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4

# Cardiovascular Disorders in Pregnancy: Diagnosis and Management



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Cardiovascular diseases (CVDs) are a major cause of complications in pregnancy worldwide and the number of patients who develop cardiac problems during pregnancy is increasing. This review summarises recent literature on the aetiology and the underlying pathophysiology, diagnostic tools, risk stratification and prognosis in women who develop heart failure during pregnancy and in the peri-partum phase as well as in patients with pre-existing cardiomyopathies undergoing pregnancy. We specifically highlight peri-partum cardiomyopathy, valvular disease and Marfan's syndrome. Furthermore, we provide overviews on established treatment concepts and novel therapeutic strategies for these different disease types, stressing the point that pregnancy-associated cardiac disease requires interdisciplinary concepts for diagnosis, management and treatment.

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## Introduction

At present, 0.2–4% of all pregnancies in Western industrialised countries are complicated by cardiovascular diseases (CVDs) and the number of the patients who develop cardiac problems during pregnancy is increasing [1]. In the first part of this chapter, we focus on heart failure in previously healthy women during pregnancy and the peri-partum phase. In the second part, we summarise the current knowledge on pre-existing cardiomyopathies, specifically valvular disease and Marfan's syndrome in women undergoing pregnancy.

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In the first group, we mainly focus on peri-partum cardiomyopathy (PPCM), a disease that is considered rare but may be often overlooked and therefore may occur much more frequently. We summarise recent knowledge on aetiology, diagnosis and management as well as the newest insights into the underlying pathomechanisms. In addition, we highlight potential biomarkers for disease monitoring and risk stratification and novel, efficient therapy concepts.

For the second group, knowledge of the risks associated with CVD during pregnancy and their management are of pivotal importance for advising patients before pregnancy. In this regard, guidelines on disease management in pregnancy are of great relevance as they give special consideration to the fact that all measures concern not only the mother, but also the foetus, as therapies favourable for the mother can be harmful for the child (i.e., foetotoxic effects of angiotensin-converting enzyme (ACE) inhibitors). Conversely, therapies to protect the child may lead to a suboptimal outcome for the mother [1].

As outlined in the recent update of the European Society of Cardiology (ESC) guidelines on the management of CVDs during pregnancy [1], a major problem in the field of pregnancy-related heart failure is that prospective or randomised studies are lacking; with a few exceptions, recommendations are mainly based on evidence level C. Therefore, registries and prospective studies are urgently needed to improve the state of knowledge. Furthermore, differences in the presentation, diagnosis and management are suspected for the pregnancy-related diseases in the focus of this review between developed Western countries and developing countries, a feature that we also address. Finally, we stress the point that pregnancy-associated cardiac disease requires interdisciplinary concepts for diagnosis, management and treatment.

### **Cardiomyopathies developing spontaneously in or shortly after pregnancy in previously healthy women**

PPCM is the major cause of pregnancy-induced heart failure and is associated with high morbidity and mortality [2,3]. The true incidence of PPCM is unknown, as clinical presentation varies. Current estimates, ranging from 1:299 (Haiti), to 1:1000 (South Africa) to 1:5556 (USA), are primarily based on case series from single-centre or retrospective questionnaires [4]. No data exist on the frequency of the disease in Europe. Our own experience suggests that PPCM occurs in 1 in 1500–2000 pregnancies in Germany (personal observation of Hilfiker-Kleiner).

The pathophysiology of the disease is still far from being understood and it is likely that multiple factors contribute to the induction and progression of PPCM. Nevertheless, decisive advances have been achieved in understanding some underlying molecular cascades that are deregulated in PPCM. Among those, elevated pro-inflammatory serum markers such as sFas/Apo1, C-reactive protein (CRP), interferon- $\gamma$  (IFN- $\gamma$ ) and interleukin (IL)-6 point to pro-inflammatory processes (pathogen-induced or auto-immune response) involved in the induction and the progression of PPCM and may have an impact on the prognosis of patients [5]. Indeed, positive effects of *Pentoxifyllin* in reducing the production of a number of inflammatory cytokines such as tumour necrosis factor (TNF)- $\alpha$  and IL-6 or immune globulin therapy have been reported [6–8]. More recent work points to an angiogenic imbalance being responsible for PPCM, involving an angiostatic and pro-apoptotic 16 kDa prolactin fragment and the soluble vascular endothelial growth factor (VEGF) receptor 1 (sFlt1), which leads to massive endothelial damage and myocardial dysfunction [9–11], a notion that is further supported by observations showing that endothelial microparticles are increased in acute PPCM [12]. Genetic factors may contribute to the susceptibility to PPCM in patients with a positive family history of cardiomyopathy, who typically have a more severe course of disease, and are therefore considered as risk factors [13,14]. Additional risk factors associated with PPCM are listed in Table 1, where pregnancy-induced hypertensive disorders such as pre-eclampsia, HELLP syndrome (where H stands for haemolysis, EL for elevated liver enzymes and LP for low platelet count) and twin pregnancy are especially prominent.

