






# The Relationship Between Peripartum Cardiomyopathy and Preeclampsia – Pathogenesis, Diagnosis and Management

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**Abstract:** Peripartum cardiomyopathy (PPCM) is a condition with an incompletely understood etiology, although many risk factors for this disorder have been mentioned. Preeclampsia (PE) is a rare but undoubtedly very important cause of PPCM. Early recognition and prompt treatment of preeclampsia and peripartum cardiomyopathy are essential to optimize pregnancy outcomes. An extensive manual search of major electronic databases was conducted in November 2021. The following literature review provides a comprehensive discussion of peripartum cardiomyopathy and preeclampsia and quantifies the prevalence of PE in women with PPCM. The authors highlighted aspects such as epidemiology, risk factors, cardiovascular changes, diagnosis and clinical presentation, and management and complications. Accumulating data indicate that both conditions have a similar pathogenesis characterized by vascular abnormalities. In both conditions we can observe an increase in interleukin-6 and gamma interferon, CCL2/MCP1, and decreased SOD activity. sFLT1 (a soluble form of fms-like tyrosine kinase 1), a substance with antiangiogenic and probably cardiotoxic effects, may be important. Preeclampsia and peripartum cardiomyopathy are characterized by recurrence rates that follow a similar pattern in subsequent pregnancies, and mortality remains a concern. Our analysis highlights the need to better understand the co-morbidity of PE and PPCM, and the need to qualify patients for the same clinical trials because of the common origin of these conditions.

**Keywords:** pregnancy, PE, PPCM, conditions

## Introduction

Peripartum cardiomyopathy (PPCM) was defined in the 1990s as heart failure developing in the last month of pregnancy or up to 5 months after delivery characterized by left ventricular systolic dysfunction.<sup>1,2</sup> As reported by Sliwa et al, in 2010 European Society of Cardiology (ESC) modified the definition of peripartum cardiomyopathy perinatal cardiomyopathy, noting that the condition occurs “at the end of pregnancy or within end of pregnancy or within a few months after delivery, when no other cause of heart failure is found heart failure”.<sup>3</sup> The revisions incorporated a broader time frame without being more specific about the month, minimizing the risk of confusion and overlooking the condition, which was very likely before when strict time criteria were followed. Elkayam et al report that peripartum cardiomyopathy is usually seen in the early postpartum period - about 75% within the first month and about 45% within the first week.<sup>4</sup>

Elevated blood pressure at week 20 of pregnancy and beyond is defined as gestational hypertension, while hypertension (systolic blood pressure values  $\geq 140$  mm Hg and diastolic blood pressure values  $\geq 90$  mm Hg) with proteinuria  $\geq 300$  mg in a daily urine collection present (a score of at least +1 on a strip test or based on a protein-creatinine ratio value  $\geq 0.3$ ) is closely associated with preeclampsia (PE).<sup>5</sup>

The association between hypertensive disease and postpartum heart failure was first described in 1938, when the authors concluded that more than 85% of cases of peripartum cardiomyopathy were related to hypertension and this was

twice as common as in the control group.<sup>6</sup> Whereas Demakis and Rahimtoola in 1971, reported that preeclampsia (PE), was detected in 22% of women affected by cardiomyopathy.<sup>7</sup> Since then, peripartum cardiomyopathy is often combined with preeclampsia and at the same time recognized as its severe complication, while hypertension is rarely the cause of heart failure itself.<sup>1,8,9</sup> It is worth mentioning that National Heart, Lung and Blood Institute (NHLBI) - 2000 and European Society of Cardiology (2010) indicate idiopathic background of peripartum cardiomyopathy when no other cause of heart failure can be identified. The diagnosis therefore becomes a diagnosis by exclusion.<sup>10</sup>

The following literature review provides a comprehensive discussion of peripartum cardiomyopathy and preeclampsia and determines the prevalence of PE in women with PPCM. The authors focused on epidemiology, risk factors, clinical features and management during pregnancy and prognosis, and wanted to summarize recent scientific reports.

