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## Review Article

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# Pulmonary vascular disease and pregnancy: current controversies, management strategies, and perspectives

B. M. Weiss<sup>1</sup> and O. M. Hess<sup>2</sup>

<sup>1</sup>Department of Anaesthesiology, University Hospital, Zürich, and <sup>2</sup>Swiss Heart Center, University Hospital Inselspital Bern, Switzerland

### Introduction

Pulmonary vascular disease, in contrast to the majority of other cardiovascular disorders, is poorly compatible with the cardiovascular burden of pregnancy and postpartum. Pulmonary vascular disease is not often encountered in pregnant women, but when pulmonary vascular disease and pregnancy coincide, there is a very high risk of maternal death. Furthermore, despite improvements in medical, obstetric, anaesthetic, and intensive care, mortality rates have remained disappointingly stable over the past decades. Apart from prevention of and early interruption of pregnancy, some recently introduced therapeutic options are raising hopes that the risk to pregnant women with pulmonary vascular disease might start to decrease in the near future.

### Cardiovascular adaptation to pregnancy in healthy women

Gestation represents a major burden upon the cardiovascular system but the necessary adjustments are usually well-tolerated in healthy women. Arterial and venous relaxation and increase of blood volume begin early after conception and govern cardiovascular adaptation to pregnancy<sup>[1–7]</sup>. Hormonal activation and circulating vasoactive substances lead to lower systemic vascular resistance, one of the earliest haemodynamic changes in pregnant women. A short-term initial reduction of effective blood volume is followed by plasma and blood volume expansion<sup>[1–5]</sup>. In the

embryonic phase, as early as the first 5 to 8 weeks of pregnancy, systemic vascular resistance decreases and the cardiac output increases by 20% to 30% as compared to preconceptional values<sup>[1–3,5–7]</sup>. Reduced vascular tone, increased arterial compliance, and arterial load alterations help to accommodate the increased circulating volume and maintain the efficiency of ventricular–arterial coupling and perfusion pressure. Heart rate, venous return, end-diastolic left ventricular volume and stroke volume contribute to the progressive increase in cardiac output<sup>[1,2,6–10]</sup>. An early and significant increase in pulmonary blood flow is countered by a decrease in pulmonary vascular resistance, resulting in no net changes in pulmonary artery pressure<sup>[11]</sup>. Blood volume usually exceeds the non-pregnant level by 10% in the 8th week and by 20–30% in the 20th week. It peaks at 40–50% between the 32nd and 36th week, then remains more or less unchanged until term<sup>[7]</sup>. Cardiac output usually exceeds the non-pregnant level by 50% between the 20th and 24th week<sup>[1,2,6–10]</sup>. In the last trimester the cardiac output may further increase, slightly decrease or remain unchanged, irrespective of method and condition of measurements<sup>[9]</sup>. Heart chamber enlargement, myocardial hypertrophy, cardiac remodelling, and multi-valvular regurgitation are characteristic findings in the latter phase of pregnancy<sup>[1,2,6–10]</sup>. Systolic function is maintained throughout most of gestation by a decreased afterload, elevated ventricular volumes, and compensatory myocardial hypertrophy; however, a reversible decrease in systolic function occurs in late pregnancy with a nadir early postpartum due to diminished contractility and low ventricular pre-load<sup>[10]</sup>. Uterine contractions increase cardiac output a further 10–40% above the pre-labour level, or 60–80% above the non-pregnant state<sup>[12]</sup>. The cardiac output changes depend upon the parturient's position (supine or lateral) and the extent of aorto-caval compression. Cardiac output increase during labour may be attenuated but is not prevented by analgesia, even though anxiety and pain are successfully relieved<sup>[6,7,12]</sup>. Delivery, aorto-caval decompression, and blood volume redistribution

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**Key Words:** Pregnancy, pulmonary vascular disease, Eisenmenger's syndrome, primary pulmonary hypertension, secondary pulmonary hypertension, mitral valve stenosis.

*Correspondence:* Branko M. Weiss, MD, Department of Anaesthesiology, University Hospital, Rämistrasse 100, CH-8091 Zurich, Switzerland.

through uterine contractions temporarily increase the venous return, ventricular volume and cardiac output. Vaginal or operative delivery with concomitant blood loss of varying magnitude leads to variable changes in heart rate, systemic arterial pressure, and circulating volume<sup>[6,7,12–14]</sup>. Heart rate, systemic vascular resistance, cardiac output, and cardiac dimensions start to decrease within hours postpartum. Despite a rapid normalization of blood volume, the complete return of the cardiovascular system to the pre-pregnant state is a slow process. The structural normalization and reversal of myocardial hypertrophy require a longer period of time than functional recovery. Cardiac output, stroke volume, ventricular volume, myocardial contractility, and pulmonary haemodynamics undergo substantial changes within 2 weeks. However, a significant reduction in left ventricular end-diastolic dimensions may not be accompanied by a parallel change in left ventricular end-systolic dimensions. Some parameters (such as mild myocardial hypertrophy and lower contractility) may not normalize until 5 to 6 months after delivery<sup>[6,13,14]</sup>. One year later some differences still persist as compared to the cardiovascular status before pregnancy<sup>[14]</sup>.

