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POSITION PAPER

Risk stratification and management of women with cardiomyopathy/heart failure planning pregnancy or presenting during/after pregnancy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy

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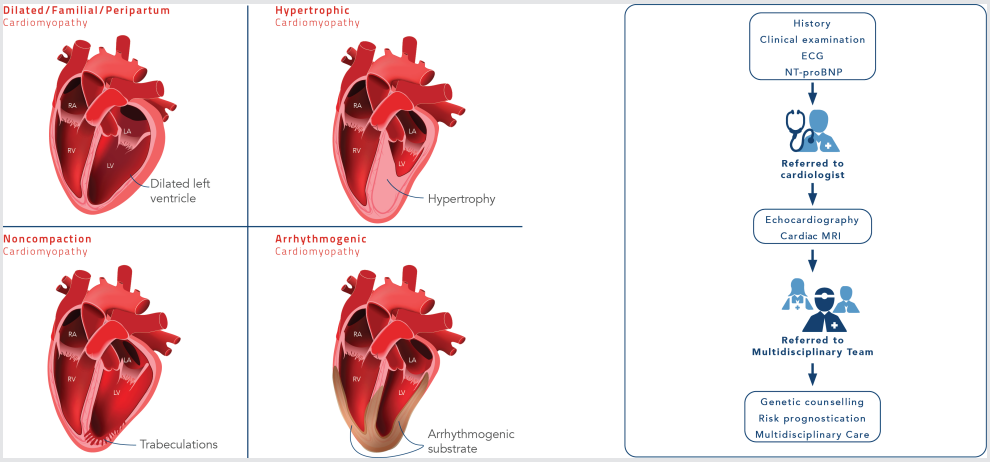
This position paper focusses on the pathophysiology, diagnosis and management of women diagnosed with a cardiomyopathy, or at risk of heart failure (HF), who are planning to conceive or present with (*de novo* or previously unknown) HF during or after pregnancy. This includes the heterogeneous group of heart muscle diseases such as hypertrophic, dilated, arrhythmogenic right ventricular and non-classified

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cardiomyopathies, left ventricular non-compaction, peripartum cardiomyopathy, Takotsubo syndrome, adult congenital heart disease with HF, and patients with right HF. Also, patients with a history of chemo-/radiotherapy for cancer or haematological malignancies need specific pre-, during and post-pregnancy assessment and counselling. We summarize the current knowledge about pathophysiological mechanisms, including gene mutations, clinical presentation, diagnosis, and medical and device management, as well as risk stratification. Women with a known diagnosis of a cardiomyopathy will often require continuation of drug therapy, which has the potential to exert negative effects on the foetus. This position paper assists in balancing benefits and detrimental effects.

Graphical Abstract



Specific cardiomyopathy and pregnancy diagnostic algorithm. ECG, electrocardiogram; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Heart failure • Pregnancy • Cancer

Introduction

The number of women with heart disease who become pregnant is increasing, thereby contributing to a significant morbidity or mortality due to heart failure (HF), peripartum thromboembolic events and arrhythmias.[1] Due to advances in genetic testing, there are also more men and women known to have a mutation associated with a cardiomyopathy and HF[2] seeking pre-conception counselling. Also, patients with a history of cardiotoxic therapies (e.g. for malignant conditions), but without HF before pregnancy, need specific advice and risk stratification. Clear guidelines/directions how to counsel those patients before, during or after pregnancy are lacking.

The aetiology of cardiomyopathies occurring *de novo*, in association with pregnancy, is diverse (*Graphical Abstract*). Cardiomyopathies are neither very rare nor common, but they are important as they may cause severe complications, contributing substantially to maternal morbidity and mortality during pregnancy, in the immediate peripartum period and up to several months thereafter. Women with these heterogeneous forms of cardiomyopathies also commonly have arrhythmias which need specific management, including device therapy. Very little information and few recommendations have been published in this important field.

Women with a known diagnosis of a cardiomyopathy or presenting with (*de novo*) HF during/after pregnancy, will often require continuation of medical therapy, which has the potential to exert a negative effect on the foetus, meaning that adequate and appropriate treatment is vital. Accurate information on the foetal effect of medication is crucial to weigh the advantages of treating the mother against the possible long-lasting negative effects on the child.

Hypertensive HF, an important and prevalent complication during pregnancy, is not covered by this position paper. During pregnancy hypertensive emergencies with increased risk for the foetus can develop, including pulmonary oedema at lower levels of blood pressure compared with non-gravid women. Treatment of hypertension can prevent the progression to HF and decrease the risk of maternal and foetal complications.[1]

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This position paper refers to other recently published papers,[1,3] but will fill important gaps in knowledge and is, therefore, a much-needed reference for cardiologists, specialist physicians, obstetricians, neonatologists, anaesthetists, intensivists, cardiothoracic surgeons, genetic counsellors and others.

Pathophysiology of heart failure in genetic, idiopathic and cardiotoxic therapy-related cardiomyopathies and its impact on the peripartum period

Recent studies linked pregnancy to a stress model (physiological changes during pregnancy are summarized in online supplementary *Table S1*) which may unmask a pre-existing genetic and/or acquired cardiomyopathy. These women are asymptomatic prior to pregnancy but develop HF and arrhythmias during pregnancy or postpartum due to volume overload and humoral stress. Frequent mutations, i.e. likely pathologic and pathologic gene variants, mostly heterozygous or compound heterozygous, have been observed in *desmoplakin* (DSP), *carnitine palmitoyltransferase 2 (CPT2)*, *TTN DSP MYH7*, *LMNA*, *BAG3*, *TNNT2*, *TNNC1*, *PLN*, *ACTC1*, *NEXN*, *TPM1*, and *VCL*.[4–6] Furthermore, metabolic factors play a role; under physiological circumstances, maternal lipid metabolism is increased during the last trimester of pregnancy and normalizes after delivery. Induced pluripotent stem cells from peripartum cardiomyopathy (PPCM) patients revealed that lipid metabolism was widely affected.[7]

