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HEART FAILURE (A MARIE CHANG, SECTION EDITOR))

Peripartum Cardiomyopathy: a Review

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Abstract

Purpose of Review Peripartum cardiomyopathy (PPCM) is an important condition with high morbidity and mortality worldwide. Patients with PPCM are at risk of developing lifelong cardiac disease, requiring regular management and medical intervention. This article conducts a review of recent literature and gives insight into this disease.

Recent Findings There is promising research in the fields of vascular, hormonal, and genetics. A number of genetic markers are being analyzed, including TTNC1, TTN, and STAT3. Mutations to these genes have been found to be prevalent in PPCM. These combined with the secretion of placental angiogenic factors potentially create imbalance in angiogenesis as the primary etiology.

Summary Current biomarkers do not differentiate between PPCM and other variants of heart failure. Women with PPCM are more likely to have a cesarean section, to have hypertensive disease, at greater risk of major adverse cardiac events, and to have lifelong morbidity.

Keywords Peripartum cardiomyopathy · Pregnancy · Cardiomyopathies · Heart failure · Preeclampsia

Introduction

In the United States (US), peripartum cardiomyopathy (PPCM) is defined as a left ventricular dysfunction with associated cardiac failure that occurs between the final month of pregnancy and up to 5 months from delivery [1, 2•]. Additional criteria include no other identifiable cause of heart failure, no other known heart disease in the last month of pregnancy, and no echocardiographic identification of left ventricular dysfunction with an ejection fraction (EF) < 45% or fractional shortening < 30% [1, 3, 4].

Cardiac dysfunction near term pregnancy was first noted in the literature in 1849, officially denoted with the current terminology in the 1990s by a workshop from the US National Heart, Lung and Blood Institute [1, 2•, 4]. The European Society of Cardiology (ESC) defined PPCM in 2010 as a heart failure that occurs in the peripartum period with no other identifiable cause [4]. A transthoracic echocardiogram is the diagnostic test of choice. An EF of < 45% is often cited as the cutoff for diagnosis, with or without left ventricular dilatation [3, 4]. The ultrasound most commonly shows features such as left ventricular dilation, left ventricular systolic dysfunction, as well as biatrial enlargement, mitral or tricuspid regurgitation, and pulmonary hypertension; however, no feature is exclusively diagnostic [1, 2•, 4]. This disease is typically a diagnosis of exclusion; many women in their childbearing years have no prior cardiac imaging.

Symptoms are typically consistent with heart failure but can be easily confused with pregnancy; palpitations, fatigue, dyspnea, and pedal edema are common complaints. Additional symptoms are consistent with heart failure: cough, dyspnea on exertion, and orthopnea. Signs include tachycardia, tachypnea, rales, increased JVP, and pitting edema consistent with left- and right-sided congestion. There may be a gallop, although an S3 can be a normal variant during pregnancy [1, 4]. Most women present postpartum within the first month after delivery [4].

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Normal Pregnancy

Pregnancy induces significant physiologic changes in the cardiovascular system. Hypervolemia and resultant anemia of pregnancy are two well-known functional alterations to compensate for increased flow and presumed blood loss in the peripartum period. In order to accommodate this increased volume, cardiac output is increased by 20–50%, and systemic vascular resistance is decreased by 30%. These key alterations occur as early in gestation as 8 weeks and persist into the third trimester. Stroke volume increases to counter the reduction of peripheral vascular resistance, both of which reach a plateau near 16 weeks [1]. Although there is an increased left ventricular mass, left ventricular contractility does not appear to change significantly during pregnancy [1]. Given these early physiologic changes, women with preexisting heart conditions tend to present with heart failure earlier in their gestation than those with PPCM.

Differential Diagnosis

Since many symptoms overlap with normal pregnancy, the index of suspicion must remain high for PPCM. The differential diagnosis includes etiologies such as preexisting mechanical heart disease, drug- or toxin-induced cardiomyopathies, HIV or hypertensive cardiomyopathy, Takotsubo, preeclampsia, valvular disease, sepsis, pulmonary embolism, myocardial infarction, myocarditis as well as "zebra" diagnoses such as lupus, amniotic fluid embolism, and thyrotoxicosis. Iatrogenic pregnancy complications, such as prolonged tocolysis should also be considered. The diagnosis is thus a diagnosis of exclusion.

