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PERIPARTUM CARDIOMYOPATHY: A PROPOSED CLINICAL PATHWAY FOR EARLY DIAGNOSIS

by

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AN ABSTRACT OF THE PROJECT OF

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Title : Peripartum Cardiomyopathy: A Proposed Clinical Pathway For Early Diagnosis

Peripartum cardiomyopathy (PPCM) is a rare but devastating disease that hits women at a time when heart disease should not be a concern. PPCM is a type of idiopathic, non-ischemic, dilated cardiomyopathy presenting with symptoms of heart failure primarily due to left ventricular (LV) systolic dysfunction that is manifested in the last trimester of pregnancy and up to 5 to 6 months after delivery. It is clear from the literature that women from black or Haitian descent are the most prone to having the condition. In Lebanon, no studies are conducted on the disorder in general. The clinical presentation can be either sudden requiring urgent admission to the intensive care unit, progressive or latent. The etiopathogeneis is still unknown but thought to be multifactorial. Signs and symptoms are similar to those in acute heart failure. The diagnosis is a diagnosis of exclusion, after ruling out cardiac-pregnancy related conditions. Echocardiography is the gold standard tool for diagnosis and cardiac magnetic resonance can be added as a complementary in critical unresponsive cases. Treatment is similar to that of conventional heart failure with consideration of contraindicated drugs in pregnancy and lactation. Novel drugs and biomarkers are promising but still in the early stages and more studies are still required to finalize and generalize their bedside uses. Since early diagnosis is the key to early recovery with less

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Table of Contents

CHAPTER I

INTRODUCTION

A. Background

Peripartum cardiomyopathy (PPCM) is a rare but potentially life-threatening condition that affects previously healthy women in late pregnancy or in the early puerperium (Hilfiker-Kleiner & Sliwa, 2014). PPCM is a type of idiopathic, non-ischemic, dilated cardiomyopathy (Anderson & Horne, 2010; Johnson- Coyle, Jensen, & Sobey, 2012; Pyatt & Copal, 201; Ramsumsson, 2007), presenting with symptoms of heart failure primarily due to left ventricular (LV) systolic dysfunction that is manifested in the last trimester of pregnancy and up to 5 to 6 months after delivery (Sliwa & Hilfiker-Kleiner, 2014; Pyatt & Copal, 2011).

PPCM strikes women at a time when heart disease should not be a concern, and can often go undetected or misdiagnosed because of its low incidence and nonspecific symptoms leading to late diagnosis (Groesdonk, et al., 2009). Therefore, PPCM has overwhelming consequences with reported mortality and morbidity rates ranging between 5% and 32% (Johnson-Coyle, Jensen, & Sobey, 2012; Pearson, et al., 2000). Earlier names of the disorder are postpartum myocardiosis, Zaria syndrome, Meadows syndrome, idiopathic myocardial degeneration associated with pregnancy, toxic postpartal heart failure (Abboud, Murad, Chen- Scarabelli, Saravolatz, & Scarabelli, 2007; Danbauchi, 2002).

PPCM has been identified as a life-threatening complication of pregnancy since the eighteenth century by Ritchie who identified a pattern of heart muscle disease in the months preceding delivery and following delivery (Ritchie, 1849, reprinted in 2011), then by Hull and Hafkesbring in 1937 (cited in Demakis & Rahimtoola, 1971), and subsequently by Gouley and Mcmillan (1937). PPCM was initially described as an "*Occult form of primary congestive cardiomyopathy made overt by the pregnant state*" (Demakis & Rahimtoola, 1971, p. 968), to be called later *"Pregnancy specific heart failure"* (Ruys, et al., 2014, p. 231). More evidence was later collected by Virchow and Porak who noticed that myocardial degeneration was causing death in women in the puerperium (the period between childbirth and the return of the uterus to normal size) (cited in Sakakibara, Seikiguch, Konno, & Kusumoto, 1970). In fact, the condition was not given enough attention until the 1930s, when pictures and depictions of post-partum women with heart biopsies showing enlarged necrotic hearts were published (Gouley, Mcmillan, & Bellet, 1937; Hull & Hafkesbring, 1937). In fact, the association between pregnancy and cardiomyopathy was not discovered until 1937 (Gouley & Mcmillan, 1937).