Pregnancy also emerges as the possible second hit that may trigger late onset cardiomyopathy after cardiotoxic cancer treatment. Women who experienced chemotherapy-induced cardiotoxicity have a higher risk for developing HF during pregnancy.[8] Moreover, previous cardiotoxic cancer therapies may trigger PPCM, even in the absence of left ventricular (LV) dysfunction immediately after cancer therapies.[9,10] In the same collective of PPCM patients with cancer, gene variants associated with an increased risk for cancer predisposition syndrome, especially in the DNA damage response pathway (DDR), were observed suggesting potential connections to pregnancy-associated cardiomyopathy as a form of late cardiotoxicity due to anticancer treatment.[6] Gene variants associated with impaired DDR may affect stress tolerance and repair ability of the heart. Mutations in the DDR genes *ataxia telangiectasia mutated (ATM)* and *breast cancer 1 (BRCA1)* not only increase the risk for cancer, but may also promote cardiomyopathies and HF *per se*,[11–14] and may also increase the risk for late cardiotoxicity.

Managing acute heart failure in patients during pregnancy or postpartum

If acute HF (AHF) develops in a pregnant patient, immediate referral to an intensive care unit and assessment of HF severity and foetal status are crucial. In addition to electrocardiogram and blood tests including natriuretic peptides (NPs), urgent echocardiography is recommended to detect left and/or right HF, valvular abnormalities, etc. To ensure rapid diagnosis, decision-making and therapy, a pre-specified interdisciplinary task force and management algorithm are recommended (*Figure 1*).[1,3] If stabilization of the patient is possible, delivery may be delayed especially in order to avoid severe prematurity of the baby.

Patients in cardiogenic shock or severe AHF requiring inotropes or vasopressors should be transferred early to a tertiary centre capable of providing mechanical circulatory support (MCS) and ventricular assist devices.[15] In these patients, urgent delivery by caesarean section (irrespective of gestation) should be considered with MCS available. PPCM patients seem to be especially sensitive to the toxic effects of beta-adrenergic agonists, which should be avoided whenever possible; levosimendan may be used as alternative inotropic drug.[15,16]

In patients with stabilized or subacute AHF, management goals are similar to AHF in non-pregnant patients, but fetotoxic agents [angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, angiotensin receptor–neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists] should be avoided.[15–17] Loop diuretics should be used in patients with symptoms or signs of congestion, with foetal monitoring due to concerns about placental blood flow. Nitrates are safe in pregnancy. After stabilization, initiation and up-titration of beta-blockers should be performed with caution. If high resting heart rate persists in the presence of beta-blockade, or intolerance thereof, treatment with ivabradine may be initiated in patients not pregnant or breastfeeding.

The European Society of Cardiology (ESC) guidelines on cardiac disease in pregnancy[1] recently added a recommendation on the use of bromocriptine in patients with PPCM (class IIb, level B). Bromocriptine (2.5 mg once daily) for 1 week may be considered in uncomplicated cases, whereas prolonged treatment (2.5 mg twice daily for 2 weeks, then 2.5 mg once daily for 6 weeks) may be considered in patients with ejection fraction <25% and/or cardiogenic shock.[1,15,18] Bromocriptine treatment must always be accompanied by anticoagulation with heparin in at least prophylactic dosages.[1]

Standard indications for anticoagulation in AHF apply during and after pregnancy.[1] In pregnant or postpartum AHF patients with very low ejection fraction, therapeutic anticoagulation may be considered to prevent thromboembolic events.

Managing pregnancies in patients with chronic heart failure

Prevalence of HF was 11% in a cohort of 5739 pregnancies in patients with congenital, ischaemic and valvular heart disease and cardiomyopathies.[1,19] Any cardiac event, including HF symptoms, admission to hospital, intensive care unit, respiratory failure, arrhythmias, and maternal death, in pregnant patients with chronic HF during pregnancy is devastating.[19]

Patients may already be known to have HF and wish to become pregnant or may present during pregnancy due to the increasing