Epidemiology

The US incidence is between 1 in 900 to 1 in 4000 live births [4, 5]. Given the nonspecific and sometimes occult nature of the disease, the true incidence is likely underreported [6]. The incidence appears to be increasing. One study showed an increase from 1 in every 4,350 births in the early 1990s to 1 in every 2,230 in the early 2000s [7]. Another showed an increase from 1 in every 1181 in 2004 to 1 in every 849 live births in 2011 [4]. This increase has been posited to be related to increasing maternal age, fertility treatments, multifetal pregnancies, and obesity [1, 8]. Worldwide incidence is similarly estimated to be about 1 in every 1,000 births with notable geographic variations [1, 3]. Nigeria reported rates up to 1%, whereas Haiti has reported 1 in every 300 births [1, 4].

Known risk factors include maternal age, hypertensive disorders of pregnancy, multifetal gestations, and race [9]. Smoking, anemia, and obesity are also likely risk factors. Twenty-five to 30% of maternal morbidity is associated with cardiovascular disease, of which PPCM is credited 50–66% [4]. Women are now more likely to have additional cardiovascular risk factors given the extension of reproductive age with fertility measures and family planning; approximately 4% of pregnancies in the Western world are complicated by cardiovascular diseases [10]. Age is an independent risk factor for PPCM—when compared with those younger than 30, the adjusted odds ratio of women over the age of 30 is 1.7–1.8 [4, 5, 11]. Additionally, multifetal gestations are related to PPCM. An estimated 9–66% of pregnancies with more than one fetus are associated with increased risk [12, 13].

There is a strong relationship between hypertensive disorders of pregnancy and PPCM. In Germany, nearly 50% of women with PPCM were found to have associated pregnancy-hypertensive disorders [3]. Recent meta-analyses showed approximately 16–22% of women with PPCM have preeclampsia and 37–38% of the cases had any kind of hypertensive disorder [5]. A retrospective Danish study found significantly increased risk ratios for PPCM with severe preeclampsia (21.2, CI 12–37.4), moderate preeclampsia (10.2, CI 6.18–16.9), and gestational hypertension (5.16, CI 2.11–12.6) [5, 11, 12]. Despite significant overlap with preeclampsia, these entities are not synonymous. Notably, preeclampsia or hypertension on their own can induce pulmonary edema even in the absence of PPCM (Table 1).

Incidence of PPCM is three to four times higher in black women than white in the US with a 5-year mortality that is up to 4 times higher in black women as compared with white [4, 5]. The Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study results suggest that black women have a lower EF at presentation and a lower rate of recovery [14•]. The IPAC was a prospective study assessing the LVEF of 100 women with PPCM until 12 months postpartum with serial echocardiography. Black women are also more likely to be younger at diagnosis and to be diagnosed later postpartum compared with counterparts of other races [4, 15]. Even after adjusting for other factors such as age, hypertension, and income, black women continue to be at increased risk of PPCM [2•]. Women of Latina descent appear to have a similar risk profile to that of white women [5].

Table 1 Risk ratio of peripartum cardiomyopathy with hypertensive disease in pregnancy

	Risk ratio	CI (lower)	CI (upper)
Severe PET	21.2	12	37.4
Moderate PET	10.2	6.18	16.9
Gestational HTN	5.16	2.11	12.6

PET preeclampsia, *HTN* hypertension, *CI* confidence interval

Pathophysiology and Research

The etiology of PPCM remains challenging to elucidate. Possible causes include infectious pathogenesis such as myocarditis, genetic predisposition, prolactin, placental angiogenic factors, and autoimmune disease.

One initial theory is that PPCM is the result of a failure to adapt to the hemodynamic changes of pregnancy. Most physiologic changes that affect parameters such as cardiac output and systemic vascular resistance occur early to mid-pregnancy. This timeline does not correlate with the timeline of PPCM, which is typically diagnosed at peri or postpartum [1, 5].

Myocarditis has long been posited as an etiology for PPCM; however, prior studies with endomyocardial biopsies showed similar proportions of women with inflammatory findings in groups with and without PPCM [1, 4, 16]. In a study utilizing cardiac MRI to assess for inflammatory changes, one of forty women with PPCM had results possibly consistent with myocarditis [17]. Additional theories include various forms of malnutrition, including anemia, selenium deficiency, microchimerism with fetal cells, and other autoimmune disorders; nevertheless, none have presented a unifying pathogenesis of PPCM [5, 18–20].

