Review Article

Thromboembolism in peripartum cardiomyopathy: a systematic review

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Background: Women with peripartum cardiomyopathy (PPCM) are at an increased risk of arterial and venous thromboembolic events. The review summarizes the evidence on the incidence of thromboembolic complications in women with PPCM, diagnostic approaches, related outcomes, and effects of therapies that have been used.

Methods: English articles were retrieved from Web of Science and PubMed using search terms to capture studies related to PPCM (or postpartum cardiomyopathy) and all combinations of thrombosis- and embolism-related keywords. A total of 347 articles from PubMed and 85 from Web of Science were obtained, and after removing duplicates, 327 articles were screened for original data and classified into four domains: epidemiology, risk factors, diagnosis, and therapy of thromboembolism in PPCM. Ultimately, 30 articles were included. Data were synthesized in summary tables for each domain.

Results: Studies in the United States and Europe reported varying incidence for thromboembolism in PPCM, up to 14% in 6 months. Risk factors include elevated levels of coagulation factors, decreased protein C and S activity, decreased fibrinolysis, and a low left ventricular ejection fraction (LVEF). Cesarean delivery and post-operative status were correlated with a higher incidence of thromboembolic complications. Diagnosis relied mostly on ultrasonography and magnetic resonance and depended on the suspected location of thrombus. Anticoagulation has been used mostly for PPCM patients with a reduced LVEF, with the duration varying across guidelines and healthcare systems. Unfractionated heparin and low molecular weight heparin (LMWH) were considered safe choices during pregnancy, while warfarin and novel oral anticoagulants (NOACs) were used postpartum. The association of bromocriptine with risk of thromboembolic complications remains debated.

Conclusions: There are important gaps in our understanding of the epidemiology, risk stratification, and optimal secondary prevention of thromboembolism in PPCM. Larger prospective studies with detailed phenotyping are required.

Keywords: Peripartum cardiomyopathy (PPCM); thromboembolism; thrombosis; embolism; anticoagulation

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Introduction

Peripartum cardiomyopathy (PPCM) is an uncommon, idiopathic cardiomyopathy characterized by slowly progressing left ventricular (LV) dysfunction late in pregnancy, during delivery, or in the postpartum months of women with no known cardiovascular disease (1,2). Most women present after delivery with nonspecific symptoms of heart failure (HF), including shortness of breath or ankle swelling. Practitioners should have a high clinical suspicion for PPCM, and appropriate diagnostic testing should be ordered immediately.

Despite a better understanding of diagnostics, management, and treatment of PPCM, mainly as a result of registry-based work, uncertainties still exist about complications associated with PPCM, especially thromboembolic events. At the time of diagnosis of PPCM, there is an increased risk of arterial and venous thromboembolic events compared to those of the general female population of the same age (3). Understanding the underlying pathophysiology and risk factors for elevated thromboembolic risk is important because of the significant morbidity and mortality associated with these complications. An unselected approach e.g., antithrombotic treatment, is also unreasonable for women of reproductive age. Therefore, identifying women in need of closer monitoring during and after pregnancy when diagnosed with PPCM can help healthcare professionals optimize management of these patients.

Generally, studies have shown age (>40 and <20 years), antepartum diagnosis, non-Caucasian race, LV ejection fraction (LVEF) <30%, LV end-diastolic diameter of >60 mm, biventricular dysfunction, and delay of diagnosis are risk factors for adverse outcomes (4). One dangerous complication of PPCM is the increased risk of arterial and venous thromboembolic events, which can eventually lead to catastrophic maternal consequences [e.g., stroke, pulmonary embolism (PE)] and potentially fetal demise. Prophylactic anticoagulation can be considered in some high-risk women, and in the presence of LV thrombus, therapeutic anticoagulation should be started immediately. Long-term antithrombotic therapy for prophylaxis, however, is unlikely to be efficacious, due to the hazard of fetal toxicity and bleeding with subsequent pregnancies. Also, compliance would also be a problem because of these issues. Therefore, risk stratification for thromboembolism after a diagnosis of PPCM and patient selection for anticoagulation would be important.

In this review, we summarize the evidence regarding the incidence of thromboembolic complications in women with PPCM, diagnostic approaches, related outcomes, and effects of therapies that have been used. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-945/rc).

Highlight box

Key findings

- The incidence of thromboembolism in peripartum cardiomyopathy (PPCM) varies worldwide, up to 14% in 6 months. Risk factors include elevated coagulation factors, decreased protein C and S activity, decreased fibrinolysis, and low left ventricular ejection fraction (LVEF). Anticoagulation has been used mostly for PPCM patients with a reduced LVEF, with varying therapy duration. Guidelines are based on expert consensus (level of evidence C), as high-quality studies are lacking.

What is known and what is new?

- Unfractionated heparin and low molecular weight heparin are considered safe choices during pregnancy for secondary prevention, although patient selection for anticoagulation is problematic and evidence is limited. Besides established concomitant indications (e.g., atrial fibrillation or left ventricular thrombus), the risk-benefit profile for anticoagulation is unclear for the remaining patients.
- Warfarin and novel oral anticoagulants can be used postpartum. The association of bromocriptine with risk of thromboembolic complications remains debated.

What is the implication, and what should change now?

- There are important gaps in our understanding of the epidemiology, risk stratification, and optimal secondary prevention of thromboembolism in PPCM. Larger prospective studies with detailed phenotyping are required.

Methods

Data source/search strategy

The search strategy aimed to identify studies in patients with established or suspected PPCM (using the terms peripartum cardiomyopathy or postpartum cardiomyopathy) in the title or abstract. Patients may not have had an established diagnosis of PPCM, but they were in the process of being worked up. The search strategy also aimed to identify articles which referred to the outcome of thromboembolism, including both arterial and venous events.