#### *Symptoms in PPCM patients*

The clinical presentation of patients with PPCM is similar to those with other forms of systolic heart failure secondary to cardiomyopathy but may be highly variable. Patients with only mild symptoms have been reported where PPCM becomes manifest in the last weeks of pregnancy up to 6 months

**Table 1**  
Predisposing factors for PPCM.[3]

Pregnancy associated factors	General risk factors
Prolonged use of $\beta$ -agonists	Smoking
Pregnancy-induced hypertensive disorders	Diabetes
Caesarean section	Hypertension
Multiple childbirth, multiparity	Substance abuse
Teenage pregnancy	Obesity
Advanced age of mother	Malnutrition
	Toxaemia
	Family history, ethnicity

following delivery in previously healthy women mainly through typical symptoms of cardiac failure such as dyspnoea on exertion, cough, orthopnoea and paroxysmal nocturnal dyspnoea [3,15]. Additionally, less specific symptoms of cardiac congestion such as abdominal discomfort, pleuritic chest pain and palpitations can occur. However, such early signs and symptoms of heart failure can be mistaken for pregnancy- or peri-partum-associated physiological discomfort [3,15]. For example, shortness of breath, leg oedema or fatigue are mild symptoms of heart failure but could also occur in normal pregnancy or early post-partum phase. This overlap in symptoms makes it difficult to sense heart failure, especially in previously healthy young women and may delay the diagnosis, which could explain why their first presentation is frequently with New York Heart Association (NYHA) III and IV classes. Such a late diagnosis is often associated with increased morbidity and mortality. Therefore, even in case of faint suspicion for PPCM, but especially in patients who have an elevated risk for the disease, an echocardiography should be performed to clarify the cardiac condition. In this regard, early biomarkers for the disease are warranted as discussed in the following paragraphs.

#### *Diagnosis of PPCM: How to distinguish it from normal physiologic discomfort in the peri-partum phase*

A redefinition of the diagnostic criteria for PPCM according to the most recent advances in clinical and experimental research has been published in a recent position paper from the Heart Failure Association of the European Society of Cardiology [3] which says: 1) PPCM is an idiopathic cardiomyopathy presenting with heart failure secondary to left-ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found and 2) it is a diagnosis of exclusion with a left-ventricular ejection fraction (LVEF) nearly always reduced below 45% but not always associated with LV dilatation.

#### *Diagnostic tools useful for PPCM*

Diagnosis of PPCM is based on exclusion criteria that include the absence of any identifiable cause for heart failure in women without known pre-existing cardiac disease and a strict time limit focussed on the last month of pregnancy and the first few months following delivery. These diagnostic criteria were intended to exclude congenital and acquired causes of heart failure that usually manifest by the second trimester due to physiological volume expansion [16,17]. Physical examination should focus on signs of heart failure, such as hypoxia, third heart sound gallop rhythm, jugular venous distension, hepatomegaly and rales [3]. The electrocardiography (ECG) presentation is quite variable: it may show normal ECG as in the majority of PPCM cases or prolongation of the PR or QRS intervals and evidence for LV hypertrophy and dysrhythmias [3].

Transthoracic echocardiography is the key tool for accurate diagnosis defined as an impairment of cardiac function manifest by a decrease in LVEF (EF <45%), fractional shortening (FS <30%) or both. Cardiac enlargement with an LV end-diastolic dimension >2.7 cm m<sup>-2</sup> is also frequently evident, particularly in those women presenting late. However, some PPCM patients display normal ventricular dimensions suggesting that dilatation may not be specific for PPCM [3].

Recently, magnetic resonance imaging (MRI) has been used for the detection of myocardial damage in PPCM disease. Interestingly, many patients with PPCM do not exhibit a disease-specific cardiac MRI

pattern. However, MRI is useful for the detection of inflammatory forms of PPCM [18] or a thrombus formation [19]. Echocardiography is sufficient for a functional analysis, especially in terms of disease progress.

In addition, as recommended by Sliwa *et al.*, [3] a number of laboratory tests should be performed in patients with suspected PPCM: Full blood count, urea and electrolytes, CRP, blood glucose, D-dimer, creatine kinase-MB (CKMB) and cardiac troponin T (cTnT). In severe heart failure, international normalised ratio (INR) and arterial blood gas should also be performed. Transaminases, urinalysis and plasma B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be considered. Arterial blood gas analysis allows assessment of oxygenation (partial pressure of oxygen,  $pO_2$ ), respiratory adequacy (partial pressure of carbon dioxide,  $pCO_2$ ), acid–base balance (pH) and base deficit and should be performed in all patients with severe heart failure.

However, it should be noted that many of these classical markers normally associated with heart failure – elevation of CKMB, cTnT and CRP – may not be present in PPCM patients. In turn, a more specific serum marker profile including elevated NT-proBNP, oxidised low-density lipoprotein (oxLDL), prolactin and IFN- $\gamma$  emerged in a more recent evaluation of PPCM patients with follow up [5]. Furthermore, serum markers involved in the prolactin-cleaving pathway, such as activated Cathepsin D and 16-kDa prolactin [9,11], increased endothelial microparticles [12], and microRNA-146a associated with these microparticles [20] may emerge as more specific diagnostic tools for PPCM.

In summary, due to the observations that early signs and symptoms of heart failure can be mistaken for pregnancy-/peri-partum-associated physiological discomfort, disease-specific biomarkers would be helpful for early diagnosis of PPCM. The diagnosis of PPCM defined as a systolic LV dysfunction can only be made by echocardiography or MRI.