In general, PPCM has been described as a heterogeneous group of problems difficult to characterize, including inflammatory autoimmune states and hypertensive heart diseases associated with toxemia of pregnancy (Young & Mill, 2001, page 34). The first PPCM definition emerged by suggesting several defining criteria. The first criteria is the time frame for when the disease first develops which is towards the beginning of the third trimester or early postpartum. The second criterion is to exclude pre-existing of cardiomyopathy that can be further exacerbated by pregnancy. Other criteria include no

determinable cause of the cardiac failure, and absence of cardiac disease before the last month pf pregnancy (Demakis & Rahimtoola, 1971). Soon after, that same definition was adopted by The National Heart, Lung, and Blood Institute and the Office of Rare Diseases Workshop, with the addition of a firm echocardiographic standard of LV systolic dysfunction demonstrated by LV ejection fraction (LVEF) < 45%, fractional shortening < 30%, or both, with or without LV dilatation (Sliwa K. , et al., 2012). The European Society of Cardiology working group on PPCM also recently released a new definition: "*An idiopathic cardiomyopathy presenting with heart failure (HF) secondary to systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%"* (Sliwa K. , et al., 2010). However, the criteria included in The National Heart, Lung and Blood Institute (NHLB) and the Office of Rare Diseases remain the most reliable and specific, and include:

- Development of PPCM in the last month of pregnancy or within five months after delivery
- Absence of an identifiable cause of heart failure
- Absence of recognizable heart disease before the last month of pregnancy
- Left ventricular systolic dysfunction, with or without LV dilatation:
  - Ejection fraction less than 45%
  - Fractional shortening less than 30%
  - End- diastolic dimension greater than 2.7 cm/cm^2 body surface area

(Pearson, et al., 2000)

B. Epidemiology

PPCM is a rare condition of indistinct etiology that accounts for an important percentage of pregnancy-related deaths (approximately 35%-55 %) (Ray, Murphy, & Shutt, 2004). Knowledge of the incidence of PPMC has a great significance on understanding its impact, and its consequences and the course of management needed. However, even today, scant information is available in the literature about the incidence of PPCM. More epidemiological studies are needed to highlight the disease in larger racial populations and geographical areas (Sliwa et al., 2010). The incidence fluctuates geographically most likely because of socioeconomic and genetic factors that vary from one country to another (Hilfiker-Kleiner & Sliwa, 2014). Yet, the real incidence of PPCM is still unknown because of the lack of population-based studies (Pearson, et al., 2000), and because the real mortality rate is not always accurately estimated and recorded (Mielniczuk et al., 2006). Generally, the incidence is low, and does not exceed 0.1% of pregnancies (Johnson-Coyle et al., 2012). PPCM is considered to be a rare disease in Western countries with an estimated incidence of 1:2300 to 1:4000 (Pearson et al., 2000; Sliwa, Fett, & Elkayem, 2006). However, the highest incidence in America has been reported in African or African-American women, the lowest in Hispanic women (Brar et al., 2007). African- American women actually have 15.7 fold higher relative risk of PPCM than non-African Americans (Gentry, et al., 2010). Although it has not been proven, there is probalby a genetic cause for the excess burden of heart disease in African-Americans who have high prevalence of hypertension, intermarriage and reproduction (Yancy C. , 2003).

PPCM also has been reported in Asian women (1 per 2, 675), in White women (1 per 4, 075), and in Hispanic women (1 per 9, 861) (Brar, et al., 2007; Pyatt & Dubey, 2010). Demakis et al (1971), and Brar et al (2007) found that African- American women were 2.9 times more likely to have PPCM than White women and seven times more likely than Hispanic women. In Africa (incidence ratio: 1:100 in a small sub-Sharan Africa; 1:1000 in South Africa) and 1:299 in Haiti (Fett, Christie, Carraway, & Murphy, 2005; Mayosi, 2007; Selle, Renger, Labidi, & Hilfiler-Kleiner, 2009). In the United States, PPCM rates have alarmingly increased from 1 per 4,350 in 1990- 1993 to 1 per 2,229 in 2000-2002 (Mielniczuk, et al., 2006); this can be attributed to the increased maternal age, the multifetal preganancies, and the easy access to reproductive therapy which can increase the chances of twin-pregnancies , and eventually the improved diagnositc techniques and early diagnosis that help in detecting PPCM (Hilfiker-Kleiner & Sliwa, 2014).

