Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pregnancy in pulmonary hypertension

Javed Khan, Majdy M. Idrees[1]

Department of Pulmonary Medicine, King Fahd Armed Forced Hospital, Jeddah, [1]Prince Sultan Medical Military City, Riyadh, Saudi Arabia

Address for correspondence:
Dr. Javed Khan, MD, Head, Pulmonary Medicine, Department of Medicine, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia.
E-mail: rjhkhan@hotmail.com

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Abstract:

Pregnancy in pulmonary hypertension (PH) is known to be associated with high morbidity and mortality.

The physiological changes occur during normal pregnancy, such as increase blood volume and cardiac output (CO) may be detrimental in PH patients.

Several practice guidelines advise against pregnancy and even recommend termination of pregnancy. Occasionally PH may be diagnosed for the first time during pregnancy, as stress of pregnancy can unmask previously undiagnosed PH in an asymptomatic individual.

This narrative review provides a detailed discussion about the physiologic parameters associated in pregnancy and their negative effect on the right ventricle. It also gives practical evidence-based recommendations about different management issues in PH pregnant patients.

Key words:

Pregnancy, pulmonary hypertension, right ventricular failure, Saudi association for pulmonary hypertension guidelines

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Pregnancy in pulmonary hypertension (PH) is known to be associated with high maternal mortality in all defined clinical groups of PH, with observational studies having estimated maternal death between 30% and 60% even in patients with little or no significant functional impairment before pregnancy.[1] Several practice guidelines advise against pregnancy and even recommend termination of pregnancy.[2-5] WHO modified risk classification considers PH of any cause as risk Class 4 (pregnancy contraindicated).

Occasionally, PH may be diagnosed for the first time during pregnancy, as stress of pregnancy can unmask previously undiagnosed PH in an asymptomatic individual.

Physiology of Pregnancy

Several physiological changes occur during normal pregnancy to meet the metabolic demands of mother and fetus. Of particular relevance to PH include increase in blood volume and cardiac output (CO) and decrease in pulmonary and systemic vascular resistance. CO increases significantly in early pregnancy due to combination of increase in stroke volume and progressive reduction in after load resulting from decrease in peripheral vascular resistance. Late in pregnancy, increase in heart rate is also a contributory factor.[6-8]

Pregnancy is also regarded as a hypercoaguable state due to several reasons, such as increase in coagulation factors, decrease serum level of protein S, and relative resistance to protein C.[9-11]

In normal pregnancy almost 50% increase in CO can be accommodated in pulmonary circulation through a subsequent decrease in pulmonary vascular resistance (PVR), and there is usually no effect on right ventricle (RV) afterload and/or function. Nevertheless, these normal physiological changes are poorly tolerated by PH patients, as these patients already have higher RV afterload from preexisting increase in PVR. Furthermore, RV is unable to cope with such an increase in CO and is overstretched. This can result in progressive RV failure and even sudden death from cardiac arrhythmias. In addition, higher RV pressures shifts intervetricular septum leftward, thus impairing diastolic filling of left ventricle which further compromises the CO.[4]

Pregnant patient with Eisenmenger syndrome or patent foramen ovale are at increased risk of having paradoxical emboli from increase in right to left shunting.[12] In addition, due to hypercoaguable state, there is increased risk of thromboembolic events, which are poorly tolerated by PH patients with already compromised RV.

Pregnant PH patients are also at increased risk of developing complications during puerperal period. Several cardiac events occur during

this period, including further increase in heart rate and blood pressure and increase in myocardial oxygen consumption, basically due to labor pains causing sympathetic nervous stimulation. The pain may also induce severe vasovagal responses resulting in hypotension and sudden death.[13,14] Another contributory factor during labor is diversion of approximately 500 ml of blood from uterine to maternal circulation due to uterine contractions and valsalva maneuvers, thus further augmenting CO.[15] Even after delivery, CO may increase by 80% due to auto transfusion from uterine involution.[16]

Clinical Features

Most PH patients complain of increasing dyspnea and fatigue due to low CO. Since these symptoms are also present during normal pregnancy, it is likely that patient and/or physician may attribute these symptoms to pregnancy and PH is not suspected, which may cause delay in diagnosis. Some patients, however, may have chest pain from RV ischemia or even syncope from low CO.

As symptoms of disproptionate dyspnea, chest pain, or syncope during pregnancy may be first manifestation of previously undiagnosed PH, hence a high index of suspicion is required.

