe PAH (top). Endothelial cells from the PA that are dysfunctional (blue) produce less prostacyclin and nitric oxide and more endothelin-1, which promotes vasoconstriction and smooth muscle cell proliferation in the PA (red). Current or new medicines in the PA target particular targets in smooth-muscle cells. Prostacyclin derivatives and nitric oxide exhibit a variety of features, including antiplatelet effects, in addition to their activities on smooth muscle cells. In addition, indicators indicate a rise in intracellular concentration. A receptor blockage, enzyme inhibition, or a drop in intracellular concentration are all indicated by minus signs.

PAH-specific therapy in pregnancy

Except for ERAs, current European Society of Cardiology/European Respiratory Society recommendations indicate those with PAH who desire to carry with pregnancy be managed with PAH-specific drugs (or continue to be treated with them). Because ERAs have been known to have teratogenic consequences, they should not be used during pregnancy.[5] Any ERA should be ceased if a woman with PAH becomes pregnant (Table 1).[10] The effective use of contemporary PAH medication in this patient population has been recorded in several case reports or case series, as well as one registry. Severe PH and delayed diagnosis have been linked to an increased risk of death; consequently, PAH therapy should be started as soon as possible.[10]

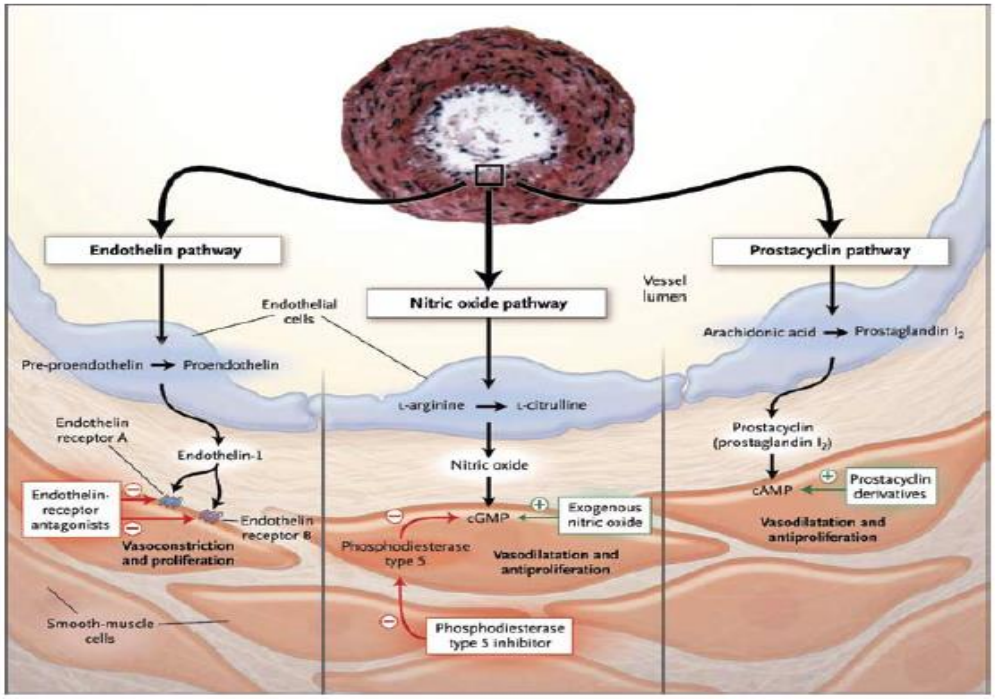

Figure 2.

Table 1. Gestation and Breastfeeding Safety of Pulmonary Vasodilator Therapy

Medication	Pregnancy	Lactation
Ambrisentan	CONTRAINDICATED	Benefit/risk discussion with patient, no human data available
Bosentan	CONTRAINDICATED	Benefit/risk discussion with patient, no human data available
Epoprostenol	Benefit outweighs risk	Safe
Iloprost	Benefit outweighs risk	Benefit/risk discussion with patient, no human data available
Macitentan	CONTRAINDICATED	Benefit/risk discussion with patient, no human data available
Nitric oxide	Benefit outweighs risk	Benefit/risk discussion with patient, no human data available
Riociguat	CONTRAINDICATED	Benefit/risk discussion with patient, no human data available
Selexipag	Benefit/risk discussion with patient No human data available, but no risk of fetal harm in animal studies at 50x MRHD	Benefit/risk discussion with patient, no human data available
Sildenafil	Benefit outweighs risk	Benefit/risk discussion with patient, limited human data available, though harm not expected based on drug properties
Tadalafil	Benefit outweighs risk	Benefit/risk discussion with patient, no human data available
Treprostinil	Benefit outweighs risk	Safe

MRHD = maximum recommended human dose.

