

Review

Anticoagulation for intra-cardiac thrombi in peripartum cardiomyopathy: A review of the literature

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Peripartum cardiomyopathy is a type of non-ischemic cardiomyopathy with a high rate of thromboembolic events. Guiding strategies for anticoagulation in patients with peripartum cardiomyopathy and thromboembolic events are limited. Literature for all cases of peripartum cardiomyopathy with intracardiac thrombi were reviewed and summarized from twelve case reports. Based on the available literature, we conclude that patients with peripartum cardiomyopathy with ejection fraction of less than 30% should strongly consider anticoagulation therapy to avoid thromboembolic events. Future studies may be able to further elucidate the optimal indication and duration of anticoagulation.

Keywords

Peripartum cardiomyopathy; thrombus; anticoagulation

1. Introduction

Peripartum cardiomyopathy (PPCM) is a relatively rare form of non-ischemic cardiomyopathy that occurs in healthy women during the final month of pregnancy and up to 5 months post-delivery (Johnson-Coyle et al., 2012). According to the National Institutes of Health consensus panel, diagnostic criteria for PPCM includes congestive heart failure symptoms of unknown cause, absence of a pre-existing heart muscle disorder, symptomatic onset during the last month of gestation or 5 months postpartum, and left ventricular systolic dysfunction demonstrated by a decreased ejection fraction (EF) (Pearson et al., 2000). Its incidence in United States varies from 1 in 1300 to 1 in 4000 live births (Elkayam et al., 2001).

In comparison to other forms of cardiomyopathies, PPCM has been associated with higher rates of thromboembolism (Elkayam, 2011). There are several factors during the peripartum period that make expectant mothers hypercoagulable. These factors include cardiac dilation, endothelial injury, and immobility (Azibani and Sliwa, 2018). Studies done by Kolte et al. (2014), show that the most frequent complication in women with PPCM was thromboembolism (6.6%) (Kolté et al., 2014). Given this increased thromboembolic risk, multiple review articles suggest that prophylactic anticoagulation in women with PPCM is advisable, especially when the left ventricular EF is < 35% (Arany and Elka-

yam, 2016; Azibani and Sliwa, 2018; Pearson et al., 2000). In 2018, the European Society of Cardiology (ESC) updated the guidelines on anticoagulation in pregnancy, recommending that women with PPCM and EF < 25% should receive prophylactic anticoagulation (Level of evidence IIB) (Seeland et al., 2018).

The current review focuses on the use of anticoagulation in patients with PPCM in the setting of known intracardiac thrombi.

2. Methods

An extensive literature search was done using MEDLINE, Google Scholar, and Cochrane review to identify original articles using search words "peripartum cardiomyopathy" and "anticoagulation". Pertinent studies were manually searched to identify additional relevant studies. Four case reports of patients with intracardiac thrombi and PPCM were excluded since they were in Turkish, French, Senegalese, and Portuguese language (Damorou et al., 2000; Koç et al., 2011; Napporn et al., 2000; Sánchez-Rubio Lezcano et al., 2004; Zehir et al., 2014).

Two case reports by Mikami and Kamiunten (2018) and (LaRue et al., 2011) were excluded because anticoagulation was administered by mechanical circulatory support (MCS) and left ventricular assist device (LVAD), respectively. A case report by Baughman (2006) mentioned the use of prophylactic anticoagulation in a patient with PPCM and no presence of thrombi and hence was excluded. Case reports with deep venous thrombosis or pulmonary embolism in the presence of PPCM were also excluded.

3. Results

A total of 12 original studies were included in our review article. All of these studies were case reports that describe individual cases. The age of women in our study ranged from 20-38 years, mean of 28.1 years. Table 1 describe all the included case reports (Altuwajri et al., 2012; Bagul et al., 2014; Bhat et al., 1986; Box et al., 2004; Corriveau et al., 2014; Ibebuogu et al., 2007; Kaufman et al., 2003; Kharwar et al., 2014; Kim et al., 2011; Nishi et al., 2002; Sakamoto et al., 2013; Shimamoto et al., 2008).

All except one patient presented during the postpartum period, which ranged from 8 days to 7 months postpartum. One patient was known to have gestational hypertension and eclampsia, while the remaining patients had no previous history of CHF, hyperten-

Table 1. Descriptive summary of case reports (1-12) describing intracardiac thrombi in patients with PPCM.

