Summary

Introduction. — Pulmonary arterial hypertension (PAH) is a rare condition characterized by sustained elevation in pulmonary arterial resistance leading to right heart failure.

Background. — PAH affects predominantly women. Echocardiography is the initial investigation of choice for non-invasive detection of PAH but right-heart catheterization is necessary to confirm the diagnosis. Conventional treatment includes non-specific drugs (warfarin, diuretics, oxygen). The endothelin-1 receptor antagonist bosentan, the phosphodiesterase-5 inhibitor sildenafil, and prostanoids have been shown to improve symptoms, exercise capacity and haemodynamics. Intravenous prostacyclin is the first-line treatment for the most severely affected patients. Despite the most modern treatment, the overall mortality rate of pregnant women with severe PAH remains high. Therefore, pregnancy is contraindicated in women with PAH and an effective method of contraception is recommended in women of childbearing age. Therapeutic abortion should be offered, particularly when early deterioration occurs. If this option is not accepted, intravenous prostacyclin should be considered promptly.

Viewpoints and conclusion. — Recent advances in the management of PAH have markedly improved prognosis and have resulted in more women of childbearing age considering pregnancy. A multidisciplinary approach should give new insights into cardiopulmonary, obstetric and anaesthetic management during pregnancy, delivery and the postpartum period.

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KEYWORDS
Pulmonary arterial hypertension; Diagnosis; Pregnancy; Treatment

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Introduction

Pulmonary arterial hypertension (PAH) is a group of disorders affecting pulmonary microcirculation resulting in sustained elevation in pulmonary vascular bed pressures. Female predominance is commonly seen in idiopathic PAH, i.e. occurring without an associated condition. The prognosis, formerly particularly poor, has markedly improved in the past few years with the development of new treatments. This article discusses the epidemiological features, pathophysiological aspects, and treatment management, particularly during pregnancy.

New classification of pulmonary hypertension

A new classification of pulmonary hypertension was defined in 2003 at the 3rd WHO World Symposium on Pulmonary Arterial Hypertension [1]. This classification identifies five categories presenting similarities in their pathophysiology, clinical presentation, and mainly their management (Table 1). This new classification defines idiopathic PAH, formerly ‘’primary’’ PAH, as onset of the disease in the absence of associated conditions such as connective tissue disease, congenital heart disease (Eisenmenger syndrome), portal hypertension, HIV infection, or exposure to toxics (anorexic derivatives of fenfluramine). These forms are characterised by intense pulmonary vascular remodelling, mainly involving the pulmonary arterioles less than 300 \( \mu \text{m} \) in diameter. These lesions are associated with concentric intimal hypertrophy, known as ‘’onion-skin pattern’’, medial hypertrophy, plexiform lesions and microthrombosis. Sometimes, this remodelling mainly involves either the pulmonary venules or the capillaries. In this case, the terms used are veno-occlusive disease or capillary haemangiomatosis.

The subclasses of pulmonary hypertension: ‘’hypoxic’’ in chronic respiratory failure, ‘’passive’’ in left-sided heart disease, and ‘’obstructive’’ in post-embolic chronic cor pulmonale, do not belong to the group of diseases previously defined and are not discussed in this article.

Epidemiology

The incidence of PAH is difficult to establish because of the absence of specific symptoms and a simple confirming examination. Recently, a French national register estimated the prevalence of PAH at 15 cases per million population and the incidence at 2.4 cases per million population per year [2]. Female predominance is typically reported in PAH. However, there are some differences between subclasses. In idiopathic PAH, the gender ratio is 1.7 females for 1 male in the North American register [3] and 1.6 to 1 in the French national register [2]. Female predominance is even more marked in familial PAH where the gender ratio varies between 2 and 2.7 females for 1 male [2,4,5]. The higher penetrance of Bone Morphogenic Protein Receptor type 2 (BMPR2) gene mutation in females presenting PAH and/or in utero loss of male fetuses who carry the mutation could be the cause of these results (see below). A very large majority of females was also observed in PAH related to anorexic drug use; 93.7% of the cases in the French register [2] and 69.5% in the IPPHS case study [6]. These results were probably related to the more frequent use of these drugs in the female population. Finally, the high proportion of females observed in PAH associated with connective tissue diseases (79.6% of cases in the French register, i.e. 3.9 females for 1 male) [2] is commonly seen in systemic scleroderma and systemic lupus erythematosus, the two main connective tissue disease complications of PAH [7,8]. However, male predominance is observed in PAH associated with HIV infection (55% of

