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POSITION PAPER

Multidisciplinary care of peripartum heart failure: A scientific statement of the Heart Failure Association of the ESC

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Heart failure is the most common cardiovascular complication during pregnancy and the postpartum period. It is associated with increased risk of maternal morbidity and mortality as well as potentially life-threatening foetal pathology. Management of heart failure in pregnancy requires expert knowledge of cardiovascular disease as well as obstetrics which underscores the importance of multidisciplinary cardio-obstetrics teams in order to optimize diagnosis, treatment and outcome. This includes counselling of women at risk before and during the course of pregnancy in order to strengthen the relationship between medical specialists and patients, as well as to allow patient-centred delivery of care and improve quality of life.

Keywords Heart failure • Pregnancy • Peripartum • Multidisciplinary approach • Counselling

Introduction

Recent data from the World Health Organization (WHO) demonstrate that maternal mortality ranges from around 12 per 100 000 live births (0.01%) in high-income countries to about 300 per 100 000 live births (0.2%) in low-to-middle income countries, with large disparities both between and within countries.[1] Importantly, risk extends beyond delivery and the immediate peripartum period since there are more postpartum (up to 42 days) and late maternal deaths (up to 1 year) from direct and indirect obstetric causes than maternal deaths during pregnancy.[2] The largest contributors to late maternal deaths are cardiovascular disease (CVD) and thromboembolism[3] and although maternal deaths due to haemorrhage and infection are decreasing on a global scale, those related to heart disease are increasing. Heart failure (HF) and arrhythmias are the most frequent cardiovascular conditions that complicate pregnancy. Maternal heart disease complicates between 1% and 4% of pregnancies and accounts for up to 15% of maternal deaths

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globally.[4] In high-income countries, it is the most important cause of maternal mortality.[4] Maternal heart disease increases the risk of hypertensive pregnancy disorders, a further frequent cause of maternal mortality, morbidity, and perinatal complications.[5] The combined occurrence of maternal heart disease and hypertensive pregnancy disorders is associated with a particularly high risk.[6] A driver of increasing maternal and fetal pregnancy risk in western societies is the substantially increasing age of women at first pregnancy,[7] with particularly high risks for women aged 40 and older.[8,9]

A significant proportion of maternal cardiovascular complications, including HF,[10] are preventable.[11] Therefore, the scope of this paper is as follows: (i) insights from models of pregnancy-related heart disease; (ii) risk factors for HF during pregnancy and identification of women at risk; (iii) usefulness of biomarkers in pregnancy; and (iv) management of pregnant women with HF (including pre-pregnancy counselling and psychological support).

Insights from models of pregnancy-related heart disease

Pre-clinical studies in experimental models are crucial to understand the pathophysiology of pregnancy-related HF and other cardiovascular complications. They are particularly important since clinical studies in pregnant women are challenging to conduct. Given the central role of the placenta in the pathophysiology of pregnancy-related cardiovascular complications, all animal models must therefore be in placental mammals. To date, such models mainly encompass pre-eclampsia and peripartum cardiomyopathy (PPCM) and are usually surgical, genetic, or pharmacological in nature. However, models of pregnancy-associated vascular aneurysms and dissection, thromboembolism and cardiac arrhythmia have also been described.[12]

Pre-eclampsia models

Rodent models like reduced uterine perfusion pressure (RUPP), induced by uteroplacental ischaemia, offer insights into pre-eclampsia pathogenesis.[13] However, ischaemia models have the limitation that characteristics of severe disease manifestations such as haemolysis, elevated liver enzymes, low platelet (HELPP) syndrome, eclampsia and abruption are not present. Anti-angiogenic response models, involving overexpression of soluble fms-like tyrosine kinase 1, mimic severe pre-eclampsia and aid in testing potential therapies (NCT02923206).[14–16] Genetic mouse models of pre-eclampsia (e.g. BPH/5, CBA/JxDBA/2, RGS2 knockout) have been established and pharmacological models (e.g. L-NAME) explore various aspects, including immune responses.[12,17,18]

Peripartum cardiomyopathy models

Diverse animal models exist for PPCM, reflecting its multifaceted origins.[12] Notable models, Myh6-Cre;Stat3lox/lox and Myh6-Cre;Ppargc1alox/lox mice, align with the vascular and hormonal nature of PPCM.[19] These models illustrate the involvement of transcription factors like activator of transcription 3 and peroxisome proliferator-activated receptor-gamma coactivator 1-alpha in disease progression.[20] However, a limitation is that these models do not fully replicate the recovery observed in women with PPCM.

Overall, these animal models provide valuable insights into the complexities of pregnancy-related cardiovascular complications, facilitating a deeper understanding of their pathophysiology.

Risk factors for heart failure during pregnancy and identification of women at risk

Risk assessment and risk scores

Risk assessment and thorough counselling about pregnancy, associated risks, options to reduce the risk before a planned pregnancy (e.g. elective treatment of valvular heart disease or aortic disease), and personal opinions regarding potential termination of a pregnancy should be performed in all women with heart disease, preferably before any pregnancy. This includes a review of medication with potential revision to ensure fetal safety.

Several risk scores are available to estimate cardiovascular risk in pregnant women. Several, such as the CARPREG II and the ZAHARA risk scores have been developed based on large populations. However, they consequently are population-specific and fail to account for some risk factors such as pulmonary hypertension or aortic dilatation, which had low prevalence in the populations used to develop the scores.[21] Currently, the most widely used and accepted system for risk prediction is the modified WHO classification, which assigns women who are pregnant or who plan to become pregnant to one of four risk WHO classes I to IV (*Table 1*).[4,22] WHO I represents a hardly increased risk of complications, while conditions that lead to WHO class IV are regarded as contraindications for pregnancy. However, it needs to be emphasized that not all risk factors are covered by the existing risk scores and that risk needs to be considered on a very individual basis. The subsequent sections discuss several specific risk factors and conditions which are associated with cardiovascular risk in pregnancy.