Relevant articles in English language were retrieved from Web of Science and PubMed queries using the following search terms: (((((((peripartum) OR (period, peripartum

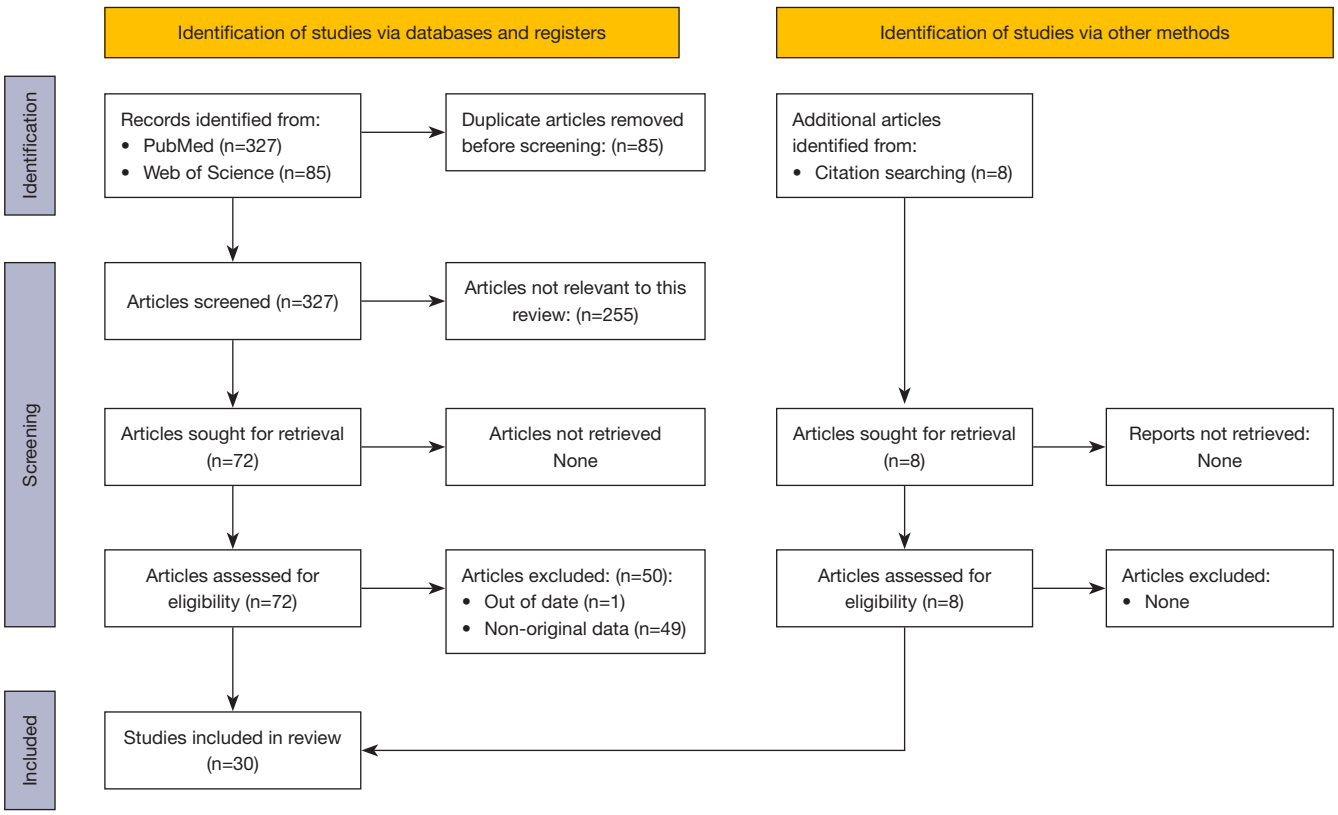

Figure 1 PRISMA flow diagram of study selection.

[MeSH terms])) OR (postpartum)) OR (postpartum period [MeSH terms])) AND ((cardiomyopath*) OR (cardiomyopathies [MeSH terms]))) OR (peripartum cardiomyopathy)) OR (postpartum cardiomyopathy) AND (English [Filter])) AND ((stroke) OR (thromb*) AND (English [Filter])). This search was done from inception until August 2022. Covidence (https://www.covidence.org/) was used to collect, review, and select relevant articles.

Study selection and classification

A total of 327 total articles were retrieved from PubMed and 85 from Web of Science. Of those, duplicates were removed, and the remaining 327 articles were screened and then classified into 4 domains: epidemiology, risk factors, diagnosis, and therapy of thromboembolism in PPCM. Initially, 72 articles were retained as relevant to this review; however, 49 were excluded because of lack of original data (e.g., review articles, case reports, commentary, etc.). Of the excluded articles, references were scanned for any other articles that could be included; this yielded 8 additional articles in addition to the 22 original included articles. One article was excluded due to being clearly outdated, leaving a total of 30 articles for this review. The workflow of the article selection process is summarized in *Figure 1*.

Study quality/data synthesis

Studies that met inclusion/exclusion criteria were included in the systematic review. A summary table describing baseline features for each study (study design, inclusion criteria, definition of PPCM, mean age, number of subjects, and follow-up period) was created for study comparison purposes, summarized in *Table 1*. The findings for the four domains of interest (epidemiology, risk factors, diagnosis, and therapy of thromboembolism in PPCM) were summarized in corresponding tables. For thromboembolism, we also reported subsequent mortality and persistent or chronic thromboembolism. Risk was reported as hazard ratio (HR), odds ratio, or relative risk, depending on the study. Finally, therapy for thromboembolism was reported as % of therapy used in each study with corresponding outcomes of