| Table 1 | Classification of pulmonary hypertension (Venice 2003). |
|-------------------------------------------------|
| Pulmonary arterial hypertension (PAH) | Idiopathic PAH |
| | Familial PAH |
| | PAH associated with |
| | Connective tissue disease |
| | Portal hypertension |
| | HIV infection |
| | Anorexics or toxics |
| | Congenital systemic-to-pulmonary shunts |
| | PAH with predominant venous or capillary involvement (veno-occlusive disease, capillary haemangiomatosis) |
| Pulmonary venous hypertension | Left-sided atrial or ventricular heart disease |
| | Left-sided valvular heart diseases |
| Pulmonary hypertension associated with hypoxia | Chronic obstructive pulmonary disease |
| | Interstitial lung disease |
| | Sleep apnoea syndrome, etc. |
| Pulmonary hypertension due to chronic thrombotic and/or embolic disease | Thromboembolic obstruction of proximal pulmonary arteries |
| | Thromboembolic obstruction of distal pulmonary arteries |
| | Non-thrombotic pulmonary embolism (tumour, parasite, foreign body) |
| Miscellaneous | PAH associated with sarcoidosis, histiocytosis X, mediastinal fibrosis |

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cases) [2,9] and in portopulmonary hypertension (60% of cases) [2]. It is probably related to the preponderance of drug addicts with HIV infection, who are more often male, and the high proportion of males with cirrhosis.

- PAH affects pulmonary microcirculation, with sustained elevation of pressures in the pulmonary vascular bed.
- A new classification of pulmonary hypertension (PH) was defined in 2003: PAH, pulmonary venous hypertension, hypoxic PH, thrombotic/embolic PH, and miscellaneous.
- Involvement is predominant in the pulmonary arterioles measuring less than 300 µm in diameter.
- In France, the prevalence of PAH is estimated at 2.4 cases per million population, and its incidence at 2.4 cases per million per year.
- There is female predominance, except for PAH associated with HIV infection, and portopulmonary hypertension.

### Clinical presentation and prognosis

Female gender is not associated with a different clinical presentation of the disease. Dyspnoea on exertion is the key symptom of the disease, but its obvious lack of specificity can be misleading when making the diagnosis. All patients present dyspnoea and it is often severe as nearly 75% of patients are New York Heart Association (NYHA) functional class III or IV when diagnosed [2]. There do not seem to be any differences in terms of severity of dyspnoea between males and females on diagnosis [2]. This is also the case for haemodynamic data. Finally, a similar proportion of males and females present acute vasodilator test response [10].

The prognosis of idiopathic PAH is very poor. Median survival in the absence of treatment is 2.8 years [3]. NYHA functional class is a major prognostic sign; patients in NYHA class III or IV have survival rates far below those of patients in class II or I [3]. There are no differences between males and females concerning prognosis in PAH, and age at time of death is similar in males and females.

- The key symptom in PAH is severe dyspnoea.
- The prognosis of idiopathic PAH is very poor.

### Pathophysiology

Three factors combine to increase pulmonary vascular resistance: vasoconstriction, remodelling of small pulmonary vessel walls, and microthrombosis. Advances in the understanding of molecular mechanisms involved in this disease suggest that endothelial cell dysfunction plays a key role [11]. Chronic impairment of production by endothelial cells of vasodilators, such as nitric oxide (NO) or prostacyclin, associated with overexpression of vasoconstrictors such as endothelin-1, not only affect vascular tone but also promote vascular remodelling. Platelet activation and inflammatory mechanisms also play a role [11].