Diabetes mellitus

One of the most common pre-existing disorders in pregnancy, with a prevalence of 1.3% among all pregnancies, is diabetes mellitus. It is either characterized by insulin resistance (type 2) or autoimmune destruction of the pancreatic β-cells (type 1). With increasing prevalence of obesity, the rates of type 2 diabetes mellitus are increasing among women of a fertile age.[23] As a result, pre-gestational diabetes, which is associated with adverse outcomes, has become more common. Specific maternal risks of pre-gestational diabetes include pre-term delivery, gestational hypertension, pre-eclampsia and delivery by Cesarean section. Foetal risks include higher rates of mortality, stillbirth, shoulder dystocia, macrosomia, small for gestational age, neonatal

Table 1 Classification of pregnancy risk in patients with cardiovascular disease[4,22]

Severity of risk	Maternal risk
Low risk	
Mild pulmonary stenosis	Morbidity: little to no increased risk
Small PDA	Mortality: no increased risk
Mitral valve prolapse with mild mitral regurgitation	
Repaired simple lesions: ASD, VSD, PDA, anomalous pulmonary venous drainage	
Moderate risk	
Uncorrected ASD or VSD	Morbidity: moderately increased risk
Repaired tetralogy of Fallot	Mortality: mildly increased risk
Marfan syndrome with aorta <40 mm	Risk varies based on individual patient
Bicuspid aortic valve with aorta <45 mm	Morbidity: moderately to severely increased risk
Repaired aortic coarctation	Mortality: intermediate increased risk
Mild-moderate MR, TR, AR, MS, AS	
Valvular heart disease with previous IE	
Mild LV impairment (EF >45%)	
Severe risk	
Mechanical valve	Morbidity: severely increased risk
Fontan circulation	Mortality: significantly increased risk
Unrepaired tetralogy of Fallot	
Marfan syndrome with aorta 40–45 mm	
Bicuspid aortic valve with aorta 45–50 mm	
Unrepaired cyanotic heart disease	
Moderate LV impairment (EF 30–45%)	
Previous PPCM without any residual left ventricular impairment	
Systemic RV with good or mildly decreased ventricular function	
Very severe risk-Pregnancy contraindicated	
Severe MS	
Severe symptomatic AS	
Uncorrected severe aortic coarctation	
Marfan syndrome with aorta >45 mm	
Bicuspid aortic valve with aorta >50 mm	
Severe systemic ventricular dysfunction (EF <30% or NYHA class III–IV)	
Previous PPCM with any residual LV impairment	

AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; EF, ejection fraction; IE, infective endocarditis; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; PDA, patents ductus arteriosus; PPCM, peripartum cardiomyopathy; RV, right ventricular; TR, tricuspid regurgitation; VSD, ventricular septal defect.

hypoglycaemia and low Apgar score. In women with type 1 diabetes, retinopathy and nephropathy can worsen during pregnancy. Multidisciplinary care is therefore required to minimize these complications.[24] Importantly, observational studies have linked gestational diabetes to an increased incidence of PPCM (by a factor of 1.8) as well as long-term risk of HF following pregnancy.[25,26]

Hypertension

Chronic hypertension is common and estimated to be present in about 3–5% of pregnancies,[27] especially because of the widespread prevalence of two contributing major risk factors, namely obesity and advanced maternal age. The vast majority of women with chronic hypertension do well during pregnancy. Nevertheless, complications, such as superimposed pre-eclampsia, pre-term birth, foetal growth restriction and placental abruption have a higher incidence than in women without hypertension.[28] Also, according to a recent analysis of more than 25 million singleton deliveries of which 2% had chronic hypertension, hypertension was associated with a five-fold increased risk of readmission for CVD in the first year after delivery (0.6% vs. 0.1%) even when the course of pregnancy was uneventful.[29] Thus, pre-pregnancy counselling should be an important part of family planning, and appropriate measures and medications to control hypertension before and during pregnancy may mitigate associated risks.[30]

Obesity

Obesity is an important factor related to pregnancy-associated complications. This is particularly relevant given the epidemic scale of obesity in industrialized nations as well as in developing countries.[31,32] Obesity is associated not only with maternal mortality, but also with increase of the risk for pre-natal mortality as well as offspring mortality in children of obese mothers,[33] which persists

even after adjustment for maternal age at delivery, socioeconomic status and other factors. Furthermore, maternal obesity harbours increased risk of neonatal injuries and hypoglycaemia.[34] In obese mothers, the risk of developing metabolic syndrome, type 2 diabetes and CVD is elevated in later life.[33,35] A recent study found the risk for PPCM increased by a factor of 1.32 in pregnant women who were overweight and by a factor of 2.03 in women with obesity as compared to women with a body mass index <25 kg/m^2.[36] Given the elevated short- and long-term risks for both mother and child, pre-pregnancy counseling, multidisciplinary monitoring during pregnancy and a heightened vigilance to identify early signs of HF are essential in women who are overweight and particularly in those with obesity.[37]

Anaemia and iron deficiency

Although it is well known that iron deficiency (ID) and anaemia are highly prevalent among women of fertile age and in pregnancy, both remain global public health issues,[38] and many women go through the entire pregnancy without achieving the minimum required iron intake. The main reasons for ID and worsening anaemia during pregnancy are pre-existing deficiencies in iron storage and the increased iron needs during pregnancy, especially in the second and third trimesters as well is iron loss during delivery.[39] Although ID and anaemia have a negative effect on maternal and foetal well-being throughout the entire pregnancy, pre-existing ID and anaemia have more pronounced effects on foetal growth than deficiencies developed later in pregnancy.[40] Foetal risks associated with maternal ID and anaemia include intrauterine growth retardation, prematurity and low birth weight, all with significant mortality risks, particularly in the developing world.[40] Risks to the mother include perinatal infection, pre-eclampsia and bleeding, post-partum cognitive impairment and behavioural difficulties.[41] While anaemia has been associated with an increased incidence of PPCM (reported odds ratios as high as 5 in women with haemoglobin <11 g/day), the influence of ID on the risk of PPCM and HF in the mother remains to be established.[42]