The mechanisms of gestational adjustment in healthy women should not be extrapolated to cardiovascular patients. A pre-existing cardiovascular disease usually implicates reduced haemodynamic reserves and a poor ability to deal with an additional, but prolonged strain upon the cardiovascular system. It is difficult to define the exact mechanisms of adaptation or to assess prospectively the individual tolerance towards pregnancy in a woman with a cardiovascular disease of relevant severity. A high percentage of women in this population miscarry, indicating either an inability of the heart and vessels to respond to the demands of pregnancy, or a lack of adequate treatment. Most patients tolerate the limited increase in blood volume and cardiac output of early gestation. However, the progressively increasing utero-placental blood flow, fetal growth, and 'peripheral' oxygen consumption with limited oxygen delivery in the third trimester<sup>[15]</sup> often exceed the patient's adaptive capabilities. A high incidence of small-for-age infants and premature deliveries in cardiovascular patients can be interpreted as a consequence of the suboptimal increase in blood volume and cardiac output, and a ceiling tolerance to cardiovascular (over)load in late pregnancy. Complications and mortality after delivery reflect the inability of cardiovascular patients (and/or the medical team) to cope with the additional and rapid haemodynamic changes associated with labour, delivery, and puerperium.

### Risks of cardiovascular diseases during pregnancy

A total of three to 20 women die per 100 000 gestations in developed countries and up to 100 to 500 women in less developed countries<sup>[16,17]</sup>. According to the latest

'Confidential Enquiries into Maternal Deaths in the United Kingdom'<sup>[17]</sup>, the maternal mortality rate in the period 1994–1996 remained unchanged at 10 to 12 cases per 100 000 gestations as compared with previous triennia. The major direct (obstetric) causes of maternal death were pulmonary embolism (18%), extra-uterine pregnancy and bleeding (10%), and hypertensive disease (toxaemia) of pregnancy (8%). Most prominent indirect causes of death were conditions involving the heart, pulmonary vessels, aorta and its branches, and systemic diseases affecting the cardiovascular system (20%), and diseases of the central nervous system (18%). Although the impact of rheumatic cardiac diseases has declined over the past decades, the cardiac diseases, in particular various types of pulmonary hypertension and aortic/arterial dissections, remain one of the most frequent causes of death during pregnancy and after delivery<sup>[17]</sup>.

Cardiovascular diseases are encountered currently in 0.5–4% of pregnant women<sup>[16–24]</sup>. The most common disorders are rheumatic mitral valve stenosis, previously surgically treated or untreated congenital heart disease, arrhythmias, cardiomyopathies, and ischaemic heart disease. In one of the largest studies published in recent years, 1000 pregnant cardiovascular patients were documented in the period 1983–1992 in São Paulo, Brazil<sup>[18]</sup>. Maternal mortality was 3%. Highest maternal death rates were found among patients with pulmonary hypertension (32%), artificial prosthetic valve (10%), and dilated cardiomyopathy (9%)<sup>[18]</sup>. Pregnancy in cardiovascular patients also involves considerable risk to the fetus/neonate. A two-centre (Turin–London), 20-year retrospective analysis of cyanotic congenital heart disease in pregnant patients found a high incidence of maternal complications (32%), resulting in one (postpartum) death among 96 pregnancies, and a 57% fetal/neonatal mortality<sup>[19]</sup>. Several studies have found the severity of congenital heart disease and cyanosis in women to be correlated to the risk of fetal/neonatal death<sup>[19–22]</sup>. In Singapore, pregnancy in patients with congenital heart disease resulted in moderate morbidity and no maternal or perinatal death<sup>[23]</sup>. In a 9-year retrospective study of 276 pregnancies in patients with various cardiovascular diseases in Ontario, Canada<sup>[24]</sup>, previous cardiac events, arrhythmias, poor functional class, cyanosis, left heart obstruction, and myocardial dysfunction were identified as risk factors for maternal cardiac events. Maternal complications (18% of cases), which occurred mostly before delivery, did not lead to maternal death. Functional class and cyanosis were associated with neonatal morbidity and mortality, involving 17% of infants<sup>[24]</sup>.

The risks of complications and death are higher in cardiovascular patients than in the general pregnant population. However, the extent of risk widely differs between various diseases. In addition, the risk may be diametrically opposite for the woman and for the fetus/neonate in certain cardiovascular conditions. Severe myocardial dysfunction, infective endocarditis, pulmonary thromboembolism, aortic dissection, and pulmonary hypertension of any aetiology primarily endanger the

pregnant woman. Other maternal conditions, e.g. severe valvular (native and prosthetic) heart disease, cyanotic congenital heart disease without pulmonary hypertension, or those requiring oral anticoagulation primarily involve low survival chances of the fetus/neonate. Both the maternal and fetal risks can often be reduced by invasive interventions before conception or even during gestation. These may improve the maternal tolerance of burden in late pregnancy, promote fetal growth and neonatal survival, and enable adjustments to cardiovascular changes postpartum<sup>[16–32]</sup>.

### Syndrome of pulmonary vascular disease

In contrast to the majority of cardiovascular diseases, pulmonary vascular disease not only shortens the patient's life expectancy in general, but its coincidence with pregnancy poses an exceptionally high risk of maternal death. Structural changes to the pulmonary vasculature can result from congenital or acquired disorders of the heart and pulmonary vessels, from parenchymal and interstitial lung affections, or from neuromuscular and skeletal disorders involving airways and the chest wall. Pulmonary vascular disease can also arise from multiple pulmonary thromboembolism, chronic disorders of the liver, systemic connective tissue, vascular and haematological diseases, or certain infections, such as those caused by human immunodeficiency virus (HIV) and schistosomiasis. Pulmonary vascular disease is found in people living at high altitude or those taking illicit and legal drugs (most notably anorectic substances). Some surgical procedures, such as large palliative shunt in congenital heart disease, pulmonary tissue resection, and heart or lung transplantation may also lead to pulmonary vascular disease<sup>[16,17,25,30,31,33–50]</sup>. In some conditions the causal relationship between primary disorder and pulmonary vascular disease is well-established, in other cases pulmonary vascular disease is less frequent and the connection speculative. Where an independent aetiological factor or disease arises in or involves the vascular system (e.g. pulmonary thromboembolism, connective tissue diseases, systemic vasculitis, HIV-infection, or drug side-effects) this is known as secondary vascular pulmonary hypertension. If no direct causes or triggers are apparent, the type of pulmonary vascular disease is termed 'primary pulmonary hypertension'<sup>[16,17,30,33,34,44–47]</sup>. Pulmonary vascular disease is rarely encountered in pregnant women but there is a very high maternal risk in Eisenmenger's syndrome, in primary pulmonary hypertension, and in secondary vascular pulmonary hypertension. In contrast, pulmonary vascular disease is more frequently encountered but at very low risk in patients with pulmonary hypertension arising from mitral valve stenosis.