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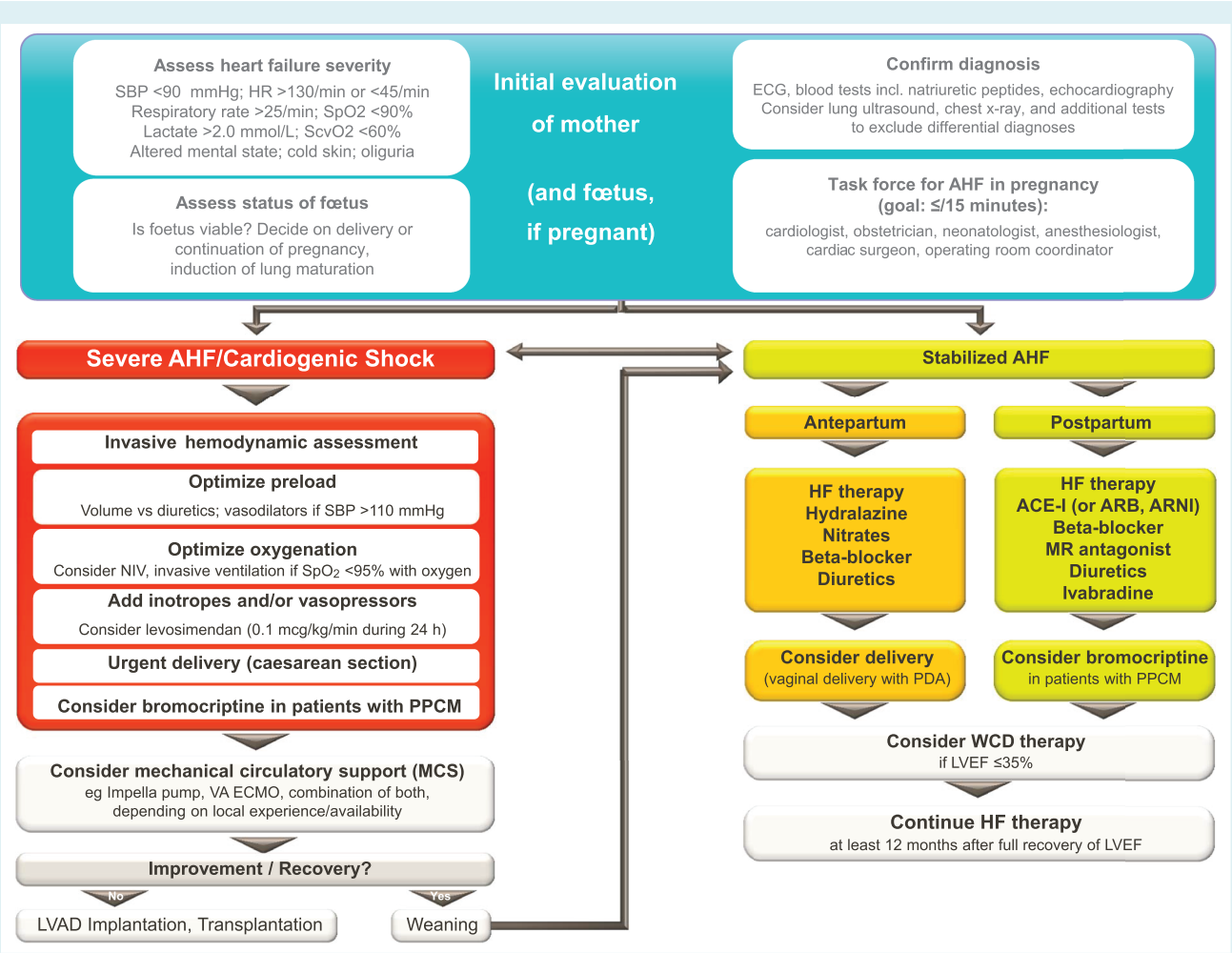


Figure 1 Management of acute heart failure (HF) during/after pregnancy: rapid interdisciplinary workup and treatment of the mother and foetus. ACE-I, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; ECG, electrocardiogram; HR, heart rate; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; NIV, non-invasive ventilation; PDA, peridural anaesthesia; PPCM, peripartum cardiomyopathy; SBP, systolic blood pressure; $ScvO_2$, central venous oxygen saturation; SpO_2, blood oxygen saturation; VA ECMO, veno-arterial extracorporeal membrane oxygenation; WCD, wearable cardioverter-defibrillator. Modified from Regitz-Zagrosek *et al.*[1]

haemodynamic burden. Distinguishing symptoms and signs of normal pregnancy from HF demands careful clinical assessment and investigation.[20]

Heart failure also places pregnant women at high risk for pre-term labour and delivery. Babies born to women with HF are at risk for prematurity, small-for-gestational-age status, infant respiratory distress syndrome, and foetal and neonatal death.[1,21]

Actions needed in order to minimize morbidity and possible mortality in pregnant HF patients are summarized in *Figure 2*. Management of HF and arrhythmias in peripartum women should be according to the underlying cardiac disease and following established guidelines.[1] Pre-pregnancy management must include modification of existing HF medications to avoid teratogenicity and minimize harm to the foetus. ACE-inhibitors, angiotensin receptor blockers, ARNI, mineralocorticoid receptor antagonists, ivabradine and sodium–glucose co-transporter 2 inhibitors are contraindicated during pregnancy as they are associated with a high risk of adverse foetal effects in all trimesters.[3,22] They should be stopped prior to conception, with close clinical and echocardiographic monitoring. If these drugs have been inadvertently taken during the first trimester, they should be stopped, and the patient monitored (maternal echocardiography and foetal ultrasound) closely. Beta-adrenergic blocking agents are generally safe in pregnancy but are associated with increased rates of foetal growth restriction. Loop and thiazide diuretics can be continued for the treatment of pulmonary congestion.

Sub-pulmonary ventricular failure (failure of the ventricle – right or left – which serves the pulmonary circulation) may also occur, especially in patients with pulmonary arterial hypertension. Bed rest and fluid balance with diuretics and inotropes could be used. In cases of pulmonary arterial hypertension, targeted therapy