Pre-existing heart failure and recovered peripartum cardiomyopathy

Patients with HF and cardiomyopathies constitute a highly diverse group. Among younger women, congenital heart disease may lead to HF.[43] Many women with cardiomyopathies may remain without significant problems throughout pregnancy (e.g. those with asymptomatic hypertrophic cardiomyopathy). However, some conditions are associated with greater risks of maternal or foetal complications. A moderately increased risk (modified WHO class II) may for example be present in patients with HF and a left ventricular ejection fraction (LVEF) >45% and pregnancy may usually be managed very well in experienced centres. However, there are groups of women with markedly elevated risk during pregnancy (for detailed overview see ESC Textbook Heart Failure; Bauersachs, Hilfiker-Kleiner, Sliwa, Chapter Pregnancy and Heart Failure). This includes patients with HF with reduced ejection fraction and an ejection fraction between 30% and 45%, women with previous PPCM but no residual left ventricular dysfunction, and patients with congenital heart disease and a systemic right ventricle with normal or mildly decreased systolic function. These women – classified as modified WHO class III (*Table 1*) – require expert pre-pregnancy counselling and close follow-up during pregnancy by a pregnancy heart team.

Patients with a prohibitively high risk of maternal mortality or severe morbidity (classified as modified WHO class IV), in whom pregnancy should be avoided, include patients with HF and an LVEF <30%, New York Heart Association (NYHA) class III–IV, previous PPCM without complete restoration of left ventricular systolic function (i.e. ejection fraction >50–55% after tapering of HF drugs), and patients with systemic right ventricles and moderately or severely decreased ventricular function.[22]

In patients on treatment for HF, any medication contraindicated during pregnancy should be adjusted during pre-pregnancy counselling in order to avoid foetal harm. Standard HF drugs that must be tapered and stopped prior to conception include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor–neprilysin inhibitors, mineralocorticoid receptor antagonists, ivabradine and sodium–glucose cotransporter 2 inhibitors. During that phase, patients must be followed closely with repeated clinical and echocardiographic monitoring. If LVEF drops significantly during tapering of HF drugs, counselling would suggest to avoid pregnancy in most cases.[22] Beta-blockers, especially beta$_1$-selective blockers, may be continued during pregnancy and therefore do not need to be stopped.

Specific counselling is required for patients with previous PPCM.[44,45] All patients should remain on combined HF medication until at least 12–24 months after full recovery of left ventrcular function (LVEF >50–55%). Women with persistent ejection fraction <50% have a high risk of PPCM relapse and death and should be strongly advised against another pregnancy. In women with ejection fraction >50% during long-term medical treatment who want to become pregnant again, drug therapy can be tapered after informed decision-making and under close monitoring as described above. If ejection fraction remains stable (>50%) 6 months after discontinuation of all HF drugs contraindicated during pregnancy, contraception may be stopped. Even wen ejection fraction remains normal, any subsequent pregnancy after PPCM is associated with a substantial risk. Hence, affected women need to be followed by an experienced team throughout pregnancy and thereafter.

Valvular heart disease in pregnancy

Cardiac output increases 30–50% and reaches a maximum of 50% between the second and third trimester,[46,47] driven by an increase in stroke volume in the first half, and by an increase in heart rate in the second half of pregnancy. Systemic vascular resistance and blood pressure fall in the first and second trimester due to placental maturation. During labour and delivery there is an increase in oxygen consumption and rapid increase in blood volume due to auto transfusion from the uterus and placenta, and relief of pressure on inferior vena cava. Together, these changes may be responsible for the clinical manifestation of different valvular diseases in pregnancy.

Severe left-sided stenotic valvular lesions are most likely to worsen during pregnancy (*Table 1*). Moderate-to-severe mitral stenosis with a valve area of <1.5 cm^2 is prone to decompensation as left atrial pressure rises due to increased cardiac output, heart rate and onset of atrial fibrillation in many cases.[48,49] While women with no or minor symptoms can be managed medically with diuretics, beta-blockers and anticoagulants when needed, women with severe symptoms require percutaneous mitral balloon valvotomy, which should preferably be done in the second trimester to avoid radiation to the foetus.[50,51] In some experienced centres, percutaneous mitral balloon valvotomy has been performed only under echocardiography guidance.[52] Surgical mitral valve replacement is generally accompanied by high foetal mortality.

The risk of maternal mortality and, consequently, the need for intervention in women with aortic stenosis is relatively low. In some instances, percutaneous aortic balloon valvotomy may be required, if feasible, as a last resort. Transcatheter aortic valve replacement has been successfully carried out in some cases of critical aortic stenosis combined with aortic regurgitation.[53]

In general, mitral, tricuspid and pulmonary regurgitation are well tolerated during pregnancy and rarely require intervention. Mild to moderate pulmonary stenosis is well tolerated during pregnancy. However, some women with severe pulmonary stenosis leading to right HF may require balloon valvuloplasty.

In the reproductive age group, surveillance and counselling for valvular heart disease should start prior to pregnancy and ought to continue postpartum, when there can be a surge of circulating volume commensurate with uterine contraction.