All these patients warrant further investigations by echocardiography for evaluation of cardiac status and in particular for PH. It is prudent first to exclude pulmonary embolism by appropriate investigations. There is no evidence of increased fetal risk or pregnancy loss at doses of radiation to pregnant mother <50 mGy.[17] Estimated fetal/maternal effective doses for various radiological procedures, such as chest X-ray ($\leq$0.01 mGy-0.1 mGy), computed tomography chest (0.3 mGy-7 mGy) and pulmonary angiogram (1.5 mGy-7 mGy) are considered safe for both fetus and mother.[18,19]

If PH is suspected by echocardiography, it should be confirmed by right heart catheterization (RHC), which can be performed safely during pregnancy.[20-22]

Prognosis of Pregnancy in Patients with Pulmonary Hypertension

Maternal outcome

Pregnancy with PH is regarded as a very high-risk pregnancy. An earlier study by Mccaffrey and Dunn in 1964 has described that 9 out of 16 patients died in 23 pregnancies; most of deaths have occurred in the last 2 months of pregnancy or early in puerperium.[16] In 1979, Gleicher *et al*. reviewed 70 pregnancies in women with Eisenmenger syndrome and found 52% maternal mortality mostly during labor, delivery and early in postpartum period. The perinatal fetal mortality was 28%.[23]

Another overview of outcome of 125 pregnancies in women with Eisenmenger syndrome, idiopathic pulmonary arterial hypertension (IPAH) and PH due to other secondary causes showed maternal mortality of 36%, 30%, and 56%, respectively.[1] Bédard *et al*. performed a systematic review of all cases of pregnancy-related death in patients with IPAH, congenital heart disease associated with PAH (CHD-PAH), or PAH associated with other diseases (APAH) published between (1997 and 2007) and compared it with data published between 1978 and 1996 to find out whether there has been any progress made in pregnancy outcome among women with PH using newer therapies.[24] The authors observed that mortality remains prohibitively high, though appears to have decreased more recently with the use of new treatments in all three major subgroups (IPAH from 30% to 17%; CHD-PAH 36% to 28%; APAH 56% to 33%), [Table 1]. Most patients died in the 1st month after delivery in both series. The main cause of death was RV failure in both reviews; other causes included sudden death and pulmonary thromboembolism.[25] Predictors of poor outcome are shown in Table 2.

Recent report from a single center of 10 consecutive pregnancies has shown significant improvement with combination of multidisciplinary approach, early initiation of specific drug therapy, and a planned caesarean delivery under regional anesthesia. There was no fetal or maternal mortality during pregnancy or in early postpartum period.[24] Another multicenter prospective study of 26 pregnancies showed better outcome with 16 (62%) patients delivering normal healthy babies without complications. Three (12%) patients died and one required urgent heart-lung transplantation.[26]

Fetal outcome

Neonatal or fetal death rate also remains high in PH pregnant patients. One series has reported death rate in IPAH, CHD-PAH, and APAH as 10%, 7%, and 13%, respectively. In addition, high rate of intrauterine growth retardation and premature delivery have been reported.[25]

Diagnosis

Once PH is suspected in pregnant woman, it always warrants further investigations by trans-thoracic echocardiography (TTE). As a screening tool, TTE has shown a good correlation between pulmonary arterial pressure (PAP) measured

Table 1: Outcome of pregnant women with PAH

Outcomes	IPAH (*n* = 29)	PAH-CHD (*n* = 29)	APAH (*n* = 15)
Follow-up days postpartum	310 (±229)	243(±147)	255 (±196)
Maternal death (%)	5 (17)	8 (28)	5 (33)
During pregnancy (%)	2 (7)	0 (0)	1 (7)
Postpartum (<90 days) (%)	3 (10)	8 (28)	4 (26)
Days postpartum	14 (7-90)	6 (0-24)	1.5 (1-21)
RV failure (%)	9 (31)	9 (31)	4 (27)
Premature delivery (37 weeks gestation) (%)	23 (85)	25 (86)	14 (100)
Neonatal or fetal death (%)	3 (10)	2 (7)	2 (13)

Adopted from reference 25, RV = Right ventricle, PAH = Pulmonary arterial hypertension, IPAH = Idiopathic pulmonary arterial hypertension, PAH-CHD = PAH associated with congenital heart disease, APAH = Associated pulmonary arterial hypertension

Table 2: Risk factors for maternal mortality

Risk factors	OR/risk
Late diagnosis	OR=5.4 (*P*=0.002)
Late hospital admission	OR=1.1/week of pregnancy (*P*=0.001)
Primigravida	OR=3.70 (95% CI=1.15–12.5, *P*=0.03) Compared with multigravida
General anesthesia	Four times more likely to die