#### *Pathophysiology involved in PPCM*

The pathophysiology of PPCM is not clear and it is likely that not one specific factor but rather the coincidental presence of multiple factors induce this disease in previously healthy women. Such factors include:

- a) Inflammation: There is some evidence that pathogen- or auto-immune-related inflammation in the peri-partum phase may promote the development of PPCM. There were virus-positive myocardial biopsies reported in PPCM patients and experimental data suggest that viral infection of the heart may enhance the PPCM phenotype [21]. Furthermore, there are reports that describe increased levels of auto-immune antibodies in the serum of PPCM patients [8]. Interestingly, the serum marker profile suggested that inflammatory conditions are very frequent in PPCM patients from South Africa with increased serum levels of pro-inflammatory cytokines (IL-6, TNF- $\alpha$  and IFN $\gamma$ ) [5,22]. In the same patient collective, the TNF- $\alpha$  inhibitor pentoxifyllin showed beneficial effects [22].
- b) Oxidative stress and prolactin cleavage: Experimental results suggest that impaired anti-oxidative defence resulting in increased oxidative stress in the heart promotes PPCM. Such an enhanced oxidative stress seems to activate enzymes like Cathepsin D, which cleaves the nursing hormone prolactin into an N-terminal 16-kDa fragment [9,10]. This 16-kDa form of prolactin injures endothelial cells and the capillary network. It promotes vasoconstriction and lowers metabolic activity and function of cardiomyocytes [9,10,20]. Pharmacological treatment with bromocriptine, an inhibitor of prolactin secretion, prevents the development of PPCM in mice [9,10]. Furthermore, first studies suggest that bromocriptine may have positive effects in patients with PPCM [9,11].
- c) Impaired vasculature and pregnancy-associated hypertension: Patients with pregnancy-induced hypertension, pre-eclampsia and HELLP syndrome have an enhanced risk for PPCM. It is hypothesised that this is caused by systemic angiogenic imbalance. In humans, the placenta in late gestation secretes anti-angiogenic factors such as 16-kDa prolactin, vasopressin and VEGF inhibitors such as soluble FLT1 (sFLT1). Pre-eclampsia and multiple pregnancies seem to be associated with increased secretion of these factors [10]. In turn, experimental data suggest that the heart needs to increase its expression of pro-angiogenic factors such as VEGF for protection against peripartal stress. This notion is supported by findings that mice which lack cardiac proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ), a powerful positive regulator of VEGF, develop

profound PPCM with massive loss of myocardial capillaries [10]. The combination of prolactin blockade with bromocriptine and a VEGF analogue prevented PPCM in these mice and might therefore be a novel and more effective treatment option in PPCM [10].

- d) Genetic background: A few studies report pregnancy-associated cardiomyopathy in patients with a family history of cardiomyopathy [13,14]. It is likely that in some of these cases the elevated haemodynamic and/or hormonal stress during pregnancy unmask a sub-clinical cardiomyopathy.
- e) Pregnancy-induced hypertension: About 5% of all pregnancies are complicated by hypertensive complications including pre-eclampsia and HELLP syndrome [23]. These conditions are also risk factors for PPCM. In fact, a recent single-centre study in Ireland reported pre-eclampsia in nine out of 12 PPCM cases [24]. Likewise, a study collective in Japan reported a high frequency of pre-eclampsia in PPCM patients [25] as did the authors in their German PPCM registry (Hilfiker-Kleiner, personal observation). Since pre-eclampsia per se can induce heart failure [23], there is some controversy among experts whether patients with pregnancy-induced hypertension should be classified as PPCM (Bachelier-Walenta et al. *Obstetric Medicine*, in press). In fact, this may be difficult as there is overlap in the pathophysiology of both disease types with regard to impairment of the endothelium and it may indeed not be possible to clearly distinguish between pre-eclampsia/HELLP syndrome and PPCM, albeit most patients with pregnancy-induced hypertensive complications do not develop heart failure and it may need a second hit to induce the PPCM condition [10].

### Treatment of PPCM

According to the newest guidelines of the ESC [1], PPCM patients should be treated with heart failure medication, mainly beta-blockers, ACE inhibitors (or angiotensin-receptor blockers, ARBs) and mineralocorticoid-receptor blockers (MRAs). Diuretics should only be used, if needed. It is important to note that PPCMs have increased the risk of thrombosis, especially if LV function is substantially decreased. Therefore, prophylactic or therapeutic anticoagulation should be used. This is of specific importance, if bromocriptine is used to stop nursing, or as therapeutic option because bromocriptine may enhance the risk of thrombosis.

Therapies involving catecholamines (inotropic substances or vasopressors) should be avoided and may lead to progression of the disease in a therapy-resistant situation. In turn, our experience suggests that even in patients with severely reduced cardiac function a well-dosed and well-supervised beta-blocker therapy appears to be beneficial. However, therapy should be induced and closely monitored by a cardiologist.

In cases of therapy-resistant patients extracorporeal life support (ECLS) may help to stabilise a patient and a left-ventricular assist device (LVAD) may be used as a 'bridge to recovery' or 'bridge to transplantation'. It is important to note that the majority of patients, even with severely reduced cardiac function, recover under optimal therapy and therefore invasive therapy options should only be used as a last resort.

Mortality due to PPCM is caused by heart failure, thrombo-embolism and ventricular fibrillation. Patients with persistent poor LV function 6 months after diagnosis need an implantable cardioverter-defibrillator (ICD). Wearable portable defibrillators should be indicated in patients with highly reduced LV function or high risk of sudden death.