## Materials and Methods

An extensive manual search of major electronic databases (PubMed, EMBASE, Web of Science, and Google Scholar) was conducted in November 2021 to identify relevant studies published on the association of peripartum cardiomyopathy with preeclampsia. No lower date limit was specified. Articles were limited to those published in English and Polish. The following search terms were used: “preeclampsia”, “peripartum cardiomyopathy”, “pre-eclampsia” in various combinations. Articles were analyzed first by title, then by abstract, and finally by full text. All articles selected were the most relevant available for this review.

## Epidemiology

The incidence of peripartum cardiomyopathy varies from 1 in 1421 to 1 in 9861 births.<sup>11</sup> In 2011, it increased to 1 in 849 live births in the United States, where it was 1 in 1200 live births among women aged 20–29 years, 1 in 790 in women aged 30–39 years, and 1 in 270 live births among women aged 40–54 years.<sup>12</sup> As reported by other sources, 58% of PPCM cases occurred in women aged >30 years, with 27–33% of women having their first live birth.<sup>4</sup> The lowest incidence is seen in Hispanic women in the United States, while the highest incidence is seen in African-American or southern African women. The authors indicate an approximate prevalence in Haiti of 1 case per 299 live births<sup>13</sup> and 1 case per 1000 live births in South Africa.<sup>14</sup>

Similar to perinatal cardiomyopathy, the prevalence of preeclampsia varies by region. Studies in the US indicate 1 in 2367 births, noting that only 4% of diagnoses were made in the antenatal period, 18% in the perinatal period, and 78% in the postpartum period.<sup>15</sup> South Korean statistics report an incidence of 1 in 1741 cases, Taiwanese data report an incidence of 1 in 3790 births, and Swedish data report an incidence of 1 in 5719 births.<sup>16–18</sup> Observations by Melamed et al showed that 17–46% of women with gestational hypertension experienced preeclampsia, and in patients without hypertension, data indicated 5–8%.<sup>19</sup>

In 2013, Bello et al conducted a meta-analysis that found the prevalence of preeclampsia in women with peripartum cardiomyopathy to be 22%, which is more than four times the estimated global average (5%).<sup>20</sup> Similar data were reported in the PPCM registry of the EURObservational Research Programme - of 411 women with peripartum cardiomyopathy, 22.8% experienced preeclampsia.<sup>21</sup> It is unclear whether the association between preeclampsia and PPCM differs between black women (both conditions are more common in black women) and women from other ethnic and racial backgrounds due to limitations in data availability and variation in previous studies from Africa and the Caribbean.<sup>20</sup>

## Risk Factors

The pathophysiological features of peripartum cardiomyopathy and preeclampsia as vascular diseases appear similar.<sup>22–24</sup> sFLT1 (a soluble form of fms-like tyrosine kinase 1), a substance with antiangiogenic and probably cardiotoxic effects, may be important. sFLT1 is secreted by the placenta as pregnancy progresses and also in the perinatal period. Subclinical dysfunction of cardiomyocytes may occur as a result of impaired mechanisms protecting the heart against anti-angiogenic factors or as a result of increased secretion of this substance observed in PPCM. Its concentration is also increased in pre-eclampsia early in pregnancy, even before the diagnosis is made.<sup>25–27</sup> It has also been noted that angiogenic imbalance in the form of an increase in sFLT1/placental growth factor (PLGF) ratio can lead to heart failure.<sup>28</sup> There are reports in the literature that another substance with anti-angiogenic effects, sVEGFR1 (soluble version of vascular endothelial growth factor receptor-1), which

disrupts homeostasis in various vascular beds, is also presumed to be important in the pathogenesis of the diseases described.<sup>24,29,30</sup>

Twin pregnancies are a risk factor for both peripartum cardiomyopathy and preeclampsia. In such pregnancies, the placenta is larger and therefore secretes more antiangiogenic factors into the maternal circulation.<sup>31</sup> In both conditions, increased levels of inflammatory factors and mediators such as interleukin-6, interferon gamma and CCL2/MCP1 have also been found.<sup>32–36</sup> It is important to mention that changes in SOD activity can lead to the development of PPCM and PE by increasing the amount of reactive oxygen species that exert negative effects on the vascular endothelium. Furthermore, it is worth noting that prolactin under physiological conditions promotes angiogenesis and has a protective effect on the endothelium. However, pregnancy-induced oxidative stress can lead to the formation of a shorter form of prolactin, 16kDa, which has cardiotoxic effects.<sup>37</sup> The use of bromocriptine as a prolactin inhibitor is still under investigation.