Adopted from reference 24, 25, OR = Odds ratio, CI = Confidence interval

by RHC and TTE. Nevertheless, the presence of PH by echocardiography requires confirmation by RHC as discrepancy between these diagnostic tools has been reported. In one study, 8 out of 25 patients diagnosed to have PH by TTE had normal PAP when measured by RHC.[17] Similarly, in another study, 30% of pregnant patients diagnosed to have PH by echocardiography did not have PH when measured by RHC.[18] Furthermore, TTE could also underestimate PAP in this patients' population, as 5 out of 8 patients were found to have more severe PH when measured by RHC.[18] RHC has been shown to be a safe procedure in the second and third trimesters of pregnancy.

Management

The class of recommendation and the level of evidence for PH management in pregnant PH patients are summarized in Table 3.

During pregnancy

At present, all guidelines consider PH as a contraindication to pregnancy. PH patients should be advised to practice safe contraception; however, should the patient become pregnant and wishes to continue with pregnancy, and then she should be managed as a high-risk pregnancy by a specialized multidisciplinary team in a center familiar with management of PH patients. Patient should be followed regularly on monthly bases and physicians are to have a low threshold for admission, should there be any deterioration or worsening of symptoms.

General management

General measure includes adjustment of activities in order to decrease extra cardiac demand, adequate rest, and low salt intake. Patient is encouraged to lay down/sleep on the left lateral position to avoid compression of the inferior vena cava, which may cause decrease in venous return. Hypoxemia should be avoided and supplementary oxygen should be provided to keep $PaO_2 \geq 70$ mmHg.[27] Pregnant women should also receive the flu vaccine.

Anticoagulation

There is no consensus on anticoagulation in a pregnant PH patient. Pregnant patients are at increased risk of thromboembolism, which is generally very poorly tolerated by PH patients. In addition as mentioned earlier, pregnant PH patient with either Eisenmenger syndrome or patent foraman ovale are also at increased risk of paradoxical emboli. This would suggest that anticoagulation should be continued throughout pregnancy. Conversely, there is an increased risk of bleeding, especially in patients with Eisenmenger syndrome and portal hypertension.[15,23,28] Bleeding risk increases further at the time of delivery, which is also poorly tolerated by PH patient. Anticoagulation should be considered on case-by-case basis. If anticoagulation is chosen, it needs to be closely monitored, as requirements change with progress of pregnancy.

Furthermore, there is no consensus regarding level of anticoagulation, and whether the patient should be fully anticoagulated or just given a prophylactic anticoagulation dosage.[29,30] Low molecular weight heparin is generally recommended during pregnancy (Food and Drug Administration [FDA] Category B), unfractioned heparin at near term and during delivery (FDA Category B), and warfarin after delivery (FDA Category D during pregnancy).[31] Fondiparinux, a factor Xa inhibitor, may be used as a prophylactic agent in patients with heparin induced thrombocytopenia; however, there is a limited data about its rule in pregnancy.[32] Anticoagulation should continue for 2-6 months after delivery as there is evidence of increased maternal morbidity and mortality during postpartum period.[33]

Table 3: Class of recommendation and level of evidence for management of PH in pregnancy

Condition	Class of recommendation	Level of evidence
General		
All pregnant PH patients are at high-risk for maternal and fetal mortality	I	C
Pregnancy in women with uncontrolled PH should be avoided or early terminated	I	C
Pregnant women with controlled PH should be managed in a specialized center by a multidisciplinary team	IIa	C
Diagnostic measure		
TTE is the preferred screening tool	I	C
RHC is safe in the second and third trimester	IIa	C
Management		
During pregnancy		
General measure	I	C
Anticoagulation (LMWH during pregnancy and unfractionated heparin during delivery)	IIa	C
PH patient who are on specific drug therapy should continue with this treatment	IIa	C
Prostanoids are safe in pregnancy	IIa	C
Sildenafil is safe in pregnancy	IIb	C
Endothelin receptors antagonists are contraindicated in pregnancy	I	C
Evaluate need to convert to other PH-specific therapies	IIa	C
During and postdelivery		
Regional anesthesia should be considered when appropriate	IIa	C
Planned cesarean/section is recommended	IIa	C
Avoid/correct PH triggers	IIa	C
Continue anticoagulation (by warfarin) for at least 2-6 months	IIa	C

PH = Pulmonary hypertension, TTE = Trans-thoracic echocardiography, RHC = Right heart catheterization, LMWH = Low molecular weight heparin