### *Eisenmenger's syndrome*

Various congenital heart disease, with direct connection(s) between the systemic and pulmonary circulation,

although morphologically different, are all characterized by a systemic-to-pulmonary ('left-to-right') shunt blood flow. Depending on the original morphology, altitude of residence, surgical interventions, and concomitant disorders, the abundant 'left-to-right' shunt may progress to pulmonary vascular disease. In patients with pulmonary artery pressure close to systemic arterial pressure, the direction of blood flow may be reversed (right-to-left shunt) or the flow may become more balanced, without net shunt along the systemic-pulmonary connection<sup>[16,25,30,33–35,48–50]</sup>. Wood explained and defined Eisenmenger's syndrome as the final stage of 'pulmonary hypertension at systemic level, due to a high pulmonary vascular resistance (over  $800 \text{ dyne} \cdot \text{s}^{-1} \cdot \text{cm}^{-5}$ ), with reversed or bidirectional shunt'<sup>[48]</sup>. The diagnosis of Eisenmenger's syndrome is usually made clinically, supported by X-ray and echocardiography<sup>[51]</sup>. In adults, Eisenmenger's syndrome is characterized by pulmonary vascular resistance values similar to those found in primary pulmonary hypertension, but by a higher pulmonary artery pressure and cardiac output, a lower  $\text{SaO}_2$ , fewer abnormalities in circulating von Willebrand factor and a more favourable survival rate than primary pulmonary hypertension<sup>[34,46,47]</sup>. On the other hand, the long-term prognosis of Eisenmenger patients is affected adversely by history of syncope,  $\text{SaO}_2$  below 85%, early onset of clinical deterioration, complexity of congenital heart disease, and ventricular dysfunction<sup>[51,52a]</sup>. Among the post-tricuspid anomalies, the survival rate is longer in patients with two ventricles (e.g. ventricular septal defect, truncus arteriosus) than in univentricular heart<sup>[52a]</sup>. Eisenmenger patients usually die in the third to fourth decade of life. Causes of death are massive haemoptysis, subarachnoid bleeding, heart failure, cerebral abscess, complications of cardiac or non-cardiac surgery, or consequences of exercise and pregnancy<sup>[30,35,51,52a]</sup>.

Wood's definition of Eisenmenger's syndrome<sup>[48]</sup> is precise but narrow. Pregnancy-induced cardiovascular changes may lead to a reaction of 'pre-damaged' pulmonary vascular bed in the presence of congenital heart disease with left-to-right shunt. Since invasive haemodynamic investigations are usually avoided in pregnant women, the severity of pulmonary vascular disease can not be assessed without exact data on pulmonary vascular resistance. In a 1978–1996 retrospective analysis<sup>[30]</sup>, an increase in pulmonary artery pressure and pulmonary vascular resistance was found during gestation in some patients with initially moderate pulmonary hypertension of congenital heart disease origin. The maternal death rate in this series of 73 Eisenmenger patients was 36%. Three women died during pregnancy and 23 at delivery or within 1 month postpartum. Mortality was strongly associated with late diagnosis and late hospital admission, while severity of pulmonary hypertension was found to be a contributing factor. Neither the mode and timing of delivery nor the type of anaesthesia and monitoring correlated with maternal outcome. Most fatalities were described as sudden death or therapy-resistant heart failure; a few were related to

thromboembolism or pulmonary artery dissection<sup>[30]</sup>. On the other hand, only one death postpartum was documented in 26 pregnant Eisenmenger patients in Trivandrum, India<sup>[51]</sup>, and all patients with pulmonary hypertension of congenital heart disease origin survived pregnancy in Ontario, Canada<sup>[24,53]</sup>. In the recent (1986–1994) Canadian analysis<sup>[24]</sup>, a systolic pulmonary artery pressure of  $71 \pm 20$  mmHg was considered as only moderately elevated (gestational age when pulmonary artery pressure values were obtained was not stated), and as not presenting a risk for the development of Eisenmenger's syndrome<sup>[24]</sup>. In a Los Angeles, California, study, no mortality was found among 16 pregnancies in patients with post-tricuspid anomalies<sup>[52a]</sup>. Only seven cases proceeded to delivery (all in the ventricular septal defect group), and four were characterized by maternal complications<sup>[52a]</sup>. The majority of studies indicate a high maternal mortality rate and frequent clinical deterioration after delivery. The outcome of pregnancy in women with Eisenmenger's syndrome has remained disappointingly 'stable' over the past 50 years, with a risk of maternal death in the range of 30% to 50%<sup>[16–18,20–22,24,25,30,35,51–59]</sup>. Survival is difficult to predict; it seems to depend on proper diagnostic evaluation and early hospitalization, the severity of Eisenmenger's reaction, the availability of interdisciplinary treatment during gestation, and intensive medical care in the highly vulnerable period after delivery.