Preeclampsia as well as peripartum cardiomyopathy is more common in pregnant women with diabetes, obesity, multiple pregnancies and late maternal age.<sup>38,39</sup>

In conclusion, the data presented above suggest that both conditions have a similar pathogenesis associated with increased release of anti-angiogenic factors from the placenta, increased levels of inflammatory factors, and decreased SOD activity.

## Cardiovascular Changes

In preeclampsia, researchers describe two theories regarding cardiac function. One indicates the presence of low cardiac output (CO) and elevated systemic vascular resistance (SVR), and the other states that cardiac output is elevated with slightly increased systemic vascular resistance.<sup>40–42</sup> In a 2012 study, untreated preeclamptic patients with increased SVR and higher CO were described.<sup>43</sup> The most commonly observed hemodynamic changes in preeclampsia are elevated CO along with a hyperdynamic left ventricle and a subsequent decrease in CO and hypertrophy of the left ventricular wall. Under increased afterload and sustained stress, such a hypertrophied ventricle develops diastolic dysfunction.<sup>10</sup> It is worth mentioning that, according to recent reports, preeclampsia can also occur in the newborn, as left ventricular hypertrophy (LVH) has been observed in the offspring of mothers who have experienced PE.<sup>44,45</sup>

Patients with peripartum cardiomyopathy often have systolic dysfunction with reduced left ventricular ejection fraction and left ventricular dilatation. Less commonly, left ventricular hypertrophy or diastolic dysfunction may be observed. Some studies suggest that patients with hypertensive disorders of pregnancy (HDP) usually have smaller left ventricular end-diastolic and systolic dimensions due to left ventricular hypertrophy.<sup>46,47</sup> However, the difference in left ventricular dimensions and wall thickness between patients with hypertensive disorders of pregnancy and patients with PPCM has not been proven in all studies.<sup>48,49</sup> Taking into account the changes in the right ventricle, it should be noted that its dysfunction may occur in patients with both PE and PPCM.<sup>50</sup> Similar findings were demonstrated by cardiac MRI.<sup>51</sup>

## Diagnosis and Clinical Presentation

In patients with severe preeclampsia and symptoms of heart failure, peripartum cardiomyopathy should always be listed as a differential diagnosis.<sup>52</sup> It is very important to recognize peripartum cardiomyopathy promptly to improve patient outcomes and facilitate earlier intervention. This condition is defined by four criteria: (1) no identifiable cause of heart failure; (2) development of heart failure late in pregnancy or within a few months after delivery (3) no recognized heart disease before the last month of pregnancy; and (4) left ventricular systolic dysfunction confirmed by classical echocardiographic criteria.<sup>53</sup> Distinguishing normal findings in late pregnancy from subtle signs of heart failure (foot swelling, exertional dyspnea, fatigue) is a challenge for the medical team.<sup>54</sup> It is largely a diagnosis by exclusion. Other causes of heart disease, both congenital and acquired, such as pulmonary hypertension, myocardial infarction causing left ventricular dysfunction, or valvular heart disease should be excluded first.<sup>1,11,55</sup>

In the last month of pregnancy, many women develop symptoms similar to those of heart failure - palpitations, exertional dyspnea, nocturnal dyspnea, cough, foot edema, fatigue.<sup>7,11,56,57</sup> On examination, features of right-sided (edema, elevated jugular venous pressure) and left-sided (pulmonary rales) overload may be found,<sup>58</sup> apical beat displacement, murmurs due to tricuspid or mitral regurgitation.<sup>56</sup> Heart failure may be manifested by pleural effusions.

