Long-term prognosis, subsequent pregnancy, contraception and overall management of Peripartum Cardiomyopathy

Practical guidance paper from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy

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ABSTRACT

PPCM is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of the pregnancy, or in the months following delivery, where no other cause for heart failure is found. Outcome varies from full recovery, to residual left ventricular systolic dysfunction and even death. Many women return to their physician to acquire information on their long-term prognosis, to seek medical advice regarding contraception or when planning a subsequent pregnancy. This position paper summarizes the current evidence for long-term outcome, risk stratification of further pregnancies and overall management. Based on the best available evidence, as well as the clinical experience of the Study Group members, a consensus on pre- and postpartum management algorithms for women undergoing a subsequent pregnancy is presented.

INTRODUCTION

Peripartum Cardiomyopathy (PPCM) is an idiopathic form of cardiomyopathy, presenting with heart failure secondary to left ventricular dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is identified.[1] Patients can present with severe acute heart failure with a high morbidity and mortality requiring a multi-disciplinary approach.[2] Even those who present with more subtle symptoms can still have long-term impaired cardiac function.[3] Until recently, data on suspected or confirmed cases of PPCM from Europe and most other regions of the world were limited. However, data from the ongoing EurObservational Research Registry on PPCM[4] have shown that this condition occurs globally.[5] Patients with PPCM are often young, have just started their families and, often, wish to fall pregnant again. The impact of a subsequent pregnancy on clinical outcome is crucial,[6] as it will not only affect the pregnant woman, but also other family members such as her partner and other children under their care. Moreover, after the traumatic experience of PPCM patients may also develop psychological disorders that need treatment.

WHAT IS KNOWN ABOUT THE LONG-TERM OUTCOME OF WOMEN WITH PPCM?

When a woman is diagnosed with PPCM, questions relating to the long-term consequences of the condition commonly arise. Women have described feeling terrified and devastated following a diagnosis of PPCM.[7] They often struggle with recommendations to avoid a further pregnancy and report damaging effects on their marriage and relationships with other family members.[7] In a review of comments from a PPCM support website, several messages were from users searching for information related to recovery, its length of time, the impact of subsequent pregnancies and the duration of medical therapy.[8] Many studies on PPCM have investigated the clinical course over 6 months or a year, but few have investigated outcomes over several years or decades. Women are understandably interested not only in outcomes during the early period following a diagnosis, but also in the long-term prognosis. Risk prediction of normalization of cardiac function and survival beyond 5 years cannot be provided based on solid prospective data. There are also no prospective long-term outcome data on larger cohorts of patients with PPCM that have received a left ventricular assist devices or cardiac transplantation to make clear recommendations on long-term benefit. Much of what we do know comes from small studies of selected populations and from restricted geographical areas **(Table 1)**.

Long-term Mortality

1-6 months postpartum

Outcomes for patients with PPCM appear to be more favourable than for those with other forms of cardiomyopathy. In a comparison of mortality, over a mean follow-up period of 4.4 years in a large single-centre study of 1230 patients with cardiomyopathy, survival was greater in patients with PPCM than in those with idiopathic cardiomyopathy (adjusted HR 0.31, 0.09-0.98).[9] Nonetheless, despite increasing recognition and understanding of PPCM, mortality rates have only been studied in a small number of countries and most available data comes from the USA, South Africa, Haiti, Turkey and Pakistan. There are very few studies from Europe which report outcomes for women with PPCM and these are mainly small case series of n≤12.[10-13] Most studies to-date have concentrated on mortality at 6 months, with a wide variation in reported rates, ranging from 2% in Germany[10] to 12.6% in a large cohort of 206 patients with PPCM from South Africa.[14] Our current focus is on outcomes beyond 6 months.

6-12 months postpartum

Mortality up to 12 months is 4-14%, with the majority towards the lower end of this range (**Table 1**). The highest rates of mortality at 6-12 months are seen in African women (12-14%).[15,16] This racial variation is evident elsewhere. For example, in the IPAC study in the United States (30% self-designated black), mortality at 12 months was 4%[17] while, in Detroit, (96% were African-American women) 11% died at a median follow-up of 12.5 months.[18] A recent trial adding the prolactin blocker bromocriptine on top of standard therapy for heart failure reported an excellent 6 months follow-up outcome in severely diseased patients having over 60% full recovery and 0% mortality, heart transplantation and/or use of assist device.[19]