Table 1 Baseline study features

Author [year]	Country	Study design	Inclusion criteria	PPCM definition	Age (years)†	Follow-up period (months)†	N
Fett [2005], (5)	Haiti	P cohort	(I) LVEF <45% or LVFS <30% on TTE	Unexplained appearance of HF in previously healthy patient during the last month of pregnancy or up to 5 months postpartum	32.2	6	98
Sliwa [2006], (6)	South Africa	P cohort	(I) Age 16–40 years; (II) NYHA II–IV; (III) PPCM definition; (IV) LVEF 40% by TTE; (V) sinus rhythm	Disorder of unknown etiology in which symptoms of HF occur between the last month of pregnancy and 5 months postpartum	31.6±6.6	6	100
Hu [2007], (7)	China	P clinical trial	(I) PPCM definition; (II) LVEF of 40% by TTE	Cardiomyopathy of unknown cause that occurs in pregnant females in during the first 5 months postpartum	28±6.5	6	106
Duran [2008], (8)	Turkey	P cohort	(I) PPCM definition; (II) LVEF <45% by TTE	Cardiac failure occurring in the last month of pregnancy or within 5 months after delivery	32±7	47.5±38.6	33
Goland [2009], (9)	USA	R cohort	(I) LVEF <45% by TTE; (II) PPCM definition; (III) absence of identifiable cause of HF	Cardiomyopathy of unknown cause that occurs during pregnancy or the first 5 months after delivery	29±7	19±25	182
Gentry [2010], (10)	USA	Case control	(I) LVEF ≤45% TTE or radionuclide ventriculography; (II) clinical symptoms of HF; (III) definition of PPCM; (IV) absence of identifiable cause of cardiac failure	HF in women without preexisting heart disease during the last month of pregnancy or within 5 months after delivery	26.3±5.2	NA	28
Mandal [2011], (11)	India	R cohort	(I) PPCM definition; (II) LVEF <45%, LVFS <30%, LVEDD >2.7 cm/m^2	Dilated cardiomyopathy with severe LV dysfunction leading to HF during the last month of pregnancy or within 5 months of delivery with no determinable etiology for the cardiac failure and no demonstrable heart disease prior to the last month of pregnancy	21–30	6	36
Renz [2011], (12)	Australia	R case series	(I) PPCM definition; (II) no family history of PPCM	Life threatening cardiac disorder affecting previously healthy women late in their pregnancy or in their early postpartum	20–40	15	6
Biteker [2012], (13)	Turkey	P cohort	(I) Symptoms of CHF developed towards the end of pregnancy; (II) PPCM definition; (III) absence of recognizable heart disease before last month of pregnancy; (IV) LVEF <45% by TTE	Idiopathic or familial cardiomyopathy presenting with HF secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery	27.0±5.2	39	42
Tibazarwa [2012], (14)	South Africa	P cohort	(I) ≥17 years old who fulfilled the diagnostic criteria for PPCM	Form of HF with poorly understood etiology, occurring between the last trimester of pregnancy and up to the first 5–6 months postpartum	29±7	6	78

Table 1 (*continued*)

Table 1 (*continued*)

Author [year]	Country	Study design	Inclusion criteria	PPCM definition	Age (years)†	Follow-up period (months)†	N
Haghikia [2013], (15)	Germany	Case control	(I) LVEF <45% by TTE; (II) PPCM definition	Diagnosis of exclusion in pregnancy or in the months following delivery, when no other cause of HF is found, characterized by a LVEF <45% but not always associated with LV dilatation	34±6	6±3	115
Laghari [2013], (16)	Pakistan	Case series	(I) PPCM definition; (II) absence of another identifiable cause for the HF; (III) absence of recognizable heart disease prior to the last month of pregnancy; (IV) LVEF <45% TTE	HF that affects women in the last month of pregnancy or within 5 months of delivery	27.4±6	6	45
Kolte [2014], (17)	USA	R cohort	(I) PPCM definition; (II) absence of another identifiable cause of HF; (III) LVEF <45%, LVFS <30% on TTE	Idiopathic dilated cardiomyopathy that presents in women during the latter part of pregnancy or the first several months after delivery	30.3±7	NA	34,219
Blauwet [2016], (18)	USA	P cohort	(I) HF in last month of pregnancy or within 13 weeks after delivery; (II) no other demonstrable cause of HF; (III) LVEF <45% within 13 weeks after delivery	Pregnancy-associated cardiomyopathy of unknown cause resulting in considerable morbidity and mortality in young, otherwise healthy women	NA	12	100
Damp [2016], (19)	USA	R cohort	(I) At least 18 years of age; (II) no previous history of cardiac disease; (III) LVEF ≤45% on TTE; (IV) non-ischemic cardiomyopathy	Development of HF late in pregnancy or in the months after delivery	30±6	12	98
Li [2016], (20)	China	R cohort	(I) PPCM definition; (II) LVEF <45% or LVFS <30% on TTE	Dilated cardiomyopathy of uncertain origin that occurs in women during pregnancy or postpartum with no preexisting heart disease	28±6	12	71
Goland [2016], (21)	NA	Case control	(I) Women at least 12 months after clinical presentation with PPCM who experienced LV recovery (LVEF >50%)	Development of idiopathic cardiomyopathy during pregnancy or within 5 months of delivery with LV systolic dysfunction as assessed by TTE with LVEF <45%	35.5±6	NA	41
Sheppard [2016], (22)	Canada	P cohort	(I) Women at least 18 years of age with no previous history of cardiac disease; (II) LVEF of <45% at the time of enrollment; (III) evaluation consistent with idiopathic nonischemic cardiomyopathy	Clinical diagnosis	30±6	12	97
Ware [2016], (23)	USA	P cohort	(I) PPCM definition	Development of maternal systolic HF late in pregnancy or early in postpartum period	~34	12	172
Ersbøll [2017], (24)	Denmark	R cohort	(I) >18 years of age; (II) PPCM definition; (III) LVEF <45% on TTE; (IV) no history of heart disease or obvious other cardiac pathology	Cardiomyopathy of unknown cause with LV systolic dysfunction towards the end of pregnancy or in the first months after delivery	31.7±6.3	12	61

Table 1 (*continued*)

Table 1 (*continued*)

Author [year]	Country	Study design	Inclusion criteria	PPCM definition	Age (years)†	Follow-up period (months)†	N
Sliwa [2017], (25)	ESC and non-ESC countries	P cohort	(I) Patients diagnosed with PPCM via exclusion clinically	Idiopathic form of cardiomyopathy presenting with HF secondary to LV dysfunction towards the end of pregnancy or in the months following delivery	30.7±6.4	6	500
Ekizler [2019], (26)	Turkey	R cohort	(I) >18 years old with PPCM	Unexplained cardiomyopathy with LVEF <45% presenting toward the end of pregnancy or soon after delivery in a previously healthy woman	29.1±6.3	12	82
Honigberg [2019], (27)	North America	P cohort	(I) ≥18 years of age; (II) absence of underlying cardiac disease; (III) LVEF <45% on TTE; (IV) excluded alternate etiologies of cardiomyopathy; (V) PPCM definition	Dilated cardiomyopathy marked by systolic dysfunction occurring at the end of pregnancy or in the early postpartum period	30±6	12	100
Sliwa [2020], (28)	Africa	P cohort	(I) Peripartum state; (II) signs and/or symptoms of HF; (III) LVEF <45% on TTE; (IV) exclusion of other causes of HF; (V) PPCM definition	HF towards the end of the pregnancy or in the months following delivery	31±6	6	740
Farhan [2021], (29)	Iraq	P cohort	(I) Peripartum state; (II) signs and/or symptoms of HF; (III) LVEF ≤45% by TTE; (IV) exclusion of other causes of HF	Clinical diagnosis (not defined in the actual study)	32.1±6.8	6	64
Hoevelmann [2021], (30)	Africa	P cohort	(I) PPCM definition; (II) no other identified causes of HF; (III) LVEF ≤45% on TTE	Pregnancy associated HF towards the end of pregnancy or within the first five months after delivery	30.0±5.9	12	35
Jackson [2021], (31)	Europe	Case control	(I) Peripartum state; (II) signs and/or symptoms of HF; (III) LVEF ≤45% on TTE; (IV) exclusion of alternative causes of HF; (V) PPCM definition	HF induced cardiomyopathy	30.5±6	6	752
Ravi Kiran [2021], (32)	India	P cohort	(I) PPCM definition; (II) >18 years of age	Cardiomyopathy with a LVEF usually <45% presenting toward the end of pregnancy or in the months after delivery in a woman without previously known structural heart disease	25.4±2.9	6	43
Petryka-Mazurkiewicz [2021], (33)	Poland	P cohort	(I) PPCM definition	cardiomyopathy presenting towards the end of pregnancy or in the months following delivery where no other cause of HF was found	30.5±5.9	12	21
Luthra [2022], (34)	USA	R cohort	(I) >18 years; (II) PPCM diagnosis	Idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction	30±7	11 years	43,986