This may be related to hypoalbuminemia and capillary leakage syndrome occurring in preeclamptic patients.<sup>59</sup> Less commonly, PPCM manifests with cardiogenic shock requiring mechanical or inotropic circulatory support or symptomatic or even unstable arrhythmias<sup>60,61</sup> and coronary artery thrombosis.<sup>62</sup>

Preeclampsia is often associated with complaints such as dyspnea, headache, epigastric pain, nausea, vomiting or visual disturbances. These symptoms are registered by the mother and are usually the first indication for diagnosis.<sup>63</sup> However, the most alarming symptoms are coexisting proteinuria and hypertension. This does not mean that deviations do not exist. It should be noted that some pregnant women present the absence of proteinuria, which determines the need to expand the diagnostic requirements.<sup>64</sup> According to studies, the criterion of headache as diagnostic for severe preeclampsia is also ambiguous and therefore unreliable.<sup>63,65</sup> There are also abnormalities in cardiocographic recordings and abnormal spectrum of flow in the placental-fetal vessels. So, how to correctly diagnose preeclampsia? According to the diagnostic scheme for preeclampsia, blood pressure should be the first concern. In women with a previously normal blood pressure after the 20th week of gestation, a blood pressure of 140/90 mmHg or higher and a proteinuria of  $\geq 300$  mg in a 24-hour collection of urine (a result of at least +1 in a strip test or a protein/creatinine ratio of  $\geq 0.3$ ) are indicative. In contrast, finding at least one of the following: BP  $\geq 160/110$  mmHg confirmed on two occasions (at least 6 hours apart) in a patient lying in bed, or proteinuria  $\geq 5$ g/day (result of 3+ on a strip test in two urine samples collected at least 4 hours apart), or signs of organ dysfunction such as acute kidney injury (serum creatinine  $\geq 1$  mg/dL, 90  $\mu$ mol/L), hepatic complications (increase in transaminase activity - AspAT or ALT  $> 40$  IU/L), pulmonary edema or cyanosis, neurological complications (eclampsia, blackouts, stroke, clonic spasm, psychiatric disorders, severe headache, and dark circles), right upper quadrant or epigastric pain, presence of thrombocytopenia (platelet count  $< 150,000/\mu$ L, DIC, hemolysis), or signs of fetal distress (abnormal flow in the umbilical artery, IUGR, or intrauterine fetal demise) change the diagnosis to severe preeclampsia. However, this definition varies from country to country.<sup>38,66</sup> Nonetheless, the non-specificity of the presenting symptoms calls for individualized attention and careful diagnosis.<sup>63,65</sup>

## Management

Blood tests are necessary in all patients diagnosed with PPCM, but troponins, creatine kinase (CK-MB), and creatinine cannot definitively confirm or exclude the diagnosis of PPCM. If peripartum cardiomyopathy is suspected, chest radiography should be ordered at every stage of pregnancy. This examination is safe because it shows little radiation to the fetus. It enables to visualize radiological signs of heart failure such as pulmonary congestion, cardiomegaly, and pleural effusion.<sup>67</sup> Another examination used is the ECG. It is classified as a non-specific test showing arrhythmias (atrial fibrillation and flutter, ventricular tachycardia) or sinus tachycardia.<sup>68</sup> We should also mention endomyocardial biopsy, which is considered controversial by many.<sup>69</sup> It has a specificity of 99% and a sensitivity of 50%, so its result may also be positive in other conditions such as myocarditis.<sup>8</sup> Biopsy is indicated when the cause causing the symptoms is unclear and a disease requiring specific treatment is suspected - infiltrative or storage diseases (amyloidosis, hemochromatosis, sarcoidosis), myocarditis. MRI has not detected a specific variable to help distinguish peripartum cardiomyopathy from other forms of cardiomyopathy but is useful in the differential diagnosis when other methods (echocardiography and coronary angiography) have failed to establish the diagnosis, especially in the diagnosis of pericardial disease and cardiac tumors.<sup>70-72</sup> This will allow the medical team to quickly implement appropriate treatment.