1-5 years postpartum

Of 182 women from the USA (56% Caucasian, 29% African-American, 10% Hispanic, 3% Asian), mortality was 7% at a mean follow-up of 19 months.[20] A significantly larger proportion of the group who died or underwent cardiac transplantation were non-Caucasian, compared with the rest of the group (76% vs. 39%, p=0.0001). At around 2 years, studies of black populations report mortality of 28% in South Africa,[21] 16% in Louisiana, USA[22] and 15% in Haiti.[23] Similarly, in a small case series of 13 women from New York, of which 69% were non-Caucasian, 23% of women had died at 2.1 years[24] In other studies from the USA, outcomes for women with PPCM are more favourable, with 2-year mortality of 0-9%.[25,26] Mortality is also lower in women with PPCM from Brazil (8% at 2.1 years),[27] and China (4% at 2.3 years). [28] Mortality between 2-5 years varies even more considerably, ranging

from 0-6% in French and American women[9,11,29-32] to 15-30% in women from China,[33], Brazil,[34], Turkey,[35-37], South Africa,[38] and the Philippines.[39]

Beyond 5 years postpartum

There are few data beyond 5 years for women with PPCM. In 3 studies from the USA mortality ranges from 7-16% at between 7 and 8.6 years.[9,40,41] In India, mortality was 23% at 6.1 years[42] and in Malaysia (n=12) 8.3% at 6.4 years.[43] In a prospective study of 181 Nigerian women with PPCM from 1989, 26% had died at 10 years.[44] There are no more recent studies of mortality beyond 5 years in African women.

Predictors of late mortality and mode of death

As recently highlighted by Sliwa et al[45] late maternal death (> 42 days postpartum) is globally poorly reported despite being an ICD10 coding recommendation. Few studies on PPCM with follow-up extending beyond 2 years have sought to identify prognostic indicators in women with PPCM. In Turkey baseline LVEF and LV end systolic diameter were identified as significant predictors of mortality due to heart failure.[35] These results conflict with other long-term follow-up studies, in which there were no differences in baseline echocardiographic parameters between deceased and surviving study participants.[1,22]

While much of the existing data suggest that the risk of death is greatest in the early postpartum period, later deaths occurring either due to deterioration of cardiac function or arrhythmia have been noted. Only 36% of deaths occurred within 6 months in a group of 80 women with PPCM from South Africa, with a further 36% at 6-12 months and 27% at 12-24 months.[21] Notably, in this cohort,[21] recovery of LV function had occurred in 29% of patients who died between 6-24 months, suggesting that even in those with early recovery, a risk of mortality persisted beyond this.[21] In a retrospective 2-centre study of 100 women from the USA, 2 out of 11 women who died had recovered LV function by a mean of 23 months and death occurred at a mean of 83 months.[40] In fact more recent data using wearable cardioverter/defibrillator (WCD) clearly demonstrate a high risk for ventricular tachyarrhythmias (VTA), and sudden death in patients with PPCM is more common in the acute phase of the disease but may even occur during recovery.[46,47] In general the recommendations of the ESC Guidelines for acute and chronic heart failure on the on the use of wearable cardioverter/defibrillators should be followed[48].

However, clear markers to identify patients at risk for arrhythmic death or non-sudden death do not exist. Consequently, although the time at which death occurs following a diagnosis of PPCM is clearly

important with regard to informing patients and also to decide whether or not continued pharmacological or device therapy may be warranted, more research to identify prognostic factors or markers associated with late death in women with PPCM is needed.

Recovery of left ventricular (LV) function

Recovery at 6 months

Studies of recovery of cardiac function with an echocardiographic left ventricular ejection fraction (LVEF) >45% have largely focussed on the trajectory over the first 6 months postpartum and rates vary markedly from one country to another. Six-month recovery rates between 46-63% have been reported in Japan,[49] China,[50], Turkey,[35] Germany,[10] and the USA[25]. Six-month recovery is worse (21-36%) in South Africa,[51,52] Nigeria,[53] Pakistan,[54] and the Philippines.[39]

Recovery beyond 6 months

Although data on early recovery of LV function is more frequently reported, the concept of myocardial recovery beyond 6 months is increasingly recognised. In the recent Investigations of Pregnancy-Associated Cardiomyopathy (IPAC) study, a prospective multicentre American study of 100 women with PPCM, recovery (LVEF>50%) was seen in 72% of women at 12 months.[17] Rate of recovery between 6 and 12 months is unavailable. In a prospective analysis of a group of 42 Turkish women with PPCM, recovery of LV function beyond 6 months was seen in 44%.[35] Of those who recovered, 60% did so beyond 12 months, with recovery seen up to 42 months postpartum. Similarly, a median time to recovery of 54 months was reported in a retrospective analysis of 44 women with PPCM in Louisiana, USA, with a 30% non-recovery rate reported up to 9 years after diagnosis.[22] Recovery at 6-monthly intervals, up to 36 months, was also illustrated in a cohort of 116 women from Haiti, with 28% of all women regaining good cardiac function.[55] At each follow-up interval, there was a steady increase in the proportion of women who demonstrated recovery of LV function. 53% of recovered patients did so beyond 18 months.