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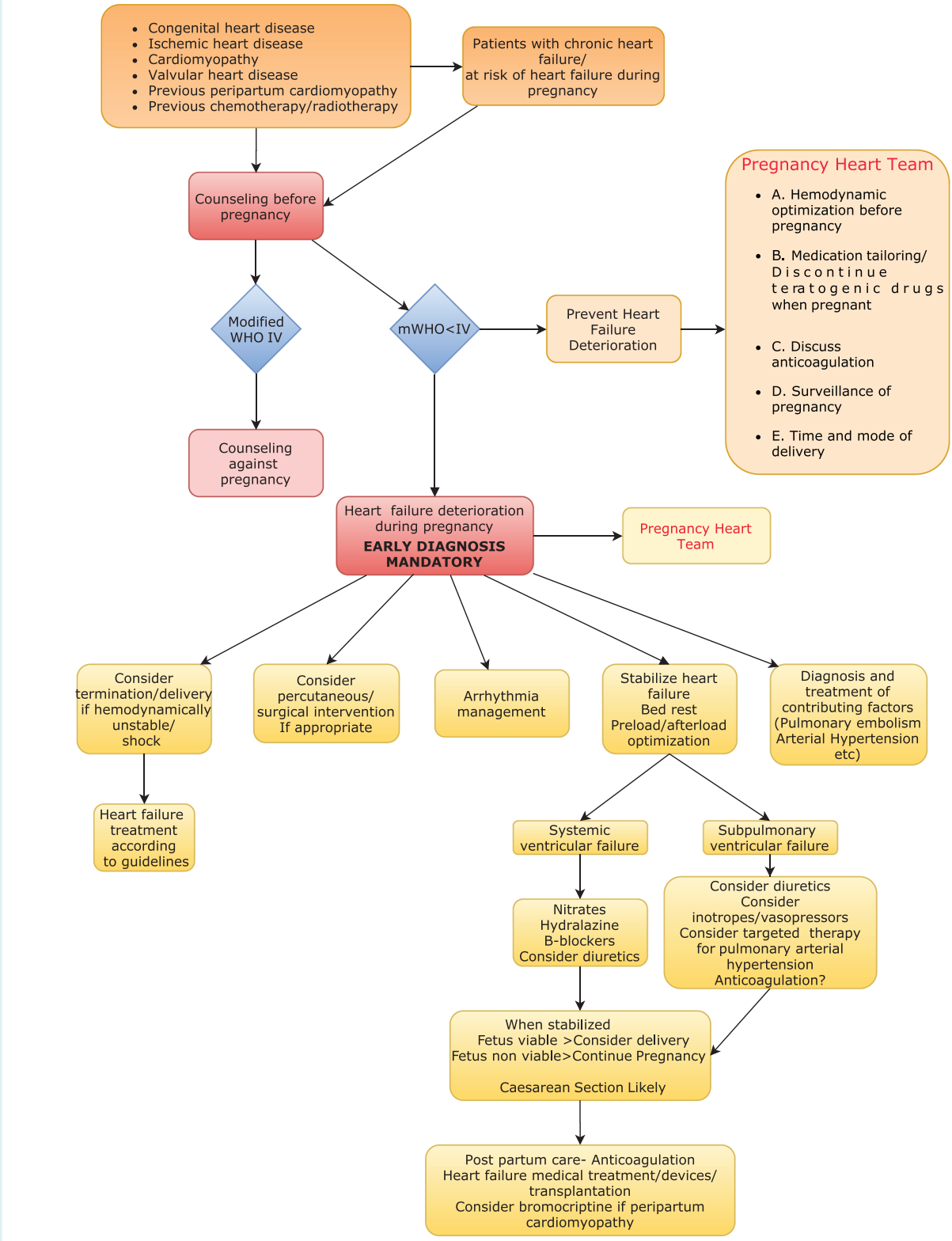


Figure 2 Management of congestive heart failure in pregnancy. WHO; World Health Organization.

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with phosphodiesterase-5 inhibitors or prostaglandins may be considered.[23–26]

Iron deficiency is common in heart failure, is often overlooked and has an independent adverse effect on cardiac function and for maternal health.[27–29] Also in pregnant women, iron deficiency (both with and without anaemia) is highly prevalent.[30,31] Iron deficiency reveals unfavourable consequences on the health status of the foetus and the mother.[31–33] Depleted iron compromises erythropoiesis, but also triggers thrombosis, coagulopathy and thromboembolic events, compromises energy metabolism in foetal and maternal tissues, impairing the functioning of myocardium and other types of muscles.[31–35] The effects of oral and intravenous iron supplementation in this particular patient population are under investigation.

Natriuretic peptides for screening and risk stratification to help ensure appropriate referral

Natriuretic peptide [B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP)], and mid-regional pro-atrial NP] concentrations are quantitative plasma biomarkers of the presence and severity of haemodynamic cardiac stress and HF.[36]

As the severity of HF is a strong predictor of the risk for cardiac complications in patients with cardiac disorders in general as well as in women during and after pregnancy in particular, quantifying the severity of HF using NP measurements may facilitate the detection of patients at high risk for cardiac complications and help appropriate referral.[37–39] During normal pregnancies in healthy women, NP concentrations remain in the normal range.[39,40] Pre-eclampsia and deterioration of cardiomyopathy/HF due to other causes will lead to an increase in NPs.[39–41] NP concentration should be checked in women diagnosed with a cardiomyopathy before pregnancy, monitored e.g. once every trimester and in case symptoms of possible deterioration such as dyspnoea occur.[39–41]

Exercise testing

Physiological exercise testing should be performed when pregnancy is planned in patients with known or previous HF but also in patients at risk for HF, e.g. with adult congenital heart disease (ACHD) or after previous chemo-/radiotherapy for malignant disease. Submaximal exercise testing (80% of predicted maximal heart rate) may also be performed in asymptomatic patients with suspected heart disease if already pregnant without increased risk of spontaneous miscarriage.

Delivery in a woman presenting with heart failure

The safe delivery of a woman presenting in HF is a challenge requiring the input of a multidisciplinary team to achieve the best outcome. In terms of timing the delivery, considerations include the gestational age at presentation, whether there is a reversible underlying reason for HF and, in its absence, the response to medical measures. Prophylactic and, in some circumstances such as persisting arrhythmia and intracardiac thrombosis, therapeutic anticoagulation should be given. Unless there is a reversible cause for HF, such as arrhythmia, anaemia or infection, then after optimization of therapy, delivery should be considered, ideally from 32 weeks, when foetal survival without major disability is expected, or earlier, including termination of pregnancy, when the response to medical therapy is suboptimal, the precipitating problem is irreversible and/or there is a significant risk to the life or long-term health of the woman of continuing the pregnancy.

Most often delivery will be by caesarean section, as advised by the ESC guidelines.[1] Only occasionally vaginal delivery may be possible; in either circumstance, meticulous attention to fluid balance is key, particularly in the context of post-partum haemorrhage.