There is still a lack of clinical trials comparing the treatment modalities for PPCM and selecting the best therapy for them, so patients should be started on standard therapeutic management dedicated to heart failure to reduce myocardial preload and afterload, increase contractility, and prevent complications and mortality. Angiotensin Converting Enzyme Inhibitors (ACEI) - hydralazine with nitrates or without them (reduction of arterial pressure, antiatherosclerotic effect, inhibition of left ventricular enlargement and fibrosis),  $\beta$ -blockers (do not use atenolol or metoprolol), digoxin (for atrial arrhythmias) and diuretics (reduce pulmonary congestion and alleviate symptoms, reducing preload) should be implemented, with loop diuretics available in the hospital setting, and fluid intake limited to 2 liters per day.<sup>7,73</sup> According to American and European guidelines, limiting sodium intake is the primary control. It is worth remembering that excessive diuresis can cause uterine hypoperfusion and hypotension in the mother. More careful observation of the risk of fetal bradycardia and monitoring of fetal growth in women taking beta-blockers may be considered.<sup>74</sup> Aldosterone receptor blockers (aldosterone antagonists) - eplerenone and spironolactone should not be used in pregnant women because they cross the placenta.<sup>68</sup> Given the safety of cardioversion or defibrillation during pregnancy, they should be performed in emergency situations.<sup>75</sup>

The medical team must also consider the safety of the neonate; therefore, it is worth remembering that angiotensin-converting enzyme inhibitors and ACEI should not be used in late pregnancy and puerperium, nor should class III (amiodarone) or class IV (verapamil) antiarrhythmics.<sup>5</sup> Pregnancy and puerperium increase thromboembolic risk, as do most types of cardiomyopathies, so low molecular weight heparin (LMWH), which does not cross the placental barrier, is recommended to prevent this.<sup>76</sup> Its dosing is more frequent, and the dose is determined by weight in early pregnancy. Warfarin, unlike heparin, crosses this barrier and therefore cannot be used in pregnancy.<sup>77,78</sup> According to European guidelines, bromocriptine is class IIB, whereas American guidelines consider it a drug still under investigation.<sup>79,80</sup> In 2016, a study with the combined use of bromocriptine was conducted in Germany. 96% of patients showed improvement and 47% showed “full recovery”. In 15% of the subjects, no improvement was proven, but their baseline LVEF was  $\leq 0.25$ .<sup>47</sup> Full recovery (LVEF  $\geq 50\%$ ) occurred in 52% of patients in the one-week bromocriptine group and 68% in the eight-week group.<sup>81</sup> Based on these two studies, bromocriptine treatment was associated with a high rate of complete LV recovery. It is worth mentioning that levosimendan is preferred as an inotropic drug in Europe, but it is not available in Canada and the United States.<sup>82</sup> The authors chose to present the drugs discussed in the text used in PPCM in Table 1.

**Table 1** Selected Drugs Used in PPCM Prepared on the Basis of Hilfiker-Kleiner et al.<sup>81</sup>

Group of Drugs	Substance Name	Comment
ACEI	Captopril Enalapril Ramipril	Contraindicated in pregnancy (risk of kidney damage, malformations and hypotension in the fetus) No data on risk during pregnancy
Sartans	Candesartan Valsartan	Contraindicated during pregnancy and lactation
Potassium-sparing drugs	Spironolactone  Eplerenone	Contraindicated during pregnancy and lactation (possible antiandrogenic effect on the fetus) Adverse effects not fully understood (FDA Category B)
Beta-blockers	Metoprolol extended-release Carvedilol Atenolol	Rare risk of bradycardia and respiratory failure in the newborn. Cardioselective agents preferred during pregnancy Risk of low birth weight and fetal bradycardia when administered in the second or third trimester
Vasodilators	Hydralazine Nitroglycerin	In combination with nitrates as a safe alternative to ACEI/sartans during pregnancy Risk of hypotension
Diuretics	Hydrochlorothiazide  Furosemide	Risk of decreased placental blood flow. Use only if there are signs of stasis in the pulmonary circulation Use only if evidence of pulmonary stasis
Inotropic drugs	Digoxin Dobutamine Milrinone	To be considered at low EF. Caution for poisoning when used in high doses Not enough evidence for safe use during pregnancy
Anticoagulants	Warfarin  Low-molecular-weight heparin	Risk of abnormal development of bones of the nose, limbs, articular cartilage, and risk of abnormalities of the visual, auditory, and central nervous systems Use if treated with bromocriptine. Include in women with EF < 35%.
Prolactin inhibitor	Bromocriptine	Increases thromboembolic risk; class of recommendation IIa, data reliability level C Medication schedule: 2.5 mg 2 ×/d for 2 weeks, then 2.5 mg once/d for another 6 weeks.
Heart rate reducing drugs	Ivabradine	Use in case of high heart rate. Contraindicated during pregnancy and lactation
Angiotensin receptor neprilysin inhibitors (ARNI)	Sacubitril/valsartan	Contraindicated during pregnancy and breastfeeding