These data illustrate that recovery can occur after 6 months and continuing recovery can be seen, at least in some countries, after several years. However, the current literature is far from comprehensive. More prospective, multicentre studies of myocardial recovery in unselected populations with long-term follow-up are required in order to describe the natural history of cardiac function in women with PPCM. More sophisticated echocardiographic investigation, including strain measurements and cardiac magnetic resonance imaging, would allow more detailed assessment of cardiac function and structure following a diagnosis. To date, recovery of cardiac function has

focussed on LVEF and the long-term effects on right ventricular function have not been studied. There is a need to investigate the long-term effects on mitral incompetence and if PPCM are left with a residual myocardial scar.

DOES MYOCARDIAL FUNCTION DETERIORATE AFTER STOPPING MEDICAL THEPAPY FOR PPCM WITH RECOVERED CARDIAC FUNCTION?

A common clinical question when myocardial recovery occurs in PPCM is: "Should medical therapy be stopped?" There are few data to guide this decision and, therefore, no recommendations within current guidelines exist. In a prospective, 2-centre study from Turkey investigating recovery in 42 patients with PPCM, 4 patients (2 who had full recovery of LV function and 2 who had partial recovery of LV function) showed delayed deterioration at 12, 24, 26 and 34 months after diagnosis.[35] In the 2 patients who had fully recovered, medication was discontinued when cardiac function improved, although the time at which medical therapy was stopped is not clear. The other 2 patients were still receiving heart failure therapy. The only other observational study is a cohort of women from North Carolina with recovered myocardial function.[29] Of the 5 patients who had discontinued treatment with both beta-blocker and angiotensin converting enzyme inhibitor, none demonstrated deterioration in cardiac function after a mean follow-up of 29 months. There is one further case series describing 3 women from the USA with recovered LV function who had a subsequent deterioration of myocardial function (unrelated to a further pregnancy) 'several months or years' later.[20] Whether these women were still receiving medical therapy is not reported. Therefore, studies evaluating criteria for treatment duration (clinical signs, biomarkers) to determine the time and composition of long-term treatment are needed.

WHAT CAN BE RECOMMENDED FOR THE LONG-TERM MANAGEMENT OF WOMEN WITH PPCM?

The current recommendation, based on consensus of the PPCM HFA Study Group members, is a six-monthly visit including echocardiography in all women until they recover to an LVEF>50%. In women with LV recovery who remain stable after tapering of heart failure drug therapy an annual visit is recommended for up to 10 years.

Patients with persistently reduced EF should continue treatment with ACE inhibitors, beta blockade and with mineralocorticoid receptor antagonist (MRA) for example ivabradine and sacubitril/valsartan according to the current ESC Guidelines for acute and chronic heart failure.[48] There is no consensus as to whether heart failure medication can be stopped in women with a

recovered left ventricular function or subclinical dysfunction. However, weaning from medication should be performed sequentially with careful and close monitoring of patients clinical and cardiac performance (see table 2, Hilfiker-Kleiner/Bauersachs, EHJ 2015).[3] Some of the Study Group members recommend life-long heart failure therapy at highest dose tolerated based on the fact that deterioration of left ventricular function has been observed in women with normalized cardiac function. If patients display signs of incomplete recovery despite recovered EF such as persistent LV dilatation or reduced myocardial strain, continuation of heart failure drugs (ACE inhibitor, betablocker, MRA) should be considered. Research in this field is urgently needed via carefully conducted studies. Genetic testing may be considered in patients with a family history for cardiomyopathy, as recent studies showed that 15% of PPCM patients carry cardiomyopathy-causing mutations. The presence of TTN truncating variants was significantly correlated with a lower ejection fraction at one year follow up [56], features important for long-term therapy concepts.

HOW CAN PATIENTS BE BEST ADVISED ABOUT THE RISKS FOR A SUBSEQUENT PREGNANCY?

Data on subsequent pregnancies in women with a previously diagnosed PPCM are limited. **Table 2** summarizes the studies of women who had a subsequent pregnancy (SSP) after being diagnosed with PPCM. However, the mode of data collection is highly variable with some studies not reporting the ejection fraction of the index pregnancy, nor the cardiac dimensions, left and right ventricular function at the onset of the subsequent pregnancy. Also the date of the last assessment post SSP is highly variable. Therefore, there are enormous gaps in our knowledge. Uri Elkayam recently summarized the available information related to SSP in women with a history of PPCM.[57] One of the largest studies to date, published in the New England Journal of Medicine in 2001, was based on information of 44 women with PPCM and SSP, collected via a retrospective survey of members of the American College of Cardiology. Twenty-eight of these women had a recovered cardiac function, while 16 pregnancies occurred in women with persistent left ventricular dysfunction. All pregnancies were associated with a reduction of mean left ventricular ejection fraction (from 49.9$\pm$12 % to 42$\pm$13 %, $p<0.001$), with no mortality in women with normalized EF at onset of a SSP (versus 19% in those women who had impaired systolic function (EF 32.0 $\pm$ 2%) at onset of a SSP (p=0.06). In the same study, frequency of premature delivery (11 % versus 37%) and therapeutic abortions (4% versus 25%) was also greater in women with impaired versus recovered cardiac function at onset of SSP. As these data were collected via a retrospective survey, information on medical therapy provided during pregnancy was not available.

