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CASE REPORT Open Access

Pregnancy in pulmonary arterial hypertension associated with congenital heart disease: an illustrative case study

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Abstract

Background: Pregnancy in patients with pulmonary arterial hypertension associated with congenital heart disease is associated with a high risk of maternal mortality.

Case presentation: An illustrative case study based on experience gained from management of patients through pregnancy is discussed. A 22-year-old female with a history of a closed patent ductus arteriosus in childhood had been diagnosed with significant pulmonary arterial hypertension at the age of 19. Her clinical condition had improved following the commencement of oral combination therapy with sildenafil 25 mg three times daily and macitentan 10 mg once daily. How should she be counselled regarding the risks of pregnancy and what are the most appropriate forms of contraception? What should the approach be if, despite adequate counselling, she subsequently becomes pregnant? Data to help guide decision-making are reviewed and a clinical approach is suggested.

Conclusions: Patients with pulmonary arterial hypertension should be advised against pregnancy and be given good contraceptive advice. If a patient with pulmonary arterial hypertension becomes pregnant and, after being fully counselled, chooses to proceed with their pregnancy, then they should be managed by an experienced multidisciplinary team.

Keywords: Pregnancy, Pulmonary arterial hypertension, Congenital heart disease, Contraception

Background

Pregnancy in patients with pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) is associated with a high risk of maternal mortality. Current guidelines therefore strongly advise against pregnancy in this patient group. In this illustrative case study, based on experience gained from management of patients through pregnancy, data regarding risks of maternal mortality in patients with PAH are reviewed and approaches to contraception and to pregnancy are discussed.

Case presentation

A 22-year-old female with a history of a closed patent ductus arteriosus in childhood had been diagnosed with significant PAH at the age of 19. Her clinical condition had improved following the commencement of oral combination therapy with sildenafil 25 mg three times daily and macitentan 10 mg once daily. She was currently in World Health Organisation functional class II. Her incremental shuttle walking test distance was 380 m. N-terminal pro B-type natriuretic peptide was modestly elevated at 485 pg/mL. Echocardiography demonstrated a mildly dilated right ventricle with moderate hypertrophy and mildly reduced systolic function and mild right atrial dilatation. Left sided chambers were of normal size and left ventricular systolic function was preserved. There was no pericardial effusion. Systolic pulmonary arterial pressure was estimated at echocardiography to be 61 mmHg

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plus right atrial pressure. She therefore had low and intermediate risk factors according to the European Society of Cardiology/European Respiratory Society approach [1]. On examination she had no evidence of peripheral oedema and her jugular venous pressure was not elevated. She had a loud second heart sound and a moderate systolic murmur at the left lower sternal edge. How should she be counselled regarding the risks of pregnancy and what are the most appropriate forms of contraception? What should the approach be if, despite adequate counselling, she subsequently becomes pregnant?

Discussion

How should she be counselled regarding the risks of pregnancy and what are the most appropriate forms of contraception?

Cardiac output increases by approximately 50% during the first 20 weeks of pregnancy in health, while systemic vascular resistance falls significantly [2]. In patients with PAH, the ability to increase cardiac output may be significantly limited. Historical reviews of maternal outcomes in PAH reported maternal mortality of 38–52% [3, 4]. A subsequent systematic review reported a maternal mortality of 25% in PAH patients managed between 1997 and 2007 [5], while case series of patients managed mainly during the last decade observed mortality rates of 10–20% [6–9]. Outcomes in 18 pregnant patients with Eisenmenger syndrome who proceeded to delivery have recently been published [10]. Maternal mortality was 6%, while severe heart failure occurred in 4 patients, 3 patients received inotropic support, and 1 patient underwent extracorporeal membrane oxygenation (ECMO). In view of these data, international pulmonary hypertension and cardiovascular disease guidelines advise against pregnancy [1, 11].

It is therefore imperative that the risks of pregnancy and the recommended forms of contraception are discussed with patients with PAH associated with CHD at the time of diagnosis and that written advice is provided. Due to concerns regarding the pro-thrombotic effects of oestrogen-containing methods, the most commonly recommended methods are the desogestrel pill (e.g. Cerazette™ or Cerelle™), etonogestrel implant (e.g. Nexplanon™) or intrauterine device (e.g. Mirena™) (Table 1). Due to the risk of syncope during insertion, the intrauterine device should be inserted in the hospital setting. Bosentan is an inducer of cytochrome P-450 and hence the efficacy of cerazette and nexplanon may be reduced [13]; additional contraceptive methods are, therefore, required.

What should the approach be if, despite adequate counselling, she subsequently becomes pregnant?