To date, neverthelss, there is no clear explanation for why PPCM incidence is higher in certain geograpgic distributions, but it is suspected that it can be related to African ancestry and the high prevalence of hypertension in the black race, lifestyle, and cultural practices (James, 2004; Pearson, et al., 2000; Sliwa, Fett, & Elkayem, 2006). Some researchers relate the variability in PPCM's reported incidence to both: the non-consistency in the criteria for diagnosis, and the lack of a comparison with same age non-pregnant women (Johnson-Coyle et al., 2012; Wiltin, Mabie, & Sibai, 1997).

Although it seems that most women who are conceiving are likely prone to develop the disorder because of the increased hemodynamic changes during pregnancy (Sliwa et al., 2007), most reports indicate higher incidence in certain populations (Anderson

et al., 2010; Ford et al., 2000), especially those of Haitian and African descent (Gentry, et al., 2010). One important aspect to note about Haitian women who are the most frequent victims of PPCM, is that not only do they have the highest rate of PPCM worldwide (ten times higher than women in the United States and Europe (Fett , Christie, Carraway, & Murphy, 2005), but they also mostly present with the alarming latent form of the disorder that happens without clinical manifestations (Sliwa, Fett, & Elkayem, 2006). It has been correspondingly documented that four out of 25 Haitian PPCM patients have unrecognized presentation of PPCM (Fett et al., 2005).

In Lebanon, there has been no research done in this area. In phone interviews conducted with two obstetricians, one mentioned that the disorder rates are low in Lebanon like anywhere else in the world, and are seen at a rate of one case per 50,000 (Ghaname, personal communication). Another obstetrician mentioned that PPCM is probably seen at a rate of one case every few years. Four cases have been witnessed by him since his career in the last decade: two patients fully recovered, and two died two months after delivery because they were diagnosed late (Al- Ali, personal communication).

Internationally, remarkable efforts have already being made in terms of PPCM, inaugurating a new era in the PPCM field with promising preliminary results in many pioneering studies . The number of PPCM-focused studies has actually increased in a significant way in the last two decades. Some novel biomarkers and treatments are being thoroughly studied because of their favourable outcomes, and will be hopefully adopted as a standard diagnostic tool/ therapy in the near future. A worldwide PPCM registry has been likewise recently established by the Peripartum Working Group of the Heart Failure

Association (HFA). This registry is known today by the ECS EURObservational Registry on PPCM, and was mainly established to promote worldwide awareness about the diseases, and to respond to the learning needs of patients. The registry encourages pregnant women to report information about PPCM like risk factors, symptoms, complications, management (Maggioni, et al., 2013). Nowadays, the registry has more than 80 centers in 50 registered countries (Hilfiker-Kleiner & Sliwa, 2014).

It is nowadays agreed that PPCM is a "*Diagnosis of exclusion*" (Ford, Barton, O'Brien, & Hollingsworth, 2000). It is a kind of idiopathic cardiomyopathy portraying signs and symptoms of heart failure accompanied by decreased LV systolic dysfunction (with or without LV dilatation). Occurrence is specifically between the last month of pregnancy and the first five months postpartum without other apparent causes contributing to the development of symptoms (Ntusi& Myosi, 2009; Sliwa, Fett, & Elkayem, 2006).

C. Significance and Purpose of the study

Even though PPMC has been considered fatal, it can have a good prognosis when diagnosed and treated early (Moukarbel & Arnaout, 2003; Shanoon-Cain, Hunt, & Cain, 2008). More importantly, a significant number of patients who present with severe left ventricular dysfunction can fully recover (with an ejection fraction of 50% or higher) when diagnosed early and followed up appropriately for six months post diagnosis (Laghari, Khan, & Kazmi, 2014). In fact, the possibility that women with PPCM have both a higher rate of spontaneous recovery of LV function and higher and better survival rates than

women with idiopathic dilated cardiomyopathy (Mayosi, 2007), has generated wide interest in its early screening and aggressive management.