Anticoagulation for mechanical heart valves poses challenges during pregnancy.[22,54] Although randomized studies are lacking, current evidence suggests that vitamin K antagonists (VKAs) with a closely monitored international normalized ratio are the safest option to prevent valve thrombosis throughout pregnancy. Continuous VKA use is recommended until 36 weeks of gestation, particularly with low-dose requirements (warfarin <5 mg/day, phenprocoumon <3 mg/day, or acenocoumarol <2 mg/day), due to minimal risks of embryopathy, foetopathy (<2%), and fetal loss (<20%), coupled with VKAs being the most effective in preventing valve thrombosis.[54,55]

In cases requiring higher VKA doses, discontinuation between weeks 6 and 12, along with replacement using adjusted-dose intravenous unfractionated heparin or low molecular wight heparin twice daily with dose adjustments based on peak anti-factor Xa levels, is a consideration. The use of low molecular wight heparins remains debatable due to an elevated risk of valve thrombosis, which can be mitigated with stringent control of anti-factor Xa levels.[54,55] Individualized discussions with the patient are crucial, especially concerning VKA dosage, pregnancy stage (with special consideration for the first trimester), patient compliance, and the type of prosthesis.

Pulmonary arterial hypertension and pregnancy

Pulmonary arterial hypertension (PAH) is a disorder of the pulmonary vascular tree and can be a manifestation of several different disease processes, ultimately resulting in right HF and death.

Despite the advancements made in understanding the disease pathophysiology and availability of more drugs, the morbidity and mortality associated with PAH remain high. Owing to the limited cardiac reserve in these patients, any form of haemodynamic fluctuation is very poorly tolerated. Pregnancy and labour are associated with several physiologic alterations that place a very high burden on the already compromised cardiovascular reserve. Therefore, regardless of the reason, PAH is associated with very high pregnancy risks and high mortality due to pulmonary hypertensive crisis, pulmonary thrombosis and right HF requiring lung transplantation in up to almost 33% of women.[56] Besides, affected patients are also at risk of complications such as pre-eclampsia, pre-term delivery and sudden foetal mortality. Therefore, guidelines recommended to avoid pregnancy, or to discuss termination if pregnancy occurs.[4,22,43] In cases of pregnancy continuation, management should be delivered by a multidisciplinary team (*Figure 1*), in an expert centre for pregnancy and cardiac disease. Of note, endothelin receptor antagonists are teratogenic and should be avoided in treatment of affected patients. Phosphodiesterase type 5 inhibitors and prostacyclins may be used with careful monitoring. Delivery is generally planned before 37 weeks and the labour is curtailed by assisted second stage. General anaesthesia is one of the risk factors for maternal death, thus epidural anaesthesia is preferred.[57] Vaginal delivery is also possible in women who are stable, but a caesarean section may also be done. The patients need to be treated in an intensive care unit setting for the initial postpartum period as the risk of complications during this period is particularly high.

Biomarkers in pregnancy

Heart failure in pregnancy is especially difficult to diagnose and manage. Natriuretic peptides (NPs), both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), may be used as diagnostic tools in pregnant women to diagnose cardiac complications, including HF and pre-eclampsia. Tanous *et al.*[58] showed that a BNP level of ≤100 pg/ml had a 100% negative predictive value for identifying cardiac events during pregnancy. A recent systematic meta-analysis, which included 13 studies, found a negative predictive value of 91% for BNP ≤100 ng/L and of 97% for NT-proBNP ≤272 pg/ml for predicting cardiac complications in pregnant women.[58] Furthermore, high-sensitivity BNP (98%) makes it a good diagnostic method for screening purposes.[59]

In PPCM, elevated NP concentrations also have an important prognostic role and are increasingly used in follow-up. Hoevelmann *et al.*[60] demonstrated that an NT-proBNP cut-off point of ≥900 pg/ml at diagnosis was useful in the risk stratification of patients with PPCM and may be used to implement more intensive treatment strategies. Recent experimental observations in PPCM have identified multiple diagnostic and prognostic biomarkers, reflective of cardiomyocyte dysfunction, endothelial dysfunction, or cardiac remodelling (*Table 2*).[17,18,20,24,27–29,31,38,61–68]

Newer biomarkers, such as altered expression of maternal circulating microRNAs (miRNAs) during pregnancy, are under evaluation (*Figure 2*).[69] While existing data are promising, further investigation is needed to directly and causally link miRNAs to cardiac pathophysiology in cardiovascular complications of pregnancy.