The high proportion of females observed in most forms of PAH (idiopathic, familial or associated with a condition) suggests that sex hormones (oestrogens and progesterone) could play a role in pulmonary vascular remodelling. Oestrogens (17β-oestradiol) and progesterone have a pulmonary vasodilator effect dependent on endothelial NO synthase whose function is deteriorated in PAH [12].

### Genetics

The familial forms (i.e. regrouping more than one case without cause occurring in the same family) were first identified by Dresdale et al. in 1954 [13] underlining a potential genetic predisposition. Since then, many other cases have been reported; familial PAH represents 6% of cases in the North American register [3] and 3.9% in the French register [2]. Germline mutations in genes encoding a TGFβ type receptor such as BMPR2 have been found in some of these patients [14,15]. These BMPR2 mutations are found in over half the cases of familial PAH, and in 10 to 30% of idiopathic PAH apparently non-familial. Studies of families with cases of PAH have shown the transmission pattern to be autosomal dominant with incomplete penetrance as only 10 to 20% of subjects who are obligate carriers of the gene mutation for the disease will develop PAH [5]. Gender ratio analysis for progeny of affected family members and healthy carriers of the mutation found abnormal female preponderance (160 females [57%] for 122 males [43%]) [5]. Wastage of male embryos in utero and/or the effects of BMPR2 gene mutation on the fecundation capacity of X or Y spermatozoa could explain this aberrant gender ratio. Moreover, calculations of penetrance for the disease based on the number of patients presenting the mutation who develop the disease compared with those at risk (healthy carriers of a mutation) show higher penetrance in females (62%) than in males (28%) [5]. These results suggest the possible role of sex hormones, particularly oestrogens. For example, the case reported of a 64-year-old woman, asymptomatic carrier of BMPR2 gene mutation, who had been prescribed hormone replacement treatment with an oestrogen-progesterone preparation for the menopause; three months later she developed PAH, confirmed by right heart catheterization [16]. The mechanisms involved remain unknown to date. Finally, there is a genetic anticipation phenomenon characterised by onset of disease and death at increasingly younger ages with passing generations in the same family. Loyd et al. thus showed that age at death for these patients was 45.6 ± 14.5 years for the first generation, 36.3 ± 12.6 years for the second, and 24.2 ± 11 years for the third (p < 0.05) [5]. However, age at death was similar in males and females with familial PAH [4]. These data were confirmed by Sztrymf et al. who found a younger age at diagnosis of patients with familial PAH compared with those presenting idiopathic PAH (36.6 ± 14.5 years against 43.1 ± 16.1 years respectively, p = 0.04) [17].
• The increase in pulmonary vascular resistance is due to vasoconstriction, remodelling of small pulmonary vessel walls, and microthrombosis.
• There is a decrease in endothelial cell synthesis of vasodilatation mediators and an increase in vasoconstriction mediators.
• Female sex hormones (oestrogens and progesterone) may play a role in pulmonary vascular remodelling.
• Germline mutations in genes encoding a TGFβ receptor are found in almost half the cases of familial PAH.
• A genetic anticipation phenomenon explains that onset of disease and death occur earlier with passing generations in the same family.