One of the most current theories of the pathogenesis includes a "two-hit hypothesis," in which women with a genetic predisposition receive a subsequent insult near-term birth with a new hormonal milieu. The genetic predisposition theory is buffered by racial, geographic, and familial clustering of PPCM [1, 4]. Various genetic markers are being researched; mutations in the genes TTNC1, TTN, and STAT3 appear to play a role [1]. Certain variants of the gene TTN that encodes for a protein called titin in the sarcomere have been found to be prevalent in PPCM and dilated cardiomyopathy [21]. Prolactin secretion and placental angiogenic factors, such as a molecule called sFlt-1 (a vascular endothelial growth factor inhibitory molecule), are also posited as potential influences, suggesting that imbalanced angiogenesis is part of the underlying etiology [1, 4, 22].

A novel paper in 2007 demonstrated that knockout mice lacking the STAT3 gene in their cardiac myocytes developed cardiomyopathy [23•]. Loss of STAT3 suppresses the expression of manganese superoxide dismutase (MnSOD), which protects against reactive oxygen species. Loss of MnSOD expression leads to an increase in the enzyme cathepsin D peptidase, which cleaves prolactin. The cleavage of prolactin produces a 16-kDa anti-angiogenic molecule called a vasoinhibin that may cause myocardial damage and subsequent ventricular dysfunction through cellular apoptosis and capillary dropout, i.e., less angiogenesis [1, 4, 24]. Bromocriptine reversed murine cardiomyopathy in mice without the STAT3 gene in their cardiomyocytes, suggesting a causal relationship with prolactin [23•]. Additionally, women with PPCM have been found to have elevated concentrations of this version of vasoinhibin and its precursor, cathepsin D [1, 6, 23•]. The 16-kDa vasoinhibin fragment has been found to upregulate microRNA-146a, which triggers the release of exosomes that are taken up by cardiomyocytes. This uptake of exosomally contained material blocks multiple pathways leading to cellular death of cardiomyocytes, which is reversible in mice with antisense oligonucleotides to miR-146a [22, 25]. Notably, this treatment did not interfere with murine lactation. Additionally, miR-146a levels are elevated in women with PPCM, suggesting that this molecule could serve as a potential biomarker and as a template for an investigational treatment [6, 22, 25]. Women treated with early bromocriptine were found to have normalized levels of miR-146a, further implicating this pathway in the development of PPCM [6].

Given the overlap between PPCM and hypertensive disorders of pregnancy, there is research into a shared pathogenesis of unbalanced angiogenesis. During near-term pregnancy, the placenta systemically secretes increased soluble fms-like tyrosine kinase receptor 1 (sFlt-1), which neutralizes VEGF in the maternal bloodstream. Certain organs, such as the heart, secrete local VEGF to counter this neutralization [5]. sFlt-1 is increased in PPCM, as are other anti-angiogenic factors such as relaxin-2 [26–28]. Unbalanced angiogenesis is a leading theory of preeclampsia; elevated sFlt-1 to placental growth factor (PIGF) ratios is being considered diagnostic biomarkers [29, 30]. One mouse model suggests that sFlt-1, in conjunction with a transcriptional co-activator called proliferator-activated receptor gamma co-activator-1alpha (PGC-1alpha), induces heart failure in PCG-1alpha knockout and wild-type mice to varying degrees. Similar to STAT3, PGC-1alpha triggers the expression of MnSOD. It also drives the expression of VEGF. Loss of PGC-1alpha thus has a two-pronged effect of initiating the 16-kDa prolactin-induced pathway and loss of the pro-angiogenic VEGF. In PGC-1alpha knockout mice, bromocriptine and VEGF both separately improved murine PPCM and both treatments together restored murine cardiac function entirely. Even in the absence of pregnancy, sFlt-1 induced heart failure in this murine model, suggesting a causal role in cardiomyocyte damage [26]. Patients with anti-angiogenic therapies, including anti-VEGF, in oncological settings, have also been found to induce cardiomyopathy as a side effect [31, 32].