†, data are presented as mean, mean ± SD, or range. PPCM, peripartum cardiomyopathy; P, prospective; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; TTE, transthoracic echocardiography; HF, heart failure; NYHA, New York Heart Association; R, retrospective; LVEDD, left ventricular end-diastolic diameter; LV, left ventricular; CHF, congestive heart failure; NA, not available; ESC, European Society of Cardiology.

Table 2 Epidemiology of thromboembolism in PPCM

Author [year]	Incidence	Outcomes[†]
Mandal [2011], (11)	14% thromboembolic events on admission (3 central, 2 peripheral)	14% mortality died due to various causes (2 from CVA, 1 from CVA and intractable HF and 2 from pump failure) at 6 months
Laghari [2013], (16)	2.4% with LV clot on admission	0% mortality at 6 months
	8.8% with stroke on admission	
Kolte [2014], (17)	No noted admission events	Major adverse events in 13.5% patient
		1.3% in hospital mortality
		6.6% thromboembolism (most common complication)
Li [2016], (20)	3% with DVT on admission	0% mortality at 12 months
	3% with acute PE on admission	
Farhan [2021], (29)	4.7% thromboembolic events on admission	4.7% mortality due to SCD, torsades, or HF at 6 months
Jackson [2021], (31)	No noted admission events	Mortality: 6.5% for PPCM-no HTN; 1.2% for PPCM-HTN; 6.9% for PPCM-PE at 6 months
		Thromboembolism: PPCM-no HTN: 6.9%; PPCM-HTN: 7.3%; PPCM-PE: 9.0% at 6 months

[†], outcomes noted such as mortality, persistent/chronic VTE/chronic thromboembolic/pulmonary HTN at X months. PPCM, peripartum cardiomyopathy; CVA, cerebrovascular accident; HF, heart failure; LV, left ventricular; DVT, deep vein thrombosis; PE, pulmonary embolism; SCD, sudden cardiac death; HTN, hypertension; VTE, venous thromboembolism.

thromboembolic events.

Risk of bias

No formal assessment for risk of bias was done, as each study had widely different types of effect estimates.

Results

Epidemiology of thromboembolism in PPCM

Although the incidence of PPCM is well documented, the incidence of thromboembolism is not. Through our literature search, we were able to find only a few articles with documentation of thromboembolism and their outcomes. In one of the earliest prospective cohort studies based in the United States, of 27 patients with PPCM, approximately 30% experienced PE and 4% experienced systemic emboli within a 20-year period (35). In a more recent United States-based retrospective cohort study of 34,219 patients with PPCM, in-hospital thromboembolism was a significant and frequent complication presenting in 6.6% of patients during late pregnancy and early postpartum along with cardiac arrest (2.1%), acute pulmonary edema (1.8%), cardiogenic shock (2.6%) (17). Globally, rates of thromboembolism were similar if not higher. In a prospective cohort study based on the European Society of Cardiology (ESC) EURObservational Research Programme (EROP) PPCM registry of 735 women, about 6% of overall patients presented with thromboembolism within 6 months of PPCM diagnosis (31). Using the EORP-PPCM registry approach, in 64 PPCM patients from Iraq, 4.1% presented with thromboembolism within 6 months. Interestingly, among participants from Pakistan, 16% of patients were administered anticoagulation prophylactically, significantly greater than that of the global registry, and may also explain Pakistan's comparatively lower thromboembolic rate (29). In a retrospective cohort study conducted in India, among 36 patients with PPCM, 14% presented with thromboembolic events (three central and two peripheral) within 4–6 months of PPCM diagnosis. The study also reported a 14% mortality rate with a significant portion due to cerebrovascular accidents, despite all patients with thromboembolism receiving therapeutic anticoagulation (11). Similarly, a 10-year case series in Pakistan with 45 PPCM patients reported that 13% of patients had either LV clot or thromboembolism (16). Lastly, in China, a retrospective study of 71 PPCM patients reported a deep vein thrombosis (DVT) rate of 3% and acute PE rate of 3% with 0% mortality by at least 12-month follow-up (20). Findings are summarized in *Table 2*.

Risk factors for thromboembolism in PPCM

Increased levels of factor VII, VIII, X, fibrinogen, and von Willebrand; decreased protein C and S activity; and decreased fibrinolysis render PPCM patients more susceptible to thromboembolic events (27,31,36).

Additionally, a LVEF <35% has been associated with a high risk of thromboembolism (37). A retrospective review of 182 patients with PPCM showed that 46 patients (25%) presented with >1 major adverse event, including thromboembolic complications. All of them had LV thrombus, three had a cerebrovascular accident (plus PE in one), and two had leg ischemia requiring amputation. In these patients, significant predictors of major adverse events were LVEF fraction <25% [HR, 4.20; confidence interval (CI): 2.04–8.64] and non-Caucasian background (HR, 2.16; CI: 1.17–3.97), with the extent of initial myocardial insult as indicated by decreased LVEF at time of diagnosis being the most powerful one. In addition, 84% of major adverse events occurred during the first year after diagnosis of PPCM. The higher likelihood of major adverse events among non-Caucasian women aligns with previous studies that have highlighted a higher relative risk of unfavorable outcomes in African American women, compared to non-Hispanic white women (9). Indeed, a retrospective cohort study of all admissions with PPCM as the primary diagnosis from the Nationwide Inpatient Sample database over an 11-year-period showed a higher incidence of LV thrombus in African American patients with PPCM compared to Caucasian Americans (50.7% *vs.* 28.8%). The study also reported a higher prevalence of LV thrombus in patients with smoking, complicated diabetes, peripheral vascular disease, coagulopathy, and drug abuse with respect to patients without LV thrombus (34).

