Pregnancy in pulmonary arterial hypertension

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ABSTRACT Despite advanced therapies, maternal mortality in women with pulmonary arterial hypertension (PAH) remains high in pregnancy and is especially high during the post-partum period. However, recent data indicates that morbidity and mortality during pregnancy and after birth have improved for PAH patients. The current European Society of Cardiology/European Respiratory Society guidelines recommend that women with PAH should not become pregnant. Therefore, the risks associated with pregnancy must be emphasised and counselling offered to women at the time of PAH diagnosis and to women with PAH who become pregnant. Early termination should be discussed. Women who choose to continue with their pregnancy should be treated at specialised pulmonary hypertension centres with experience in managing PAH during and after pregnancy.

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While pregnancy is not recommended in PAH, there is increasing experience in managing PAH in pregnant women http://ow.ly/N6b2305Aur3

Introduction

Current guidelines clearly recommend the avoidance of pregnancy in women with PAH and termination when pregnancy does occur [1, 2]. This recommendation is of particular significance given that PAH often affects women of childbearing age [3]. Historically, high rates of maternal and fetal death have been reported for pregnant women with PAH (30–56% and 11–28%, respectively) [4–6]. The causes of poor maternal outcomes are varied and include risk of death from right heart failure and stroke from intracardiac shunting [7]. Furthermore, there is a high peri-/post-partum risk due to haemodynamic stress, bleeding complications and the use of general anaesthesia, which can all lead to right heart failure [8, 9]. The most common risk to the fetus is death, with premature birth and growth retardation being reported in successfully delivered children [6].

Despite the risks to both the mother and unborn child, some women decide to continue with their pregnancy and more women with PAH are considering having a family. As the PAH landscape changes and patients are living longer with better quality of life, there is an increasing amount of experience in managing PAH in pregnant women. This article reviews the current data and guidelines on the management of PAH in pregnancy.

Physiological changes during pregnancy

Extensive physiological changes take place in the mother during pregnancy to meet the growing demands of the fetus and some of these changes may contribute to right ventricular failure in women with PAH (figure 1). Blood volume, red cell mass, left ventricular mass and cardiac output (CO) increase during

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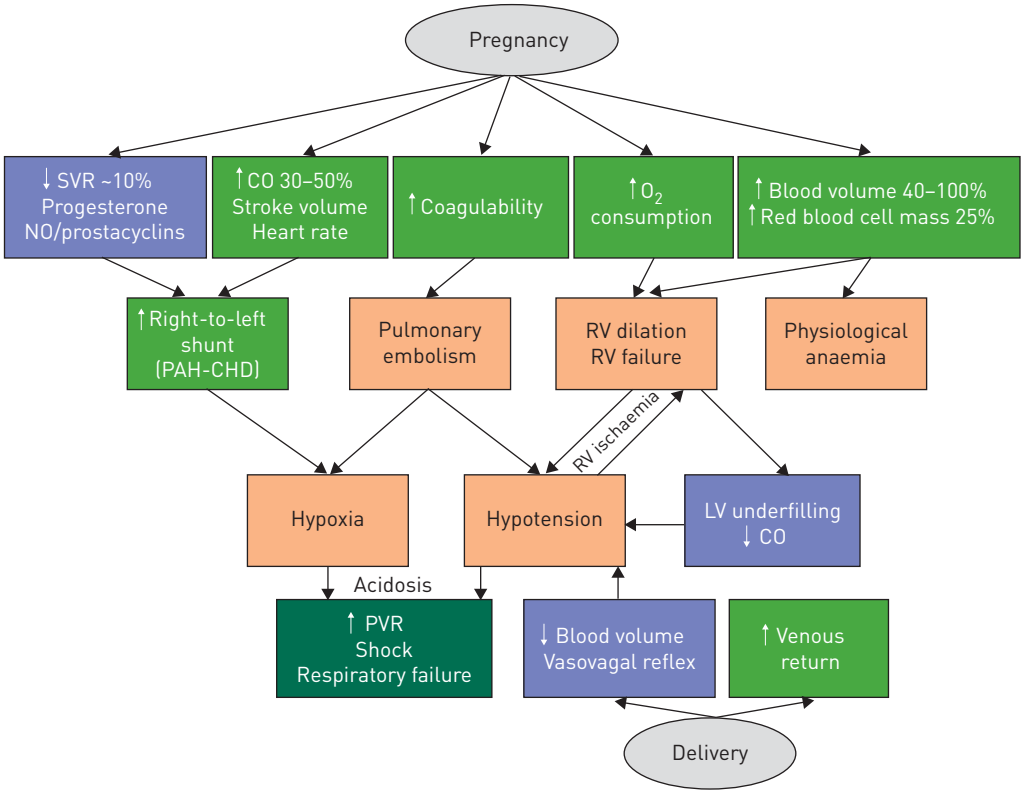