Newer, more specific therapy options derive from experimental research where, for example, a pathophysiologic effect could be assigned to the cleaved 16-kDa prolactin fragment. The first pilot trials and healing attempts in PPCM patients in South Africa and Germany using bromocriptine to block prolactin yielded positive effects [9,11]. While the treatment is now used regularly in South Africa, further clinical evidence for the efficacy of this therapy is needed and a larger multicentre randomised trial is currently underway in Germany (ClinicalTrials.gov, NCT00998556).

### Prognosis

Very little is known about the incidence of PPCM. Prospective, population-based, epidemiologic studies have not been performed in Europe and the US. The number of patients with a benign course of the disease is unknown.

End-stage heart failure (transplantation and death) due to PPCM is seen in 10–23% of patients, while recovery of an LVEF over 50% is reported in about 50% of the patients. Predictors of therapy failure seem to be poor LV function (LV-EF <30% or fractional shortening <20%), an LV end-diastolic diameter >6 cm and an elevated Troponin T [3,5,15,26].

Nevertheless, while it seems that both poor LV function at the time of diagnosis and dilated LV have a higher chance for an adverse outcome, it should be noted that many patients with poor baseline conditions recover as well. In fact, improvement of LV function during treatment has been observed even years after diagnosis [27]. In turn, we observe that in some patients with normalised LV function worsening of heart failure occurs after discontinuing medication. A reason could be a sub-clinical irreversible injury of the myocardium or vascular system in PPCM. Therefore, careful evaluation of whether a recovered PPC patient is really stable without heart failure medication is required.

### *Interdisciplinary management*

When PPCM occurs in pregnancy, the situation is life threatening for the foetus. The heart failure condition in PPCM and the heart failure treatment may cause placental insufficiency, leading to intrauterine foetal death or premature birth. Therefore, interdisciplinary management is required to treat a pregnant woman with heart failure, requiring a team of cardiologists, obstetricians, neonatologists, anaesthetists and, if necessary, cardiac surgeons who have to confer among each other and manage the situation together. The guidelines of the ESC for the management of CVD in pregnancy are helpful instructions [1].

As mentioned above, the unborn child has also to be carefully monitored as the cardiac re-compensation therapy in the mother could be followed by placental insufficiency causing the death of the foetus. Therefore, decisions have to be taken which help to rescue the mother's and, if possible, also the foetus' life, by considering a premature delivery with a timely use of corticosteroids for foetal lung maturation.

The mode of delivery should be adapted to the condition of the mother considering the ESC guidelines, also with regard to anaesthesia in severe heart failure [1].

### *Subsequent pregnancy*

After recovery from PPCM, there is an elevated risk of heart failure in a subsequent pregnancy. In general, the severity of PPCM in a subsequent pregnancy increases [3,15]. Patients with persistent reduced LV function before subsequent pregnancy have an especially high risk of a recurrence of PPCM [3,15]. A pilot study in South Africa and case reports from Germany indicate that patients with subsequent pregnancy after PPCM appear to profit from an early treatment with bromocriptine starting right after delivery and induction of heart failure medication as soon as haemodynamic stability is reached [9].

Therefore, all patients have to be informed about the relatively high risk of a relapse of PPCM in a subsequent pregnancy. If the LV function has not recovered to a normal range, patients should be advised not to get pregnant again. If a patient becomes pregnant again, a continuous obstetrics- and cardiology-based care during pregnancy is necessary. Physicians experienced in treating PPCM should counsel patients with subsequent pregnancies. For example, it is important to note that PPCM may not be prevented by an early termination of pregnancy because the trigger for the disease seems to be associated with the peri-partum physiology and because we have cases where PPCM started after a miscarriage in the first trimester.

The ESC guidelines on the management of CVD during pregnancy point out the importance of pregnancy status for treatment of chronic heart failure as foetotoxic treatment, such as ACE inhibitors and ARBs (Table 1), has to be stopped in pregnant women, while the treatment with  $\beta$ -blockers could be continued [1].

### *Differential Diagnosis of PPCM*

PPCM is a diagnosis of exclusion. It is, by definition, a disease that occurs in the last month of pregnancy and the months following delivery. Maternal heart failure that appears before that last

trimester may therefore have other causes. For example, pre-existing congenital or acquired cardiac diseases that were unmasked under a growing haemodynamic workload, or hypertensive heart disease caused by untreated hypertension or pregnancy-induced hypertension may be a reason for these types of heart failures.

Notably, patients after chemotherapy often develop heart failure in pregnancy. In patients with chemotherapy-induced cardiomyopathy, the worsening under a pregnancy does not fulfil the definition of PPCM. In turn, patients who do not develop cardiomyopathy after chemotherapy but who develop heart failure peri-partum may be considered PPCM.

Thus, chemotherapy has to be considered a risk factor for peri-partum heart failure. As both patient types seem to benefit from an early heart failure treatment, we advise cardiologic assessments before, during and after pregnancy to these patients.

Peri-partum myocardial infarction is a rare complication. Its pathophysiology, diagnosis, treatment and prognosis is reviewed by El-Deeb and co-workers [28].

Another differential diagnosis is a pulmonary embolism. Thrombo-embolic complications have also been observed in patients with PPCM caused by lowered cardiac output [1].