Cesarean delivery and post-operative status after cesarean section have also been correlated with a higher incidence of thromboembolic complications (DVT, stroke, and PE) in women with PPCM, with endothelial injury, immobility, and ventricular dilatation representing other potential contributors (4,38).

Furthermore, the expression of certain plasminogen activator inhibitor-1 (PAI-1) promoter variants has been reported to be higher and more prevalent in PPCM patients compared to healthy controls, and has been associated with a higher risk of thromboembolic complications, miscarriages, and mild pre-eclampsia (39).

Interestingly, 30 cases of stroke and 9 cases of myocardial infarction have been reported among postpartum women taking bromocriptine, most at higher dosages (40,41).

Finally, estrogen-containing preparations carry an increased risk of thrombosis, therefore they should be avoided in patients with PPCM (42). Findings are summarized in *Table 3*.

Diagnosis

Two-dimensional (2D) and three-dimensional (3D) echocardiography are valuable tools for evaluation of intraventricular thrombi (43). Considering the evidence linking thromboembolic complications to a LVEF of <0.30 at the time of PPCM diagnosis, recent studies suggest that earlier diagnosis, when cardiac function is more likely to be preserved, is important for preventing thromboembolism (44).

In a retrospective study using surgical confirmation as the gold standard, contrast-enhanced magnetic resonance imaging (MRI) demonstrated higher sensitivity and specificity in diagnosing such thrombi compared to transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). However, its adoption in clinical practice is limited due to the time required for the study and high cost (37,43).

When there is suspicion of lower extremity DVT, manifesting as extremity pain or swelling, the recommended initial diagnostic test is compression ultrasonography of the proximal veins. If there is still a suspicion of iliac vein thrombosis despite negative results, further evaluation with non-gadolinium-enhanced magnetic resonance venography is advised (45).

The initial evaluation of PE should include electrocardiogram, chest X-ray, and blood tests, while D-dimer testing for the exclusion of PE remains controversial. To establish a conclusive diagnosis, imaging techniques such as lung scintigraphy (ventilation/perfusion scan) or coronary tomographic angiography are necessary. Recently, pregnancy-adapted decision algorithms have shown promising preliminary data, but their effectiveness needs to be validated in larger-scale studies (46). Findings are summarized in *Table 4*.

Therapy

In an American Heart Association (AHA) scientific statement for the diagnosis and treatment of specific dilated cardiomyopathies, anticoagulation is recommended for patients with PPCM who present with a LVEF <30% (47). In a guidance for the care of acute PPCM, the ESC recommends anticoagulation with heparin to avoid cardio-embolic

Table 3 Risk of Thromboembolism in PPCM

Author (year)	Risk factor	Risk (HR, OR, or RR)
Fett [2005], (5)	Baseline echo features	28% patients with LVEF >50%
		Deceased *vs.* survivors: LVEDD 6.2 *vs.* 5.8 cm (P=0.08), LVEF 22% *vs.* 25% (P=0.12), LVFS 16% *vs.* 15% (P=0.46)
		2/15 deaths caused by thromboembolic events
Hu [2007], (7)	cTnT concentration	cTnT >0.04 ng/mL more persistent LV dysfunction (84.8% *vs.* 31.5%, OR =12.17, 95% CI: 4.17–35.57, P=0.0001)
Duran [2008], (8)	Baseline echo features	24.2% with recovered LVEF
		LVESD 5.5 cm (sensitivity 100%, specificity 76%, PPV 57%, NPV 100%), LVEF >27% (sensitivity 100%, specificity 80%, PPV 62%, NPV 100%)
		10% death (50% due to SCD)
Goland [2009], (9)	Non-Caucasians	Predictors of MAE: LVEF ≤25% (HR =4.20, CI: 2.04–8.64), non-Caucasian background (HR =2.16, CI: 1.17–3.97)
	Low baseline LVEF	Predictors of death or HTx: LVEF ≤25% (HR =5.38, CI: 1.87–15.50), non-Caucasian background (HR =4.78, CI: 1.81–12.66), delay of diagnosis ≥1 week (HR =5.51, CI: 1.21–25.04)
	Delay of diagnosis	7% death (27% due to SCD)
		4 patients with thromboembolic events all developed LV thrombus
		3 severe embolic complications including PE, CVA, leg ischemia
Sliwa [2006], (6)	Inflammatory markers (FAS/APO)	Independent predictors of death: FAS/APO-1 (OR =3.56, 95% CI: 1.35–9.42, P=0.01)
Gentry [2010], (10)	African American women	African American compared to other races: OR =15.7, 95% CI: 3.5–70.6, P<0.001
	HTN	HTN: OR =10.8, 95% CI: 2.6–44.4, P=0.001
	Not married	Unmarried: OR =4.2, 95% CI: 1.4–12.3, P=0.009
	Multiparity	Multiparity: OR =2.9, 95% CI: 1.1–7.4, P=0.025
		African American ethnicity multivariable predictor of PPCM: OR =31.5, 95% CI: 3.6–277.6, P=0.002
Tibazarwa [2012], (14)	T-wave abnormalities	Presence of major T-wave changes associated with 9% (95% CI: 1–16%; P=0.03) reduction in LVEF compared to those without T-wave changes
Haghikia [2013], (15)	Baseline LVEF	NIMP had lower LVEF compared to IMP (17%±5% *vs.* 28%±9%, P<0.0001)
	LVEDD	NIMP has greater LVEDD compared to IMP (70±8 *vs.* 59±7 mm, P=0.002)
Blauwet [2016], (18)	RV FAC	RV FAC independent predictor of:
		(I) Adjusted HR for lack of LV recovery or unfavorable clinical event (0.95, 95% CI: 0.92–0.99, P=0.02)
		(II) Adjusted HR for persistent LVEF ≤35% or unfavorable clinical event (0.93, 95% CI: 0.87–0.99, P=0.04)
Damp [2016], (19)	Relaxin-2	Elevated relaxin-2 associated with higher LVEF (P=0.01) and LVSD (P=0.006) at 2 months postpartum
	sFlt1	Elevated sFlt1 associated with more severe NYHA (P=0.01) and women who died or required LVAD support during first year postpartum (P=0.03)
Goland [2016], (21)	VEGF sFlt1	Patients with post-PPCM have significantly higher plasma sFlt1 concentration (P<0.001) with a trend of somewhat higher levels of VEGF (P=0.1) and significantly decreased VEGF/sFlt1 ratio (P=0.01)
Sheppard [2016], (22)	African American GNB3 TT gene	GNB3 TT genotype had lower LVEF at 6 months (P=0.007) and 12 months (P=0.001) from GNB3 CT and GNB3 CC at 6 months (P=0.02) and 12 months (P=0.008)