FIGURE 1 Physiological changes in pulmonary arterial hypertension (PAH) patients which occur in response to pregnancy. NO: nitric oxide; CO: cardiac output; PAH-CHD: PAH associated with congenital heart disease; LV: left ventricle; RV: right ventricle; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance. Reproduced from [7] with permission from the publisher.

pregnancy, whereas systemic vascular resistance (SVR) and blood pressure decrease [3, 10]. Between 28 and 34 weeks of gestation, blood volume increases to reach maximum levels of 40–100% above the pre-pregnancy baseline levels and then remains stable until delivery [7, 10]. Red cell mass only increases to 25% above the non-pregnancy level, potentially resulting in physiological anaemia [10]. The heart can increase in size by up to 30%, partially due to dilation [11]. CO increases sharply during the first trimester and then rises to reach a peak of 30–50% above the pre-pregnancy baseline level. This is initially due to an increase in stroke volume, whereas in late pregnancy an increase in heart rate (by 15–20 beats per minute) can be a contributing factor [3, 11]. Haemostatic changes can occur during pregnancy, such as an increase in coagulation factors and fibrinogen, a decrease in protein S, and acquired protein C resistance [12]. Together, these changes result in a tendency towards hypercoagulability and an increased risk of thromboembolic events [10, 11]. Hormonal changes that can occur during pregnancy include increased levels of progesterone and oestrogen, which can have vasodilatory effects, further exacerbating the decrease in SVR and leading to a significant drop in diastolic blood pressure [3]. Mechanical compression of the vena cava, caused by enlargement of the uterus, can occur during mid-pregnancy and potentially results in a reduction of venous return to the right ventricle [10]. All of these changes can put considerable strain on the right ventricle and lead to right ventricular failure in pregnant women with PAH.

For women with PAH, the risk of right heart failure is particularly high during labour, delivery and the post-partum period, reflecting the high risks related to pressure and volume changes that occur during these stages. During labour, a blood volume of 500 mL is diverted to maternal circulation from the uterus during each contraction, resulting in increased CO and systemic and diastolic blood pressure [7, 11]. Systemic blood pressure can increase by 15–25% during uterine contractions [7, 10, 11]. In contrast, during delivery, hypotension associated with blood loss or a vasovagal response can lead to a drop in systemic blood pressure [7]. These opposing physiological changes highlight some of the complexities of managing labour and delivery in women with PAH. Increases in CO vary greatly: increases of 15% are observed in early labour and increases of up to 80% are observed post-partum due to the additional autotransfusion associated with uterine involution and resorption of leg oedema [11]. In addition, anaesthesia, analgesia, haemorrhage and infection during delivery and in the post-partum period may put considerable stress on the maternal cardiovascular system [11].

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Advice and counselling for women at the time of PAH diagnosis

Given that PAH often affects women of child-bearing age, it should be made clear to women at the time of their PAH diagnosis that pregnancy is not recommended due to the high maternal and fetal risks [1–3, 7]. Counselling should be offered to women and their families at the time of PAH diagnosis, together with an individual patient risk assessment, in a pulmonary hypertension centre with experience in the management of pregnancy in PAH [1–3, 10, 13, 14].