### Pre-existing disease requiring special consideration

#### *Aortic dissection during pregnancy*

In women under the age of 40 years, 50% of type A aortic dissection occur in the obstetric population [29,30]. With an overall reported incidence of 0.4–3.5 cases per 100,000 patient-years, it represents a rare condition [30,31]. However, it is associated with a high neonatal and maternal mortality (up to 83%) [32]. This fatality occurs during the third term or within the early post-partum period [1].

Several inheritable connective tissue disorders and congenital heart diseases are associated with aortic pathologies predisposing to aortic dissection (Table 2). The underlying vascular pathology consists of degeneration of collagen and elastin of the aortic wall [33], causing media necrosis. Among these, Marfan's syndrome represents the leading, single, underlying disease of pregnancy-related aortic dissection. Arterial hypertension plays a pivotal role in this situation. Hypertension has been observed in up to 90% of patients, either as the single underlying disease or in combination with a predisposing disorder, for example, Marfan's syndrome [30]. Additionally, the overall risk of dissection increases with older maternal age and with growing aortic diameters; however, dissections have been observed in only mildly dilated aortas as well [34]. It has been discussed controversially whether pregnancy itself might be a predisposing condition as related haemodynamic and hormonal changes during pregnancy might promote aortic dissection. Particularly oestrogen, a hormone that increases gradually during pregnancy, has been identified to alter the structural integrity of the aorta, facilitate its remodelling and render it relatively more susceptible to injury during or shortly after pregnancy [30,35].

#### *Risk assessment*

In all women with known predisposing conditions (Table 2), the risk of pregnancy should be discussed prior to conception. Individual risk assessment is based on the underlying disease, absolute or increasing aortic diameters and a family history of dissection. Imaging of the entire aorta before

**Table 2**  
Prevalence and risk of aortic dissection during pregnancy.

Disorder (Selection of important disease entities)	Prevalence	Very high risk of dissection
Marfan's Syndrome	1:3,000–5,000	Yes
Loyes-Dietz Syndrome	Unknown	Yes
Ehlers-Danlos-Syndrome (Type IV)	Rare	Yes
Familial thoracic aortic aneurysm	Rare	Depending on type
Turner-Syndrome	1:3,000	No
Bicuspid aortic valves	1:50–100	No
Complex congenital heart disease with aneurysm (e.g. Tetralogy of Fallot, D-Transposition)	1:5,000–10,000	No

pregnancy is recommended [1]. In Marfan's syndrome and other disease entities with high risk of aortic dissection, except for Ehlers–Danlos type IV pre-pregnancy, surgery is recommended in aortas  $\geq 4.5$  cm ( $\geq 27$  mm m<sup>-2</sup>) and in other conditions in ascending aortas  $\geq 5$  cm ( $\geq 28$  mm m<sup>-2</sup>). In case of a family history of dissection, or growing aortic size pre-pregnancy, surgery is suggested in aortas  $\geq 4$  cm. In women of short stature, absolute values might underestimate the risk of dissection. Therefore, diameter indices ( $\geq 27$  mm m<sup>-2</sup>) must be used. In women with diameters larger than these values, pregnancy should be discouraged. The Ehlers–Danlos type IV syndrome represents a condition with extraordinary tissue fragility resulting in large-vessel rupture, bruising and uterus rupture. This syndrome is regarded a contraindication for pregnancy [1,36].

However, despite pre-pregnancy surgery clinicians should be aware of the residual risk of dissection as the native part of the aorta might be a source of aortic fatalities. In addition, although rare, dissections occur in aortic sizes below the addressed values outlining that an absolutely safe diameter does not exist [34].

#### *Genetic counselling*

Genetic counselling is important to inform about risk. Marfan's syndrome as an autosomal inherited disorder is associated with a 50% risk. By contrast, the bicuspid aortic valve is associated with various genetic entities resulting in an overall risk of 9%. All women with congenital cardiovascular disorders should be offered a detailed 20-week foetal cardiac scan to detect foetal lesions potentially influencing the mode of delivery or requiring special paediatric care.

#### *Management of pregnancy*

Risk management during pregnancy is based on both risk detection and prevention.

For risk detection, patients with Marfan's syndrome or entities associated with pregnancy-related risk of aortic dissection require repeated assessments (1–3 months intervals) of aortic diameters during pregnancy and assessments up to 6 months post-partum are recommended. In a particular risk situation, defined either by aortic enlargement or by the disease itself (Table 2), monthly assessments are advisable during the third term and the early post-partum period [1].

There is an ongoing discussion whether patients with Marfan's syndrome should take  $\beta$ -blockers to prevent aortic growth during pregnancy. A meta-analysis from 2007 did not show a beneficial effect of  $\beta$ -blockers on aortic growth. However, a recent prospective analysis found that the absence of  $\beta$ -blocker medication is associated with progressive aortic dilatation [37,38]. Currently,  $\beta$ -blocker medication is recommended during pregnancy and the early post-partum period. In 53 non-pregnant women with Ehlers–Danlos syndrome type IV, celiprolol was effective in preventing aortic fatalities. Current guidelines recommend celiprolol during pregnancy in this particular situation. In patients with Ehlers–Danlos syndrome type IV, celiprolol is recommended [1,39].