Diagnosing

Diagnosis can be challenging. Pregnant women often have shortness of breath, weight gain, and edema [3]. Interestingly, in a study using a European Society of Cardiology (ESC) worldwide cohort, the disease presentation was similar across ethnic and socio-economic backgrounds [33]. Most women are diagnosed with PPCM within 1 month

postpartum. A recent study found that 2/3 of women were diagnosed at readmission after their childbirth index hospitalization, indicating likely delay in diagnosis [6, 33, 34]. There is no current laboratory biomarker that confirms the diagnosis of PPCM; however, markers such as B-type natriuretic peptide (BNP) and pro-BNP have been utilized to aid in the diagnosis. Of note, in healthy women, BNP/NT pro-BNP levels can be elevated within 48 h postpartum without PPCM [1]. There is no threshold for diagnosis. Other biomarkers are under research, including certain micro RNAs such as miR-146a and anti-angiogenic factors, namely prolactin [18].

It is recommended that evaluation includes workup for sepsis, preeclampsia, anemia, liver, kidney, and thyroid disease. An EKG, troponin, and chest radiograph are additional adjuncts. The typical EKG is normal or may show sinus tachycardia or low-voltage QRS complexes with inverted T waves [2•, 3, 5]. Chest radiography can show typical features of pulmonary edema, pleural effusions, and/or cardiomegaly [4, 5]. The role of cardiac MRI is debated; echocardiography is preferred [35]. A TTE is the gold standard for diagnosis with an EF of < 45% at presentation. LV enlargement is not required for diagnosis.

Treatment and Interventions

Management

The timing of diagnosis has important consequences regarding treatment and interventions of the woman with PPCM. If diagnosed during pregnancy, medical management until delivery is typically indicated. An interdisciplinary team should be convened to assess the timing and method of delivery to best assess indications for delivery and weigh risks and benefits to the newborn. Although vaginal delivery is preferred, over 50% of US women with cardiomyopathy (of any type) deliver via Caesarian section [36]. There is no data to suggest that early delivery improves fetal or PPCM outcomes [5]. Apgar scores, birth size, and mean birth weight are all lower in neonates born to women with PPCM [5]. The neonatal death rate from an ESC prospective cohort is estimated at 3.1% [33].

The diagnosis is more often made postpartum when more treatment modalities are available. Medical therapy is utilized in both groups and is based on typical therapy for heart failure with reduced EF, including symptomatic treatment, altering the neurohormonal response and reducing long-term complications like thromboembolism and arrhythmia [1]. There is no disease-specific treatment regimen at this time.

Current guidelines include the 2013 ACCF/AHA heart failure, the 2016 AHA dilated cardiomyopathies, the 2016 ESC severe acute PPCM, and the 2018 ESC cardiovascular disease in pregnancy guidelines [2•, 37–39]. Recommendations are similar for standard medical therapies for HFrEF, medications, devices, and care of the pregnant women; however, European guidelines recommend the use of bromocriptine (class IIB) while American guidelines do not. The latest American guidelines from 2016 indicate that bromocriptine treatment is experimental [33]. Additionally, levosimendan, a drug not available in the US, is the inotrope of choice in European guidelines [4].

Medications

Loop diuretics, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs), calcium channel blockers, and beta blockers are all commonly utilized [33, 40, 41]. Notably, ACE-I are teratogenic and are thus only used in the postpartum period. Other vasodilatory medications can be substituted until postpartum, such as hydralazine [1, 41]. Aldosterone antagonists are generally avoided during pregnancy due to lack of safety data [35]. Diuretics such as furosemide can be used with caution, preventing hypotension and uterine hypoperfusion is paramount [5]. Beta blockers are recommended as class IA medications for HFrEF; in a German PPCM cohort, they were noted to improve outcomes when given in conjunction with ACE-I and bromocriptine [6]. Preference among beta blockers is for beta 1–selective agents to avoid beta 2 stimulation of uterine contraction [4]. Digoxin is also safe during pregnancy, although typically reserved after maximization of other therapies. Very few, small trials have been conducted for PPCM-specific therapy, and some experimental treatments such as pentoxifylline and intravenous immunoglobulin have been considered, but do not currently have data-driven usage [5]. Sodium restriction is commonly recommended.