A recently published prospective study reported the management and outcome of SSPs in 34 PPCM

patients in Germany, Scotland and South Africa.[6] Persistently reduced LVEF (<50%) prior to entering SSP was present in 47%, while full recovery (LVEF ≥50%) was present in 53% of patients. The majority of these patients were of African ethnicity (75%). Overall relapse rate (LVEF < 50% or death after at least 6 months follow-up) was 56% with 12% (4/34) mortality). All 4 deaths occurred in the women with persistently reduced LVEF prior to SSP. Patients obtaining standard therapy for heart failure, and bromocriptine immediately after delivery, displayed significantly better LVEF at follow-up and a higher rate of full recovery, with no patient dying, compared to patients obtaining standard therapy for heart failure alone. This was independent of African or Caucasian race. Bromocriptine was provided to a number of patients, based on previous research suggesting that the nursing hormone, prolactin, which is highly elevated during delivery, and periodically in nursing mothers, is a key player in the pathophysiology of PPCM.[58] A number of factors, such as oxidative stress, promote the cleavage of prolactin in an antiangiogenic 16kDa-PRL fragment being causally involved in PPCM.[59] Furthermore, experimental studies in mice and small clinical pilot studies suggest a beneficial effect of the prolactin blocker bromocriptine to improve outcome of acute PPCM[60] or prevent relapse after a SSP.[6] Recent data from the EuroObs PPCM global registry has demonstrated that of 411 patients, 21.1% received bromocriptine in their index pregnancy.[5] However, breastfeeding should be encouraged in women with mild cardiac dysfunction, particularly in areas of poor sanitation and unsafe water supply.

Based on published data [57],[6] and consensus by the HFA PPCM Study Group our position is that full recovery of LVEF before a SSP is associated with lower mortality and better cardiac function at follow-up. However, all patients have a risk of deterioration of cardiac function. Women with impaired LV function at the onset of a SSP have a high risk of relapse, heart failure and death and pregnancy should be avoided.

Data have shown that patients with a history of PPCM could have subclinical cardiac dysfunction[61,62] demonstrated reduced myocardial strain after recovery in women with PPCM at least 12 months after the diagnosis. There are no published data on the impact on subsequent pregnancy in this group of patients.

Addition of bromocriptine to standard therapy for heart failure immediately after delivery was found to be safe and seemed to be associated with a better outcome of SSPs in African and Caucasian patients.

The current recommendation based on published data [57],[6] and consensus of the HFA PPCM Study Group members on the management of pregnancy and postpartum period in women with a previous PPCM is summarized in **Figure 1.**

Patients can be stratified according to impaired or recovered left ventricular function at onset of subsequent pregnancy. However, each case would need to be assessed by a multidisciplinary team, which includes a cardiologist, obstetrician, neonatologist, anaesthetist and possibly other specialists. Neonatologists could provide advice on neonatal outcome if delivery needs to occur prematurely. Anaesthetists need to provide input in patients delivering with symptoms and signs of heart failure. In addition, overall health system factors and maternal factors such as e.g. age and sub-clinical thyroid disease need to be considered.

In pregnant women renin-angiotensin receptor inhibitors need to be terminated because of fetal toxicity. In addition Hydralazine/nitrate combination should be used instead of angiotensin blockers for management of heart failure as well prevention of further deterioration.[63] Anticoagulation with low molecular weight heparin during pregnancy in PPCM women with LV dysfunction should be considered.

In terms of pregnancy from an obstetric standpoint, scans for fetal growth should be performed every 4 weeks from week 24. Timing of the delivery, for obstetric reasons, should be driven by the usual parameters including fetal growth restriction or pre-eclampsia. For cardiac reasons, early delivery should be considered with deteriorating cardiac function and particularly with heart failure. Ideally the target would be to reach 37 weeks. However, the best compromise will be achieved by discussion with the multidisciplinary team to balance maternal health and fetal maturity.

Figure 2. Provides a check box for all women with a diagnosis of a PPCM - either newly diagnosed or with a PPCM and subsequent pregnancy. Anticoagulation for 6-8 weeks after the delivery could be considered because of the hypercoagulability during this period of time.