Diuretics

Patient may need diuretic therapy for cardiac failure and hypervolemia. Furosemide is preferable choice (FDA Category C). Spironolactone should be avoided because of its anti-androgenic effect (FDA Category D).[34]

Pulmonary arterial hypertension specific therapy

Recent guidelines on management of pregnant patient with heart disease advise that PH patient who are on specific

drug therapy should continue with this treatment, (class of recommendation II a, level of evidence C).[2] Patients who are well-controlled on calcium channel blockers should continue with same drug. Prostacyclin (Flolan) is effective and safe in pregnancy and is the drug of choice (FDA Category B).[35,36] Inhaled Iloprost has also shown good efficacy, but some studies have reported adverse fetal effects (FDA Category C).[37] Oral agent sildenafil is find to be safe in animal and human studies (FDA Category B).[38] Endothelin receptors antagonist (bosentan and ambrisentan) are contraindicated because of their teratogenic effects (FDA Category X).[39] Patients already on these drugs should be advised about fetal risk and switched to other drugs. It is perhaps plausible to use prostacyclin analog or/and oral Sildenafil early in pregnancy as specific pulmonary vasodilators.

During delivery, puerperium and postdelivery

Pulmonary hypertension pregnant patients should be closely observed through the second trimester onwards and admitted for any deterioration of condition. A planned admission for delivery is advised. General measures include control of labor pain, anxiety and avoidance of hypovolemia, and hypoxemia. Please refer to the review of "perioperative management in patient with PH" in this issue of the journal for more details.

Although, there is no optimal mode of delivery, earlier reports suggest higher mortality due to cesarean section particularly when performed under general anesthesia. More recent reports however suggests better outcome of planned cesarean delivery using regional anesthesia.[25] Cesarean delivery avoids prolonged labor and associated hemodynamic stress.

Several physiological changes occur during vaginal delivery. Blood volume shifts during contractions and sympathetic stimulation from labor pains may result in sudden increase in CO, which is often poorly tolerated by PH patient. In addition, pain may also produce serous vasovagal response, though assisted vaginal delivery has shown low mortality rate in some centers.[15] Since general anesthesia is associated with several disadvantages, including increase PVR during intubation and positive pressure ventilation and cardiac depression from anesthetic agents, all producing hypotension, therefore regional anesthesia is preferred which may avoid these complications.

Patient is usually monitored for weeks after delivery. Several reports have suggested increased mortality during peripartum period, and so anticoagulation and specific pulmonary vasodilators agents should be continued after delivery.

References

1. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: A systematic overview from 1978 through 1996. J Am Coll Cardiol 1998;31:1650-7.
2. European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, *et al*. ESC Guidelines on the management of cardiovascular diseases during pregnancy: The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2011;32:3147-97.
3. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, *et al*. Guidelines for the diagnosis and treatment of pulmonary hypertension: The 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 the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493-537.
4. Madden BP. Pulmonary hypertension and pregnancy. Int J Obstet Anesth 2009;18:156-64.
5. Idrees MM, Al-Hajjaj M, Khan J, Al-Hazmi M, Alanezi M, Saleemi S, *et al*. Saudi guidelines on diagnosis and treatment of pulmonary arterial hypertension. Ann Thorac Med 2008;3(1):1-57[Supplement].
6. Ueland K. Maternal cardiovascular dynamics. VII. Intrapartum blood volume changes. Am J Obstet Gynecol 1976;126:671-7.
7. Pritchard JA. Changes in the blood volume during pregnancy and delivery. Anesthesiology 1965;26:393-9.
8. Lund CJ, Donovan JC. Blood volume during pregnancy. Significance of plasma and red cell volumes. Am J Obstet Gynecol 1967;98:394-403.
9. Pechet L, Alexander B. Increased clotting factors in pregnacy. N Engl J Med 1961;265:1093-7.
10. Walker MC, Garner PR, Keely EJ, Rock GA, Reis MD. Changes in activated protein C resistance during normal pregnancy. Am J Obstet Gynecol 1997;177:162-9.
11. Hellgren M, Blombäck M. Studies on blood coagulation and fibrinolysis in pregnancy, during delivery and in the puerperium. I. Normal condition. Gynecol Obstet Invest 1981;12:141-54.
12. Kansaria JJ, Salvi VS. Eisenmenger syndrome in pregnancy. J Postgrad Med 2000;46:101-3.
13. Slomka F, Salmeron S, Zetlaoui P, Cohen H, Simonneau G, Samii K. Primary pulmonary hypertension and pregnancy: Anesthetic management for delivery. Anesthesiology 1988;69:959-61.
14. Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. Br Med J (Clin Res Ed) 1987;295:1169-72.
15. Warnes CA. Pregnancy and pulmonary hypertension. Int J Cardiol 2004;97 Suppl 1:11-3.
16. Mccaffrey RM, Dunn LJ. Primary pulmonary hypertension in pregnancy. Obstet Gynecol Surv 1964;19:567-91.
17. Osei EK, Faulkner K. Fetal doses from radiological examinations. Br J Radiol 1999;72:773-80.
18. Brent RL. The effect of embryonic and fetal exposure to x-ray, microwaves, and ultrasound: Counseling the pregnant and nonpregnant patient about these risks. Semin Oncol 1989;16:347-68.
19. ACOG Committee on Obstetric Practice. ACOG Committee Opinion. Number 299, September 2004 (replaces No. 158, September 1995). Guidelines for diagnostic imaging during pregnancy. Obstet Gynecol 2004;104:647-51.
20. Penning S, Robinson KD, Major CA, Garite TJ. A comparison of echocardiography and pulmonary artery catheterization for evaluation of pulmonary artery pressures in pregnant patients with suspected pulmonary hypertension. Am J Obstet Gynecol 2001;184:1568-70.
21. Wylie BJ, Epps KC, Gaddipati S, Waksmonski CA. Correlation of transthoracic echocardiography and right heart catheterization in pregnancy. J Perinat Med 2007;35:497-502.
22. Damilakis J, Theocharopoulos N, Perisinakis K, Manios E, Dimitriou P, Vardas P, *et al*. Conceptus radiation dose and risk from cardiac catheter ablation procedures. Circulation 2001;104:893-7.
23. Gleicher N, Midwall J, Hochberger D, Jaffin H. Eisenmenger's syndrome and pregnancy. Obstet Gynecol Surv 1979;34:721-41.