There is a tight relationship between aortic dissection and arterial hypertension [30,32,40]. Therefore, close monitoring of blood pressure is advised. At our institution, all at-risk patients are advised to perform 24-h ambulatory blood pressure monitoring at initial evaluation. In pregnancy without potential aortic complications, depending on the underlying situation, a blood pressure from 140/90 mmHg to 150/95 mmHg can be accepted; treatment consists of fluid and salt restriction [41]. Currently, data on optimal blood pressure control during pregnancy in Marfan's syndrome and associated at-risk lesions are lacking. At our institution, in presumed high-risk situations, treatment goals consist of a mean blood pressure below 130/90 mmHg and avoidance of peak values beyond 160 mmHg. This tight blood pressure control necessitates foetal growth monitoring.

#### *Management of delivery*

In high-risk situations, delivery should be performed in hospitals providing cardiovascular surgery and neonatal intensive care facilities.

Vaginal delivery is preferable in all patients with stable aortic diameter  $\leq 4.5$  cm ( $< 27$  mm m<sup>-2</sup>). In Marfan's and Loyes–Dietz syndrome, an aortic diameter  $\geq 4$ – $4.5$  cm ( $\geq 27$  mm m<sup>-2</sup>) requires special consideration. The therapeutic goal during labour and delivery consists of cardiovascular stress reduction to avoid blood pressure peaks potentially inducing aortic dissection. This can be achieved by regional anaesthesia, expedited second stage of delivery and maintenance of  $\beta$ -blocker medication.

However, in Marfan's syndrome regional anaesthesia might be difficult in the presence of scoliosis or dural ectasia. In this situation, in patients with aortas sized  $\geq 4$ – $4.5$  cm and in those with aorta size exceeding 4.5 cm caesarean section should be considered.

In the absence of data and guidelines for patients with a presumed lower risk of dissection, for example, bicuspid aortic valves, we recommend caesarean section in aortas  $\geq 5$  cm ( $\geq 28$  mm  $m^{-2}$ ). In case of aortic sizes  $\geq 4.5$ – $5$  cm, the risk versus benefit of the mode of delivery is discussed with the patient and decision is made on an individual basis. As in Marfan's or Loyaes–Dietz syndrome, all patients are offered regional anaesthesia, independent of the diameter of the aorta.

Progressive dilatation represents a high-risk factor of dissection requiring aortic surgery. In case the foetus is not viable, surgery should be considered with the foetus *in utero*. When the foetus is viable, at first caesarean section followed by immediate aortic repair is recommended [1].

#### *Clinical presentation and management of acute dissection*

The leading clinical symptom consists of a sharp thoracic pain. Differential diagnosis includes pulmonary embolism and myocardial infarction. Patients require close monitoring on an ICU and immediate therapeutic intervention. A senior cardiologist and a cardiothoracic surgeon should be informed immediately.

Initial evaluation should include blood pressure measurements of all four extremities. The diagnosis of dissection is quite likely, if low blood pressure or loss of pulses of one or more extremities, cardiac murmur in particular due to aortic regurgitation, murmurs over the abdomen or carotid arteries and/or neurological symptoms exist.

Basic evaluation should include a 12-lead ECG and measurement of troponin and D-dimer, lactate, liver enzymes, creatinine and full blood count. These parameters might be helpful in the differential diagnosis and diagnosis of complications. However, initial blood tests alone are not sufficient for definite diagnosis or to rule out any complication of acute dissection.

Therefore, imaging modalities are mandatory. Only about half of the patients with acute aortic dissection present with a widened mediastinum on chest radiograph outlining the limited value in making the diagnosis. Transthoracic echocardiography is helpful in the detection of complications such as pericardial effusion/tamponade, or aortic regurgitation, right-heart failure favouring pulmonary embolism or regional wall-motion abnormalities to be expected in acute myocardial infarction. Conversely, known complications in aortic dissection are rupture into the pulmonary artery, or dissection of coronary arteries misleading us to the diagnosis of pulmonary embolism or myocardial infarction as the primary course of deterioration. All three imaging modalities, CT scan, MRI and transesophageal echocardiography, have a nearly 100% sensitivity and specificity in detecting aortic dissection [42].

However, CT scans are associated with radiation exposure and, in case of MRI, contrast enhancement with gadolinium should be used with caution, because gadolinium passes the placenta barrier and the long-term effect on the foetus is yet unknown. Trans-oesophageal echocardiography carries the risk of aspiration due to gastric atony. To its advantage, it can be done quite safely as a bedside test after a stomach tube has been inserted. The mode of imaging is chosen on the base of centre's experience and rapid availability.

As soon as the diagnosis is made, surgery should be performed starting with caesarean section in cardiac theatres and directly proceeding to repair of aortic dissections. Rapid diagnosis and an interdisciplinary approach have reduced in-hospital mortality significantly [1].

#### *Valvular lesions*

Valvular lesions at the childbearing age usually consist of chronic valvular problems. In underdeveloped countries, rheumatic lesions represent the vast majority of lesions (1% of all pregnancies), whereas in Western industrial countries degenerative and congenital disorders are more common. The risk in pregnancy is related to the ability to cope with haemodynamic changes during pregnancy. Pregnancy in asymptomatic patients with regurgitant lesions and preserved ventricular function is usually uncomplicated. This is in contrast to LV stenotic lesions, which are associated with a limited ability to adapt to the haemodynamic changes related to pregnancy. Therefore, in the case of known

valvular lesion pre-pregnancy cardiac evaluation is recommended. Pre-pregnancy valve repair should be performed according to current guidelines [43].