### *Primary and secondary vascular pulmonary hypertension*

Classification of the syndrome of pulmonary vascular disease, particularly the distinction between primary and secondary pulmonary hypertension, is controversial<sup>[30,33,38–47,60–69]</sup>. Morphology of the pulmonary vessel changes, endothelial dysfunction, unbalanced metabolism and vasoactive mediators, and altered haemostasis affect primary pulmonary hypertension and various types of secondary pulmonary hypertension in a strikingly similar way<sup>[33–50,60–69]</sup>. Some forms of secondary vascular pulmonary hypertension have been 'differentiated', for example, by lower pulmonary artery pressure in HIV-infection as compared to non-HIV primary pulmonary hypertension<sup>[41]</sup>, variable pulmonary vascular involvement in Gaucher's disease<sup>[43]</sup>, or hypoxic pulmonary vasoconstriction in a limited form of scleroderma<sup>[39,66]</sup>. Primary pulmonary hypertension has been 'characterized', as compared to secondary pulmonary hypertension, by the pronounced abnormality of von Willebrand factor<sup>[47]</sup>, by the monoclonal endothelial cell proliferation<sup>[70]</sup> or by the absence of large broncho-pulmonary collaterals, as found in thromboembolic pulmonary hypertension<sup>[71]</sup>. Furthermore, the titre of phospholipid binding antibodies is frequently high in chronic thromboembolic PH<sup>[72]</sup>. Antiphospholipid syndrome can also dominate various

manifestations, including pulmonary hypertension, of connective tissue diseases<sup>[73–76]</sup>. The influence of these 'differences' between primary pulmonary hypertension and secondary vascular pulmonary hypertension on the tolerance towards and outcome of pregnancy is largely unknown, except for a documented high incidence of pregnancy loss and thrombosis in antiphospholipid syndrome<sup>[72–76]</sup>. Primary pulmonary hypertension or secondary vascular pulmonary hypertension starts occasionally during pregnancy or postpartum. The connection between primary pulmonary hypertension and gestation, more as chronological coincidence than causal relationship, was documented in only 7–17% of female patients<sup>[77,78]</sup>. Presentation during or after pregnancy was found to be associated with longer survival in one series of primary pulmonary hypertension patients<sup>[79]</sup> but others could not confirm this relationship<sup>[77]</sup>.

In pregnant patients with primary pulmonary hypertension, according to the 1978–1996 overview<sup>[30]</sup>, the maternal mortality rate (30%) is similar to that of Eisenmenger patients (36%), while mortality is much higher (52%) in secondary vascular pulmonary hypertension. Typically, primary pulmonary hypertension and secondary vascular pulmonary hypertension patients die after delivery due to sudden or progressive heart failure. Neither the individual patient's characteristics nor aspects of peripartum management influence maternal outcome in primary pulmonary hypertension. In the secondary vascular pulmonary hypertension group, however, late hospital admission, operative delivery, pulmonary vasculitis of a systemic disease, and illicit drugs were identified as factors contributing to maternal death<sup>[30]</sup>. The differences in outcome might result from a more homogenous population in primary pulmonary hypertension (lowest mortality), variable presentation of Eisenmenger's syndrome, and a non-homogenous population in secondary vascular pulmonary hypertension (highest mortality). A diagnostic search and differentiation between primary pulmonary hypertension and secondary vascular pulmonary hypertension are warranted. Despite similar levels of pulmonary artery pressure<sup>[30]</sup>, the identification of underlying disease or potential trigger and concomitant organ involvement may be helpful to properly assess the risk of death and severe complications in patients with primary pulmonary hypertension and secondary vascular pulmonary hypertension.

### *Mitral valve stenosis*

Rheumatic mitral valve stenosis mainly affects women and is the most frequent heart disease encountered in the pregnant population worldwide<sup>[16,18,31–33,36,37]</sup>. The clinical presentation and the woman's tolerance of pregnancy depend upon the severity of the valve disease, the heart rate and rhythm, atrial compliance, circulating blood volume, and pulmonary vascular response. Reflectory pulmonary vasoconstriction (which balances the distribution of blood flow), endothelial dysfunction,



and remodelling of pulmonary vessels may progress to significant pulmonary hypertension and decrease right heart function<sup>[36,37,46,80,81]</sup>. The severity of pulmonary hypertension in mitral valve stenosis before conception correlates with the occurrence of gestational heart failure<sup>[82,83]</sup>. A systolic pulmonary artery pressure above 50 mmHg was associated with cardiac complications during pregnancy<sup>[82]</sup>, and functional status worsened more rapidly in pregnant than in non-pregnant patients with mitral valve stenosis<sup>[83]</sup>. However, pulmonary hypertension in mitral valve stenosis seems to be a less ominous finding than pulmonary hypertension in other types of pulmonary vascular disease<sup>[16–18,20,25,30,31,33–59,66–69,77–84]</sup>. Although patients with mitral valve stenosis are more likely to develop pulmonary oedema, they are less prone to right heart failure which is more difficult to treat. The lower severity of pulmonary hypertension, the lower incidence of full-blown pulmonary vascular disease, and the availability of therapeutic measures contribute to a favourable outcome in most cases of mitral valve stenosis.