If vaginal delivery is attempted, effective pain relief is essential and an instrumental delivery, without prior maternal effort, is likely to be the safest approach. Vaginal delivery is associated with less blood loss and lower risk of infection, venous thrombosis, and embolism, and should be advised for most women. For the third stage careful use of uterotonics, avoiding agents like ergometrine and carboprost and the early or even prophylactic use of mechanical approaches, including brace suture and balloon compression, for the management of post-partum haemorrhage are advised. Once delivery is achieved and after the immediate peripartum period, important consideration is effective contraception. Progesterone-based contraception methods have the advantage of not increasing the risk of thrombosis and are the most effective.[1]

Specific cardiomyopathies

There is a heterogeneous group of heart muscle diseases such as PPCM, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and LV non-compaction (LVNC) (*Graphical Abstract*) as well as others such as arrhythmogenic right ventricular cardiomyopathy (ARVC), Takotsubo syndrome (TTS), ACHD with HF.

Peripartum cardiomyopathy

Peripartum cardiomyopathy is HF that occurs towards the end of pregnancy or in the months following delivery.[42] Major geographical variations in incidence exist (1–100 in 10 000 live births),[42] compounded by the fact that patients are usually only diagnosed when they have severe symptoms[43] – raising the possibility that those with less severe presentation might go undiagnosed. A high index of suspicion is encouraged from midwives and obstetric teams. Investigations for possible PPCM should include an electrocardiogram and/or BNP (and echocardiography if either of these are abnormal). As there are no specific biomarkers for PPCM established to date, differentiation from other cardiomyopathies is not easily possible.[3] Recently, circulating plasminogen activator inhibitor-1 and miR-146a have been suggested as potential specific biomarkers for PPCM but are not used yet in clinical practice.[44]

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Peripartum cardiomyopathy is associated with a mortality rate of around 6% at 6 months, but has a high chance of myocardial recovery of around 50% reported up to 3 years after diagnosis.[43,45] A management plan should be formulated, taking into account the wellbeing of the mother and baby.[3] For those who are still pregnant, a delivery plan will involve obstetricians, paediatricians, cardiologists and cardiac surgeons (in case MCS is necessary). Medical therapy pre-delivery invariably involves decongestion with diuretics but should avoid drugs that are deleterious to the foetus (see *Table 3* in Bauersachs *et al.*[3]). If PPCM is diagnosed post-delivery there are several key aspects of management. Therapy should include drugs that are safe during lactation[3] or, if not breast-feeding, medical therapy should follow conventional guideline-directed HF therapy. Anticoagulation (HF and pregnancy are both pro-coagulant conditions, and the rate of thromboembolic events is relatively high)[45] and bromocriptine should be considered.[1,3,18,46] Implantable cardioverter-defibrillators and cardiac resynchronization therapy can have a role, but care should be taken to avoid implantation in women who are likely to recover on conventional medical therapy.[3] Prior to discharge, counselling should include advice about contraception and the risk of subsequent pregnancies.[47] When and whether to stop medical HF therapy when myocardial recovery is seen is uncertain.[48] The risk of subsequent pregnancies depends upon whether or not the woman has experienced myocardial recovery (usually defined as a LV ejection fraction >50%).[47] For those who have recovered, the rate of death is <1% and a risk of recurrent HF is around 10% but for those who have not recovered, the risk of death is around 10% and recurrent HF 25–50%.[47]

Hypertrophic cardiomyopathy

The observed incidence of HCM in pregnancy is <1:1000. Maternal mortality is low (0.5%) and complications or worsening of symptoms occur in 29% of cases.[1,49] Foetal mortality is comparable to the general population. However, the risk of premature birth is increased (26%). Risk is higher in women who are symptomatic before pregnancy or exhibit diastolic dysfunction, severe LV outflow tract obstruction or arrhythmia. Symptoms and medication before pregnancy are also risk factors for maternal cardiac events. Echocardiography is crucial for diagnosis.

Women with HCM should be risk stratified according to the ESC guidelines for cardiac disease in pregnancy according to the modified World Health Organization (WHO) class.[1] Women in WHO class II should be assessed during each trimester and those in class III assessed monthly or bi-monthly. A recent randomized study on the effectiveness of implanted cardiac rhythm recorders for detecting arrhythmias in pregnant women with structural heart disease suggests that those devices could be considered in HCM facilitating early detection of arrythmia or re-assurance of the mother and avoiding harm-full medication.[3,50] Beta-blockers should be continued if they are already being taken and foetal growth monitored. Beta-blockers should be started when new symptoms occur, for rate control in atrial fibrillation and to suppress ventricular arrhythmias, with verapamil as a second choice. Cardioversion should be considered for poorly tolerated persistent atrial fibrillation. Therapeutic anticoagulation is recommended for those with paroxysmal or persistent arrhythmias.

Low-risk cases may proceed with vaginal delivery. Caesarean section should be considered in patients with severe LV outflow tract obstruction, pre-term labour while on oral anticoagulation or severe HF. In the Registry Of Pregnancy And Cardiac disease (ROPAC), only 5% of patients required emergency caesarean section.[49] During delivery, heart rate and rhythm should be monitored in patients with a high risk of developing arrhythmias.

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy is a rare inheritable chronic and progressive cardiomyopathy. Its prevalence is 0.02–0.05%, but it is one of the leading causes of sudden cardiac death in young women.[51,52] For women not having a cardioverter-defibrillator implant before pregnancy,[53] ARVC severity score is highly predictive for the occurrence of ventricular arrhythmias, and echocardiographic and signal-averaged ECGs are markers of ventricular arrhythmias. Ventricular arrhythmia and disease progression in ARVC are worsened by vigorous exercise.[54] Pregnancy could be regarded as a state of prolonged haemodynamic stress and might affect disease progression in ARVC. However, in a recently published large population, pregnancy did not affect cardiac structure or function in ARVC, supporting previous reports of well-tolerated pregnancies in this patient group.[52] Given the exacerbation induced by exercise, then vaginal delivery with an epidural and assisted delivery is likely to be the safest approach.

Moreover, serious cardiac symptoms did not worsen during pregnancy, number of pregnancies was not associated with arrhythmic events, and higher number of pregnancies was not associated with worse outcome in women with ARVC. Thus, the long-term effect of pregnancy is well tolerated, and pregnancy appears relatively safe in women with ARVC.