Despite being counselled regarding the risks of pregnancy, some patients with PAH may actively choose to conceive or choose to proceed should they become pregnant. Other patients may present with PAH during pregnancy. For all pregnant patients the risks of proceeding versus termination should be discussed. If a patient decides to proceed, then a multidisciplinary approach to supporting pregnancy is required, involving experienced healthcare professionals (PAH/adult CHD physicians and nurses, obstetricians, midwives, anaesthetists, intensivists and neonatologists) [6]. Figure 1 summarises an approach to the management of a PAH patient who chooses to proceed with pregnancy. Endothelin receptor antagonists are potentially teratogenic and should, therefore, be stopped before conception or at the very early stages of pregnancy [14]. Several case reports and case series support the safety of sildenafil in pregnant PAH patients, with no reports of adverse effects on the

Table 1 Contraception in pulmonary arterial hypertension

Method	1-yr failure rate: typical use (%)	1-yr failure rate: perfect use (%)	Comments
Male condom	15	2	Efficacy is not high enough in typical use to use as sole method
Combined oral contraceptive pill	8	0.1	Not recommended due to increased thrombotic risk
Desogetsrel (e.g. Cerazette™)	8	0.1	Efficacy is reduced in patients receiving bosentan and an additional method is therefore required (e.g. barrier)
Medroxyprogesterone acetate injection (e.g. Depo-Provera™)	3	0.3	Increased risk of thrombus compared with other non-oestrogen hormonal methods
Etonogestrel implant (e.g. Nexplanon™)	0.05	0.05	Efficacy is reduced in patients receiving bosentan and an additional method is therefore required (e.g. barrier)
Copper coil	0.8	0.6	
Levonorgestrel coil (e.g. Mirena™)	0.1	0.1	Requires placement in hospital due to the risk of vaso-vagal events.
Male sterilisation	0.2	0.1	
Female sterilisation	0.5	0.5	Requires laparotomy (ligation) or hysteroscopy (Essure)

Adapted from Condliffe et al [12].