It is important that advice on effective contraceptive methods is given early following a PAH diagnosis and that there is appropriate collaboration and follow-up with a community gynaecologist. A summary of contraceptive methods is given in table 1. Progestogen-only methods of contraception can be used in women with PAH [3]. However, there have been concerns over the association between injectable progestin and venous thromboembolism (VTE), with one meta-analysis demonstrating a two-fold increase in the risk of VTE with this type of contraceptive [14]. Furthermore, intrauterine devices can lead to vasovagal reactions when inserted, which can have severe adverse effects in women with PAH, such as a profound drop in CO and cardiovascular collapse [3, 13]. Oestrogen-containing contraceptives increase risk of VTE [3, 10], but may be used when patients are on anticoagulation. Barrier methods are safe to use in women with PAH but can be unpredictable [1, 2]. Permanent contraception *via* tubal ligation or a device implanted into the fallopian tubes may be considered. However, such a permanent contraceptive method may not be a desirable option for many women, who may wish to use temporary methods. Furthermore, the procedure also bears the risk of complications and anaesthesia. Given the risk of drug–drug interactions, the potential contraindication of hormonal methods and the unreliability of barrier

TABLE 1 Contraceptive methods for women with pulmonary arterial hypertension (PAH)

Type of contraceptive (trade name)	Comments
Hormone-based methods	
Progestogen-only	
Progesterone-only pill	May have reduced efficacy in women taking bosentan and should not be used as the sole method of contraception in these patients [1, 2, 10, 13]
Injectable progestin (Depo-provera®)	One meta-analysis has shown an increased risk of VTE when injectable progestin is administered [14]
Progestogen implant (Implanon®)	May have reduced efficacy in women taking bosentan and should not be used as the sole method of contraception in these patients [1, 2, 10, 13]
Hormone-releasing IUS (Mirena)	Risk of infection at time of insertion [13] Occasional vasovagal reaction when inserted, which is poorly tolerated in severe PAH [10, 13]
Emergency hormonal contraception	Emergency contraception is not recommended as a regular long-term contraceptive technique due to its high annual failure rate, plus its lack of protection against sexually-transmitted infections [13] May have reduced efficacy in women taking bosentan [13]
Oestrogen and progestin combination	
Combined oral contraceptive pill Transvagal ring (NuvaRing#) Contraceptive patch (EVRA#)	The oestrogen component is associated with increased risk of arterial thromboembolism and VTE [3, 10, 13]; anticoagulation does not protect entirely against the thrombotic risk [13]
Non-hormonal methods	
Copper-T IUD	Less frequent replacement required than the Mirena IUS [13] Risk of endocarditis likely to be greater than the Mirena IUS [13]
Barrier methods	Barrier contraceptive methods are safe for the patient, but with an unpredictable effect [1, 2]
Permanent methods	
Female sterilisation	Sterilisation can be performed electively, post-abortum, post-partum or at the time of caesarean section, avoiding the risks of a separate procedure; however, the failure rate is reportedly higher in this setting [10] Hysteroscopic methods are associated with the potential for lower procedural risks than other permanent contraception methods [3] If tubal ligation is planned, a mini-laparotomy may be a safer method than a laparoscopic approach due to procedural risks [3]
Male sterilisation	Male sterilisation can be performed under local anaesthesia. It is also cheaper and associated with a lower failure rate and fewer complications compared with female sterilisation [10]

VTE: venous thromboembolism; IUS: intrauterine system; IUD: intrauterine device. #: not available in the UK.

methods, two methods of contraception may be used at the same time [1, 2]. Dual contraception is indicated in women taking the endothelin receptor antagonist (ERA) bosentan, due to the interaction between the drug and progesterone-based methods of contraception [1, 2, 10].