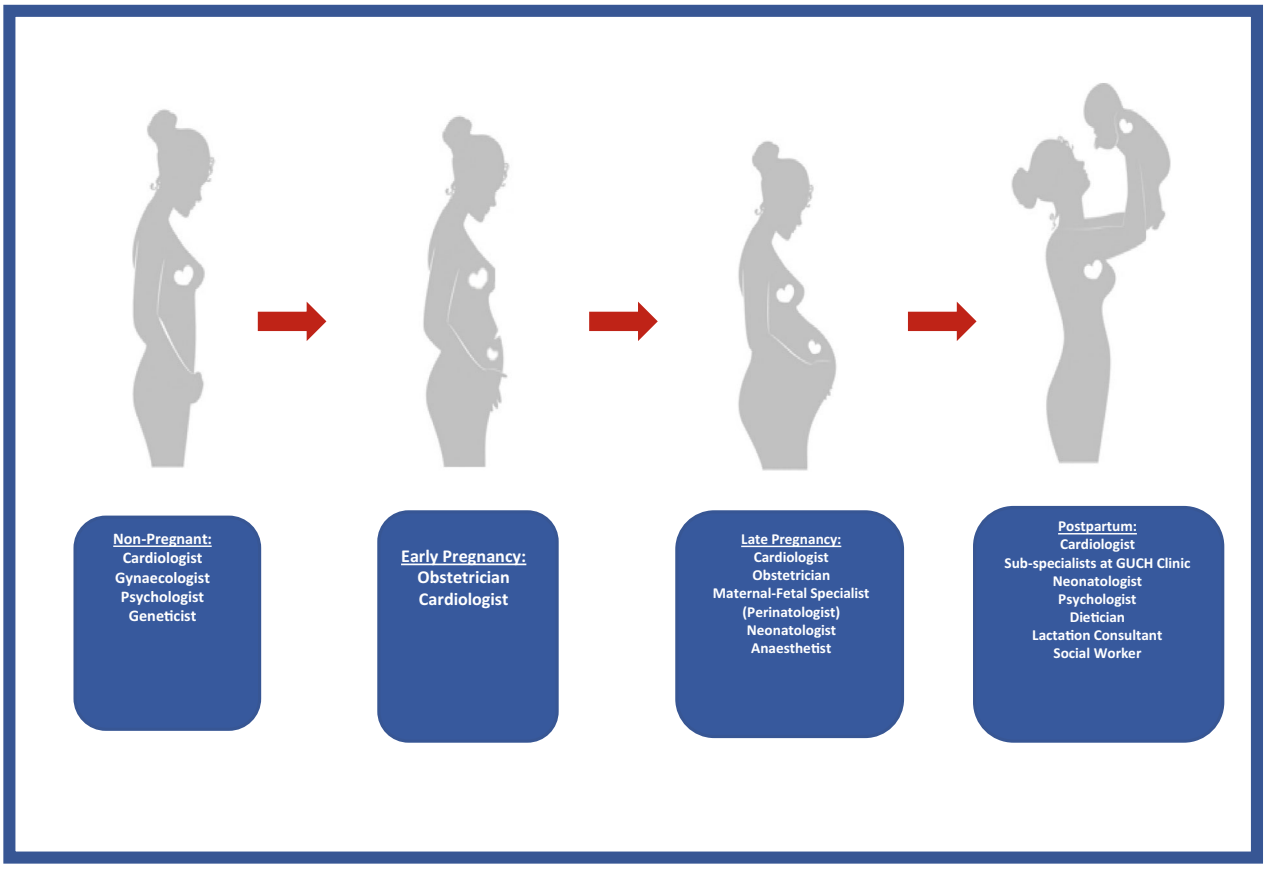

Figure 1 Multidisciplinary care for women with peripartum cardiac disease. GUCH, grown-up congenital heart.

Management of pregnant women with heart failure

Multidisciplinary approach

An important general principle to manage complex medical conditions is to follow a multidisciplinary approach. This is especially applicable to pregnant women who are in modified WHO classes II to IV in order to improve both maternal and foetal outcomes. The multidisciplinary approach is presented in *Figure 1*. The pregnancy heart team[4,22,70] should include cardiologists, obstetricians, and obstetric anaesthesiologists, which all should have specific expertise and experience in the management of high-risk pregnancies in women with heart disease. Optimally, the team should also involve maternal and foetal medicine specialists, neonatologists, nursing staff with experience in pregnancy and heart disease, psychologists and social workers.[4,22,62] Other medical specialists such as haematologists, cardiothoracic surgeons, paediatric cardiologists, pulmonary specialists and others may be required in specific cases.

There are multiple goals for the pregnancy heart team, from preconception counselling through labour and delivery planning and, importantly, including close postpartum follow-up and long-term care.[63] Ideally, pre-conception counselling should be carried out jointly by a cardiologist and obstetrician/obstetric physician. The prenatal maternal evaluation encompasses a thorough assessment of symptoms and signs, overall health status, risk stratification with the modified WHO score and medication review. In conditions classified as modified WHO class IV, patients should be advised against pregnancy.[4,22]

In the real world, the majority of high-risk women will present when already pregnant, which requires coordination of care, treatment of complications and the mitigation of risks during the further course of the pregnancy. The required level of expertise of the managing centre and the visit frequency are based on the severity of the condition and the maternal and foetal risk.[63–65] Often, pregnant women at moderate and high risk will require advanced care and, therefore, must be transferred to a centre where HF specialists, pulmonary hypertension specialists, interventional cardiologists, cardiothoracic surgeons and others are available. Breast-feeding and subsequent contraception should be planned before delivery, taking into consideration both medical factors as well as the mother's preferences.[71]

Anaesthetic management of pregnant patients with heart failure

Multidisciplinary delivery planning in expert centre is required to manage HF pregnant patients[72] (*Figure 3*). Two situations must

Table 2 Diagnostic and prognostic biomarkers in peripartum cardiomyopathy[61]

Nursing hormone	Cardiomyocyte dysfunction	Endothelial dysfunction	Cardiac remodelling
PRL[a,18,24]	BNP[a,18,24,62–65]	microRNA-146[a,18,27]	TGF-β[a,24,66]
16 KDa-PRL[a,20]	NT-proBNP[b,24,65]	sFlt[b,31]	MMP-2[a,17]
	cTnT[c,67]	sFlt1/PlGF[a,29]	sST2[a,29]
	Cathepsin D[a,18,20,24]	Ox-LDL[b,24]	Fas/Apo1[b,17,24,28]
		MR-proADM[a,29]	TNF-α[a,17,24,28,29]
		Relaxin-2[c,31]	IL-6[a,28]
			IL-4[a,38]
			IFN-γ[b,24,38]

Apo1; apolipoprotein 1; BNP, B-type natriuretic peptide; cTnT, cardiac troponin T; IFN-γ, interferon-gamma; IL, interleukin; MMP-2, matrix metalloprotienase- 2; MR-proADM, mid-regional pro-adrenomedullin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ox-LDL, oxidized low-density lipoprotein; PlGF, placenta growth factor; PRL, prolactin; sFlt, soluble fms-like tyrosine kinase; sST2, soluble suppression of tumorigenesis 2; TGF-β, transforming growth factor-beta; TNF-α, tumour necrosis factor-alpha.
[a]Diagnosis biomarker.
[b]Diagnosis and prognosis biomarker.
[c]Prognosis biomarker.