Contraception for women with a recent PPCM and for patients at high risk in a subsequent pregnancy

Contraceptive counselling should begin early – i.e. as soon as PPCM has been diagnosed. A review on the use of contraceptives in women with heart disease has been published recently by Roos-Hesselink and colleagues.[64] Types of the most commonly used contraceptives are summarized in **Figure 3**. Appropriate advice may be complex and will require the input of both a cardiologist and an obstetrician to identify the optimal approach. As no studies have been performed in women with heart disease, and in particular in women with PPCM, the relative risks and benefits of different contraceptive methods are based on consensus only. As women with PPCM with LV dysfunction are at a substantial risk of thrombo-embolic events,[5] hormonal contraceptives with a pro-thrombotic effect should be avoided. The risk of venous thrombosis is significantly increased (up to 7-fold) by

the oestrogen component in oral contraceptives - irrespective of type of progestin used. However, the risk is in the general population is small in absolute numbers (8-10/10,000 women-years exposure).[65,66] The risks of using a combined oral contraceptive must be weighed against that of an unplanned pregnancy. However, since oestrogen-containing oral contraceptives not only increase the risk of venous thrombosis, but also of arterial thrombosis and hypertension,[67,68] they are contraindicated in with most forms of cardiac disease, particularly those associated with an increased venous or arterial thrombotic risk, hypertension or ischaemic heart disease. Further, given that the most effective types of contraception are the long-acting reversible forms (intrauterine contraceptive devices or progesterone cutaneous implants) and that they have no prothrombotic effects, this group of contraceptives should be advised in most cases. They are at least as effective as sterilization, the finality of which some women struggle to accept. The progestogen (etonogestrel), implant known as Implanon, has no cardiac effects, is effective and has fewer side-effects, such as irregular bleeding, than other implants.[64] The progesterone releasing intrauterine system, Mirena, is preferred to the older copper IUCDS as the majority of users have no periods. Due to high failure rates barrier methods should only be recommended in addition to other contraceptive methods.

In reaching a decision about type of contraception given the significant maternal morbidity and mortality risk of a subsequent pregnancy, the partner of the women should be involved in reaching the decision about type of contraception. In the decision making the following issues should be considered:

1) The risk of pregnancy for the mother and the consequences of an unplanned pregnancy.

2) The impact of any pregnancy on the entire family, which could include to hospitalization due to heart failure, embolic events and death.

3) The risks and benefits of the type of contraception - in particular pro-thrombotic effects.

4) Failure rates of the type of contraception.

5) The availability and affordability of different types of contraception.

6) The individual's preferences, which may include the option of sterilization for the women or her partner.

7) For the majority of women, a long-acting reversible form such as an intrauterine contraceptive device will be most favourable.

CONCLUSION AND WAY FORWARD

The current evidence for long-term outcome is based mostly on single-centre studies or small registries. All patients with a previously diagnosed PPCM and their partners should receive careful counselling about the longer-term prognosis and undergo a risk stratification if further pregnancies are considered. Patients who undergoing a subsequent pregnancy should be monitored by an experienced multi-disciplinary team throughout the pregnancy and for at least 1 year postpartum. Based on recently published data, women undergoing a subsequent pregnancy with an impaired systolic function are at substantial risk for a relapse and death and should therefore be advised against pregnancy. Breastfeeding is not advisable in cases with severely impaired systolic function. In those patients inhibition of prolactin with bromocriptine should be considered. The ongoing EURObservational Program on PPCM will provide much needed longer-term outcome data.[5]

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Legends

Tables: uploaded as separate files

Table 1: Long-term outcome of patients with PPCM

Table 2: Studies of PPCM patients undergoing a subsequent pregnancy

Figures: (in TiFF format 300 pixels and as separate files)

Figure 1: Counselling of women with PPCM regarding subsequent pregnancy and a guide to management.

Figure 2: Post discharge check box for women diagnosed with PPCM

Figure 3: Sketch illustrating different types of contraceptives

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The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European journal of heart failure 2016.

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Yours sincerely

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2 October 2017

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RE: Long-term Prognosis and Management of Peripartum Cardiomyopathy (PPCM): Contraception, Subsequent Pregnancy, Drug Treatment. Practical guidance paper from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy

The authors confirm that all material is original to this submission.