Bromocriptine, a prolactin antagonist, has also been utilized for treatment outside of the US. Although there is growing evidence to suggest improved ventricular function may occur with bromocriptine, the FDA has not approved bromocriptine for PPCM in the US. Multiple small studies have shown reduced morbidity and mortality with bromocriptine as compared with women on standard heart failure treatment alone [8, 42]. The BOARD treatment regimen (Bromocriptine, Oral heart failure treatments, Anticoagulation, vasoRelaxing agents, and Diuretics) is a post-partum regimen arising from recent promising research in bromocriptine usage in Europe [43, 44]. The European PPCM registry reported bromocriptine usage at 20% [18].

Breastfeeding Effects

An individualized approach is recommended regarding breastfeeding. Although there is early research to suggest that cessation of breastfeeding in order to inhibit prolactin may be beneficial, such claims remain under investigation. Given the

significant benefits to the infant, if the mother can tolerate breastfeeding, it may be prudent to pursue this avenue. Women in cardiogenic shock or with LVEF < 25% may be more likely to benefit from pharmacologic prolactin inhibition [4].

Long-Term Management

Contraception should be provided to prevent unintended repeat pregnancies. Hormone-free contraceptives are preferred as estrogen-containing compounds may interfere with standard heart failure therapies and have a pro-thrombotic risk [3, 35]. Progestin-only compounds and intrauterine devices are reasonable options since there is no increased risk of thromboembolism and there are various long-term preparations.

Prognosis

With treatment, the prognosis is fair; studies showing LVEF improvement range from 23 to 85% worldwide [6, 41]. In the IPAC cohort, 72% of women recovered an LVEF of > 50%, with only 13% having a major event or persistently low EF (< 35%) [14•]. Another study noted that 60% of women recover completely within 1 year, whereas an additional 47% recover partially, and only 3% remained in heart failure [44].

Partial recovery is considered a 10% increase in LVEF or an improvement by one NYHA class [3]. Predictors of recovery include left ventricular size and LVEF at the time of diagnosis [4–6]. In the IPAC study, women with higher LVEF at presentation had higher LVEF at 1 year. Of women with LVEF ≥ 30% at presentation, 86% progressed to LVEF > 50% at 1 year whereas in women who presented with an LVEF < 30%, 37% progressed to LVEF > 50%, and 37% had a major event (death, transplant or left ventricular–assisted device) or LVEF at 1 year of < 35% [14•]. A major event in this study was defined as death, LVAD, or heart transplantation. Left ventricular end diastolic diameter (LVEDD) was inversely associated with LVEF; women with LVEDD ≥ 6 cm had a lower baseline LVEF than women with LVEDD < 6 cm. This trend continued at 6 and 12 months [14•]. Of women who presented with an LVEF ≥ 30% and an LVEDD < 6 cm, 91% recovered to an LVEF ≥ 50% as compared with 61% of women who had just one of those characteristics. No women who presented with LVEF < 30% and LVEDD > 6 cm had a final LVEF of > 50% [14•]. Recovery, as measured by LVEF, typically occurs within the first six months [5].

Notably, black women tend to fare worse regarding both disease acquisition and progression. Worldwide estimates reflect this; mortality in Europe and Japan is noted to be between 2 and 4%, whereas mortality in African studies tends to be much higher, 13–17% [13, 18]. A North Carolina–based study found a 4-fold increase in mortality in women of African descent [45]. Despite similar levels of left ventricular systolic dysfunction at the time of diagnosis, a retrospective study found that 61% of white women versus 41% of black women experienced complete recovery of LVEF. At the 12 months follow up, not only was LVEF lower in African American patients but also LVEDD was significantly larger [15].

Complications and Mortality

Major adverse cardiac event (MACE) rates were higher for women with PPCM as compared with controls at 1 year postpartum [46]. MACE rates were also higher as compared with other types of cardiomyopathies during pregnancy [46, 47]. Concurrent preeclampsia is associated with increased morbidity and mortality, while pulmonary hypertension, obesity, renal failure, multiparity, long-term anticoagulation, CAD, and drug use were all found to be related to hospital readmission [13, 48, 49]. Readmission rates are estimated between 13 and 15% [48, 49].

In the IPAC study, 6 of 97 women experienced a major event, including 4 deaths, 3 early LVAD implants, and 1 heart transplantation. Of the women who had LVADs implanted early (within 3 months postpartum), 2 died, and 1 had a subsequent cardiac transplantation [14•].