Many studies have been conducted to understand the disorder and its complexity, and to develop reliable biomarkers to diagnose it. However, there have not been clear clinical guidelines on how women at risk can be screened since risk factors are not clearly determined and interconnected. Additionally, the discovery of biomarkers is still in the early stages of research. It can take years before a final, reliable test might be adopted to confirm diagnosis. Therefore, the focus of this project will be on primary prevention and early diagnosis, and how health care providers can screen pregnant women for this deadly condition before it attacks the cardiovascular system and other vital organs, and cause irreversible and disastrous sequelae on the expecting mother and the fetus.

Since early diagnosis is the key in reversing PPCM, a screening tool/ algorithm will be developed in this project to be used early in the last month of pregnancy and at any time there is a need to screen for PPCM in high risk women. The assessment tool will help to detect the early signs of PPCM that can be confused with the normal discomfort of pregnancy itself and can be used by gynecologists/ general physicians and registered nurses. Afterwards, high risk patients who have enough alarming signs and symptoms and/ or enough risk factors will be sent for thorough testing for early diagnosis. A clinical pathway guiding referral and management will also be developed.

Despite the fact PPCM is not a frequently encountered disorder in clinical practice, it is a serious condition leading to lethal outcome if not diagnosed early and treated appropriately and aggressively. Since health care professionals working in pre and post-

partum units may not be skilled or experienced in cardiac disorders, dealing with such a disorder may be puzzling for them. This could delay the management of PPCM as normal complains in the last part of pregnancy might mimic the manifestations of heart failure. Therefore, in this project, a literature review is conducted and a clinical pathway developed for women presenting with PPCM so that early diagnosis prompt treatment can be initiated.

CHAPTER II

LITERATURE REVIEW

As mentioned in chapter I, PPCM is a rare disorder that has a distinct clinical entity. The diagnosis is made by exclusion, so among the cardiac and pulmonary manifestations, certain chronological, clinical and echocardiographic criteria have to be met. PPCM is defined as the development of heart failure in the last month of pregnancy or the five months after delivery. Further diagnostic criteria have been added to increase the diagnosis specificity of the disorder. These include the absence of an identifiable cause of heart failure, no known previous heart disease, and clear evidence of left ventricular systolic dysfunction (Pearson, et al., 2000). In this chapter, the etiology/ risk factors, pathophysiology, diagnosis and management of PPCM are reviewed.

The pathophysiologic mechanism of PPCM is still poorly outlined. However, the increased accumulation of risk factors have attracted more research attention in order to understand the intriguing pathophysiological transformations upon the cascade activation of lethal triggers that may take place in pregnancy. Pregnancy is considered as a "*Physiologic stress test*" that can disclose serious conditions like hypertension, diabetes and heart failure. During pregnancy, there is an increase of cardiac output by 30 to 50 %. There is also an increase in cardiac workload due to the increase in plasma volume, which can precipitate heart failure (Ruys, et al., 2014). Geva, Mauer, Striker, Kirshon, and Pivarnik (1997) studied the effects of the physiologic load of pregnancy

on left ventricular contractility and remodeling. They found that during pregnancy there is 10% increase in left ventricular end-diastolic volume, a 45% increase in cardiac output, a 26% to 28% decrease in end systolic wall stress, a sensitive measure of myocardial afterload. Furthermore, the left ventricle remodels in response to the substantial hemodynamic stress of pregnancy, resulting in transient hypertrophy (Geva et al., 1997). Therefore, pregnancy itself activates a unique hemodynamic stress response that, by going aberrant, can have overwhelming consequences on the myocardium and its functions. This unique hemodynamic stress of pregnancy can also disclose previously undiagnosed cardiomyopathy in previously medically stable people (Wiltin, DO, Mabie, & Sibai, 1996). The proposed triggers of this hemodynamic aberration that leads to PPCM are described next.