Table 3 (*continued*)

Table 3 (*continued*)

Author (year)	Risk factor	Risk (HR, OR, or RR)
Ware [2016], (23)	TTN gene	At 1-year follow-up patients with TTN had lower EF compared to those without 44±17 *vs.* 54±8, P=0.005
Ersbøll [2017], (24)	Baseline LVEF	LVEF: (OR =1.05, 95% CI: 0.97–1.14, P=0.244), cabergoline: (OR =4.64, 95% CI: 1.18–18.24, P=0.028), HDP: (OR =2.66, 95% CI: 0.75–9.43, P=0.129)
	Cabergoline HDP	14.8% suffered a major adverse event with 3.3% mortality, 8.2% mechanical circulatory support requirement and/or heart transplantation, and 4.9% persistent severe HF
Ekizler [2019], (26)	Positive T-waves in avR	Positive TaVR independent predictor of primary composite endpoint (cardiac death, arrhythmic event, or persistent LV systolic dysfunction) (OR =6.21, 95% CI: 1.45–26.51, P=0.014)
		Thromboembolic events (OR =1.86, 95% CI: 0.330–10.209, P=0.475)
		Stroke (OR =0.51, 95% CI: 0.155–1.675, P=0.267)
Honigberg [2019], (27)	EKG abnormalities (LAA)	LAA associated with lower LVEF at 6 months (44% *vs.* 52%, P=0.02) and 12 months (46% *vs.* 54%, P=0.03)
		LAA predicted decreased event-free survival at 1 year (P=0.008). Six women experienced 9 major events: 4 deaths, 4 LVAD implantations, and 1 cardiac transplantation
Farhan [2021], (29)	Baseline LVEF	LVEF ≥50%: 36.7% patients and GLS ≤–17%: 33.3% patients
	GLS	4.7% patients with SCD, torsade de pointes, or HF
		4.1% patients with Thromboembolic events
Hoevelmann [2021], (30)	NT-proBNP	Baseline NT-proBNP ≥900 pg/mL multivariate predictor of failure to recover LVEDD (OR =0.22, 95% CI: 0.05–0.95, P=0.043) and LVEF (OR =0.20, 95% CI: 0.04–0.89, P=0.035)
Jackson [2021], (31)	HTN	Greater likelihood of LVEF >50% in women with PPCM-PE *vs.* women with PPCM-noHTN (adjusted OR =2.08, 95% CI: 1.21–3.57)
		2.2% stroke in PPCM-noHTN, 2.5% PPCM-HTN, 2.8% PPCM-PE (P=0.93)
		6.9% thromboembolism PPCM-noHTN, 7.3% PPCM-HTN, 9.0% (P=0.72)
Ravi Kiran [2021], (32)	LAVi	Multivariate predictors of composite endpoint (rehospitalization for HF decompensation, all-cause mortality, and poor recovery):
	RV FAC	(I) LAVi: OR =1.18, 95% CI: 1.1–1.9, P=0.04
		(II) RV FAC: OR =0.7, 95% CI: 0.5–0.9, P=0.02
		0% thromboembolic events
Luthra [2022], (34)	Smoking history	Multivariate predictors of LVT:
	Pregnancy related HTN	(I) Smoking history: OR =2.22, 95% CI: 1.12–4.04, P=0.01
	CHF	(II) Pregnancy related HTN: OR =0.21, 95% CI: 0.09–0.43, P<0.001
	Anemia	(III) CHF: OR =1.86, 95% CI: 1.19–2.94, P=0.01
		(IV) Anemia: OR =2.05, 95% CI: 1.21–3.37, P=0.01
		CVA in PPCM with LVT: 10.17%
		CVA in PPCM without LVT: 1.24%

PPCM, peripartum cardiomyopathy; HR, hazard ratio; OR, odds ratio; RR, relative risk; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVFS, left ventricular fractional shortening; cTnT, cardiac troponin T; LV, left ventricular, CI, confidence interval; LVESD, left ventricular end-systolic dimension; PPV, positive predictive value; NPV, negative predictive value; SCD, sudden cardiac death; MAE, major adverse events; HTx, heart transplantation; PE, pulmonary embolism; CVA, cerebrovascular accidents; HTN, hypertension; NIMP, non-improvers; IMP, improvers; LAVi, left atrial volume index; RV FAC, right ventricle fractional area change; LVSD, left ventricular systolic dysfunction; NYHA, New York Heart Association; LVAD, left ventricular assist device; HDP, hypertensive disorder in pregnancy; HF, heart failure; aVR, aortic valve replacement; TaVR, transcatheter aVR; EKG, electrocardiogram; LAA, left atrial appendage; GLS, global longitudinal strain; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LVAi, indexed left atrial volume; LVT, left ventricular thrombus; CHF, congestive heart failure.