Both *in vitro* fertilisation and harvesting of eggs are not advised in PAH. Although there are no data for *in vitro* fertilisation in PAH, common serious adverse events in healthy individuals include ovarian hyperstimulation and risks of VTE, which would have potential detrimental effects on women with PAH. For a woman with PAH who wishes to become pregnant, genetic screening and counselling should be considered [15]. If the patient has heritable PAH and a mutation in a PAH-associated gene has been identified, the risk of the child inheriting the mutation and developing PAH should be discussed. It is important to consider disease aetiology in women with PAH who are pregnant, or who plan to become pregnant, as this may affect treatment strategies not just for PAH but also for the underlying disease. For example, patients with PAH associated with connective tissue disease may be receiving treatment with immunosuppressants, which may be contraindicated in pregnancy.

Currently there are no long-term data on patient outcomes after pregnancy in PAH. However, considering the limitations of the underlying disease, this issue should be discussed with the patient on an individual basis.

Management of PAH during pregnancy

If a woman with PAH becomes pregnant, counselling should be offered and therapeutic abortion seriously considered [10]. Patients should also be advised that PAH can worsen during the post-partum period [3]. If a therapeutic abortion is accepted, it is recommended that this occurs before 22 weeks of gestation [10]. One study has shown that of six planned terminations in women with PAH (mean gestational weeks±SD, 10±3), all proceeded without complication [8]. In contrast, a case study has shown that late surgical termination is associated with an increased risk of death [16].

It is important that a woman with PAH who becomes pregnant is referred to a PAH specialist centre that has experience in managing PAH in pregnancy. Specialist centres typically encourage a close multidisciplinary collaboration between pulmonary hypertension specialists, obstetricians, critical care specialists and neonatologists. Such a team is essential for the successful management of PAH during pregnancy [7, 17]. In addition, a pregnancy care plan should be detailed from early on, including timing and mode of delivery for the woman with PAH [7].

For women with PAH who decide to carry on with their pregnancy, regular close follow-up at a PAH centre is recommended and, in some cases, elective hospitalisation for optimisation of medication leading up to delivery may be advised. In addition to a full clinical evaluation, close follow-up should include regular echocardiographic monitoring and monitoring of the fetus for growth retardation [3, 18]. Some publications outline factors that are associated with a lower risk pregnancy in women with PAH. These include well-controlled PAH with PAH-specific therapy, a low pulmonary vascular resistance (PVR) and response to calcium channel blockers (CCBs) [8]. Conversely, a higher risk pregnancy in women with PAH is associated with uncontrolled PAH, first pregnancy and high PVR [8, 9, 19]. A Japanese case study has also shown that the level of pulmonary artery blood pressure before or in the early stages of pregnancy may be an important predictor of pregnancy outcome [20].

Hospitalisation of women with PAH in the second trimester is sometimes appropriate due to the increased risk of premature labour and of haemodynamic complications [17, 21]. Evaluation for lung transplantation should be performed in a timely manner, as this may be required in case of emergencies, especially in high risk patients who decide to continue with their pregnancy [8].

PAH-specific therapy

The current European Society of Cardiology/European Respiratory Society guidelines recommend that women with PAH who choose to continue with pregnancy should either be treated with (or continue treatment with) PAH-specific therapies [1, 2], except for ERAs [10, 22–24]. There is an increasing body of evidence on the successful and safe use of PAH-specific therapies during pregnancy, such as CCBs [5, 8, 9], prostacyclin and its analogues [8, 17, 25–29], and phosphodiesterase type-5 inhibitors [17, 30]. However, no controlled studies have been reported to date and there are no comparative studies of different PAH treatment regimens.

It has been reported that some women with PAH may benefit from CCBs during pregnancy [5, 8, 9]. For example, in a prospective registry of PAH patients, eight women were identified who had uncomplicated pregnancies whilst using CCBs [8]. There have also been several case reports on the successful use of intravenous (*i.v.*) epoprostenol during pregnancy and delivery, *via* either spontaneous vaginal delivery or caesarean section, in women with PAH [27–29]. Inhaled iloprost has also been used successfully to treat PAH during pregnancy [8, 17, 25, 26]. Two case reports have been published on the successful use of the phosphodiesterase type-5 inhibitor sildenafil during pregnancy in women with PAH [17, 30].