Cardiac decompensation and pulmonary oedema may occur in pregnant women with overt or silent mitral valve stenosis during the second or third trimester<sup>[16,31,36,37,82,83]</sup>. Fluid restriction, diuretics, and control of atrial fibrillation are basic measures that can prevent pulmonary congestion. Although elective Caesarean section is the preferable mode of delivery to avoid the risks of protracted labour and sudden cardiac decompensation<sup>[16,84–92]</sup>, vaginal delivery was well-tolerated even in patients with severe mitral valve stenosis and pulmonary hypertension<sup>[85–87]</sup>. Epidural block is the preferable anaesthetic or analgesic technique, as it minimizes haemodynamic fluctuations peripartum, but general anaesthesia was also used successfully for emergency or elective Caesarean section in parturients with mitral valve stenosis<sup>[16,84–92]</sup>. Monitoring with a pulmonary artery catheter was recommended in patients with a markedly reduced valve area<sup>[84–86,88,90,91]</sup>. Such a case requires organization of trained personnel and combined expertise for the haemodynamic, anaesthetic, and obstetric management of delivery and postpartum. In a series of 15 parturients with a mitral valve area of 0.7–2.5 cm<sup>2</sup> (mean 1.4)<sup>[92]</sup>, only one patient required monitoring with a pulmonary artery catheter. Moderate complications occurred postpartum in five cases, and all women and neonates were discharged between day 5 and 20 after delivery<sup>[92]</sup>.

In patients with mitral valve stenosis, gestational volume overload, poor compliance with drug treatment, and/or pre-eclampsia lead occasionally to severe heart failure and maternal death<sup>[87–89]</sup>. Acute decompensation requires either an urgent delivery, a surgical intervention, or percutaneous balloon-valvuloplasty to be done before or after delivery<sup>[16,31,32,83,84,87–89]</sup>. Surgical commissurotomy antepartum resulted in uneventful labour and delivery, low fetal/neonatal mortality, and maternal survival in almost all cases<sup>[16,32,83,92,93]</sup>. With percutaneous balloon-valvuloplasty becoming a routine treatment of mitral valve stenosis, the necessity for surgical

therapy has decreased<sup>[31,36,37,81,83,90–98]</sup>. For example, in the series of non-pregnant young patients (mean age  $\pm$  SD, 27  $\pm$  10 years) with severe mitral valve stenosis and PH<sup>[81]</sup>, percutaneous balloon-valvuloplasty decreased systolic pulmonary artery pressure only moderately (from 65  $\pm$  13 to 50  $\pm$  13 mmHg), without significant changes in pulmonary vascular resistance. However, a relevant reduction in systolic pulmonary artery pressure (38  $\pm$  9 mmHg) and pulmonary vascular resistance was found at the follow-up 7–14 months later<sup>[81]</sup>. Markedly reduced valve area ( $\leq$  1.2 cm<sup>2</sup>) and poor response to medical therapy are indications for an invasive intervention in both pregnant and non-pregnant patients<sup>[16,31,32,36,37,81,83,84,87,92–97]</sup>. In 80 pregnant mitral valve stenosis patients treated by percutaneous balloon-valvuloplasty at a gestational age of 10 to 34 weeks<sup>[31,94–97]</sup>, percutaneous balloon-valvuloplasty increased valve area to 1.5–2.0 cm<sup>2</sup>, decreased the pressure gradient to 2–8 mmHg and lowered pulmonary artery pressure to 23–32 mmHg. A surgical correction of the valve was required only in one case. Fetal radiation exposure was reduced by appropriate shielding or eliminated altogether by the use of echocardiography. Normal neonates were delivered at term, except for two premature deliveries and two stillbirths<sup>[31,94–97]</sup>. Since improvement in pulmonary artery pressure and pulmonary vascular resistance after percutaneous balloon-valvuloplasty is slow, more intensive care and monitoring are required during the remainder of pregnancy and in subsequent gestations. The rate of mitral re-stenosis following surgical commissurotomy or percutaneous balloon-valvuloplasty is generally low in the short term, but relevant re-stenosis with pulmonary hypertension and high pulmonary vascular resistance may complicate a further pregnancy<sup>[85,90–92]</sup>. A second percutaneous balloon-valvuloplasty should be considered, although the risk of complications is higher than for the first intervention<sup>[98]</sup>.

### Antithrombotic treatment, risk of bleeding, and haemoptysis

The use of antithrombotic drugs in pregnant women continues to generate controversy<sup>[16,99–109]</sup>, but a thromboembolic prophylaxis is generally recommended in pulmonary vascular disease patients. This treatment strategy is based upon the observation that increased thrombogenicity is characteristic of all types of pulmonary vascular disease. The postulated mechanisms of thrombogenicity include vascular inflammation, cell proliferation, endothelial dysfunction with abnormalities of von Willebrand factor, enhanced platelet and leukocyte activation, circulating cellular aggregates, diminished fibrinolysis, and sluggish pulmonary blood flow<sup>[33–37,44–47,49,61–70,72–74]</sup>. However, a long-term follow-up of Eisenmenger patients<sup>[52,52a]</sup> found that anticoagulant drugs frequently led to haemorrhagic complications and recommended such treatment

only for patients with established thrombotic problems. Platelet antiaggregant drugs prevented cerebral complications but not pulmonary thromboembolism<sup>[52]</sup>. It seems that the risk–benefit ratio of chronic anticoagulation may differ according to the individual characteristics of the patient and the type of pulmonary vascular disease. During pregnancy, on the other hand, intra-abdominal compression, peripheral venodilation with decreased venous blood flow velocity<sup>[110]</sup>, and activated coagulation and fibrinolytic cascades<sup>[111,112]</sup> further increase the risks of thromboembolism. Patients with a history of thromboembolism or venous thrombosis, atrial fibrillation, echocardiographic findings of intracardiac thrombi, or the presence of phospholipid binding antibodies are particularly endangered. They require a higher level of anticoagulation and more frequent clinical and laboratory monitoring<sup>[16,17,33–37,44–47,65,72–73,99–103,105–109,113]</sup>.