Calcium Channel Blockers

A small percentage of IPAH patients are responded to CCB, meaning they have normal or near-normal hemodynamics after treatment.[10] A small percentage of IPAH patients are "responders" to calcium channel blockers, meaning they have normal or near-normal hemodynamics after treatment. While pregnancy, calcium channel blockers are regarded to be harmless. Eight women met the responder criteria in a recent studies database, and every one of them had uncomplicated and normal pregnancies. This type of condition may be the only subset of PAH patients in whom pregnancy may be carried to term, although there is little evidence, requiring more research.[10]

Prostacyclin analogs

Epoprostenol

Epoprostenol is a pregnancy category B drug because it is a naturally occurring prostaglandin and vasodilator.[9] At 2.5–4.8 times the approved human dose of epoprostenol, reproductive investigations in experimental rats indicated neither decreased fertility nor fetal toxicity.[10] Epoprostenol has been shown to be effective in treating PAH in pregnant women. Intravenous epoprostenol should be used to initiate patients since it has a short half-life and allows for quick dosage titration. The infusion of epoprostenol should be continued throughout the gestation, even throughout the Cesarean section as well as the post-partum period. If patients are hemodynamically stable, they can be gradually weaned off prostanoids several months after delivery.[8]

Treprostinil

There seems to be still no information on the use of treprostinil during pregnancy. Treprostinil, like epoprostenol, is classified as a class B drug by the Food & Drug Administration.[10]

Iloprost

This prostacyclin analog can lower blood pressure and vascular resistance. There have been five examples of pregnant women who got nebulized iloprost for PAH. Despite the fact that iloprost is a pregnancy class C drug, no fetal anomalies were found in any of the babies, and there was no post-partum mother or newborn death.[9] Furthermore, if there are no other options and the benefits outweigh the hazards, Iloprost is only suggested for usage during pregnancy.[8]

Inhaled nitric oxide

A pregnant patient with PAH who presented at 30 weeks gestation and had an atrial septal defect and HIV was managed with sildenafil and inhaled NO, according to one case report. Despite having a Cesarean section scheduled, she went into spontaneous labor. Inhaled NO was gradually reduced, while sildenafil was maintained. She was given digoxin and enoxaparin subcutaneouly, as well as antiviral drugs.[8]

Phosphodiesterase-5 inhibitors

Sildenafil promotes pulmonary vascular bed vasodilation as well as systemic circulation. Sildenafil is a drug under the pregnancy category B.[9] A pregnant with Eisenmenger syndrome was medicated with L-arginine and sildenafil during pregnancy, birth, and post-partum, with satisfactory infant and patient outcomes, according to one case report. It's worth noting that L-arginine isn't approved by the FDA in the United States. Sildenafil has been demonstrated to enhance uterine muscle layer thickness in those who have had in vitro fertilization with an initial poor endometrial response. Furthermore, premature, term, newborn, and pediatric pulmonary hypertension have all been effectively treated with sildenafil and NO.[8]

Table 2. Drugs used to treat pulmonary hypertension in pregnancy[8]

Class	PDE-5 inhibitors		Endothelin receptor antagonist		Prostacyclin			
Mode of action	Blocks degradation of cGMP		Competitive antagonists of endothelin receptor		Provides exogenous prostanoid			
Individual drugs	Tadalafil	Sildenafil	Ambrisentan	Bosentan	Epoprostenol	Treprostinil	Iloprost inhaled	Tresprostinil inhaled
Individual dose	40 mg	20 mg	5–10 mg	62.5–125 mg	0.5->100 mg/kg/min	0.5 ->100 mg/kg/min	2.5 or 5 µg	9–12 breaths
Frequency of administration	Daily	Three times daily	Daily	Twice daily	Continuous infusion	Continuous infusion	Every 2 h	Four times daily
Elimination half life	17.5 h	3–5 h	15 h	5.4	2–3 min	3-4 h	20–30 min	3-4 h
Route of administration	Oral	Oral	Oral	Oral	Intravenous	Intravenous, subcutaneous	INH	INH
Side effects	Headache, myalgia, back pain, flushing, dyspepsia, diarrhea nausea pain in extremity	Headache, myalgia, back pain, flushing, dyspepsia, diarrhea	Peripheral edema, headaches, dizziness, nasal congestion	Peripheral edema, headaches, dizziness, cough, syncopy, abnormal hepatic function	Headache, flushing, jaw pain, anxiety/nervousness, diarrhea, flu-like symptoms, nausea, and vomiting	Headache, diarrhea, nausea, jaw pain, flu-like symptom Subcutaneous infusion: site pain, reactions, and bleeding	Headache, flushing, flu-like symptom, nausea, and vomiting, jaw muscle spasm, cough, tongue pain, and syncope	Cough, headache, pharyngolaryngeal pain, throat irritation, nausea, flushing, and syncope

cGMP, cyclic guanosine monophosphate; INH, inhalation treatment; PDE-5, phosphodiesterase-5.

The FDA has licensed tadalafil, a long-acting phosphodiesterase-5 inhibitor, for the treatment of PAH patients, although there have been no studies on the use of tadalafil in parturient PAH patients.[8]

Treatment of Pregnancy-related Manifestations6

Because of a reduction in protein S and acquired protein C resistance, as well as greater amounts of thrombin, the coagulation process is triggered during pregnancy.

To lessen the chance of VTE in pregnant women with PAH, anticoagulation may be used.