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ERAs have shown teratogenic effects [22, 24, 31] and are therefore contraindicated during pregnancy [22–24]. If a woman with PAH becomes pregnant, any ERA should be discontinued. Once the ERA is discontinued, the woman should be switched to another therapy if these treatments are not being used already. In women with a desire to have children, ERA therapy should generally not be discontinued until the woman actually becomes pregnant.

Physiological changes and complications that occur during pregnancy, such as hyperemesis gravidarum, can affect the absorption, excretion and bioavailability of drugs [11, 32]. Therefore, it is vital to monitor patients carefully and make dose adjustments as necessary throughout the pregnancy and delivery [11].

Treatment of pregnancy-related manifestations

The coagulation system is activated in pregnancy due to a decrease in protein S and acquired protein C resistance, and higher levels of thrombin [12]. However, there are no data indicating whether pregnant patients with PAH are at increased risk of VTE. Therefore, anticoagulation may be considered in pregnant women with PAH to reduce the risk of VTE [10]. Vitamin K antagonists are contraindicated in the first trimester of pregnancy due to their potential to lead to fetal craniofacial abnormalities [10]. The use of vitamin K antagonists at any stage of pregnancy may lead to fetal haemorrhage, spontaneous abortion and malformation of the central nervous system. It is recommended that pregnant women with PAH are treated with low-molecular-weight heparins [10, 33]. Due to increased fluid retention and blood volume during pregnancy, it is particularly important to manage peripheral oedema, a symptom of right heart failure in PAH [1, 2]. Pregnant women with PAH should avoid lying on their backs to help prevent compression of the inferior vena cava [3]. Although diuretics can reduce blood flow over the placenta [11], they may be required for the treatment of right heart failure in women with PAH [3, 7, 17], or during delivery to reduce fluid overload [3]. If required, the diuretics torasemide or furosemide can be used, whereas spironolactone should be avoided because of anti-androgenic effects in the first trimester [3, 11].

It is important to manage hyperemesis gravidarum as this could otherwise result in fluid and electrolyte imbalances and reduce the efficacy of oral medications during the pregnancy. The use of laxatives should be limited as these can reduce the intake of other therapies.

Modes of delivery for pregnant women with PAH

The optimal timing and mode of delivery for pregnant women with PAH has not been determined but women with PAH should ideally not go into labour naturally. Practices vary across centres, with successful vaginal births (using induction and assisted delivery) and caesarean sections being reported. Assisted delivery is conducted early to avoid spontaneous vaginal delivery, the timing of which cannot be controlled and which can potentially lead to labour at night or during weekends with inexperienced teams managing the labour and delivery. This is particularly important to consider since pre-term labour is common in women with PAH.

There are practical considerations regarding the different modes of delivery for women with PAH. A vaginal birth is usually associated with less blood loss, fewer infections, less thromboembolic risk, and less abrupt haemodynamic changes compared with a caesarean section [10, 34, 35]. However, a prolonged labour can be detrimental, with haemodynamic changes that can be problematic for the mother, including an increase in CO and venous return. Further disadvantages that are associated with vaginal births include labour-induced acidosis, hypercapnia or hypoxia that can lead to increases in pulmonary arterial pressure [3, 21, 35]. Women should be monitored by electrocardiogram at all times throughout labour and should have regular measurements of pulse oximetry, central venous pressure, and intra-arterial blood pressure taken [3, 7]. Nitrous oxide (N_2O) should be avoided as pain-relief during vaginal birth because of its ability to cause vasoconstriction of the pulmonary vasculature [3].

A scheduled caesarean section delivery is a means of avoiding an often lengthy labour. Caesarean sections can be performed in a controlled environment, with close monitoring and extracorporeal membrane oxygenation on standby, and under regional anaesthetic where possible [36, 37] as general anaesthesia poses a risk for women with PAH [8, 9]. Planned caesarean sections are usually arranged for gestational weeks 32–36 as a compromise between maternal health and sufficient fetal maturation, and to reduce the risk of the woman going into spontaneous labour during unsociable hours.