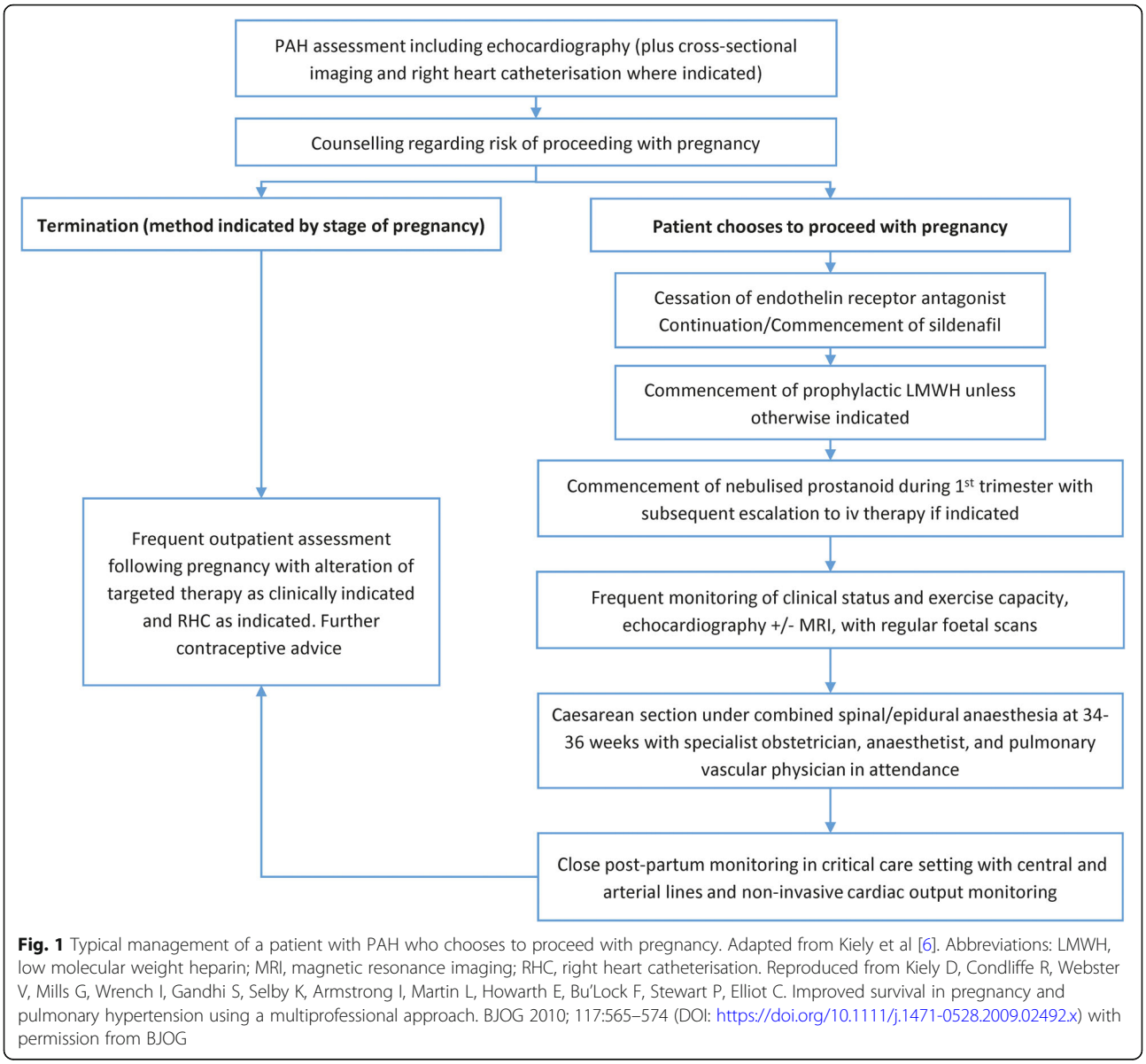

Fig. 1 Typical management of a patient with PAH who chooses to proceed with pregnancy. Adapted from Kiely et al [6]. Abbreviations: LMWH, low molecular weight heparin; MRI, magnetic resonance imaging; RHC, right heart catheterisation. Reproduced from Kiely D, Condliffe R, Webster V, Mills G, Wrench I, Gandhi S, Selby K, Armstrong I, Martin L, Howarth E, Bu'Lock F, Stewart P, Elliot C. Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. BJOG 2010; 117:565–574 (DOI: https://doi.org/10.1111/j.1471-0528.2009.02492.x) with permission from BJOG

foetus [7–9, 15, 16]. Prostanoid therapy may also often be required via either the nebulised or intravenous route [6, 17, 18]; in our centre we routinely add in nebulised iloprost to sildenafil during the first trimester. Unless full-dose anticoagulation is indicated, we routinely commence patients on prophylactic low molecular weight heparin.

Patients should be carefully monitored throughout pregnancy, with regular assessments including exercise capacity and echocardiography or cardiac magnetic resonance imaging. Significant deterioration occurring during the first trimester suggests an inability to increase cardiac output sufficiently and should stimulate further discussions regarding termination. If termination is not performed, or if worsening of right ventricular (RV) function occurs later in pregnancy, then we would recommend switching from nebulised to intravenous prostanoid. The aim should be to deliver early at around 34–36 weeks' gestation although this may be brought forward if there are concerns regarding worsening RV function or impaired foetal growth. Although there is debate regarding the optimal method of delivery, many experienced centres deliver via elective Caesarean section under regional anaesthesia [19]. Indeed, in their systematic review, Bedard et al. found general anaesthesia to be associated with a four-fold increased risk of death as compared with regional anaesthesia, although patients receiving general anaesthesia were those with more severe disease [5].

Patients require close haemodynamic monitoring during the peri-partum period. Measurement of central venous pressure and saturation via a central line, systemic

blood pressure via an arterial line and non-invasive cardiac output monitoring enable manipulation of RV preload (with fluid boluses or diuretics), RV afterload (with parenteral prostanoid), systemic vascular resistance (with pressor agents) and cardiac contractility (with inotropes) [14]. Certain agents often used during delivery may increase pulmonary vascular resistance (PVR); nitric oxide should be avoided, whilst oxytocin should be used with caution as a low dose infusion [6]. After delivery, significant fluid shifts into the systemic vasculature occur, which may be poorly tolerated in patients with pulmonary hypertension. The postpartum period is therefore a period of increased risk of mortality and close monitoring in the critical care setting for at least 72 h is advised [14].

Outcome

Despite full counselling, the patient became pregnant. The risks of proceeding with pregnancy were re-discussed and termination was offered. The patient, however, chose to proceed with the pregnancy. Macitentan was stopped during pregnancy and she was commenced on nebulised iloprost in addition to sildenafil. She was commenced on prophylactic-dose low molecular weight heparin, which was continued for 6 weeks following delivery. She was followed regularly during pregnancy, and her clinical state and echocardiographic parameters remained stable. Elective Caesarean section was performed under combined spinal-epidural anaesthesia at 36 weeks' gestation. Low-dose intravenous iloprost was commenced 48 h prior to delivery and continued for 72 h post-partum. She had an uneventful peripartum period. Following discussion regarding future contraceptive wishes, a Levonorgestrel coil was inserted following delivery. Macitentan was restarted and she was weaned off nebulised iloprost by 3 months post-partum.

Conclusion

Although outcomes in patients with PAH may have improved over recent years, pregnancy is still associated with a high risk of maternal mortality. Patients with PAH should therefore be advised against pregnancy and be given good contraceptive advice. If a patient with PAH becomes pregnant and, after being fully counselled, chooses to proceed with their pregnancy, then they should be managed by an experienced multidisciplinary team.

Abbreviations

ECMO: Extracorporeal membrane oxygenation; PAH: Pulmonary arterial hypertension; PVR: Pulmonary vascular resistance; RV: Right ventricular

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Consent for publication

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Competing interests

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