Vitamin K antagonists should not be used during the first trimester of pregnancy because they might cause fetal craniofacial deformities. Vitamin K antagonists can cause fetal bleeding, spontaneous miscarriage, and brain abnormalities if used during pregnancy.

Low-molecular-weight heparins should be used to manage pregnant women who have PAH.

Peripheral edema, a sign of right heart failure in PAH, is especially crucial to control during pregnancy owing to enhanced fluid retention and blood volume.

To reduce compression of the inferior vena cava, pregnant women with PAH could perhaps avoid laying on their backs

Despite the fact that diuretics can restrict blood flow across the placenta, they may be essential to treat right heart failure in women with PAH or to minimize fluid overload after labor.

Torasemide or furosemide might be taken if needed.

For its anti-androgenic capabilities, spironolactone should be discouraged throughout the first trimester.

It's essential to control hyperemesis gravidarum, as it can cause fluid and electrolyte abnormalities, as well as impair the efficiency of oral drugs during pregnancy.

Laxatives should be used cautiously since they can decrease the absorption of other medicines.

Post-natal care for the mother and newborn

Women with PAH should be monitored closely after birth, as this is when the majority of fatalities occur, and observation should remain for many days or even weeks after delivery. The first four weeks following birth are the most dangerous for mortality, with right ventricular failure accounting for most deaths. Thrombo embolic events, blood autotransfusion, and severe elevations in PVR are all factors that contribute to right ventricular failure.[6]

Nebulized NO, i.v. Epoprostenol, and inhaled iloprost are among the medications used to minimize the chances of right ventricular failure after childbirth. In some cases, systemic vasopressors and inotropes are recommended.[6]

Following birth, mothers with PAH are given lactation instruction as part of their ongoing care. Lactation is not generally suggested because pulmonary vasodilators may be secreted in breast milk, and a harmful effect of prolactin on the myocardium in these individuals cannot be ruled out. After pregnancy, women with PAH should have a lengthy close follow-up.[6]

Conclusion

Pregnant patients with PAH is linked to a significant risk of maternal death. It is highly suggested that PAH experts and pregnant women with PAH have a detailed consultation. Careful clinical supervision is suggested in the first and second trimesters and weekly clinic visits in the third trimester.[8]

For those with deteriorating right heart failure should be offered a choice to abort their pregnancy, especially if it is early in the pregnancy. If they intend to carry the pregnancy, specific PAH medication should be enhanced to maximize the chances of a successful ending. A collaborative strategy involving a cardiologist, a pulmonary vascular physician, an obstetrician, and an anesthesiologist is strongly advised in this case. Despite a comprehensive approach, the death rate for pregnant PAH patients remains high.[8]

Acknowledgement

Author acknowledged the assistance of Abdul Majid Halim, MD and Andreas Hartanto Santoso, MD as research fellow in Congenital Heart Disease and Pulmonary Hypertension Registry (COHARD-PH Registry) who engaged in the completion of this manuscript.

References

1. Smedstad KG, Cramb R, Morison DH. Pulmonary hypertension and pregnancy: a series of eight cases. Can J Anaesth. 1994;41(6):502-512. doi:10.1007/BF03011545
2. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913. Published 2019 Jan 24. doi:10.1183/13993003.01913-2018
3. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119. doi:10.1093/eurheartj/ehv317
4. Pieper PG, Hoendermis ES. Pregnancy in women with pulmonary hypertension. Neth Heart J. 2011;19(12):504-508. doi:10.1007/s12471-011-0219-9
5. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018;39(34):3165-3241. doi:10.1093/eurheartj/ehy340
6. Olsson KM, Channick R. Pregnancy in pulmonary arterial hypertension. Eur Respir Rev. 2016;25(142):431-437. doi:10.1183/16000617.0079-2016
7. Hartopo AB, Anggrahini DW, Nurdiati DS, Emoto N, Dinarti LK. Severe pulmonary hypertension and reduced right ventricle systolic function associated with maternal mortality in pregnant uncorrected congenital heart diseases. Pulm Circ. 2019;9(4):2045894019884516. Published 2019 Nov 18. doi:10.1177/2045894019884516
8. Safdar Z. Pulmonary arterial hypertension in pregnant women. Ther Adv Respir Dis. 2013;7(1):51-63. doi:10.1177/1753465812461680
9. Huang S, De Santis ER. Treatment of pulmonary arterial hypertension in pregnancy. Am J Health Syst

Pharm. 2007;64(18):1922-1926. doi:10.2146/ajhp060391

10. Lindley KJ, Bairey Merz CN, Asgar AW, et al. Management of Women With Congenital or Inherited Cardiovascular Disease From Pre-Conception Through Pregnancy and Postpartum: JACC Focus Seminar 2/5. J Am Coll Cardiol. 2021;77(14):1778-1798. doi:10.1016/j.jacc.2021.02.026

11. Olsson KM, Jais X. Birth control and pregnancy management in pulmonary hypertension. Semin Respir Crit Care Med. 2013;34(5):681-688. doi:10.1055/s-0033-1355438