Unfractionated or low molecular-weight heparins, which are unable to pass the placenta, are the drug of choice for antithrombotic treatment/prophylaxis in the first 12 to 16 weeks of gestation. Early intrauterine exposure to oral anticoagulants can cause coumarin (warfarin)-embryopathy during the critical period of organogenesis. Later, these drugs may contribute to fetal bleeding and relevant neonatal morbidity and mortality. Pregnancy loss and neonatal complications ranged in the recent years from <5% up to 69% of gestations in women receiving coumarin<sup>[16,26,99–105,108]</sup>. After the first 16 weeks of pregnancy, continuation of heparin treatment (with or without platelet antiaggregant drug) or, in high-risk cases, a switch to oral anticoagulation should be considered. The re-institution of heparin therapy is recommended 2 to 4 weeks before delivery, since antagonism of heparin activity is easier to achieve than that of oral anticoagulants<sup>[16,99–105]</sup>. On the other hand, inadequate antithrombotic protection, thrombocytopenia, osteoporosis, spontaneous fractures, and persistence of anticoagulant effects for up to 28 h after the last injection are complications of heparin treatment<sup>[16,99–103,105,107–109,113]</sup>. Low molecular-weight heparins offer some advantages (higher bioavailability, longer half-life, and lower propensity to induce thrombocytopenia and haemorrhagic complications) as compared to unfractionated heparin, and provide similar protection in patients at high-risk for thromboembolism<sup>[100,102,105–107,109,113–116]</sup>. Unfortunately, the ongoing use of any anticoagulant provides a potential for serious complications a priori. Bleeding and haemodynamic instability peripartum, surgical intervention, and fetal/neonatal bleeding are frequent and occasionally fatal consequences in parturients receiving antithrombotic drugs<sup>[16,30,108]</sup>. In addition, lumbar anaesthesia contributes to the risk of spinal haematoma in patients receiving antithrombotic drugs. Strategies and concepts for providing regional anaesthesia during labour and delivery in anticoagulated patients (drugs and doses, laboratory tests, time intervals, etc.) are controversial, and differ widely between different countries and institutions<sup>[16,109,113,115,116]</sup>.

In a retrospective analysis covering two decades, the use of antithrombotic drugs could not be correlated with maternal outcome of Eisenmenger and primary pulmonary hypertension patients, and in the secondary vascular pulmonary hypertension group it actually increased the risk of maternal death<sup>[30]</sup>. However, different institutions used various drugs and various administration protocols. On the other hand, routine anticoagulation peripartum contributed in some studies to improved survival in patients with Eisenmenger's syndrome and other types of pulmonary vascular disease<sup>[30,53,54]</sup>. Occasional findings of pulmonary thrombi suggest that thromboembolism is a less frequent direct cause of death in pregnant pulmonary vascular disease patients than clinically suspected<sup>[30,52]</sup>; however, the data on post-mortem examinations are frequently missing. Nevertheless, in addition to adequate hydration, use of elastic stockings, and regular mobilization, an antithrombotic drug prophylaxis should be used in pregnant patients with Eisenmenger's syndrome and primary pulmonary hypertension. Possibly, prophylaxis with lower doses should be considered in secondary vascular pulmonary hypertension patients as well. The treatment should be started early with subcutaneous heparin, e.g. at hospitalization in the second trimester<sup>[54]</sup>, and monitored by frequent clinical and laboratory control. It should be interrupted at short intervals (12 to 24 h) before delivery and re-instituted as soon as possible postpartum<sup>[16,17,30,53,54,99–109]</sup>.

A recent or active haemoptysis intrapulmonary haemorrhage and/or pre-existing coagulation defects also constitute clinical challenges in pregnant patients with pulmonary vascular disease. Haemoptysis results from embolism or rupture of the dilated bronchial vessels, broncho-pulmonary or other systemic arterial-pulmonary collaterals, or rupture/dissection of a large pulmonary artery. It is a relatively frequent manifestation of Eisenmenger's syndrome and is less common in other types of pulmonary vascular disease in non-pregnant patients<sup>[16,30–37,44,45,48,50–59,117–121]</sup>. Haemoptysis associated with pregnancy or arising from the use of oral contraceptives was previously described as leading to worsening of clinical status or death<sup>[117]</sup>. Gleicher *et al.* did not identify haemoptysis as a relevant cause of mortality in pregnant women with Eisenmenger's syndrome<sup>[25]</sup>. Recent reports suggest that haemoptysis is only an occasional complication of pregnancy in pulmonary vascular disease women, occurring at a similar rate in Eisenmenger's syndrome and other types of pulmonary vascular disease<sup>[30,35,51–59,120,121]</sup>. Angiography and embolization of bronchial arteries or surgical pulmonary resection are the treatment of choice in some cases of severe haemoptysis during pregnancy<sup>[16,32,120,121]</sup>.

## Neonatal outcome

Over the last 20 years, infant survival has depended more strongly on maternal tolerance towards late

pregnancy and the presence or absence of congenital anomalies than on the mother's type of pulmonary vascular disease. Neonatal survival rates of 87%, 89% and 88% were found in the Eisenmenger, primary pulmonary hypertension and secondary vascular pulmonary hypertension group, respectively<sup>[30]</sup>. According to other reports, neonatal survival may exceed 90% in patients with Eisenmenger's syndrome<sup>[16,17,20–22,24,52–59]</sup>. The differences between maternal (50–70%) and neonatal (90%) survival rates confirm the existence of a 'conflict of interest' between the pregnant woman with pulmonary vascular disease and the fetus.