**Notes:** Red, contraindicated during pregnancy; blue, no studies on harm to the fetus.

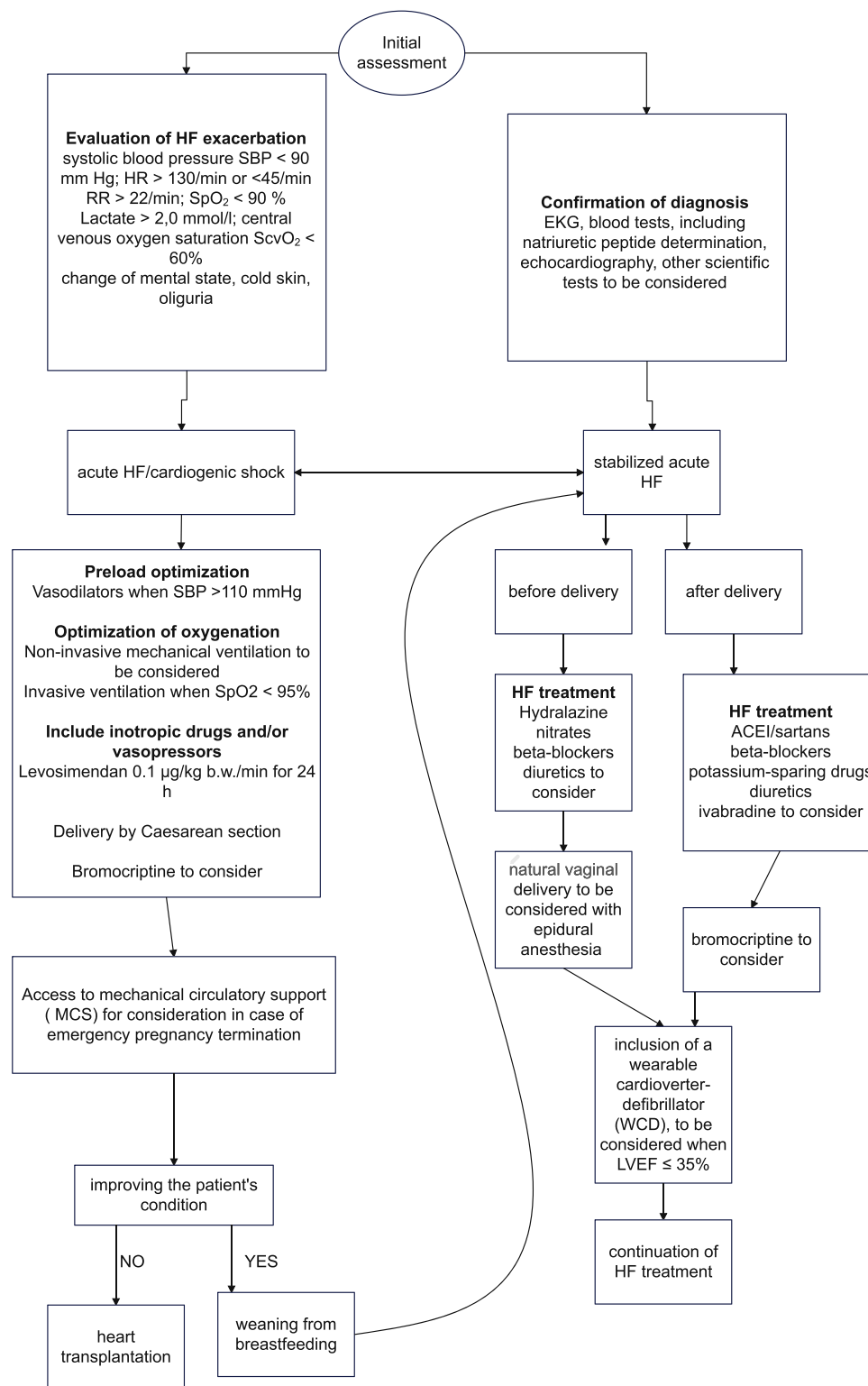


The management of pregnant women with PPCM is based on obstetric guidelines and recommendations. Vaginal delivery is chosen instead of cesarean section. It has the advantage of greater hemodynamic stability, low blood loss, and lower risk of postoperative infection. Cesarean section is associated with an increased risk of uteritis and pulmonary embolism.<sup>83</sup> However, according to AHA and ESC guidelines, cesarean section should be considered for acute heart failure and obstetric indications.<sup>80,84</sup> In patients in whom PPCM is diagnosed before delivery, it is advisable to appoint a team of physicians - obstetricians, anaesthesiologists and cardiologists, who will individually select the management regarding the time and mode of delivery.<sup>80,85</sup> The treatment algorithm is outlined by the authors below (Figure 1).

The 2018 Guidelines of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) disagree, citing the possibility of treating patients with mild preeclampsia in the outpatient setting and emphasizing that preeclampsia is an indication for hospitalization, where both maternal and fetal status can be monitored. Urgent hospitalization is recommended for women with systolic blood pressure  $\geq 160$  mmHg and/or diastolic RR  $\geq 110$  mmHg in multiple measurements over 15–30 minutes. Efforts should be made to lower blood pressure pharmacologically with labetalol or nicardipine and magnesium sulfate. If there is no improvement, termination of pregnancy may be considered. As with gestational age  $>37$  weeks, significant worsening of liver function markers, renal function, hemolysis, decreased platelet count, intravascular coagulation syndrome (DIC), eclampsia or other neurologic signs with visual disturbances, headache, signs of premature placental separation, fetal life threatening, or intrauterine fetal death. If premature termination of pregnancy is necessary, a 48-hour intramuscular course of steroid therapy with betamethasone or dexamethasone at a total dose of 24 mg in pregnancies  $< 34$  weeks is used to stimulate fetal lung maturity. Treatment for preeclampsia includes hypotensive therapy-until blood pressure values  $<160/110$  mmHg are achieved in women with severe hypertension, followed by implementation of chronic oral drug therapy in the puerperium, treatment with low-molecular-weight heparin (with daily proteinuria  $> 3.5$  g) and intravenous magnesium sulfate, which prevents eclampsia and is responsible for fetal neuroprotection, is continued. In the puerperium, hypotensive treatment and surveillance are continued for at least 48 hours after delivery due to the risk of postpartum eclampsia.<sup>5</sup>