Table 4 Diagnosis of thromboembolism in PPCM

Author [year]	Baseline features	Diagnostic method	Yield
Renz [2011], (12)	Median EF: 22.5% (IQR, 26.3%)	CMR	Patients showing LGE, persistent elevation of T2 ratio, and EGER had a non-favorable clinical course
	Median LVEDD: 29.8 mm/m^2 (IQR, 8.3)		PPCM patients showed elevated T2 which decreased to normal values during follow up except for one patient
Tibazarwa [2012], (14)	Mean LVEF: 30.5%±9%	EKG	Presence of major T-wave changes associated with 9% (95% CI: 1–16%; P=0.03) reduction in LVEF compared to those without T-wave changes
	Mean LVEDD: 5.8±0.7 cm		
	90% NSR EKG		
Honigberg [2019], (27)	Mean LVEF: 34%±10%	EKG	LAA associated with lower LVEF at 6 months (44% *vs.* 52%, P=0.02) and 12 months (46% *vs.* 54%, P=0.03)
	Abnormal EKG in 51% of patients		LAA predicted decreased event-free survival at 1 year (76% *vs.* 97%, P=0.008)
			ST depression correlated with decreased LV recovery at 6 months (LVEF 40% *vs.* 52%, P=0.003) and 12 months (45% *vs.* 54%, P=0.025)
			"Normal EKG" predicted greater LVEF at 6 months (53% *vs.* 48%, P=0.02) and associated with recovery to an LVEF ≥50% by 12 months (84% *vs.* 49%, P=0.001)
Petryka-Mazurkiewicz [2021], (33)	Mean LVEF: 35.9%±13.7%	CMR	LV stroke volume index (50.3±11.8 *vs.* 44.5±10.5 mL/m^2, P=0.04)
	Mean LVEDVI for PPCM: 138.3±50.1 mL/m^2		Higher right atrial minimal and pre-systolic volumes (47.2±16.0 *vs.* 37.2±8.2 mL, P<0.01 and 68.7±18.3 *vs.* 58.4±13.9 mL, P=0.02)
	Mean LVESVI for female DCM: 101.3±39.1 mL/m^2		RA EF (42.4±10.0 *vs.* 48.6±9.8 mL, P=0.02)

PPCM, peripartum cardiomyopathy; EF, ejection fraction; IQR, interquartile range; CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; EGER, early gadolinium enhancement ratio; LVEDD, left ventricular end-diastolic diameter; EKG, electrocardiogram; CI, confidence interval; LVEF, left ventricular ejection fraction; NSR, normal sinus rhythm; LAA, left atrial abnormality; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; DCM, dilated cardiomyopathy; RA, right atrial.

complications in patients with LVEF ≤35% or treated with bromocriptine (if no contraindication exists) (48). The level of evidence for these recommendations is C (i.e., expert consensus), as higher quality evidence is scarce. Some experts suggest starting anticoagulation and continue until 8 weeks postpartum in all women with PPCM (27,41). In contrast, in some healthcare systems anticoagulation is administered only to PPCM patients with a definite indication for anticoagulation, such as atrial fibrillation or LV thrombus (49). Therapeutic anticoagulation should be administered to patients with intracardiac thrombus identified through imaging or those presenting with systemic embolism, as well as to those experiencing paroxysmal or persistent atrial fibrillation (40).

Some experts suggest continuing anticoagulation therapy until full recovery of LV function. Therefore, regular assessments of LVEF should be conducted over a period of 6 to 12 months (41). Although a full recovery is usually achieved within 2 to 6 months from diagnosis, a potential delay up to 5 years has been reported (50). A cohort study of 36 patients with PPCM [100% with ejection fraction (EF) <45% and 75% with EF <35%] not on prophylactic anticoagulation, showed that, during the 2-year follow-up period, 5 (14%) thromboembolic complications occurred and 2 patients with stroke died. The authors concluded that prophylactic anticoagulation should be given at least for the first 6 months after delivery (41).

Both unfractionated heparin and low molecular weight heparin (LMWH) represent safe choices in pregnancy since they do not cross the placenta (49). Some evidence suggests subcutaneous heparin (5,000 IU twice daily), especially in patients presenting with a LVEF <35% (51). Although warfarin is contraindicated during pregnancy because of its teratogenic potential, it is recommended in the postpartum

period (especially in the first several months) in patients with LVEF <30% or in the presence of other indications, such as atrial fibrillation, DVT or PE, or LV thrombus. Anticoagulation for other conditions is based on clinical experience. Data on use of novel oral anticoagulants (NOACs) in PPCM are scarce (52).

Finally, bromocriptine, a dopamine agonist that inhibits the release of prolactin, has demonstrated a high rate of full LV recovery in PPCM (50). Although some case reports suggested that bromocriptine is associated with thromboembolic complications, two prospective cohort studies in ESC and non-ESC countries reported no difference in thromboembolic events with bromocriptine compared [5 events in 84 patients (6%) on bromocriptine *vs.* 26 events in 463 patients (6%) not on bromocriptine; P=0.802] (2,28). Most experts recommend anticoagulation with heparin (LMWH or unfractionated heparin), at least in prophylactic dosages, in PPCM patients receiving bromocriptine (53). Findings are summarized in *Table 5*.

Discussion

Thromboembolic complications in women with PPCM pose a significant clinical challenge, with potential life-threatening consequences. In this systematic review, we summarized the epidemiology, risk factors, diagnosis, and therapy of thromboembolic complications in PPCM patients, shedding light on the current understanding of this important clinical issue.

The epidemiology of thromboembolism in PPCM is not extensively studied, and the available literature provides limited information. Our review identified several studies reporting on the incidence of thromboembolic events in PPCM patients across different geographical regions. Although the incidence varied, ranging from 3% to 16%, it was consistently higher than that observed in the general population. These findings highlight the need for heightened awareness and monitoring for thromboembolic complications in women with PPCM.

Several risk factors have been associated with thromboembolic complications in PPCM patients. Hormonal changes during pregnancy contribute to a hypercoagulable state, which can persist for several weeks after delivery, rendering these patients more susceptible to thromboembolic events (27,36). LV systolic dysfunction, which characterizes PPCM, further contributes to blood stasis and the formation of intracardiac thrombi and subsequent systemic embolism, potentially leading to cerebrovascular events and other arterial embolic events, and venous thromboembolic events and PE.

Our review identified LVEF <35% as a significant risk factor for thromboembolism in PPCM patients. Non-Caucasian background and the extent of initial myocardial insult were also identified as predictors of major adverse events, emphasizing the importance of considering individual patient characteristics when assessing thromboembolic risk in PPCM and, therefore, highlighting the need for targeted risk factor modification in these high-risk groups (34).

Cesarean delivery and the post-operative period have been associated with a higher incidence of thromboembolic complications in women with PPCM. Endothelial injury, immobility, and ventricular dilatation likely contribute to the increased risk observed in these patients. Furthermore, elevated circulating levels of PAI-1 in some PPCM patients, due to genetic variability, may play a role in increased thrombotic susceptibility. However, further studies are needed to establish the precise relationship between PAI-1 levels and thromboembolic complications in PPCM (39).

Despite its current indication for treatment of PPCM, it has been postulated that the use of bromocriptine has been associated with high risk of thromboembolic complications, most at higher dosages. Whether concomitant anticoagulation should be given remains an open question.