### Family planning, interruption of pregnancy, and sterilization

The issues involved in pregnancy and pulmonary vascular disease are complex and multifaceted. The woman's well-being, reproductive desires, family pressures, chances of delivering a viable infant, and chances of surviving postpartum all represent potential areas of 'conflict of interest'. Women with congenital heart disease and pulmonary hypertension, established Eisenmenger's syndrome, primary pulmonary hypertension and secondary vascular pulmonary hypertension should be strongly advised against pregnancy. This recommendation is occasionally not followed, and some women with pulmonary vascular disease become pregnant and decide to continue until term, despite all risks<sup>[16–18,20–25,33–35,51–59,122]</sup>. In contrast, mitral valve stenosis of itself presents no barrier to pregnancy, and these patients rarely require a 'therapeutic' interruption of gestation<sup>[123]</sup>. Even severe mitral valve stenosis with pulmonary hypertension can be treated before an interruption and tubal ligation becomes indicated for cardiac reasons<sup>[16–18,31,32,36,37,82–97]</sup>.

Prevention of or early interruption of pregnancy are the relevant measures to improve long-term survival in women with pulmonary vascular disease. Spontaneous termination of pregnancy makes a 'natural' contribution to maternal survival in severe cardiovascular diseases<sup>[16–29]</sup>. In contrast, a high number of patients with Eisenmenger's syndrome, primary pulmonary hypertension or secondary vascular pulmonary hypertension are able to tolerate pregnancy, deliver a viable neonate near term, but die after delivery<sup>[16–18,20–25,30,35,51–59]</sup> or sustain symptomatic deterioration<sup>[52a]</sup>. On the other hand, an interruption of pregnancy and tubal ligation in pulmonary vascular disease patients is connected with a higher rate of complications and mortality than in healthy women. Perioperative (combined anaesthetic and surgical) risk of death in patients with complex (congenital heart disease, primary pulmonary hypertension, and secondary vascular pulmonary hypertension) undergoing interruption of pregnancy and/or laparoscopic, open or transvaginal sterilization may be as high as 4% to 6%<sup>[16,17,35,52,124–128a]</sup>.

## Therapeutic perspectives and hopes for the future

### *Atrial balloon septostomy*

With progression of primary pulmonary hypertension (and also secondary vascular pulmonary hypertension), a high pulmonary artery pressure leads to right heart failure, and frequently early death. Congenital or iatrogenic intraatrial communication may postpone the occurrence of right heart failure or acutely decompress the right heart at the expense, of course, of the 'right-to-left' shunt blood flow<sup>[129]</sup>. In one series of primary pulmonary hypertension patients, the survival rate was better in subjects with an open foramen ovale than in those with an intact septum<sup>[79]</sup>. More recently, balloon atrial septostomy has been successfully used in severe, therapy-resistant primary pulmonary hypertension in non-pregnant patients. It was possible to unload the right heart and to improve pulmonary and ventricular haemodynamics<sup>[129,130]</sup>. In the majority of patients, atrial septostomy increased cardiac output, and improved systemic oxygen transport (despite a fall in SaO<sub>2</sub>) and exercise capacity. It resulted in a prolonged survival compared with patients receiving conventional therapy<sup>[129,130]</sup>. The intervention was not performed or considered indicated in pregnant women. Despite the improvement of a woman's status by right ventricular unloading, an acute decrease in SaO<sub>2</sub> would certainly endanger the fetal life. However, primary pulmonary hypertension and secondary vascular pulmonary hypertension patients are more likely to decompensate and die of pulmonary hypertensive crisis and right heart failure after than before delivery<sup>[30]</sup>. Thus, an atrial septostomy remains an option postpartum, reserved for those cases who fail to respond to other therapeutic interventions.

### *Surgical options*

Surgical pulmonary thrombendarterectomy is a treatment option for patients with chronic thromboembolic disease involving proximal pulmonary arteries<sup>[44,45,131]</sup>. Excellent functional results have been reported after surgery, including a few cases of uneventful course of pregnancy<sup>[130]</sup>. In patients with heart, lung, or heart-lung transplants (indicated in a minority of cases of Eisenmenger's syndrome and primary pulmonary hypertension), moderate morbidity rates, delivery of small-for-age neonates, and excellent maternal survival rates have been reported in over 50 cases<sup>[16,44,45,132–134]</sup>. A recent study of adult heart transplant recipients identified previous pregnancy, rather than female gender per se, as associated with an increased frequency of organ rejections<sup>[132]</sup>. The long-term effects of gestation on transplant organ function, severity and rate of complications, and survival remain unknown.

### Medical options

Conventional medical therapy of primary pulmonary hypertension and secondary vascular pulmonary hypertension, following an individual assessment of the responsiveness of the pulmonary vascular bed, includes a selection of oral (calcium-channel blockers, angiotensin converting-enzyme inhibitors) or parenteral vasodilating drugs (adenosine), cardiac glycosides, anticoagulants, diuretics, and supplemental oxygen. However, no combination of drugs in primary pulmonary hypertension and secondary vascular pulmonary hypertension has resulted in a long-term response or an improvement in life expectancy<sup>[44,45,66–69,135]</sup>. Similarly, according to the retrospective analyses<sup>[52,52a]</sup>, the long-term survival of Eisenmenger patients seems to be poorly influenced by drug therapy. A non-significant trend towards an improved outcome was found with the use of platelet antiaggregant drugs, diuretics, and digitalis, and the use of anticoagulants and vasodilators showed a trend towards a reduced survival<sup>[52]</sup>.