#### *Mitral and aortic regurgitation*

Usually, both entities are not associated with an increased risk of obstetric complications. Adverse outcomes may be due to heart failure in already symptomatic patients or patients with impaired ventricular function prior to pregnancy [44]. In rare cases, for example, in antiphospholipid syndrome or endocarditis, acute severe regurgitation might occur requiring urgent surgical therapy [45–47]. In chronic regurgitation, obstetric complications are rare. However, there is an increased incidence of premature labour, particularly in pregnancies with an unfavourable situation before pregnancy. Vaginal delivery is preferable. In mildly symptomatic patients, regional anaesthesia and expedited second-stage labour are recommended. Caesarean section may be considered in symptomatic patients, in particular those with New York Heart Association-Classification (NYHA) III and IV and those with impaired ventricular function [1].

#### *Mitral stenosis*

##### *Pre-pregnancy consideration*

Mitral stenosis due to rheumatic heart disease represents the most common lesion in underdeveloped countries, being associated with a high foetal and maternal mortality [48]. In a cohort of pregnant patients with severe mitral stenosis, 67% developed a maternal cardiac event and 44% of infants were born prematurely or died (25%) [49]. By contrast, mild mitral stenosis rarely results in cardiac events. Women with valve areas  $<1.5 \text{ cm}^2$  poorly tolerate the haemodynamic burden of pregnancy and are particularly prone to develop heart failure during the second and third terms. These patients should be counselled against pregnancy. It is advisable to perform percutaneous commissurotomy, open-heart commissurotomy or valve replacement preferably with a valve made out of biological materials prior to pregnancy.

##### *Haemodynamic considerations*

In mitral stenosis, cardiac output is dependent on the mitral valve area. Particularly in mitral valve areas  $<1.5 \text{ cm}^2$ , the increase in cardiac output is limited. Patients cannot cope with the 30–50% increase in cardiac output during pregnancy resulting in decompensation in the second or third trimester.

Haemodynamic considerations are important for medical management, anaesthesia and in the presence of tachycardia. The impact of both preload and afterload reduction requires special consideration. All drugs should be given with caution. Afterload reduction can cause reflex tachycardia with declining diastolic filling of the left ventricle promoting cardiac decompensation. In addition, preload reduction is associated with the risk of declining cardiac output. Patients should be advised to take preferentially a lateral or upright position during delivery to avoid 'vena cava' compression.

##### *Management of severe mitral stenosis in pregnancy*

The severity of mitral stenosis predicts the risk of cardiac decompensation. This may be due to increasing pulmonary congestion related to valve stenosis and/or due to atrial fibrillation occurring in  $<15\%$  of cases. Medical heart failure treatment, bed rest, arrhythmia control and anticoagulation are important in the management of symptomatic patients.

Atrial fibrillation may present as a medical emergency with haemodynamic instability associated with pulmonary oedema and high risk of thrombo-embolism. Whenever it is possible, transoesophageal echocardiography should be performed before cardioversion. In acute onset, both resolution of pulmonary congestion via diuretics and heart rate control are important to prolong diastole, which improves cardiac output and lessens heart failure symptoms ( $\beta$ -blocker, digoxin).

Anticoagulation at onset of atrial fibrillation is essential to prevent thrombo-embolic complications. This should be continued for at least 4 weeks after cardioversion. In recurrent or persistent atrial fibrillation, anticoagulation is essential to prevent thrombo-embolic complications. Anticoagulation should be considered in large atria with spontaneous echo contrast. Dependent on the clinical situation, either low-molecular-weight heparin or vitamin K antagonists can be chosen. Special care should

be taken for dosing of the vitamin K antagonist in the first term since there is a dose-dependent risk of this drug for malformation in the developing embryo and foetus and for miscarriages.

In highly symptomatic patients and/or pulmonary hypertension unresponsive to optimal medical treatment (echocardiographically estimated systolic pulmonary artery pressure >50 mmHg), percutaneous valvuloplasty should be performed in suitable cases. This procedure is associated with favourable maternal (mortality <2%) and foetal outcome (mortality <4%) [50,51]. As there is a risk of urgent surgical valve replacement, this procedure should not be performed in asymptomatic patients. Closed commissurotomy remains an alternative in developing countries when percutaneous commissurotomy is not available. Open-heart surgery should only be performed in cases of persisting decompensation unresponsive to all treatment modalities [1,51].

#### *Delivery in mitral stenosis*

In mild mitral stenosis and severe mitral stenosis with NYHA class I/II without pulmonary hypertension, vaginal delivery should be considered. Delivery should be performed in a left lateral upright position. Management should be aimed to achieve a fast labour with excellent anaesthesia to avoid pain-related stress and the consideration of assisted second stage of labour. In situations where there is doubt about the functional adequacy of the cardiac condition, induction of labour can be considered. In these cases, individual management will be based on the parturient's cardiac status, foetal well-being and lung maturity and the inducibility of the cervix. However, long induction times should be avoided. In a favourable situation, according to the Bishop score oxytocin and artificial rupture of membranes are recommended. With respect to obstetric contraindications, local prostaglandin might be used with caution in an unfavourable cervix as systemic absorption can cause hypotension with reflex tachycardia.