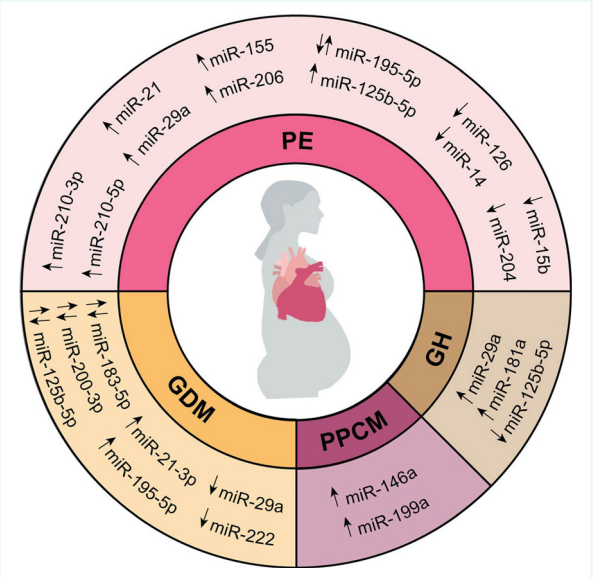

Figure 2 Dysregulated circulating cardiac-related microRNAs (miR) in cardiovascular complications during pregnancy. Depicted miRNAs have been shown to be involved in animal models of heart disease. GDM, gestational diabetes mellitus; GH, gestational hypertension; PE, pre-eclampsia; PPCM, peripartum cardiomyopathy.[69]

be distinguished: (1) planned and (2) emergency delivery. Vaginal delivery is associated with lower blood loss, reduced infection and thrombosis rates, and remains the safest option to avoid cardiac decompensation.[4,22]

Cardiac monitoring and intravenous access during labour

The main objective of cardiac monitoring is to prevent and to early detect cardiac events.[73] Pulse oximetry is a simple non-invasive tool allowing continuous monitoring of heart rate, rhythm (to detect bradycardia and tachycardia) and occurrence of desaturation. Maternal 5-lead electrocardiographic telemetry (ECG) should be considered for patients at high risk for arrhythmia and myocardial ischaemia. To date, no recommendation concerning non-invasive blood pressure is available concerning intervals between measures, but according to the severity of cardiac disease, repeated measures with intervals of 1 min may be necessary. In case of cardiac instability and/or a high risk of cardiac decompensation, invasive blood pressure monitored by arterial catheter is an option. Transthoracic echocardiography (TTE) is an important examination in pregnant patients with HF. Baseline TTE is necessary before delivery. A new cardiac assessment using TTE may be required, notably in case of new and/or modification of clinical signs leading to assess cardiac function. Finally, non-invasive and invasive devices used to monitor cardiac output (PiCCO™, LiDCO™, FloTrac™) have never been evaluated and no recommendation can be made in this context.

Labour and delivery analgesia

Painful labuor is one of the most important and frequent factors involved in decompensation of cardiac disease[73] inducing catecholamine release with tachycardia, hypertension, hyperventilation and increased cardiac output.[72] Severe haemodynamic variations can induce cardiac ischaemia, increased myocardial oxygen demand, and arrhythmia.[46] Whatever the type of delivery, neuraxial anesthesia (i.e. epidural, spinal and combined spinal techniques) should always be considered,[73] to limit cardiovascular and haemodynamic risks of general anaesthesia and mechanical ventilation.[73] However, haemodynamic changes following neuraxial anaesthesia by decreasing venous return and systemic resistances, need to be prevented by reducing and titrating medication doses, and/or precociously using vasopressors while maintaining optimal analgesia. Close haemodynamic monitoring associated with restrictive fluid therapy is mandatory in these patients. Haemodynamic changes induced by spinal anaesthesia are more pronounced, when compared to epidural anaesthesia.[73] Bupivacaine is associated with a lower risk of haemodynamic fluctuation.[74,75] General anaesthesia