Pregnancy

Haemodynamic modifications in pregnancy

Pregnancy is accompanied by considerable physiological cardiovascular modifications [18]. From the first few weeks of pregnancy, hormonal activation and circulation of vasoactive substances (prostaglandins) result in a fall in systemic vascular resistance, an increase in blood volume (up to +50% in late pregnancy) and cardiac output (+50% in late pregnancy) [18]. During labour, uterine contractions further accentuate these haemodynamic modifications by increasing cardiac output by an extra 10 to 40% [18]. After delivery, aorto-caval decompression and modifications in blood volume cause variable modifications in heart rate and systemic arterial pressure. Thus these physiological cardiovascular modifications, usually without adverse effects, can worsen the haemodynamic status of patients with PAH and precipitate them into irreversible right heart failure. Moreover, several cases of onset of PAH during pregnancy have been reported. Whether PAH is present before pregnancy and is worsened by the haemodynamic modifications of pregnancy, or whether pregnancy, via the hormonal modifications, can be considered to be a risk factor for PAH remains to be elucidated. For these reasons, pregnancy is contraindicated in women with PAH, and effective contraception is strongly recommended in women of childbearing age [19]. However, improvements in management and prognosis for this disease have resulted in an increase in the number of patients of childbearing age whose state of health allows them to consider a pregnancy. Centres managing patients with PAH will thus probably be increasingly confronted with this problem.

Maternal risk

Maternal mortality is very high, between 30 and 50% in the series of cases published before the introduction of modern treatments for PAH [20–22]. Recently, Bonnin et al. reported a series of 15 pregnancies in 14 patients with severe PAH treated between 1992 and 2002 [23]. One patient was able to carry two pregnancies to term six years apart. The distribution of types of PAH was: four idiopathic, six associated with congenital heart disease, one associated with anorexigen drug use, one associated with a mixed connective tissue disease, one associated with HIV infection, and two post-embolic [23]. The diagnosis of PAH had been made during pregnancy in four patients. Pregnancy worsened the clinical status of most patients (10 out of 14). Overall maternal mortality was 36%, comparable with rates reported in older series [23]. Two patients died early in pregnancy, at 12 and 23 weeks amenorrhoea, with a clinical picture of haemodynamic failure and before termination could be considered. Three other patients died shortly after delivery [23].

Modes of delivery

Discussions continue in the literature concerning mode of delivery. In the recent Bonnin et al. series, there were four vaginal deliveries under regional anaesthesia and nine caesarean sections, five under peridural anaesthesia [23]. Elective caesarean section is the delivery mode most often used [18,24,25]. However, general anaesthesia can worsen the haemodynamic status of severely afflicted patients; regional anaesthesia seems to be an interesting alternative.

Fetal risk

Neonatal survival is between 87 and 89% in contrast with the high maternal mortality rate [20,22]. In the series reported by Bonnin et al., two fetuses died: one after termination at the 21st week of amenorrhoea, and the other was stillborn at 36 weeks gestation [23]. Fetal risk is related to maternal hypoxaemia leading to intra-uterine growth restriction and premature birth.

Specific treatments for PAH in pregnancy

There are no known specific treatments for PAH (prostaglandins, endothelin receptor antagonists, phosphodiesterase inhibitors) in pregnant women. They were, quite obviously, never included in the clinical trials to evaluate the effectiveness of these treatments [26–30]. Thus there are no recommendations concerning the use of specific treatments for PAH in pregnant women.

• During pregnancy, we note a fall in systemic vascular resistance, and an increase in blood volume and cardiac output.
• In PAH, the haemodynamic variations of pregnancy, usually without repercussions, can trigger irreversible right heart failure.
• Pregnancy is thus contraindicated in PAH.
• Maternal mortality varies between 30 and 50% in the series published before the introduction of modern treatments for PAH, and is currently 36%.
• The neonatal survival rate varies between 87 and 89%.
• Fetal risk is related to maternal hypoxaemia.
• The effects of specific treatments for PAH during pregnancy are unknown.
Anticoagulants