Thromboembolism has been found in 2.2–6.8% of women with PPCM, a higher percentage than with other types of cardiomyopathy [1, 33]. It is posited that this risk is increased due to enlargement of the heart chambers, immobility, and endothelial injury [1, 5]. Pregnancy is an independent risk factor for thromboembolism [4]. Consideration of prophylactic anticoagulation is advised by the AHA guidelines with LVEF < 30% [2•]. Heparin and unfractionated heparin remain the anticoagulant of choice for pregnant women as there is limited data regarding efficacy and safety of direct oral anticoagulant use in pregnancy [4, 50].

Arrhythmias are a common cause of sudden death in this population; ventricular tachycardia is thought to be related to approximately 25% of deaths [1, 4]. Cardioversion and defibrillation are safe in pregnancy and should be implemented in emergent situations. The AHA guidelines suggest consideration of wearable devices in women with LVEF < 35% [2•]. Many women will recover, thus, implantable devices are discouraged early in the disease [4, 5].

Cardiogenic shock is an uncommon presentation, estimated at 2.6% of women with PPCM in the US. Mechanical support with LVAD (1.5%) and transplantation (estimated between 0.5–11%) are also potential therapeutic modalities [2•, 4]. Despite treatment, 5% of cardiac transplants in women in the United States are related to PPCM [1]. Patients should be treated aggressively given likely improvement and can be bridged with mechanical assistive devices, such as LV and biventricular assist devices, ECMO, and intra-aortic balloon

pumps [5]. In a nationwide US sample from 2004 to 2011, in-hospital mortality was found to be 1.3% [51]. Longer term mortality estimates vary significantly, possibly up to 11 to 16% in the United States based on three small studies [5]. In a 2018 meta-analysis of 46 studies with a mean follow-up of 2.6 years, developed countries had lower mortality than developing countries, 4% vs. 14% [13].

Minimizing Future Risk and Safety with Additional Pregnancies

Repeat echocardiography is recommended at 6 months postpartum, with subsequent ultrasounds every year once ventricular function has recovered [1]. Future pregnancies are at risk for recurrent PPCM, which should be part of prenatal counseling. Before any future pregnancies, a baseline cardiac ultrasound and BNP are recommended. The risk of PPCM associated with subsequent pregnancies is extrapolated from retrospective data; reported repeat incidence is between 66 and 100% [6]. In a small retrospective study, all subsequent pregnancies were noted to have a reduction in LVEF whether or not prior LVEF function had returned after the first pregnancy [1, 52]. Women who did not have complete recovery of their EFs after the first pregnancy appeared to be more susceptible to recurrent heart failure and had a higher mortality and fetal complication rate [1, 4, 42, 52]. There may be a genetic predisposition to recovery; women in a study of the TTN gene with PPCM, who had truncating variants of TTN, were also more likely to have reduced EF at 12 months follow-up [21]. The AHA guidelines counsel against repeat pregnancy if LVEF does not recover after the initial pregnancy [2•, 4]. The role of long-term medication and a firm definition of recovery remain unclear, as some studies have reported recurrence after discontinued therapy, while others have not [18]. The AHA recommends indefinite therapy as long as LVEF does not recover [2•]. The fact remains that there is no disease-specific therapy for PPCM.

A quality-of-life study ($n = 116$) found that 56% of respondents never recovered their emotional baseline after PPCM and 73% were unsatisfied with their level of symptoms. Moreover, 41% did not return to their prior exercise level and 28% left their jobs secondary to the diagnosis [53]. These findings suggest a significant emotional, financial, and health-related burden of PPCM that remains to be addressed.

Conclusions

PPCM is a rare disease that imparts a high level of maternal morbidity and mortality worldwide. Although the etiology has not been fully elucidated, there are promising areas of research in vascular, hormonal, and genetic arenas. Despite this, there are no disease-specific treatments. No biomarker is available for PPCM; BNP does not differentiate between PPCM and other variants of HF and variable information is available about prognostic factors for women who have recovery of LVEF regarding subsequent pregnancies and lifetime recovery. Women of African descent appear to be at greater risk; including later initial diagnosis, worse initial presentation, and lower rates of LVEF recovery. Further investigations are ongoing, including an ESC-driven observational study and PPCM registry, which will provide more baseline data to characterize the disease and improve understanding of its etiology, specific biomarkers, and treatment options [41].

Compliance with Ethical Standards

Conflict of Interest Lindsay Ballard and Adrian Cois declare no conflict of interest.

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