A. Etiology/ pathogenesis

Despite many attempts to discover the unique etiology underlying PPCM, the real mechanism behind PPCM is still not adequately explained today (Ntobeko & Mayosi, 2009). However, many studies suggest that PPCM can be multifactorial, and that many of these factors result in a common final pathway. Some of these factors range from viral myocarditis, enhanced oxidative stress, and Cathepsin D cascade activation, to abnormal immune response, fetal microchimerism and chromosomal interaction, and genetic predisposition.

a. Myocarditis

The prevalence of myocarditis in PPCM patients is high in the literature (Sanderson, Olsen, & Gatei, 1986). It has been suggested that PPCM is actually a type of myocarditis stemming from an infectious, autoimmune, or idiopathic process (Brown & Bertolet, 1998). A 62% prevalence of myocarditis was reported in PPCM patients on endomyocardial biopsy (Felker, et al., 2000). In an older report of endomyocardial biopsy done on 18 patients with PPCM, 14 were found to be positive for myocarditis (Midei, Feldman, Hutchins, & Baughman, 1990). In this context, many investigators suggested that viral myocarditis (Melvin, Richardson, & Gatei, 1986; Sanderson, Olsen, & Gatei, 1982), and eosinophilic myocarditis (Borczuk, van Hoeven, & Factor, 1996) are possible causes of PPCM. Dense lymphocyte infiltrated, myocytes edema, necrosis, and fibrosis were identified in positive endomyocardial biopsies (Melvin, Richardson, & Gatei, 1982). Bültmann et al (2005) highlighted the viral culprit in PPCM patients who were diagnosed with myocarditis, and found different virus species in the studied specimens, such as parvovirus B19, human herpes virus 6, Epstein-Barr virus, and cytomegalovirus (Bültmann, Klingel, Näbauer, Wallweiner, & Kandolf, 2005).

In some cases, the myocarditis was related to inflammation and inappropriate immune response (Hjalmarson, Fu, & Mobini, 2002), and mild inflammatory cell infiltration within the myocardium with foci of necrosis and variable amounts of hypertrophy and fibrosis (Sanderson, Olsen, & Gatei, 1986). However, myocarditis in PPCM can resolve naturally in some cases, which is associated with a major improvement in LV function (Midei, Feldman, Hutchins, & Baughman, 1990).

b. Abnormal immune response

The immune system activation has been widely documented in the literature in PPCM (Hjalmarson, Fu, & Mobini, 2002; Sliwa, Fett, & Elkayem, 2006), and has led many researchers to believe that PPCM is an "*organ-specific autoimmune disease*" (Sunstrom, Fett, Carraway, & Ansari, 2002). Some suggest the hypothesis of an underlying autoimmune mechanism characterized by infiltrating auto-reactive lymphocytes and antibodies in the cardiac tissue (Lamparter, Pankuweit, & Maisch, 2007). The abnormal autoimmune process is described as abnormal auto-immune antibodies, which attack human cardiac tissue protein (Ansari, et al., 2002). This reaction can be triggered by reactivation of latent viral infections, and a variety of host-specific factors. Viral genomes determine the outcome of the disorder (Bültmann, Klingel, Näbauer, Wallweiner, & Kandolf, 2005). For instance, elevated IgG3s levels in PPCM were found to be specific to PPCM patients compared to dilated idiopathic cardiomyopathy. These levels were also indicative of poorer prognosis as they were associated with advanced disease at the time of diagnosis (Warraich, et al., 2005).

c. Apoptosis, Prolactin, oxidative stress and Cathepsin D cascade activation

Neurohormonal activation (Adesanya, et al., 1991), and the loss of myocytes and histological apoptosis (Narula, et al., 1996) have long been described in different types of cardiomyopathy patients. These processes are thought to cause myocardial dysfunction and have been linked to the progression and prognosis of heart failure in these patients (Midei, Feldman, Hutchins, & Baughman, 1990). A balance between oxidative stress and antioxidant capacity is highly required late in the pregnancy and in early postpartum as a

compromised antioxidant defense system can increase the production of oxidative stress, therefore, predisposing women to PPCM (Hilfiker-Kleiner & Sliwa, 2014). Unbalanced oxidative stress, and high levels of the nursing hormone prolactin and serum levels of IFN-y are now thought to be interlocked in a vicious circle during pregnancy. They are associated with an increased inflammatory response and poor outcome in PPCM (Forster, et al., 2008). Elevated levels of cytokines and Fas receptors in PPCM patients are additionally related to increased LV dimension and lower EF at presentation (Sliwa, et al., 2005), and are thought to play an important role in the pathogenesis and the prognosis of the disorder (Sliwa, et al., 2000).