Thrombosis, the most often in situ, plays an indisputable role in the pathophysiology of the disease, as attested by the presence of partly recanalised thrombotic lesions in pulmonary arterioles. Two uncontrolled studies have demonstrated the effectiveness of curative anticoagulant treatment in improving the survival rates of patients with PAH [31,32]. Prescription of oral anticoagulants is thus standard, at a dose to obtain an INR between 1.5 and 2.5 [19]. Pregnancy and postpartum are two well-known risk factors for venous thromboembolic disease that can aggravate PAH. Continuation of effective anticoagulation is thus recommended throughout the pregnancy and postpartum period. Contrary to oral anticoagulants, heparin (unfractionated or low molecular weight) does not cross the placental barrier and represents the anticoagulant of choice in the first trimester. Low molecular weight heparin at curative dose is the easiest to use (one to two subcutaneous injections a day, better bioavailability, better predictability of anticoagulant effect, no laboratory surveillance apart from platelet count) and can be used during pregnancy [33]. After 12 to 16 weeks gestation, treatment can be switched to oral anticoagulants under strict surveillance of INR. Finally, interruption of oral anticoagulants and resumption of treatment with heparin is recommended one month before the expected delivery date because heparin is easier to manage (shorter half-life). In the postpartum period, treatment is switched to oral anticoagulants to obtain an INR between 1.5 and 2, in the absence of a history of thromboembolism.

- Curative anticoagulation is effective and improves the survival rates of patients with PAH.
- Effective anticoagulation must be continued throughout the pregnancy and the postpartum period.
- Low molecular weight heparin at curative dose is the anticoagulant of choice in the first trimester.
- Oral anticoagulants are switched to heparin one month before the expected delivery date, with return to oral anticoagulants in the postpartum period.

Calcium channel blockers

High doses of calcium channel blockers can, in a minority of responders to acute vasodilator testing with NO, improve and sometimes normalise pulmonary haemodynamics in these patients [10]. The survival rate for responders is practically normal with high doses of calcium channel blockers [10]. Clinical and haemodynamic stability with calcium channel blocker treatment for at least a year is usually recommended before a patient can consider a pregnancy under strict medical surveillance [34]. In the series reported by Bonnin et al., one patient in NYHA functional class I was thus able to carry her pregnancy to term without aggravation of clinical or haemodynamic status [23].

Prostaglandins

To date, continuous infusion of prostacyclin is the most effective and only approved treatment for the severest cases in NYHA class IV [19]. It improves haemodynamic parameters, short- and medium-term survival rates, and quality of life in severe PAH resistant to conventional medical treatment [26,35]. Animal studies do not show any direct of indirect harmful effects on gestation, embryo and fetal development at doses of prostacyclin 2.5 to 4.8 times superior to those used in human diseases. In women, several cases of good outcomes without fetal malformations have been reported with administration of intravenous prostacyclin during pregnancy [23,34,36—40]. Some of the patients were administered prostacyclin from the beginning of pregnancy [34,39,40]; in the majority of cases, prostacyclin was started a few weeks before, even just before delivery [34,36—38]. In the series reported by Bonnin et al., continuous infusion of prostacyclin was started postpartum in three patients; two were stable one year after delivery [23].

Stable prostacyclin analogues are easier to use and have been evaluated in PAH. These are treprostinil (subcutaneous route) and inhaled iloprost that have both been granted marketing authorizations in NYHA functional class III PAH. Some cases of good results have been reported for the mother, and without malformations for the new-born, using inhaled iloprost in pregnant women, particularly during the first trimester [38,41].

Endothelin receptor antagonists

Bosentan is the leader in this new therapeutic class. It is a non-selective endothelin receptor A and B antagonist. Its short-term (12 and 16 weeks) effectiveness has been demonstrated in two randomised placebo controlled clinical trials [29,42], and medium-term (two years) [43]. This treatment has been granted a marketing authorization for NYHA class III PAH. Sitaxsentan is a selective endothelin receptor A antagonist. Its effectiveness has been evaluated in two randomised placebo controlled studies [44,45]. This treatment has been granted a marketing authorization for NYHA class III PAH. Animal studies have shown teratogenesis and embryotoxicity for bosentan. Very little data are available, and only one case has reported the use of bosentan (interrupted in the first trimester) and sildenafil in a 27-week pregnant woman [46]. The risk is still unknown in humans; however, bosentan must be considered to be teratogenic and must not be used during pregnancy. No pregnancy should be considered for at least three months following stoppage of treatment with bosentan. Women of childbearing age should thus use a reliable contraceptive method during treatment with bosentan and for at least three months following stoppage of treatment (see ‘Contraception’ below). A pregnancy test is recommended once a month during treatment with bosentan. The teratogenic effect of bosentan has been demonstrated in rats at plasma concentrations over 1.5 times the therapeutic concentration. The teratogenic effects, such as malformations of the head, face and main vessels, were dose-dependent. The similarity with the malformations observed with other endothelin receptor antagonists in endothelin-deficient ‘endothelin knockout’ mice, indicates this is a class effect. The use of sitaxsentan is thus also contraindicated during pregnancy.
**Phosphodiesterase-5 inhibitors**