For all modes of delivery, it is important that the underlying PAH is well controlled first. There is a preference at some centres to initiate *i.v.* epoprostenol in women with PAH immediately prior to delivery, regardless of whether or not their PAH is well controlled. However, it is unknown whether this approach improves outcomes and not all women will choose to start parenteral prostanoid therapy prior to induction or a caesarean section. Even if women have well compensated PAH prior to delivery, acute deterioration and death can occur post-partum; therefore, treatment with *i.v.* epoprostenol is continued at some centres for some time after delivery.

Post-natal care for the mother and neonate

Post-partum monitoring of women with PAH is very important as most deaths occur in this period and monitoring should continue for several days to weeks following delivery [5, 10, 35]. The highest risk of mortality is during the first 4 weeks after delivery [9, 36] with the majority of deaths due to right ventricular failure [8, 9]. Contributing factors to right ventricular failure include autotransfusion of blood, excessive increases in PVR and thromboembolic events [10]. Therapies to reduce the risk of right ventricular failure post-partum include inhaled nitric oxide, *i.v.* epoprostenol and inhaled iloprost [5]. Systemic vasopressors and inotropes may also be required [10]. Prevention of bleeding complications after a caesarean section is of high importance and oxytocin remains the first-line drug [38]. However, oxytocin has to be used carefully as it can cause hypotension and reflex tachycardia [38], potentially leading to an increase in pulmonary artery pressure in PAH patients [39, 40]. Further management of women with PAH following delivery includes advice with regards to breastfeeding. Breastfeeding is not usually recommended as pulmonary vasodilators may be excreted in breast milk [17, 31] and a negative effect of prolactin on the myocardium cannot be excluded in these patients [41]. A close long term follow up should be secured in women with PAH after pregnancy

There is a high chance that babies born to women with PAH will be premature, being delivered during gestational weeks 32–36 [5, 9]. These babies are generally smaller than a full-term baby and may require management in the premature care unit. Based on clinical experience, these babies are generally healthy.

Women who develop PAH during pregnancy

PAH may manifest during pregnancy and some women are diagnosed with PAH during this time. Current data and our experience suggest that there is a higher risk of complications associated with this group of women, potentially due to a late diagnosis of PAH and a subsequent delay in initiating appropriate PAH therapy [7, 31]. As some of the most common PAH symptoms, such as fatigue and dyspnoea, are also common during pregnancy, this can contribute to a delayed PAH diagnosis [10]. Although echocardiography can be a useful screening tool for PAH during pregnancy, a "false positive" echo is not uncommon [42], likely due to the increased CO and the concomitant mild increase in pulmonary arterial pressures seen in pregnancy.

The psychological aspects of PAH and treatment in women who develop PAH during pregnancy must be managed. Counselling is essential at the time of PAH diagnosis to highlight the risks to the mother and fetus. Depending on the stage of pregnancy, counselling for termination should also be offered.

Conclusion

Pregnancy in PAH is an extremely sensitive topic. Pregnancy is not recommended in women with PAH, yet interactions with patients in the clinic and discussions in internet chat rooms indicate that an increasing number of women with PAH are expressing their desire to have a family. The wishes of these women cannot be ignored and they should be made aware of the options that are currently available, as well as the risks associated with pregnancy. There is increasing experience in managing PAH in the setting of pregnancy [8, 17, 25–30]. Recent studies report improved outcomes of pregnancy in PAH patients compared with the era before advanced therapies [8, 20], provided that PAH is well controlled, and particularly in long-term responders to CCBs [8]. These data must be confirmed using data from larger series before the general recommendation to avoid pregnancy is reconsidered [1, 2]. Furthermore, caution is warranted as the number of published cases is few and there is likely to be a bias towards publication of cases with positive outcomes. With improved long-term outcomes for PAH patients in general, it will become more common to manage and treat pregnant women with PAH.

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