24. Kiely DG, Condliffe R, Webster V, Mills GH, Wrench I, Gandhi SV, *et al*. Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. BJOG 2010;117:565-74.
25. Bédard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 2009;30:256-65.
26. Jaïs X, Olsson KM, Barbera JA, Blanco I, Torbicki A, Peacock A, *et al*. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J 2012;40:881-5.
27. Moore LG, Rounds SS, Jahnigen D, Grover RF, Reeves JT. Infant birth weight is related to maternal arterial oxygenation at high altitude. J Appl Physiol Respir Environ Exerc Physiol 1982;52:695-9.
28. Pitts JA, Crosby WM, Basta LL. Eisenmenger's syndrome in pregnancy: Does heparin prophylaxis improve the maternal mortality rate? Am Heart J 1977;93:321-6.
29. Oakley CM. Anticoagulation and pregnancy. Eur Heart J 1995;16:1317-9.
30. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: A systematic review of safety and efficacy. Blood 2005;106:401-7.
31. American College of Obstetricians and Gynecologists. ACOG Committee Opinion: Safety of Lovenox in pregnancy. Obstet Gynecol 2002;100:845-6.
32. Mazzolai L, Hohlfeld P, Spertini F, Hayoz D, Schapira M, Duchosal MA. Fondaparinux is a safe alternative in case of heparin intolerance during pregnancy. Blood 2006;108:1569-70.
33. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, *et al*. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:35-62S.
34. Hecker A, Hasan SH, Neumann F. Disturbances in sexual differentiation of rat foetuses following spironolactone treatment. Acta Endocrinol (Copenh) 1980;95:540-5.
35. Easterling TR, Ralph DD, Schmucker BC. Pulmonary hypertension in pregnancy: Treatment with pulmonary vasodilators. Obstet Gynecol 1999;93:494-8.
36. Geohas C, McLaughlin VV. Successful management of pregnancy in a patient with eisenmenger syndrome with epoprostenol. Chest 2003;124:1170-3.
37. Elliot CA, Stewart P, Webster VJ, Mills GH, Hutchinson SP, Howarth ES, *et al*. The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. Eur Respir J 2005;26:168-73.
38. Villanueva-García D, Mota-Rojas D, Hernández-González R, Sánchez-Aparicio P, Alonso-0Spilsbury M, Trujillo-Ortega ME, *et al*. A systematic review of experimental and clinical studies of sildenafil citrate for intrauterine growth restriction and pre-term labour. J Obstet Gynaecol 2007;27:255-9.
39. Madsen KM, Neerhof MG, Wessale JL, Thaete LG. Influence of ET(B) receptor antagonism on pregnancy outcome in rats. J Soc Gynecol Investig 2001;8:239-44.

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