Sildenafil is a phosphodiesterase-5 inhibitor, a degrading enzyme of a second NO messenger, cyclic GMP. It has a vasodilator effect on pulmonary arteries and inhibits smooth muscle cell proliferation in pulmonary vessels [47]. It has shown its short-term (12 weeks) and medium-term (one year) effectiveness in a randomised placebo controlled study [27]. Animal studies have not shown any direct or indirect harmful effects on gestation, and embryo and fetal development. Animal studies have shown toxicity in postnatal development. The experience in pregnant women remains limited to the publication of two clinical case studies [46,48]. In the absence of studies evaluating the apparent absence of teratogenesis in particular, the use of sildenafil is not recommended in pregnant women.

On this point, in summary, despite the development of effective treatments, the mortality rates for pregnant women with severe PAH remain very high. Under these conditions, pregnancy remains formally contraindicated, apart from the very exceptional case of women responders to acute vasodilator testing with NO and perfectly stable (practically normalised haemodynamic status and clinically asymptomatic) under treatment with high doses of calcium channel inhibitors for over a year. In all other cases, pregnancy termination must be discussed, particularly in rapid clinical and haemodynamic deterioration. If this option is not accepted, early introduction of continuous intravenous prostacyclin should be considered. Finally, birth by elective caesarean section under regional anaesthesia appears to be advisable. Multidisciplinary management (chest physicians, obstetricians, anaesthesiologists) in an experienced centre is indispensable.

- Prostacyclin analogues (treprostinil, iloprost) are also effective.
- Bosentan, an endothelin receptor antagonist, is effective but teratogenic.
- Phosphodiesterase-5 inhibitors have a vasodilator effect on pulmonary arteries and inhibit proliferation of smooth muscle cells in pulmonary vessels.
- In the absence of precise data, they should be avoided in pregnant women.


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**Table 2**  Failure rates for different contraception methods and their possible interaction with bosentan (from Thorne et al. [49]).

<table>
<thead>
<tr>
<th>Contraceptive method</th>
<th>% of women with unplanned pregnancies in the 1st year of use</th>
<th>Effect of bosentan on contraceptive activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Typical use</td>
<td>Perfect use</td>
</tr>
<tr>
<td>No method</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Condom</td>
<td>15–32</td>
<td>2–26</td>
</tr>
<tr>
<td>Oestrogen-progesterone</td>
<td>3–8</td>
<td>0.1</td>
</tr>
<tr>
<td>Progestogen</td>
<td>5–10</td>
<td>0.5</td>
</tr>
<tr>
<td>Cerazette®</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Intra-uterine device</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Oestrogen-releasing IUD</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Female sterilisation</td>
<td>0.5</td>
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</tr>
</tbody>
</table>