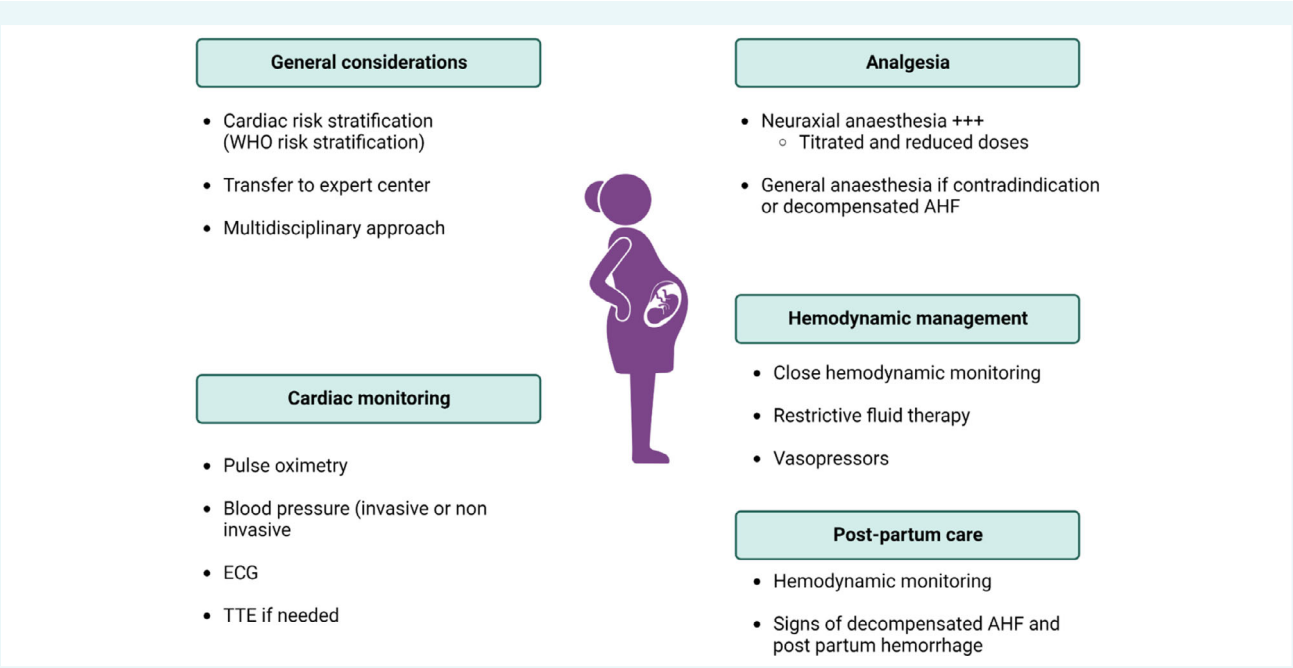

Figure 3 Key points of anaesthetic approach of pregnant heart failure patients. AHF, acute heart failure; ECG, electrocardiogram; WHO, World Health Organization; TTE, transthoracic echocardiography.

is advised in those with cardiac decompensation, current anticoagulation, thrombocytopenia, or maternal refusal of neuraxial anaesthesia.[76] The presence of desaturation, dyspnoea or hypoxaemia before labour or delivery must alert the anaesthesiologist on the high risk of cardiac decompensation after delivery (due to the aortocaval decompression, followed by acutely increased preload).[76] In case of uterine atony and/or postpartum haemorrhage, oxytocin could be used (risk of hypotension), but the risk balance benefit must be in favour of the use of the uterotonic, compared to the risk of cardiac decompensation.

Postpartum anaesthetic care

Postpartum is a period of high risk of cardiac decompensation. Maternal monitoring (including vital parameters [e.g. heart rate, blood pressure, pulse oximetry, diuresis, temperature], signs of postpartum haemorrhage and cardiac decompensation) will be used according to the cardiac disease and the occurrence of cardiac events during during labour and delivery. Further TTE may be appropriate for evaluation of cardiac function combined with ECG and troponin levels if indicated.

Postpartum care

Ensuring appropriate postpartum monitoring is essential for all women, particularly those at high risk for CVD.[45,63,77] Postpartum is a critical period for diagnosis of HF, with the majority of cardiovascular deaths occurring within the first 6 weeks after delivery, and most venous thromboembolisms happening within 1 week of delivery.[66,78] Extended monitoring is especially important for women with pre-existing HF, pulmonary arterial hypertension, or valvular heart disease, given the heightened risks associated with haemodynamic changes in the postpartum period.[22,44,77] Telemonitoring is recommended for those at high risk of significant arrhythmias. The duration of planned postpartum stay depends on the specific cardiovascular condition, with high-risk individuals monitored for at least 72 h.[77] Patients should promptly report any pathological symptoms. The postpartum period is also crucial for addressing breastfeeding, family planning, contraception, mental health, and the need for long-term cardiovascular follow-up if not previously discussed. Most cardiovascular medications can be continued during lactation.[22]

Contraception in women with heart failure

Sexually active women with HF require effective contraception to avoid complications from an unintended pregnancy and drug interactions must also be considered. Barrier methods are not advised due to their high failure rates.[75] Surgical or tubal sterilization in some women may be an option.[76] Copper intra-uterine devices (IUD-CU) are safe, but increased menstrual flow with resulting anaemia may arise. Because of their high efficacy, hormonal contraceptives may be an option.[75] They do not increase the risk of HF.[79] Short-acting reversible contraceptives (short-acting reversible contraceptives, i.e. the pill, vaginal ring, transdermal patch) require optimal patient compliance and should be avoided in those who have difficulty to correctly or consistently use this method.[75] Oestro-progestins should be avoided because of the possible effects of oestrogens on blood pressure, fluid retention, increase in ventricular mass and stroke volume, arrhythmias and

Table 3 Contraception in presence of cardiac risk factors

Conditions	IUD-CU	Progestin contraceptives (pill, IUS, implant, DMPA)	Oestroprogestin contraceptives (pill, ring, patch)
Cardiomyopathy			
Normal cardiac function	Not contraindicated	Not contraindicated	Not contraindicated
Impaired cardiac function	Not contraindicated	Not contraindicated	Contraindicated
Atrial fibrillation	Not contraindicated	Not contraindicated	Contraindicated
Hypertension	Not contraindicated	Not contraindicated	High risk
Vascular disease	Not contraindicated	Not contraindicated. High risk for DMPA	Contraindicated
Vascular and congenital heart disease, complicated	Not contraindicated	Not contraindicated	Contraindicated
Diabetes mellitus, complicated	Not contraindicated	Not contraindicated	High risk
Obesity, BMI >35 kg/m^2	Not contraindicated	Not contraindicated	High risk
Multiple risk factors for CVD	Not contraindicated	Not contraindicated. High risk for DMPA	High risk

BMI, body mass index; CVD, cardiovascular disease; DMPA, depot medroxyprogesterone acetate; IUD-CU, copper intra-uterine contraceptive device; IUS, intrauterine system. Modified by UK Medical Eligibility Criteria April 2016, Amended September 2019 (https://www.fsrh.org/documents/ukmec-2016).

increase in venous thrombosis.[80–82] These effects are higher with ethynilestradiol but cannot be excluded for preparations with natural oestrogens.