Haemodynamic monitoring should include maternal blood pressure and heart rate control and continuous foetal heart rate control. Invasive haemodynamic monitoring is rarely indicated, as in severe highly symptomatic mitral stenosis, because a Swan–Ganz catheter is associated with bleeding complications, arrhythmias and thrombo-embolic complications (authors' personal experience and published data) [1,52].

Caesarean section is considered in the presence of pulmonary hypertension, moderate-to-severe highly symptomatic mitral stenosis or after failure of percutaneous valvulotomy [1]. In these patients, aesthetic management is challenging as a decrease in systemic resistance might result in reflex tachycardia promoting the development of cardiac decompensation. In addition, hypovolaemic states might result in declining cardiac output. Thus, these patients warrant invasive haemodynamic monitoring during delivery [52].

#### *Aortic stenosis*

##### *Pre-pregnancy consideration*

In childbearing-age women, severe aortic stenosis represents a rare condition [32]. The site of obstruction can be of sub-, or supra- or valvular origin. As in mitral stenosis, cardiac morbidity depends on the severity of obstruction highlighting the importance of cardiac evaluation before pregnancy. Mild-to-moderate asymptomatic stenosis usually is well tolerated. In asymptomatic women with severe aortic stenosis (mean gradient >50 mmHg, valve area <0.6 cm<sup>2</sup> m<sup>-2</sup>), stress testing can unmask symptoms. Risk factors consist of severe LV hypertrophy, proven recent progression of stenosis, severe symptomatic aortic stenosis or asymptomatic aortic stenosis with impaired ventricular function. These patients should be counselled against pregnancy. Pre-pregnancy corrective surgery should be performed according to current guidelines [43]. However, maternal cardiac complications (13%) and obstetric complications (38%) are reported after aortic valve replacement despite low maternal mortality [53].

The bicuspid aortic valve represents the most frequent cause of aortic stenosis. It is associated with aortic dilatation requiring assessment of diameters of the ascending aorta before and during pregnancy. Pre-pregnancy surgery is recommended in aortas exceeding 50 mm (28 mm m<sup>-2</sup>) [1].

##### *Haemodynamic consideration*

The increase in cardiac output in pregnancy is adversely related to the degree of aortic stenosis. Haemodynamic changes during pregnancy such as increasing blood volume and decreasing systemic

peripheral resistance contribute to an incremental aortic valve gradient. While usually systolic function is preserved, diastolic function is impaired. An increasing aortic gradient requires adequate ventricular filling to maintain cardiac output. In addition, tachycardia impairs diastolic filling. Hypovolaemia will enforce both tachycardia and reduction of peripheral resistance promoting an unfavourable haemodynamic situation with a declining cardiac output [54,55].

#### *Management of pregnancy*

Depending on cardiac status, patients require monthly or bimonthly cardiac follow-up. In symptomatic patients,  $\beta$ -blockers, diuretics and restriction of physical activities are recommended. However, in particular diuretics have to be given with caution. Symptomatic aortic stenosis is associated with a 10% maternal mortality [56,57]. In symptomatic patients unresponsive to medical treatment with favourable anatomy, percutaneous valvuloplasty can be performed. This procedure should be restricted to symptomatic patients due to a procedure related to risk of stroke, intraprocedural death, coronary occlusion, severe aortic regurgitation or tamponade [58].

#### *Management of delivery*

In mild-to-moderate asymptomatic aortic stenosis, vaginal delivery is preferred. In severe symptomatic aortic stenosis, caesarean section with endotracheal intubation and general anaesthesia should be preferred because regional anaesthesia carries a high risk of decrease in peripheral vascular resistance contributing to unfavourable haemodynamic effects [1].

### **Conclusions**

In summary, counselling and management of women of childbearing age with suspected cardiac disease should start before pregnancy. Pregnant women with cardiomyopathies, either known or developed during pregnancy, should be managed by interdisciplinary teams and high-risk patients should be treated in specialised centres where diagnostic procedures and interventions should be performed by specialists with expertise in the individual techniques and experience in treating pregnant patients [1].

### **Conflict of interest statement**

None of the authors has anything to disclose.

#### **Practice points**

- Symptoms of heart failure in the peri-partum phase: dyspnoea on exertion, cough, orthopnoea and paroxysmal nocturnal dyspnoea, abdominal discomfort, pleuritic chest pain and palpitations.
- Early signs and symptoms of heart failure can be mistaken for pregnancy/peri-partum-associated physiological discomfort; therefore, perform an echocardiogram or a magnetic resonance tomography (MRT) to confirm or exclude peri-partum heart failure. Note, ECG may be normal even in severe peri-partum heart failure.
- Treatment of heart failure in the peri-partum phase should always be performed according to the guidelines of the European Society of Cardiology (ESC). Note that heart failure medication may harm the foetus. In turn, the mother's condition may be difficult for anaesthesia during delivery. Therefore, interdisciplinary management is always required.
- Careful counselling of women with cardiac disease for pregnancy and especially subsequent pregnancy in an interdisciplinary setting with a cardiologist, cardiac surgeon and geneticist (especially in patients with genetic disorders such as Marfan's or Ehlers–Danlos type IV) is required.

## Research agenda

- Importance to find specific biomarkers for heart failure in pregnancy and post-partum for diagnosis and risk stratification.
- Importance to understand pathomechanisms behind different types of pregnancy-induced heart failures.
- Clinical studies to analyse risk factors, therapy concepts and outcome in pregnancy-associated heart failure.

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