**Contraception**

The pregnancy-related risks thus require the use of effective contraception in women of childbearing age with PAH. Several contraception methods exist, highly variable in efficacy (Table 2) [49]. The combined oral contraceptive pill, mini- or microdose, is effective but theoretically contraindicated because of the increased thromboembolic risk [50]. However, its use can be considered in women under effective anticoagulant treatment and without any history of thromboembolism or known thrombophilia. Microdose progestogens can be used but are slightly less effective than combined oral contraceptives and can cause bleeding between cycles. Cerazette® represents a new class of oral progestogen contraceptive that does not increase thromboembolic risk and shows excellent efficacy and tolerance. It could thus be the oral contraceptive of choice in women with PAH. It is however very important to note that treatment with bosentan can diminish the efficacy of hormonal contraception due to induction of metabolising liver enzymes; women of childbearing age should not use hormonal contraceptives (including oral, injectable, implantable or transdermal contraceptives) as their only contraceptive method. They should thus be advised to use a supplementary contraceptive method (condom) or use a different reliable contraceptive method. An intrauterine device, even definitive sterilisation, remain the two most effective methods devoid of potential interaction with PAH treatments.

- High doses of calcium channel inhibitors are effective in some patients who are responders to NO testing.
- Continuous prostacyclin infusion is to date the most effective and only approved treatment in the most severe PAH.
- Prostacyclin can be used during pregnancy.
• Effective contraception must be proposed in PAH in women of childbearing age.
• Progestogen-only oral contraceptives are preferable to combined oral contraceptives.
• Bosentan diminishes the efficacy of hormonal contraception requiring the recommendation of a supplementary contraceptive method.

Preimplantation genetic diagnosis

It is technically possible to sort embryos according to BMPR2 genotype. It is thus theoretically conceivable to apply this technique in the context of familial PAH with BMPR2 mutation, as proposed in other genetic disorders. Preimplantation genetic diagnosis would be particularly indicated when the father carries the mutation, as pregnancy is in any case contraindicated in women with PAH. Cases of asymptomatic female carriers of BMPR2 mutations are far more difficult. The risks of developing PAH after hormonal stimulation and during pregnancy in genetically predisposed women remain largely unknown.

Genetic counselling

The American College of Chest Physicians (ACCP) recommends that genetic testing and genetic counselling be proposed to relatives of patients with familial PAH, and that patients with sporadic idiopathic PAH and their relatives be informed of the possibility of genetic testing and genetic counselling [51]. The situation is very complex because of the genetic characteristics of PAH: the variable penetrance indicates that being a carrier of BMPR2 mutation, an obvious source of anxiety, does not necessarily mean that the person will develop the disease. A genetic counselling consultation has thus been set up by the PAH National Reference Centre.

Conclusion

PAH is a rare disease that mainly afflicts women. Despite the considerable progress in the past few years in understanding the pathophysiology of PAH, no curative treatments are available to date. Improved prognosis, particularly in the most severe cases, has resulted in an increase in the number of patients of childbearing age. The maternal mortality rate is very high (30 to 50%). Therefore, pregnancy is contraindicated in women with PAH and an effective method of contraception is recommended in women of childbearing age. Therapeutic termination should be discussed, particularly in the case of clinical deterioration. If this option is not accepted, intravenous prostacyclin should be considered promptly. Multidisciplinary specialised management is in any case indispensable.

KEY POINTS

• PAH, predominant in women, is characterised by sustained elevation in pulmonary vascular bed pressures.
• A distinction is made between idiopathic PAH and PAH associated with other disorders such as connective tissue disease, congenital heart disease, portal hypertension, HIV infection, and exposure to toxins (anorexics).
• It causes remodelling, predominant in pulmonary arterioles less than 300 μm in diameter.
• Predominance is mainly female and varies depending on the subtype, but is male in the types related to HIV infection, and due to portopulmonary hypertension.
• The key symptom in PAH is severe dyspnoea.
• The prognosis is poor, the same in females and males.
• The increase in pulmonary vascular resistance has three causes: vasoconstriction, vascular remodelling, and microthrombosis.
• The predisposing (or triggering) factors are: pulmonary vasomotor dysfunction (via the endothelial cells), platelet dysfunction, female hormones, genetic predisposition.
• Pregnancy can worsen haemodynamic status and is contraindicated in PAH, requiring effective contraception.
• The specific treatments for PAH are not recommended in pregnant women.

References