Study, Year, Country	Age of patient	Gravidity	Presentation	Postpartum presentation (PP)	Mode of delivery	LVEF (%)	LVED diameter (cm)	Location of thrombus	Appearance/features of thrombus	Anticoagulant used	Clinical outcome	Embolie episode	Days for resolution of thrombus	Follow up Echo	Follow up EF (%)	LVED diameter (cm)	Total follow up period
Nishi et al., 2002 Japan	23	1	Palpitation, nocturnal dyspnea, orthopnea	6 weeks PP	Vaginal	18	5.7	Apical thrombi in ventricle	spherical, shaggy and irregular in both configuration, and freely mobile, suggesting that they were fresh	IV heparin → Warfarin	Resolution of thrombus	No	4	2 months	48	4.7	1 year
Kim et al., 2011 Bangladesh	22	N/A	Dyspnea, weakness	4 months PP	Vaginal	17	6.4	Biventricular thrombi	Larger in the RV, Smaller LV [Septal location]	Subcutaneous heparin and Warfarin	Resolution of thrombus	No	Smaller LV- 16 days, larger RV-21 days	2 months	17	N/A	2 months
Corriveau et al., 2014 Canada	29	3	Dyspnea, fatigue, orthopnea and LE edema	2 weeks PP	Vaginal	16	N/A	LV	Large, mobile	Heparin → Warfarin	N/A	Yes-CVA	N/A	N/A	N/A	N/A	N/A
(Sakamoto et al., 2013) Japan	37	2	Dyspnea	4 months PP	C-Section	29	6.5	1. LV apex RV apex	2. Mobile, large [2.8 x 2 cm] -Larger LV and 1.6 x 1 cm -RV]	Heparin → Warfarin	Resolution of thrombus	Yes-CVA	N/A	1 year	62	4.8	13 months
Bagul et al., 2014 India	26	1	Dyspnea	8 days PP	Vaginal	20	N/A	1. Apex RV free wall 3. RA Roof	2. 2.5 x 2 cm, 3.5 x 1 cm, 1 x IV heparin → Warfarin farin	Warfarin	Resolution of thrombus	No	2 clots [smaller] -3 days; 1 larger [apex]- 1 month	1 month	40	N/A	1 month
Kharwar et al., 2014 India	30	4	Dyspnea, Orthopnea	3 weeks PP	Vaginal	32	3.05 cm/m2 (LVEDD index)	LV-Septum	Pedunculated 2.5 x 2 cm	Warfarin	Resolution of thrombus	No	1 month	1 month	43	N/A	N/A
Altunajiri et al., 2012 Canada	25	4	Dyspnea, Orthopnea, PND	7 months PP	N/A	<20	N/A	Multiple LV, lateral wall	large layered echodense mass	Heparin	Resolution of thrombus	No	4 days	N/A	N/A	N/A	N/A
(Box et al., 2004) USA	31	N/A	Edema, Fatigue	4 weeks PP	Vaginal	20	6.9	LV Apex	N/A	N/A	N/A	Yes-coronaries	N/A	N/A	N/A	N/A	6 months

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(Shimamoto et al., 2008) Japan	32	2	N/A	10 days	PP	C-section	20	6	35 X 20 mm (initially immobile → development of 3 mobile) 20X9, LV apical 10X10, 10X10 masses → immobile	Warfarin → +Heparin → Warfarin	Needed surgical removal as it became mobile	No	24 days	30 days	33	5.5	2 years
(Kaufman et al., 2003) Canada	38	7	Acute dyspnea	30 weeks gestation	C-section	45	N/A	Lt MCA thrombi	N/A	heparin → Warfarin	Improved clinically	Yes-CVA	N/A	N/A	N/A	N/A	N/A
Ibebuogu et al., 2007 USA	24	5	Epigastric, RUQ pain, Nausea, Vomiting	5 months PP	Vaginal	<15	6.5	LV anterior wall thrombus → BiV thrombi	N/A	Yes (not mentioned what kind)	Underwent b/ILE thrombectomy	Yes- liver, bilateral kidneys, common iliac and right external iliac arteries	5 days	N/A	N/A	N/A	2 weeks
Bhat et al., 1986 India	20	N/A	Exertional SOB, Fatigue, Palpitation, PND	4 months PP	Vaginal	39	6.5	Biventricular apices	N/A	Heparin → oral AC	Underwent bilateral femoral thromboembolctomy	Yes- bilateral femoral artery	NA	N/A	N/A	N/A	N/A

sion, or pregnancy related hypertension (Shimamoto et al., 2008). None of the patients had previous history of thromboembolic episode or family history of hypercoagulable state. One out of 12 patients was anticardiolipin antibody positive after the thrombotic event (Kaufman et al., 2003).

All cases had echocardiographic evidence of an intracardiac thrombus except one, where the patient had a stroke that was presumed to be cardioembolic. Left ventricular ejection fraction (LVEF) varied from < 15% to 45%. Six out of 12 had an embolic episode to the brain (3), coronaries (1), liver and kidney (1), or lower extremity arteries (2). Seven studies that included left ventricular end diastolic diameter (LVEDD) in the case report ranged from 5.7 to 6.9 cm (average 6.4 cm) (normal 3.9-5.3 cm). Seven case reports mentioned the timing of clot resolution, which ranged from 4 days to 1 month. Most studies did not mention the duration of anticoagulation; however, the two that did reported durations of 12 months and lifelong anticoagulation.