Nevertheless, since data are still scarce, we suggest that these patients should be referred to an experienced centre for structured follow-up from early pregnancy until after delivery.

Left ventricular non-compaction cardiomyopathy

Left ventricular non-compaction is a rare congenital heart disease (CHD), which is characterized by hypertrabeculation of the myocardium with deep intertrabecular recesses, and a subset of patients develop LV dysfunction, with an increased risk of thromboembolic events. During normal pregnancy, there is a transient increase in LV trabeculation which occurs in one quarter of women. This makes diagnosis of LVNC during pregnancy challenging.[55] Pregnancy in LVNC is often complicated by HF and arrhythmias, but no mortality during pregnancy has been reported.[56] There is no specific treatment, but anticoagulation is recommended for patients with LVNC and a history of thromboembolic events, atrial fibrillation, intracardiac thrombi or impaired LV function.[57]

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Takotsubo syndrome

Takotsubo syndrome is an acute and usually reversible HF syndrome with initial presentation similar to acute coronary syndrome.[58] Often triggered by emotional stress and much more common in women than men, TTS is characterized by reversible LV dysfunction with extensive apical cardiac akinesia. Cardiac function recovers almost entirely within a few days/weeks if the patient survives the acute phase. Unfortunately, cardiac dysfunction can be sufficiently severe to cause life-threatening complications such as fulminant HF, cardiogenic shock, heart rupture and ventricular fibrillation. Many aspects of TTS are incompletely understood or characterized, and knowledge to guide optimal clinical management is limited. Treatment recommendations are based on expert opinion. It is advisable to seek expert support in TTS patients at high risk. Most of the reported TTS cases in pregnant women happened after childbirth with caesarean delivery, but TTS has also been reported in women during pregnancy. Similar to non-pregnant patients with TTS, recovery occurred between 4 days and 3 months.[59]

The European task force position statement suggests classifying TTS into lower-risk and higher-risk categories[58] and to consider ACE-inhibitor/ARNI and a beta-blocker in higher-risk groups. However, ACE-inhibitors/ARNI are contraindicated in pregnancy and evidence for beta-blockers is not established in TTS; these agents should not be used in pregnant women with TTS. In severe cases with life-threatening haemodynamic instability (lung oedema, cardiogenic shock), MCS should be considered early in the clinical course. Occasionally, thrombus formation may occur in the dyskinetic segment. Even though a visualized thrombus mandates anticoagulation, routine anticoagulation for dyskinesis without thrombus is not recommended, because of the rapid resolution of the condition.

Dilated cardiomyopathy

The term DCM encompasses acquired and inherited conditions characterized by LV dilatation and systolic dysfunction in the absence of significant abnormalities in loading conditions or coronary artery disease.[60] Causes include pathogenic gene variants in 20–35%, and/or acquired triggers including prior viral infection, immune-mediated and drug-induced LV dysfunction.[4] To date, >50 gene mutations have been described associated with DCM phenotype,[17,61] but the genetic contribution of 12 of them has recently been re-enforced.[5]

Although PPCM and DCM are considered distinct disease entities, with differentiation largely supported by the timing of presentation, they may share a genetic predisposition.[62,63] When the patient presents during the course of pregnancy, differentiation may be challenging.[4,64]

Patients with pre-existing DCM receiving current disease-modifying treatment may show substantial/complete recovery of LV systolic function.[62] However, pregnancy is poorly tolerated in women with DCM, carrying with it the potential for significant deterioration in LV function (depending on the residual severity of LV dysfunction).[19,65] Predictors of maternal mortality include the degree of symptoms (approximately 7% for New York Heart Association class III or IV) and ejection fraction <40%.[19,66] Significant risk factors include ejection fraction <20%, mitral regurgitation, right ventricular failure, atrial fibrillation and/or hypotension. All patients with DCM who are pregnant therefore require appropriate joint cardiac and obstetric care, since there is a high risk of overt HF, irreversible deterioration in ventricular function and foetal loss, as well as maternal mortality.

Standard indications for anticoagulation in DCM apply during pregnancy, including the presence of intracardiac thrombus and paroxysmal/persistent atrial fibrillation. The choice of the anticoagulant agent (low molecular weight heparin or vitamin K antagonists) will depend upon the stage of pregnancy and patient preference.[67] Non-vitamin K antagonist oral anticoagulants are not recommended for use in pregnancy.

When a new diagnosis of DCM is made, there are potential implications not just for the patient, but also for other blood relatives potentially requiring clinical screening of family members and referral to experts in cardiovascular genetics.[62]

Cardiac transplantation

Female patients represent around 20% of overall cardiac transplants, with around 25% of these of childbearing age.[68] There are risks to the transplanted mother and foetus, but also to a foetus whose father is a cardiac transplant recipient.[69] Multidisciplinary care is mandatory, preferably coordinated by the transplant centre.[70] Successful conception (including *in vitro* fertilization) and delivery have been reported in patients with cardiac transplantation and also in patients with long-term ventricular assist devices but data are scarce and of low quality.

Pre-conception counselling includes the risks to the mother and the foetus including graft rejection, graft dysfunction, infection, and teratogenicity of immunosuppressive agents. Some centres recommend paternal HLA testing prior to conception, as if the donated heart and father have the same HLA antigen, and the recipient develops donor-specific antibodies, the risk of autograft rejection is high.[71] The reason for the indication for transplantation should also be considered in pre-conception counselling; children of mothers with pre-transplant CHD have up to 10% risk of congenital disease in the foetus.[72,73] Here, early foetal screening is indicated. Female transplant patients should be advised to avoid pregnancy for at least 1 year post-transplantation, that their risk of spontaneous abortion is around 10–20%, and that they will undergo more intense surveillance of graft function during and after any pregnancy. Successful pregnancy is most likely where there is normal graft function and no evidence of rejection. If clinically indicated, standard investigations, up to and including endomyocardial biopsy, should be undertaken prior to pregnancy. In those at high risk of rejection and/or with poor baseline graft function before pregnancy, it should be strongly discouraged/delayed until these risks can be reduced. All medications (including immunosuppression) should be reviewed prior to conception, with cessation/substitution of teratogenic drugs, and close monitoring of drug levels (where their metabolism can be altered by pregnancy, e.g. cyclosporine).