Progestin only contraceptives are therefore more appropriate. Women with HF should be advised to use long-acting reversible contraceptives, including intra-uterine devices containing levonorgestrel or subdermal implants with etonogestrel, which show higher contraceptive efficacy than short-acting reversible contraceptives and reduced bleeding with menses.[83] Progestins with glucocorticoid activity must be avoided because of possible fluid retention. The other progestins are not contraindicated. Progestins with anti-mineralocorticoid activity, drospirenone, should be advised in these women, although no specific data exist. The choice of the hormonal method must consider the presence of concomitant risk factors (*Table 3*).

Pharmacological approaches for emergency contraception include a single dose of 1.5 mg of levonorgestrel, although interaction must be considered in those taking concomitant warfarin. Ulipristal and mifepristone may also be used and are more effective than levonorgestrel. IUD-CU insertion within 120 h after intercourse is also very effective in those who cannot be managed medically.[84]

Pregnancy management and decision on termination or continuation

Pregnancy is one of the most important events in a woman's life. Clearly, pregnancy brings about a particular need for consultation and informed decision when it is associated with increased maternal or foetal risk. Therefore, pregnancy counselling should be provided for women of child-bearing age with either clinically overt HF, or at risk of developing HF during pregnancy in order avoid unnecessary maternal and foetal risks.[4,22]

In patients with pre-existing cardiac conditions, HF may complicate the natural course of the pregnancy and is associated with adverse maternal and foetal outcomes.[63,84–86] It is important to avoid unplanned pregnancies as HF medications, potentially teratogenic, during the first trimester, may significantly harm the foetus's life. On the other hand, the hypervolaemic status of the pregnancy, especially during the second and third trimesters, may trigger decompensation. Therefore, pregnancy counselling is the most critical preventive measurement in patients at risk or with overt HF.[4,22] In cases of unplanned pregnancy, a careful risk–benefit evaluation should be performed for both mother and foetus. Multidisciplinary discussions on a case-by-case scenario should involve a cardiologist and obstetrician, and psychological support is often required.

Pregnancy termination should be discussed in high-risk cases with high maternal risk of morbidity and mortality, and/or significant and potential life-threatening foetal abnormalities.[4,22] After careful and open counselling, the ultimate decision on pregnancy continuation or termination should be made by the pregnant woman. The woman and her partner must be carefully informed of the potential risks of miscarriage/foetal abnormalities and pregnancy-related complications, including HF decompensation, permanent disabilities, and maternal or foetal death. Similarly, rates of major maternal complications of undergoing surgical termination, specifically after the first trimester of pregnancy, should be discussed before an informed decision is made.

If a decision towards pregnancy termination is made, either surgical or medical, the patient should be managed in an experienced centre to reduce adverse outcomes. A multidisciplinary approach involving the patient's cardiologist and obstetrician, with the help of psychological support, should be sought for the procedure. If continuation of pregnancy is advocated, the pregnant woman must be offered careful follow-up from both the cardiologist and obstetrician to reduce the risk of adverse events.

Ethical considerations both of the patient and of medical professionals may play a significant role in counselling pregnant women with, or at risk of HF. Care must be taken that the explanation of potential risks and benefits of either decision are provided accurately, completely, and without bias. The ultimate decision, with all

the bearing of ethical and personal implications, should be reserved for the woman and her family. It is fundamental to consider the psychological, social, religious, and personal contexts to provide support, in order help the patient towards making her decision. Structured follow-up should be offered in all situations.

Psychological support

Pregnancy is both a joyful and stressful time in a woman's life. In patients with, or at risk of HF, stress is increased by the knowledge of potential maternal and/or foetal risk of increased adverse events and teratogenicity, and psychological needs should be carefully considered. Psychological distress is associated with a higher incidence of HF and its complications.[87,88] Social and psychological support should be provided during the entire course of pregnancy in patients with HF.[61,67,89] Multidisciplinary management, ideally with involvement from a psychologist, should be offered during pregnancy and continued into the postpartum period.

Discussions around pregnancy termination or continuation should include impartial patient-centred information that is accurate and comprehensive to inform the pregnant woman of the risks and benefits of either decision and to reduce the psychological burden of that decision. Social and psychological support is crucial in improving coping mechanisms and reducing the stress of the pregnant woman.

Behavioural therapy may help the patient to cope and manage the stress of the pregnancy. Given the potential disadvantages of medical therapy for mental health issues during pregnancy, the role of behavioural therapy has increased importance. Furthermore, it may help the pregnant woman to cope better with the distress of a potentially challenging decision which may occur during the pregnancy.

Multidisciplinary approaches involving the caregivers, the community services and the medical services are required to provide comprehensive management. Preventing or mitigating emotional distress is pivotal to strengthening the therapeutic alliance and improving quality of life. The design of programmes addressing clinical and psychological needs in pregnant women at risk of, or with overt HF, is critical. Programmes should address care planning to prevent adverse outcomes and reduce patients' distress.

When local expertise is limited, the management of pregnant women with, or at risk of, HF should be referred to tertiary centres which have the ability to provide a multidisciplinary approach, including psychological support.

In conclusion, our paper provides a thorough discussion of HF during pregnancy, emphasizing the necessity for preventive measures, risk assessment, and meticulous management. We cover insights from pregnancy-related heart disease models, risk factors, biomarkers, and holistic management strategies, highlighting the complexity of this medical challenge.

The discussion on risk factors emphasizes the significance of pre-pregnancy risk assessment and counselling, introducing various risk scores with acknowledgement of their limitations. Each risk factor is carefully examined, emphasizing its implications for both maternal and foetal health. In essence, our paper not only highlights the clinical intricacies of managing HF during pregnancy but also emphasizes the importance of comprehensive, patient-centred care. By addressing each facet with diligence, from risk assessment to psychological support, it serves as a valuable resource for clinicians and researchers striving for improved outcomes in this challenging medical scenario.

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