4. Discussion

4.1 PPCM and Thromboembolism

Peripartum cardiomyopathy is a form of non-ischemic cardiomyopathy that causes systolic dysfunction in women during the last month of pregnancy or within 5 months post-delivery (Al-tuwaijri et al., 2012). There are several factors in the coagulation cascade that make the peripartum period hypercoagulable such as increased endogenous thrombin generation, acquired activated protein C resistance, increased levels of coagulation factors VII, VIII, X and plasma fibrinogen, and decreased activated partial thromboplastin time (aPTT) (Hellgren, 2003). These hemostatic changes usually normalize 4-6 weeks after delivery. Additionally, if left ventricular dysfunction persists from PPCM, it leads to blood stasis in the heart making a patient hypercoagulable. In a prospective study from South Africa (n = 100), LV thrombus was found in 16% of the patients with PPCM (Sliwa et al., 2006). In another study by Amos et al (N = 55), 17% of patients developed LV thrombus and none of them had full recovery of LV function (Amos et al., 2006). Kido and Guglin (2019) recently summarized 4 case reports for use of anticoagulation in patient with PPCM with intracardiac thrombi. In our review, we found additional data sources from women with PPCM that developed intracardiac thrombi and received anticoagulation therapy.

4.2 Anticoagulation in PPCM: What do the guidelines say?

Anticoagulation in a patient with PPCM is a topic that lacks extensive medical literature. The guidelines are based on expert opinion and do not delineate clearly the indications for anticoagulation in patients with PPCM. According to the ACCF/AHA guideline in 2013, anticoagulation is recommended for patients with PPCM if ventricular dysfunction is persistent (Writing Committee et al., 2013). However, the terms "ventricular dysfunction" and "persistent" need to be clearly defined. Recently, the guidelines from the ESC 2018 recommend anticoagulation in women with PPCM with LVEF < 25% (level of evidence IIB) (Seeland et al., 2018).

Studies done by Sheppard et al. (2014) referred to the following as indications for anticoagulation in a patients with PPCM: atrial fibrillation, LV thrombus, systemic embolism, bromocriptine use,

and EF less than 30% . All except one patient in our review with intracardiac thrombi had EF < 30%. This finding reiterates the possible need for prophylactic anticoagulation or a closer follow up with serial echocardiograms in patients with low EF. Additionally, all the patients in our review who had LV dimensions measured were found to have large left ventricular end diastolic dimension (LVEDD) and mean of 6.4 cm (range 5.7-6.9 cm). These parameters need to be studied further, and may help categorizing patients with PPCM that might benefit from prophylactic anticoagulation.

4.3 Bromocriptine for PPCM and anticoagulation

Bromocriptine, typically used for lactation suppression, continues to be studied for the treatment of PPCM. In a multicenter randomized study by Hilfiker-Kleiner et al. (2017), bromocriptine treatment was associated with high rate of full LV recovery and low morbidity and mortality in PPCM patients compared to PPCM cohorts that are not treated with bromocriptine. Currently, it is not approved by the US Food and Drug Administration (FDA) for treatment of patients with PPCM, but continues to be investigated. There are few case reports suggesting a prothrombotic effect of bromocriptine like cases of myocardial infarction (Hopp et al., 1996; Loewe and Dragovic, 1998). Due to the prothrombotic effect; however, it is advised to implement a full dose of anticoagulation when bromocriptine is used.

4.4 Type and duration of anticoagulant

As discussed above, the first 6-8 weeks postpartum have a persistent hypercoagulable state that requires anticoagulation. Both unfractionated heparin and low molecular weight heparin are safe to use during pregnancy because they do not cross the placenta (Gerald et al., 2009). Due to its shorter half-life and reversible effect, unfractionated heparin is preferred during pregnancy whenever an urgent delivery is suspected due to maternal or fetal instability. Warfarin crosses placenta, and is considered a category D drug for use during pregnancy. In postpartum women, neither warfarin nor heparin are secreted into the breast milk and can be offered during breast-feeding (Gerald et al., 2009). The use of novel oral anticoagulants in pregnancy and embryopathy still has significant data gaps. NOACs have not been reported to be used in the setting of PPCM.

The duration of anticoagulation is another ambiguous topic. As per the heart failure guidelines for PPCM, anticoagulation therapy should be continued until LV function normalizes (Johnson-Coyle et al., 2012). In PPCM patients, it has been reported that 23% to 72% achieve full recovery of normal LV systolic function (McNamara et al., 2015). It occurs within 2 to 6 months of diagnosis, but can be delayed for up to 5 years (Fett et al., 2005). In our review, 7 patients had clot resolution within 1 month, 3 patients required a surgical procedure for thrombectomy, and the remaining two patients lacked data on clot resolution.

4.5 Limitations

Since PPCM with intracardiac thrombi is a rare condition, our systematic review only includes case reports. We rely on the information published and cannot conclude certain aspects because they are not included in the study literature.

5. Conclusion

Thromboembolism is a serious complication in patients with PPCM. Our systematic review summarizes twelve case reports that mentioned the presence of intracardiac thrombi in patients with PPCM. Although this topic lacks well defined guidelines, we conclude that in patients with PPCM with EF < 30%, anticoagulation should be strongly considered to avoid a thromboembolic event. Future studies with longer follow-up of larger cohorts of patients with PPCM might be able to elucidate further the optimal duration of anticoagulation.

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Conflict of Interest

There are no conflicts of interest to declare.

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