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Hypertension is the commonest maternal complication during pregnancy and may result in foetal growth restriction and pre-term delivery.[74] Hyperemesis gravidarum may result in poor/partial absorption of immunosuppressive medication and requires careful monitoring. Venous and pulmonary thromboembolic disease is more common in cardiac transplant recipients,[75] and clinical suspicion should remain high. All immunosuppressive medications enter the foetal circulation, thus the management of immunosuppression in the pregnant post-transplant recipient should be conducted by the experts. As all immunosuppressive agents are excreted into breast milk with unknown long-term effects, breastfeeding is not recommended.

Pregnancy, cancer and heart failure

Cardiovascular risk during pregnancy in female cancer survivors

There is a growing population of female cancer survivors of child-bearing age following treatment and cure of a malignancy as a child or young adult. Curative treatment pathways frequently include cardiotoxic therapies, including anthracycline (AC) chemotherapy (~60% of all paediatric malignancies) and/or radiation to the chest.[76] There is a sixfold increased risk of HF at long-term follow-up in paediatric cancer survivors who were treated with AC chemotherapy.[77] The risk is dose-related for both AC and radiation therapy, and lifelong cardiomyopathy surveillance in cancer survivors is recommended.[78]

Risk of pregnancy-related cardiovascular complications, predominantly HF, increases after cardiotoxic cancer therapies. In a large retrospective study[79] with 847 female cancer survivors completing 1554 pregnancies, 43 women presented with cardiomyopathy, the majority either prior to pregnancy or 5+ months post-pregnancy. Only three women (0.3%) developed a new pregnancy-associated cardiomyopathy. The total cumulative AC dose was higher in women presenting with cardiomyopathy compared to the cohort who did not develop HF. Of 58 female cancer survivors with pregnancy,[80] 17 (27.6%) developed new LV dysfunction (ejection fraction <50% on two successive echocardiograms), compared to 15% in a control female cancer survivor group without pregnancy. Risk factors included high total cumulative AC dose, and younger age at treatment. In a recent smaller cohort of female cancer survivors,[8] four women developed overt HF during their pregnancy (5%), and all four had history of pre-existing cardiomyopathy. Thus, the incidence of pregnancy-induced HF was 31% (4/13) vs. 0% (0/65) in women with vs. without pre-existing cardiomyopathy.[8]

In summary, the absolute risk of pregnancy-induced HF in female cancer survivors is low, but in female cancer survivors who received AC chemotherapy or chest radiation the risk is higher than in healthy untreated female populations. Risk factors for pregnancy-induced HF in female cancer survivors are summarized in *Table 1*. The main risk factor is pre-existing LV dysfunction prior to pregnancy.

We recommend that all female cancer survivors who received AC or chest radiation are counselled about the potential cardiovascular risks associated with pregnancy and are advised to have a cardiology review including resting ECG, echocardiography, NP measurements and risk assessment prior to all planned pregnancies. Establishing NP levels either before pregnancy or early in pregnancy and following the levels during pregnancy can help diagnose early haemodynamic deterioration. We recommend all female cancer survivors who received AC or chest radiation should be reviewed by a pregnancy heart team with clinical history, examination, NP measurement and echocardiography to assess LV function at the end of the trimester (12–14 weeks) and a personalized surveillance plan developed to monitor cardiovascular health during their pregnancy. The frequency of further assessments with NP measurement and echocardiography depend upon the presence and severity of abnormalities detected, and monitoring using the ESC guidelines for the management of cardiovascular diseases in pregnancy is recommended.[1] Female cancer survivors identified as high risk of pregnancy-induced cardiovascular complications should have their obstetric care delivered by a pregnancy heart team.[1]

Cardiovascular risk in women receiving chemotherapy during pregnancy

Women without known HF requiring AC chemotherapy during pregnancy often are at higher risk and cardiac monitoring is recommended, with delivery involving the pregnancy heart team. There is a small population of women who present with a new malignancy during pregnancy which requires treatment with potentially cardiotoxic cancer therapies. This includes pregnancy-associated breast cancer (2% of all breast cancer cases) and Hodgkin's lymphoma where AC chemotherapy is indicated. There are no studies on the rate of cardiovascular complications in this patient cohort, but the consensus and experience of the co-authors is that these women requiring AC chemotherapy during pregnancy are at higher risk and cardiac monitoring is recommended and delivered by the pregnancy heart team in collaboration with a cardio-oncology team with appropriate risk assessment before starting chemotherapy.[14] Finally, the constant flux of new antineoplastic agents, such as immune checkpoint inhibitors, with new cardiac side-effects that may occur unexpectedly, requires an infrastructure allowing fast and intense interaction between cardiologists, oncologists and gynaecologists.