Excessive prolactin production has been suggested as a potential factor in the pathogenesis of PPCM (Kothari, 1997; Podewski, Hilfiker, Hilfiker-Kleiner, Kaminski, & Drexler, 2004), along with the cascade activation of oxidative stress and inflammation (Forster, et al., 2008) .Studies have actually shown a decrease in the cardioprotective signaling pathway STAT3, which results in a decrease in the production of the superoxide dismutase antioxidant enzyme leading to an unopposed activation of the reactive oxygen species. As a result, an activation of oxidative stress and cathepsin is initiated (Hilfiker-Kleiner, Sliwa, & Drexler, 2008). Prolactin, the nursing hormone, is excessively secreted from the pituitary gland into the circulation during lactation. Prolactin is cleaved into the 16-KDa-prl, the harmful form of prolactin, under certain conditions of excess oxidative stress by the myocardium therefore causing adverse effects on the angiogenesis. This will consequently induce endothelial apoptosis, capillary dissociation, vasoconstriction; therefore, cardiomyocyte metabolism

and function will be impaired, thus promoting PPCM (Chopra, Verghese, & Jacob, 2012; Hilfiker-Kleiner, et al., 2007; Hilfiker-Kleiner, Sliwa, & Drexler, 2008; Hilfiker-Kleiner & Sliwa, 2014). Knowledge of the angiostatic and proapoptotic effects of 16kDa prolactin and its potential role in the initiation and progression of PPCM, has generated great interest in developing drugs that inhibit prolactin production. This is done by using the D_2 dopamine- receptor agonist like bromocriptine that is showing promising results for PPCM patients (Hilfiker-Kleiner & Sliwa, 2014).

Significant levels of BNP and NT-proBNP (the N terminal of the pro-hormone brain natriuretic peptide that is assessed along with the hormone BNP for screening and prognosis in heart failure), oxidized LDL, interferon gamma (IFN-γ) and prolactin are associated with poor prognosis in PPCM. This suggests a close connection of these factors to the pathophysiology of PPCM and risk stratification of PPCM patients (Forster, et al., 2008). Another angiogenic factor, FLT-1, is released by the placenta in large amounts during mid to late pregnancy, and high levels of it are closely related to triggering pre-eclampsia that is known to be common among PPCM (Levine, et al., 2004)

d. Fetal microchimerism and chromosomal interaction

In chimerism, fetal cells reside in the mother's circulation, or vice versa (Ramaraj & Sorelli, 2009). Fetal microchimerism is a normal process in all pregnancies, in which levels of fetal cells are detected in the maternal circulation. They peak in the third trimester, and then fade after delivery (Sunstrom, Fett, Carraway, & Ansari, 2002). However, some

studied PPCM patients showed stubborn levels of male chromosomal DNA in the third trimester persisting for more than one month post –partum (Ansari, et al., 2002). Also found are some specific chromosome replication in PPCM patients, indicating a genome-wide association between genetics and the disorder (Horne, et al., 2011).

e. Familial disease

There is a suggestion in the literature that a subset of PPCM is part of familial dilated cardiomyopathy and shares genetic roots with it (van Spaendonck-Zwarts, et al., 2010). Familial PPCM is likely to reoccur in first –degree relatives (Massad, Reiss, Mutch, & Haskel, 1993). Mutations associated with familial forms of PPCM have been identified and include mutations in MYBPC3, MYH6, MYH7, PSEN2, SCN5A, TNNC1, and TNNT2 (Morales, et al., 2010; van Spaendonck-Zwarts, et al., 2010). Yet, additional studies are needed to determine the genetic predisposition to PPCM (Anderson & Horne, 2010). Patients with suspected familial disease should undergo thorough interviews about their family history, and should be sent for routine genetic testing if they are confirmed to have familial DCMO or PPCM (Hilfiker-Kleiner & Sliwa, 2014).