Yours sincerely

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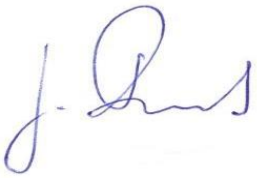

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Supplementary Material

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Table 1. Studies of n≥8 after 1985 describing long-term (> 6 months) mortality in women with PPCM stratified by region

First author	Year	Study period	Location	Study type	Number	Mean age (years)	Mortality (%)	Follow-up in months/years (mean or median)
6-12 months								
Libhaber	2015	2008-2014	South Africa	Prospective, 2 centres	206	30	12	6 m
Hagikhia	2013	2004-2012	Germany, Hannover	Prospective, 1 centre	115	34	2	6 m
Barbosa	2012	NA	Brazil	Prospective, 1 centre	9	29	0	7.9 m
Isezuo	2006	2003-2005	Sokoto, Nigeria	Prospective, 1 centre	65	28	12	9.7 m
Desai	1995	1986-1989	Durban, South Africa	Retrospective, 1 centre	97	29	14	7 m
Kamiya	2011	2007-2008	Japan	Survey, nationwide	102	32	4	9.4 m
Ravikishore	1991	NA	New Delhi, India	Prospective, NA	20	28	5	10 m
12-23 months								
Briasoulis	2016	2009-2014	Detroit, USA	Retrospective, 1 centre	47	29	11	12.5 m
McNamara	2015	2009-2012	USA	Prospective, multicentre	100	30	4	12 m
Goland	2013	1993-2007	Louisiana + South California, USA	Retrospective, 2 centre	156	29	7	19 m
Goland	2009	NA	USA	Retrospective, NA	182	29	7	19 m
Bernstein	2001	1985-1995	Connecticut + New York, USA	Retrospective, 2 centre	23	30	13	12 m
O'Connell	1986	NA	Illinois, USA	Prospective, 1 centre	14	28	43	12.1 m
Carvalho	1989	1982-1988	Sao Paulo, Brazil	Prospective, 1 centre	19	26	16	21 m
Prasad	2014	2006-2012	Maharashtra, India	Prospective, 1 centre	16	25	6	12 m
~ 2 years								
Cooper	2012	2002-2008	USA	Prospective, multicentre	39	30	0	2.1 y
Modi	2009	1992-2003	Louisiana, USA	Retrospective, 1 centre	44	25	16	2 y
Elkayam	2005	1997-1998	USA	Survey, American College of Cardiology	100	30	9	2 y
van Hoeven	1993	1982-1990	New York, USA	Retrospective, 1 centre	13	30	23	2.1 y
Cole	1987	NA	Boston, USA	Prospective, NA	14	30	7	2 y
Fett	2005	2000-2005	Haiti	Prospective, 1 centre	98	32	15	2.2 y
Moreira	2005	1994-2002	Sao Paulo, Brazil	Retrospective, 1 centre	12	24	8	2.2 y
Sliwa	2011	2006-2010	Soweto, South Africa	Prospective, 1 centre	80	29	28	2 y
Liu	2016	1983-2014	Beijing, China	Retrospective, 1 centre	28	27	4	2.3 y
2.5-5 years								
Gunderson	2011	1995-2004	North California, USA	Retrospective, population	110	NA	2	3 y
Habli	2008	2000-2006	Ohio + Kentucky, USA	Retrospective, 2 centre	70	NA	0	3.4 y
Brar	2007	1996-2005	South California, USA	Retrospective, population	60	33	3	4.7 y
Amos	2006	1990-2003	North Carolina, USA	Retrospective, 1 centre	55	29	0	3.6 y
Felker	2000	1982-1997	Baltimore, USA	Retrospective, 1 centre	51	29	6	5 y
de Souza	2001	1990-1999	Sao Paulo, Brazil	Prospective, 1 centre	29	28	28	3.3 y
Ntusi	2015	1996-2009	Cape Town, South Africa	Prospective, 1 centre	30	31	17	3.5 y
Li	2016	2004-2011	Beijing, China	Retrospective, 1 centre	71	28	0	3.6 y
Cuenza	2016	2005-2015	Quezon City, Philippines	Retrospective, 1 centre	39	28	26	4.5 y
Akil	2016	2002-2012	Turkey	Retrospective, 3 centre	58	31	15	2.7 y

Biteker	2012	2005-2009	Istanbul, Turkey	Prospective, 2 centre	42	27	24	3.3 y
Duran	2008	1995-2007	Istanbul, Turkey	Prospective + retrospective, 1 centre	33	32	30	4 y
Mouquet	2012	1999-2006	Lille, France	Prospective, 1 centre	8	28	0	4.2 y

>5 years								
Pillarisetti	2014	1999-2012	Kansas + Michigan, USA	Retrospective, 2 centre	100	30	11	8.2 y
Harper	2012	2002-2004	North Carolina, USA	Retrospective, population	85	NA	17	7 y
Felker	2000	1982-1997	Baltimore, USA	Retrospective, 1 centre	42	29	7	8.6 y
Adesanya	1989	1969-1972	Zaria, Nigeria	Prospective, 1 centre	181	NA	26	10 y
Chee	2013	2000-2009	Kuala Lumpur, Malaysia	Retrospective, 1 centre	12	32	8	6.4 y
Mishra	2006	1995-2005	Cuttack Orissa, India	Prospective, NA	56	31	23	6.1 y
Lamparter	2007	1989-2003	Marburg, Germany	Prospective, registry	10	30	0	5.8 y