Adult congenital heart disease and pregnancy

In the large prospective ROPAC registry, ACHD is the most prevalent diagnosis (58%).[81] Women with ACHD have a relatively favourable pregnancy outcome, with a mortality rate of 0.2%. However, due to the heterogeneity of this group, the type and complexity of CHD needs to be considered. Indeed, the HF rate was 7% for the total group and, in patients with complex CHD this was 13%, while it was 5% and 6% for the simple and moderate

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Table 1 Risk factors for pregnancy-induced heart failure in female cancer survivors

Left ventricular dysfunction (LVEF <50%) pre-pregnancy (higher risk if LVEF <40% pre-pregnancy)
Previous AC chemotherapy (higher risk in women who received a total cumulative doxorubicin dose ≥250 mg/m^2 or equivalent)
Previous chest radiation therapy (higher risk if total cumulative chest radiation dose ≥35 Gy)
Cancer diagnosis and treatment at young age (<10 years)
Time from cancer treatment to pregnancy >15 years
Recommendations for the management of pregnancy in female cancer survivors
All female cancer survivors who received AC or chest radiation should be counselled about the potential cardiovascular risks associated with pregnancy
All female cancer survivors who received AC or chest radiation are recommended to have a cardiology review including resting echocardiography and risk assessment prior to all planned pregnancies
All female cancer survivors who received AC or chest radiation should be reviewed with clinical history, examination and echocardiography to assess left ventricular function at the end of the trimester of all pregnancies
All female cancer survivors who received AC or chest radiation should have personalized surveillance plan developed to monitor cardiovascular health during their pregnancy
All female cancer survivors who received AC or chest radiation are recommended to have their obstetric care delivered by a multidisciplinary team including an obstetrician and a cardiologist
All female cancer survivors who are at high risk of pregnancy-induced cardiovascular complications should have their obstetric care delivered by a multidisciplinary team specialized in the care of high-risk pregnancies: the pregnancy heart team
Baseline cardiac assessment pre-chemotherapy and cardiac monitoring during chemotherapy is recommended for all women requiring AC chemotherapy during pregnancy
All women requiring AC chemotherapy during pregnancy should have their obstetric care delivered by a multidisciplinary team specialized in the care of high-risk pregnancies: the pregnancy heart team

AC, anthracycline; LVEF, left ventricular ejection fraction.

defects, respectively. The vast majority of these patients had their condition treated at a very young age, creating ample opportunities for pre-pregnancy counselling and the optimization of cardiac status prior to pregnancy, perhaps accounting for the relatively good outcomes.[19] Maternal mortality complicates pregnancy in 0.1% of women with corrected CHD and in 0.7% with uncorrected CHD.[19,81] HF occurs in about 5% of women with corrected CHD, and 8% of women with uncorrected CHD, of whom 3% are solely post-partum. Signs of HF before pregnancy, pulmonary hypertension and medication use before pregnancy were found to be predictors for mortality or HF.[82] Cyanosis is a risk factor for maternal cardiovascular events and associated with a high risk of miscarriage. Women with a Fontan circulation are also at high risk and need counselling. Although, in general, patients with regurgitant lesions often tolerate pregnancy well, severe valve regurgitation both left- or right-sided, can cause HF. Left heart obstruction can also cause HF, and mitral stenosis is especially not well tolerated.[83]

Concerning the timing of the event of HF, in the ROPAC registry there was a peak around the end of the second trimester (typically women with a shunt lesion) and the second shortly after delivery (women with diminished LV ejection fraction).[84]

Treatment of HF is essentially the same as outside pregnancy but avoiding embryo/fetotoxic drugs. In patients with a systemic right ventricle (transposition of the great arteries operated with a Senning/Mustard procedure or congenitally corrected transposition of the great arteries patients), there is no evidence that medication such as ACE-inhibitors are effective. Finally, early delivery is advised when HF cannot be stabilized with bedrest and medication.

Diagnostics

Patients with an unexpected phenotype of a cardiomyopathy before and after pregnancy need further certification. According to current recommendations, this is usually based on cardiac magnetic resonance imaging.[2] In cases of uncertainty and to evaluate differential diagnosis with potential therapeutic consequences an endomyocardial biopsy can be helpful. Such a scenario could be in the difficult setting of suspected post-partum cardiomyopathies in patients who do not recover adequately over time.

Medication during pregnancy and breastfeeding

The recently published position paper on PPCM[3] summarizes in *Table 3* the safety or potential detrimental effects of common HF medications during pregnancy and lactation. Breastfeeding is tolerated by many women with mild HF and many drugs for HF are not contraindicated in breastfeeding mothers and may be used with caution.

Pregnancy induces significant changes in maternal physiology that interfere with pharmacokinetic and pharmacodynamic actions of the drugs (*Table 2*). A greater fluctuation in the unbound drug concentration occurring during the dosing interval may potentiate the pharmacodynamic effects at peak or reduce therapeutic effect at trough. This is of relevance for cardiovascular drugs with direct effect on physiological parameters (heart rate, blood pressure, etc.). Therefore, during pregnancy it is recommended to employ a more frequent dosing with an adjustment according to the

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Table 2 Factors affecting pharmacokinetics in pregnancy

Cardiovascular system, lungs and blood
• Increases in plasma volume, cardiac output, stroke volume, and heart rate
• Decreases in serum albumin concentration and serum colloid osmotic pressure
• Increases in coagulation factors and fibrinogen
• Compression of the inferior vena cava by the uterus
• Increase in tidal volume and minute ventilation
Liver, stomach, and intestines
• Changes in oxidative liver enzymes, such as increased activity of cytochrome P450 enzymes (e.g. CYP2D6 and CYP3A4)
• Nausea and vomiting
• Delayed gastric emptying
• Prolonged small bowel transit time
• Gastrointestinal reflux
Kidneys
• Increase in renal blood flow and glomerular filtration rate

observed pharmacodynamic effect on the mother and the foetus (i.e. heart rate, blood pressure, international normalized ratio, activated partial thromboplastin time, etc.).[1]

Conclusion

Risk stratification and management of pregnancy and the post-partum period for women with a diagnosis of structural heart disease and a history of HF is complex and requires the input of a multidisciplinary team. Women with a history of chemo-/radiotherapy for cancer or haematological malignancies need specific pre-pregnancy assessment and counselling.

Women with a known diagnosis of a cardiomyopathy will often require continuation of drug therapy, which has the potential to exert adverse effects on the foetus. This position paper provides guidance in balancing benefits and detrimental effects for the mother and the child.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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