## Complications

It is important to note the importance of monitoring and follow-up of patients in the form of annual echocardiographic evaluation to catch possible complications of PPCM and side effects of treatment more quickly.<sup>86</sup> For this condition, the prognosis largely depends on the return of left ventricular function and size within 6 months after delivery.<sup>87</sup> Another study concluded that patients with PPCM, should be followed for 6–12 months after diagnosis.<sup>88</sup> Demakis et al concluded that left ventricular dysfunction was evident in about half of 27 women, with a 5-year mortality rate of 85%.<sup>53</sup> Other authors have concluded that the disease is irreversible if left ventricular systolic function does not return to normal within 6 months after delivery.<sup>78</sup> The most common complication of PPCM appears to be thromboembolism, occurring in 6.6% of women with PPCM in the United States;<sup>12</sup> a similar incidence (6.8%) was recorded in the EURObservational Research Programme Worldwide Registry study.<sup>21</sup> Thrombosis may occur in both the right and left ventricle.<sup>89–91</sup> Another noteworthy complication of peripartum cardiomyopathy is cardiogenic shock found in 2.6% of women in the United States between 2004 and 2011. In the face of these complications, mechanical circulatory support was used in 1.5% of cases and heart transplantation was performed in only 0.5% of women.<sup>12</sup> It is worth noting that between 2004 and 2011 in the United States, 2.9% of women underwent cardiac implantation and 2.1% suffered cardiac arrest.<sup>12</sup> Another analysis of 9841 cases with PPCM found that arrhythmias were present in 18.7% of cases, including ventricular tachycardia in 4.2%.<sup>8</sup> The statistics are alarming, as peripartum cardiomyopathy accounts for 5% of cases eligible for heart transplantation among women in the United States.<sup>92</sup> Within 5 years of diagnosis, as many as 25% of women die from PPCM in developing countries,<sup>93</sup> while neonatal mortality ranges from 0% to 75%.<sup>94,95</sup> Return of left ventricular size and function in patients with peripartum cardiomyopathy has been described in relation to hypertensive disorders of pregnancy as a variable predictor. Researchers have demonstrated a protective effect of hypertensive disorders in pregnancy and more significant left ventricular recovery among patients with PPCM.<sup>46,96,97</sup> On the other hand, another study demonstrates that concurrent hypertensive disorders in pregnancy and PPCM leads to higher mortality.<sup>47</sup> Haghikia et al conducted the largest prospective cohort study that verified the effect of hypertension in pregnancy on outcomes among women with PPCM and did not prove an association between outcomes and HDP.<sup>48</sup>



**Figure 1** Treatment algorithm for PPCM prepared on the basis of Hilfiker-Kleiner et al.<sup>81</sup>

A characteristic of preeclampsia and peripartum cardiomyopathy is the recurrence rate, which follows a similar pattern in subsequent pregnancies. Early pre-eclampsia is considered to be the more severe phenotype, with a 34% risk of recurrence,<sup>98</sup> and in patients with PPCM these figures are 15–50%.<sup>81,99</sup> Despite the full recovery of some women, there is concern about the risk of recurrence of the condition during a subsequent pregnancy.<sup>1,100,101</sup> Elkayam et al in

their study showed that among women after PPCM in whom left ventricular dysfunction persists, 54% develop cardiac dysfunction and 9% die in subsequent pregnancies.<sup>102</sup> Currently, authors have not reached consensus on guidelines for future pregnancy in women who have experienced peripartum cardiomyopathy, but left ventricular function is the most important prognostic factor.<sup>103</sup> It is worth remembering that the Mirena and Implanon intrauterine system (progestational contraceptive methods) are considered the safest and most effective methods of contraception in women who have experienced PPCM.<sup>78</sup>

For preeclampsia, maternal mortality two years after onset ranges from 0% to 9%, with higher rates seen in women of African descent, like PPCM.<sup>104</sup> When, at the time of diagnosis, the level of heart failure reaches Class I or II according to the New York Heart Association (NYHA), outcomes are generally better than for Class III and IV.<sup>104,105</sup>

## Conclusions

Linking the pathogenesis of these conditions - preeclampsia and peripartum cardiomyopathy - can provide a wealth of information regarding treatment, risk of recurrence in subsequent pregnancies, and accurate diagnosis. Although PPCM is a rare complication of preeclampsia, the interdisciplinary medical team should be aware of its likelihood in patients with preeclampsia.

Further extensive research into effective, causal treatments, such as the use of anti-SFLT1, is needed. Future publications should also provide more evidence on the importance of the role of prolactin in PPCM. Then perhaps bromocriptine will be included in the ESC guidelines as an indispensable part of the treatment of patients. It is also important to answer the question of why some patients who have relapsed experience a recurrence of heart failure after a subsequent pregnancy, despite the initiation of effective treatment.

Our analysis highlights the need to better understand the comorbidity and common etiology of PE and PPCM, and the need to include patients with these conditions in equivalent clinical trials.

## Disclosure

The authors report no conflicts of interest in this work.

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