Table 2: Studies of PPCM patients undergoing a subsequent pregnancy

First author	Year	Number	Pregnancies *	Post index pregnancy LV function		Persistent LVSD post subsequent pregnancy** n (%)	Maternal death		Miscarriage/ fetal death n (%)
				Recovered n (%)	Unrecovered n (%)		Total death n (%)	Number of deaths in unrecovered LV function (% of total deaths)	
Sutton[a]	1991	4	4	4 (100)	0	0	0	-	0
Witlin[a]	1997	6	7	NA	NA	NA	1 (17)	1 (100)	0
Albanesi Filho[b]	1999	12	16	6 (50)	6 (50)	NA	1 (8)	1 (100)	0
de Souza[a]	2001	7	7	NA	NA	7 (100)	0	-	0
Elkayam[c]	2001	44	35	28 (64)	16 (36)	9 (20)	3 (7)	3 (100)	0
Avila[b]	2002	18	19	7 (39)	11 (61)	4 (44)^	1 (6)	1 (100)	0
Sharieff[b]	2003	9	NA	2 (22)	7 (78)	5 (56)	2 (22)	NA	NA
Sliwa[d]	2004	6	6	2 (33)	4 (67)	5 (83)	2 (33)	2 (100)	0
Chapa[a]	2005	6	8	4 (67)	2 (33)	5 (83)	0	-	NA
Fett[b]	2006	15	16	1 (7)	14 (93)	7 (47)	1(7)	NA	NA
Mishra	2006	9	NA	NA	NA	NA	5 (56)	NA	NA
Hilfiker-Kleiner[b]	2007	12	12	12 (100)	0	6 (50)	3 (25)	0	NA
Habli	2008	37	21	NA	NA	NA	0	-	0
Modi[c]	2009	NA	15	4 (27)	11 (73)	NA	0	-	6 (40)
Chee[c]	2009	2	1	2 (100)	0	NA	0	-	0
Fett[e]	2010	56	61	29 (52)	27 (48)	9 (15)^^	1 (2)	1 (100)	NA
Mandal[f]	2011	6	6	5 (83)	1 (17)	1 (17)	1 (17)	1 (100)	1 (17)
Hilfiker-Kleiner[c]	2017	34	31	18 (53)	16 (47)	17 (53)[∞]	4 (12)	4 (100)	1 (3)

** Number without therapeutic abortion* ***at last follow-up* *^n=9 with follow-up data* *^^denominator is number of pregnancies* *[∞]n=32 with follow-up data*

[a] Fractional shortening 30% used as cut off *[b] Unknown cut-off* *[c]EF 50% used as cut off* *[d] EF 40% used as cut off* *[e]EF 55% used as cut off* *[f] EF 45% used as cut off*

Figure 1

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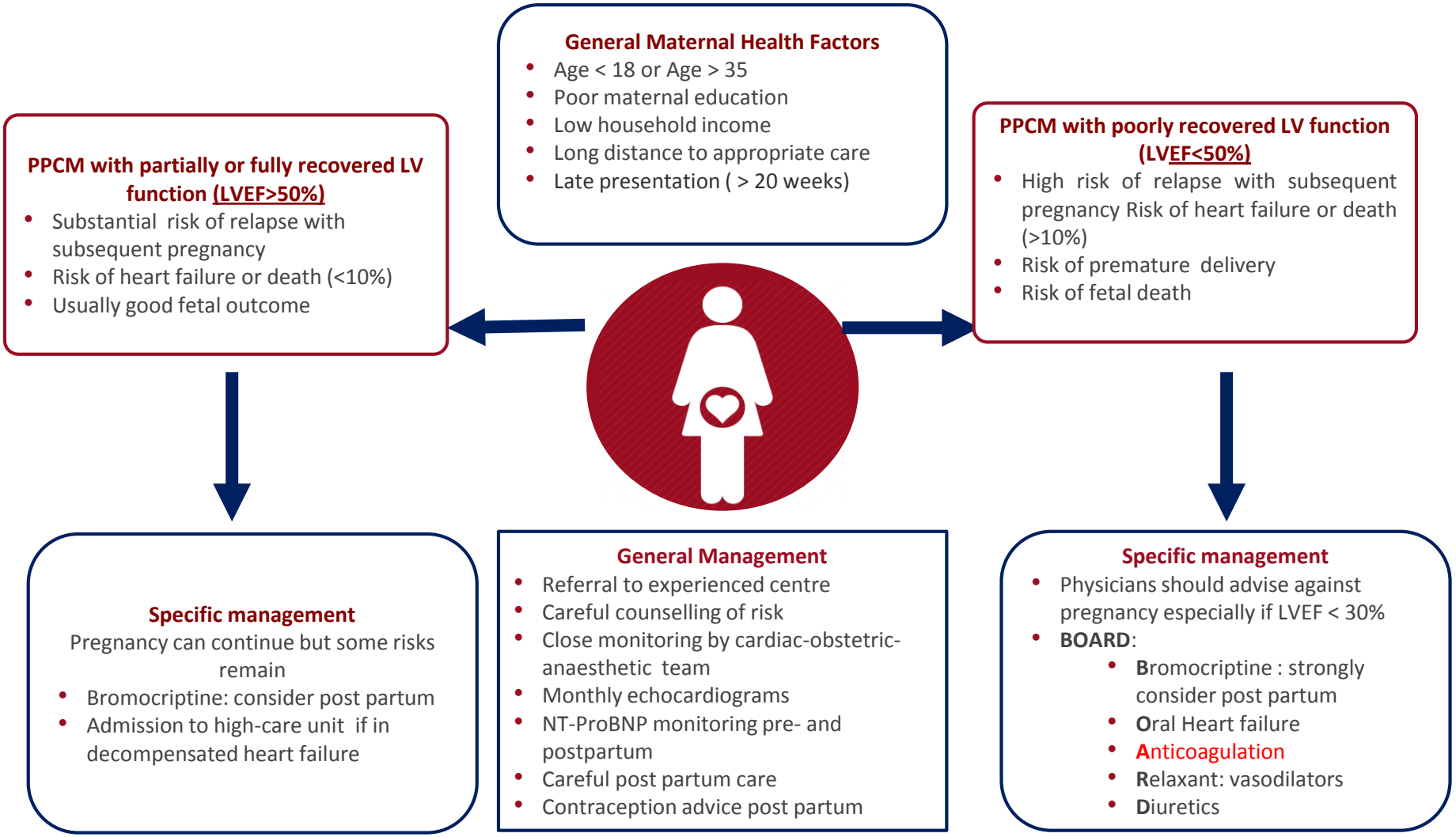

