Special Situations in Pulmonary Hypertension

Pregnancy and Right Ventricular Failure

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KEYWORDS

• Pregnancy • Pulmonary arterial hypertension • Pulmonary vascular disease
• Right ventricular failure

KEY POINTS

- Pregnancy remains a high-risk hemodynamic state for patients with PAH despite some improvement in outcomes with the advent of modern PAH therapies and multidisciplinary management strategies.
- Right ventricular (RV) failure predicts a poor prognosis in patients with pulmonary arterial hypertension (PAH).
- Evidence-based therapy for PAH should be initiated early in the disease course to decrease RV wall stress and prevent RV remodeling and fibrosis.
- In patients with acutely decompensated RV failure, an aggressive and multifaceted approach must be used with a combination of oxygen, intravenous (IV), or inhaled pulmonary vasodilators; inotropic agents; and diuretics; a thorough search for triggering factors for the decompensation is a key part of the successful management strategy.
- At specialized centers, atrial septostomy, extracorporeal membrane oxygenation (ECMO), and mechanical circulatory support devices are options to bridge patients to lung or heart-lung transplantation.
- Patients with refractory RV failure who are not candidates for surgical intervention should be referred to palliative care to maximize quality of life and symptom relief.

PREGNANCY

Introduction

PAH frequently affects women of childbearing age. Pregnancy is known to be associated with a high incidence of maternal and fetal mortality and morbidity in patients with PAH: the largest systematic review to date reported a maternal mortality of 30% to 56% and neonatal mortality of 11% to 13% in patients with PAH.[1] The hemodynamic stressors of pregnancy can sometimes lead to a new diagnosis of PAH in previously asymptomatic women. Current guidelines recommend strict avoidance of pregnancy and early pregnancy termination in women with PAH.[2] The treatment of PAH has been revolutionized, however, in the past 2 decades with new classes of medications, including endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors, soluble guanyl cyclase stimulator, and prostacyclin analogs, resulting in dramatic improvement in quality of life, functional status, and, with epoprostenol, mortality outcomes. This article reviews the physiology of pregnancy in women with PAH and the therapeutic options and treatment outcomes in pregnancy in the modern era of PAH therapy.

Hemodynamic Effects of Pregnancy

Gestation: a hyperdynamic and hypercoagulable state

Progressive expansion of plasma volume is one of the physiologic hallmarks of pregnancy. Plasma volume expansion begins at 6 to 8 weeks'

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gestation and increases by 50% during an average pregnancy to reach a peak intravascular volume of 4700 mL to 5200 mL at 32 weeks.[1,2] The resultant increase in stroke volume (SV) and a smaller-magnitude increase in resting heart rate (10–20 beats per minute) combine to increase cardiac output (CO) by 35% to a maximum of 9 L/min at term.[1,3] The highly compliant pulmonary vasculature of a healthy young woman coupled with further progesterone-mediated reduction in pulmonary vascular resistance (PVR) is able to accept this high CO without a rise in pulmonary pressure; in women with PAH, the vasoconstricted, remodeled pulmonary vasculature cannot respond with fall in PVR and there is a paradoxic increase in pulmonary pressures.[2] The dangerous combination of increased CO and elevated PVR presents a pressure overload to the RV with attendant high incidence of acute RV failure and maternal mortality during the peripartum, intrapartum, and postpartum periods in pregnant women with PAH.

Pregnancy is associated with a markedly hypercoagulable state due to increased fibrin generation, decreased fibrinolytic activity, increased levels of clotting factors, decrease in free protein S, and a high incidence of acquired resistance to protein C. These risk factors for thromboembolism are further exacerbated by a 50% reduction of venous flow velocity in the lower extremities due to compression by the enlarged uterus starting at 25 to 29 weeks' gestation and lasting until 6 weeks postdelivery.[4] These changes combine to raise the overall risk of thromboembolic events 5-fold in a pregnant woman even in the absence of PAH[5] but no data currently exist to quantify the precise incremental risk to pregnant women with PAH.

Peripartum and postpartum: a time of rapid hemodynamic shifts

The peripartum state is a time of large-scale volume shifts and rapid fluctuations in CO that poses further stress the RV in patients with PAH. In late gestation, the gravid uterus can compress the inferior vena cava, resulting in rapid decreases in venous return and drastic changes in preload to the RV merely with positional changes. Vaginal delivery is associated with blood loss of approximately 500 mL, or 10% loss of total blood volume, whereas caesarean section can amount to as much as 1000 mL, or up to 30% total plasma volume blood loss.[4] Uterine smooth muscle contraction postdelivery results in a rapid infusion of 300 mL to 500 mL of blood from the uterus into the maternal circulation.[6] Uterine contraction, anxiety, and pain also cause further increases in heart rate and thus CO during labor.[5]

The hemodynamic changes of pregnancy persist in the immediate postpartum period making this time one of the most dangerous in the course of pregnancy. There is a rapid increase in both systemic vascular resistance (SVR) and PVR that occurs immediately after delivery. The relief of compression of the inferior vena cava by the gravid uterus can result in rapid preload increase postpartum.[5] Reabsorption of extravascular volume can also contribute to increased preload to the RV. CO continues to remain elevated for or up to 48 hours postdelivery. All these factors contribute to the development of acute RV failure.

Pulmonary Arterial Hypertension Outcomes in Pregnancy

Studies from the 1960s and 1970s first defined the extreme risk of pregnancy with PAH, reporting a maternal mortality of greater than 50%, with most deaths occurring in late gestation, during labor, or early in the postpartum period.[7,8] Data from a systematic overview of outcomes in 125 pregnant patients with PAH from 1978 through 1996 by Weiss and colleagues[6] defined an overall maternal mortality of 38%, with a range of 30% in idiopathic PAH, 36% in congenital disease/Eisenmenger syndrome, and 56% in secondary pulmonary hypertension (PH) (including PH associated with thromboembolic and connective tissue disease). A comparative analysis by Bedard and colleagues[8] of 73 pregnancies with PAH from 1997 to 2007 reported a significant decrease in overall maternal mortality (25% vs 38%; $P = .047$), with concomitant decreases in mortality within each cause of PH (17% in idiopathic PAH, 28% in congenital disease/Eisenmenger syndrome, and 33% in secondary PH). Most deaths occurred in the first month postpartum in both studies. Independent risk factors for maternal mortality were late diagnosis (odds ratio [OR] 5.4; $P = .002$), late presentation to the hospital (OR 1.1 per week of pregnancy; $P = .01$), primigravida (OR 3.70; $P = .03$) and the use of general anesthesia (OR 4.37; $P = .02$).[1,9]

Table 1 summarizes the results of key studies of maternal and fetal outcomes published to date with particular emphasis on improved maternal mortality outcomes and the more widespread utilization of PAH-specific therapies in the past 2 decades. The most recent report from a prospective, international registry by Jaïs and colleagues[10] followed 26 pregnant women with PAH and reported a significantly decreased maternal mortality (3 women died from right heart failure and 1 required urgent heart and lung transplantation); the investigators note that patients with successful