Selective pulmonary vasodilators have emerged as a promising treatment in pulmonary vascular disease. Continuous epoprostenol (prostacyclin, PG12) infusion lowered pulmonary vascular resistance and improved right ventricular function in several series of primary pulmonary hypertension and secondary vascular pulmonary hypertension patients. The prolonged mechanisms of action have been attributed to selective pulmonary vasodilatation, inhibition of platelet aggregation, and/or vascular remodelling<sup>[44,45,66–69,135a]</sup>. Intravenous alprostadil (PGE1) and inhaled nitric oxide (NO) favourably influenced pulmonary haemodynamics in patients immediately after mitral valve replacement<sup>[136,137]</sup>. Short-term application of aerosolized PG12 or its analogue iloprost more effectively reduced pulmonary artery pressure as compared to intravenous PG12 and inhaled nitric oxide in patients with primary pulmonary hypertension, secondary vascular pulmonary hypertension and pulmonary hypertension of ischaemic cardiomyopathy<sup>[138,139]</sup>.

Intravenous PGE1, tested in a small series of patients with Eisenmenger's syndrome, provoked mostly undesirable reactions, such as systemic arterial hypotension and a fall in SaO<sub>2</sub><sup>[140]</sup>. More recently, a combined use of oxygen and nitric oxide was found to decrease pulmonary vascular resistance in pulmonary hypertension of congenital heart disease more effectively than each gas alone<sup>[140a]</sup>. Chronic administration of intravenous PG12, despite a lack of acute response, decreased pulmonary artery pressure and pulmonary vascular resistance in these patients, as well<sup>[140b]</sup>. Although pulmonary vasodilators also induce side-effects (bleeding, formation of toxic nitrate metabolites, and methaemoglobinaemia following inhalation of nitric oxide; diarrhoea, jaw pain, headaches, and cutaneous flushing following PG12 infusion) and complications are sometimes associated with the drug-delivery system, the overall risk-benefit of these drugs is favourable in patients with pulmonary vascular disease<sup>[44,45,66–68,135a–142]</sup>. Oral

or long-acting transdermally-delivered prostacyclin analogues, endothelin receptor antagonists and converting-enzyme inhibitors, thromboxane inhibitors and antagonists, or new angiotensin converting-enzyme inhibitors with specific affinity for pulmonary vasculature might be expected to further improve the efficacy of treatment and life expectancy in patients with pulmonary vascular disease<sup>[44,45,69,143–146]</sup>. The effects of selective pulmonary vasodilators in pregnant women are almost unknown. Although it might be expected that such treatment would improve the tolerance towards the outcome of pregnancy, a negative impact on fetal/neonatal growth, labour, delivery, and the risk of maternal pulmonary, haematologic or other complications cannot be excluded a priori. Pulmonary vasodilators have been given in late pregnancy for a short period of time or after the failure of other therapeutics in a small number of parturients with pulmonary vascular disease. They could not reverse a progressive deterioration in some parturients, particularly those with Eisenmenger's syndrome<sup>[17,30,56,58]</sup>. A poor response to nitric oxide and maternal death postpartum was reported in a case of scleroderma complicated by secondary vascular pulmonary hypertension<sup>[147]</sup>, while another patient with HIV-infection was successfully managed with nitric oxide peripartum<sup>[148]</sup>. In women with primary pulmonary hypertension, a treatment with intravenous PGI2 was recommended for 12 to 15 months before conception<sup>[149]</sup>. PGI2 was able to reduce pulmonary artery pressure and normalise ventricular function, resulting in an uneventful course of subsequent pregnancy. When the diagnosis of primary pulmonary hypertension was made during gestation, PGI2 contributed to survival in one patient, but another woman failed to respond and died before delivery<sup>[149]</sup>. In a recent report<sup>[150]</sup>, severe primary pulmonary hypertension was controlled by an intravenous infusion of PG12 after delivery. Postpartum bleeding was thought to be a secondary effect of PG12. The treatment was gradually changed to aerosolized PG12, resulting in cessation of bleeding and the patient's recovery<sup>[150]</sup>. Aerosolized PG12 or its analogue iloprost is the current drug of choice for patients with primary pulmonary hypertension and secondary vascular pulmonary hypertension. It should be made available to pregnant patients, particularly to prevent pulmonary hypertensive crisis and right heart failure postpartum<sup>[138,139,150]</sup>.

### Conclusions

The prevention of pregnancy and its associated cardiovascular burden remains one of the major means of improving survival among women with pulmonary vascular disease. Patients who decide to continue a pregnancy should be hospitalized in the second trimester and treated by an interdisciplinary team. Late pregnancy and particularly the period after delivery carry a high risk of maternal death. The fetal/neonatal chances of



survival are relevantly better than those of the mother. In the past decades, maternal mortality ranged between 30% to 40% in pregnant Eisenmenger patients. A diagnostic differentiation between primary pulmonary hypertension and various types of secondary vascular pulmonary hypertension is relevant, as the risk of death postpartum differ, being 30% in primary pulmonary hypertension and exceeding 50% in secondary vascular pulmonary hypertension. Under favourable circumstances, combining early hospitalization and established therapeutic measures with newly available selective pulmonary vasodilators, the chances of maternal survival could be expected to increase in patients with primary pulmonary hypertension, secondary vascular pulmonary hypertension, and, possibly, Eisenmenger's syndrome. The availability of medical and invasive therapeutic options for mitral valve stenosis, even in the presence of severe pulmonary hypertension, make it possible for these patients to bear children without or at very low additional risks.

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