Figure 1: Management of women with PPCM and a subsequent pregnancy

Figure 2

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- Adequate post diagnosis counselling, including future pregnancies and prognosis
- Counselling and education of families
- Prescription of formula milk provided if women is not breastfeeding
- Adequate dose of heart failure medication
- Contraceptive advice provided
- Referral to appropriate centre if unable to come back to expert centre
- Referred to social worker if unable to work/low income circumstances

Figure 2: Post Discharge Check Box for women diagnosed with PPCM

Figure 3

Contraception (Female)

- **Intrauterine contraceptive device** (e.g. Mirena or copper IUCDs)
- Oral contraceptive (combined or progestin only pills)
- Depomedroxyprogesterone acetate (DMPA) injections
- Tubal ligation
- Diaphragm
- Contraceptive implants
- Contraceptive patch
- Hysteroscopic tubal occlusion (HTO)
- Vaginal ring
- Safe period

Contraception (Male)

- Condom
- Vasectomy

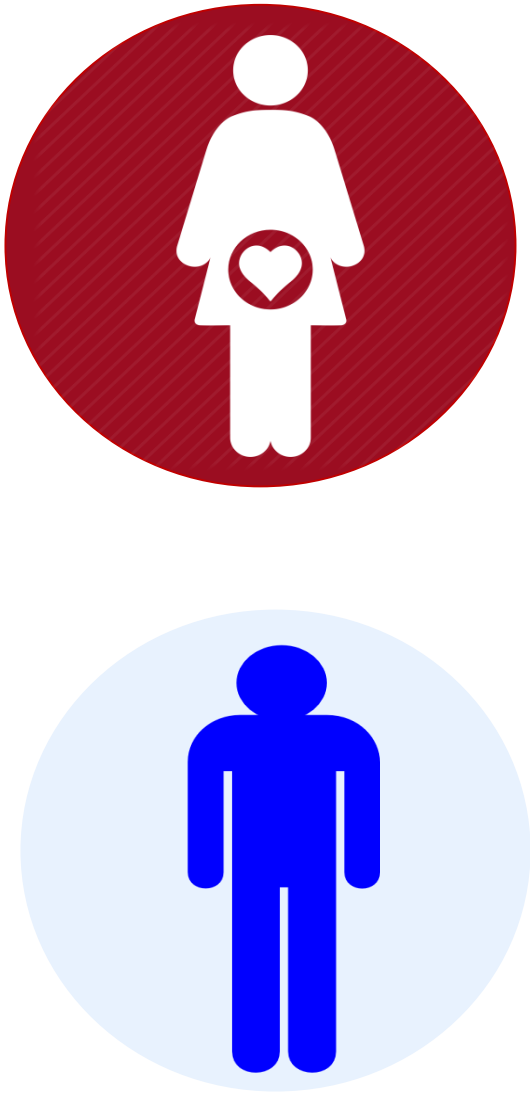

Figure 3: Types of contraception