Timely diagnosis of thromboembolic events is crucial for appropriate management. However, there is limited evidence regarding the diagnostic methods used to assess thromboembolic events in PPCM. MRI has shown higher sensitivity and specificity compared to echocardiography for intracardiac thrombi, but its use is limited due to cost and time requirements. Compression ultrasonography and non-gadolinium-enhanced MRI are recommended for diagnosing DVT. Diagnosis of PE remains challenging and requires a high index of suspicion, since one-third of patients do not present symptoms, with imaging techniques such as lung scintigraphy or coronary tomographic angiography being necessary for definitive diagnosis.

Despite the high rate of thromboembolic events in women with PPCM, the decision of anticoagulant therapy remains a subject of ongoing debate and there is limited evidence to guide management options as well as duration of therapy in these patients. Also, practice varies substantially across healthcare systems. The debate also concerns the decision of therapeutic *vs.* prophylactic anticoagulation in these patients, as evidence is limited (4). Current guideline statements address the use of anticoagulation in patients with PPCM. However, they primarily rely on expert opinions rather than conclusive empirical evidence. Therefore, which

Table 5 Therapy for thromboembolism in PPCM

Author [year]	Therapy used	Outcome
Biteker [2012], (13)	100% diuretics, 93.8% BB, 81% ACEI/ARB, 35.7% digoxin, 0% bromocriptine use	47.6% recovered EF
		23.8% died (5 due to HF progression, 5 due to SCD)
		30% with early recovery, 70% with delayed recovery
		28.6% with persistent left ventricular dysfunction
		0% LV thrombus in early and delayed recovery patients *vs.* 18.2% PLVD patients had a thrombus (P=0.184)
		Early recovery: normalization of LVSF at 6 months post-diagnosis
Sliwa [2017], (25)	83.6% diuretics, 78.8% ACEI, 79.9% BB, 21.2% bromocriptine, <10% ivabradine, <50% MRA	At 1-month, persistent symptomatic HF more common in non-ESC *vs.* ESC countries (92.3% *vs.* 81.3%, P<0.001)
	Significant differences in prescribing pattern of those medications in ESC *vs.* non-ESC countries (P<0.001)	Within 1 month, 2.4% died mostly due to HF, some due to stroke, and cardiac death
	More common among ESC *vs.* non-ESC: AC (27.9% *vs.* 15.9%, P=0.022), BB (91.9% *vs.* 70.3%), ivabradine (17.1% *vs.* 1.4%)	After 1 month, PPCM with HF higher in non-ESC (92.3% in non-ESC *vs.* 81.3% in ESC, P<0.001)
	More common among non-ESC *vs.* ESC: bromocriptine (32.6% *vs.* 7.1%), diuretics (91.3% *vs.* 68.8%), digoxin (37.0% *vs.* 18.0%)	6.8% of patients with thromboembolic events, CVA, arterial embolism (no significant differences between ESC *vs.* non-ESC)
Sliwa [2020], (28)	15% received bromocriptine with significant regional variation (Europe 15%, Africa 26%, Asia-Pacific 8%, the Middle East 4%, P<0.001)	46% recovered EF [commonly in Asia-Pacific (62%), and least commonly in the Middle East (25%)]
	85% with ACEI, 81% betablockers, 45% MRA, 21% digoxin, 74% diuretics	42% HF death, 30% sudden death
		Thromboembolism occurred in 7% by 6 months (highest in Europe)
		Stroke occurred in 3% of patients
Farhan [2021], (29)	91.8% BB, 73.5% ACEI/ARB, 40.8% MRA, 22.45% AC, 8.2% digoxin, 8.2% bromocriptine	36.7% recovered EF
		4.7% died due to SCD, torsades de pointes, or HF
		4.1% with thromboembolic events
Hoevelmann [2021], (30)	94.3% BB, 80% ACEI/ARB, 45.7% ARB, 91.4% diuretic, 41.1% bromocriptine	51.4% recovery of EF

PPCM, peripartum cardiomyopathy; BB, beta-blockers; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; EF, ejection fraction; HF, heart failure; SCD, sudden cardiac death; LV, left ventricular; PLVD, persistent left ventricular dysfunction; LVSF, left ventricular systolic function; MRA, mineralocorticoid receptor antagonists; ESC, European Society of Cardiology; AC, anticoagulant; CVA, cerebrovascular accidents.

women with PPCM necessitate anticoagulation remains controversial.

The decision to initiate anticoagulation is often based on LVEF thresholds, ranging from <30% to <35%. Prophylactic anticoagulation may be considered for all PPCM patients, especially during the first 6 months after delivery, while therapeutic anticoagulation is recommended for patients with intracardiac thrombus or systemic embolism. There is no consensus on the duration of anticoagulation therapy, with some experts suggesting continuation until clinical and echocardiographic recovery (41). Factors such as patient compliance, the severity of HF, and other clinical considerations should be taken into account when determining need for anticoagulant treatment (50).

Bromocriptine, a dopamine agonist which inhibits the release of prolactin, continues to be studied for the treatment

of PPCM and results about whether it is associated with an increased risk of thromboembolic events is controversial. Therefore, the question remains whether anticoagulation should be administered in women with PPCM treated with bromocriptine (41,50).

Conclusions

In conclusion, thromboembolic complications in women with PPCM represent a significant clinical challenge. Thromboembolism in PPCM is consistently higher than in the general population of pregnant women, emphasizing the need for increased awareness. Risk factors include LV systolic dysfunction and individual patient characteristics such as non-Caucasian background. Cesarean delivery and the post-operative period are associated with a higher risk of thromboembolism in PPCM, along with other factors like endothelial injury, immobility, ventricular dilatation, and genetic variability affecting PAI-1 levels. Diagnosis of thromboembolic events in PPCM remains challenging, with limited evidence for specific diagnostic methods. The decision regarding anticoagulant therapy in PPCM is subject to ongoing debate and lacks conclusive empirical evidence. Guidelines primarily rely on expert opinions, and the decision to initiate anticoagulation is often based on LVEF thresholds, presence of intracardiac thrombus or systemic embolism. The duration of therapy and the use of anticoagulation in PPCM patients treated with bromocriptine remain controversial. Overall, further research is needed to better understand the epidemiology, risk factors, diagnosis, and optimal management of thromboembolic complications in women with PPCM.

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