B. Risk factors

Many risk factors are described in the literature since PPCM was discovered two centuries ago. Based on the literature, risk factors for PPCM are classified into general risk factors and pregnancy – related risk factors. General risk factors are similar to cardiovascular risk factors, with some additions, and include:

- History of hypertension (Bhattacharyya, Basra, Sen, & Kar, 2012)

- Diabetes; obesity; smoking, alcohol abuse (Amos, Jaber, & Russel, 2006; Lampert & Lang, 1995; Wiltin, DO, Mabie, & Sibai, 1996)
- Maternal cocaine abuse (Mendelson & Chandler, 1992)
- Advanced maternal age (over 30 years (Hasan, Quereshi, Ramejo, & Kamran, 2010; Hu, et al., 2007); yet, some cases can still develop in younger age (Ford, Barton, O'Brien, & Hollingsworth, 2000; Johnson-Coyle, Jensen, & Sobey, 2012)
- Genetic predisposition such as black race (Desai, Moodley, & Naidoo, 1995; Gentry, et al., 2010), and familial PPCM (Massad, Reiss, Mutch, & Haskel, 1993).
- Low selenium levels there are conflicting data as to whether selenium deficiency is (Cenac, Simonov, Moretto, & Djibo, 1992; Kothari, 1997) or is not a risk factor for PPCM (Fett, Sunstrom, & Combs, 2002). Some data suggest that selenium deficiency makes women more susceptible to viral infection, which can cause cardiomyopathy (Levander & Beck, 1999).

On the other hand, pregnancy- related risk factors are very specific to pregnancy and include:

- Pre- eclampsia or pregnancy induced hypertension has been frequently reported in PPCM patients and thought to be correlated (Reuwer, et al., 2010). However, PIH is rarely reported as a single risk factor for PPCM, but always associated with other related risk factors such as gestational hypertension leading altogether to PPCM (Selle, Renger, Labidi, & Hilfiker-Kleiner, 2009). However, PIH has been reported in isolated cases as a single risk factor that can cause PPCM in some women (Cunningham, Rivera, & Spence, 2011) .

- Multiparity (Homans, 1985). Some PPCM cases have been reported in primigravidas (Bhattacharyya, Basra, Sen, & Kar, 2012).
- Twin pregnancy (Elkayam, et al., 2005) is observed in 13% of patients with PPCM, which is significantly higher than the 1% to 2% reported in healthy women (Holge, Hutoon, KA, Barrett, & Hannah, 2003)
- Teenage pregnancy (Selle, Renger, Labidi, & Hilfiker- kleiner, 2009).
- Prolonged tocolytic therapy such as use for more than four weeks of β-sympathomimetic drugs used to suppress contractions in premature labor (terbutaline, salbutamol, ritodrine, magnesium sulfate) (Lampert, et al., 1993)
- Gestational hypertension or pregnancy induced hypertension (PIH), a type of hypertension that can develop during pregnancy in certain women (6-8% of all pregnant women, and can lead to preeclampsia if not diagnosed and treated promptly (The American Congress of Obstetricians and Gynecologists, 2014). (American Congress of Obstetricians and Gunecologists (ACOG), 2014) A strong association has been found between PPCM and gestational hypertension (Desai, Moodley, & Naidoo, 1995), with an incidence of approximately 43% compared to the 8.5% to 10% incidence in the overall pregnant population (Murali & Baldisseri, 2005)
- Cultural practices and lifestyle (such as the high salt intake by ingesting dried lake salt “kanwa” in Nigeria and some areas of Africa), and sunbathing in heated mud beds in the early postpartum period, which can theoretically lead to a high level of volume overload) (Adesanya, et al., 1991; Johnson-Coyle, Jensen, & Sobey, 2012;

Ntobeko & Mayosi, 2009; Pearson, et al., 2000; Selle, Renger, Labidi, & Hilfiker-kleiner, 2009).

C. Diagnosis

The diagnosis of PPCM can be "elusive" (Pope, 2006, p. 43) as signs and symptoms can be overlooked with the physiological changes that occur in the pregnant body (Groesdonk, et al., 2009). The clinical presentation in PPCM is extremely different from other types of dilated cardiomyopathy, and may briskly develop into end- stage heart failure within days. Yet, spontaneous recovery is always possible, and both options seem to happen in two extreme ends in certain patients (Sliwa K. , et al., 2010). The sudden onset of left ventricular failure in pregnancy, with occasional evidence for pulmonary or systemic embolization, is usually indicative of PPCM (Lee & Cotton, 1989) .

The most common presentation of PPCM is of symptoms and signs of systolic heart failure (Fett, Dowell, King, & Perre, 2002; Sliwa, et al., 2000). Although symptoms may emerge any time in the period of the last trimester to five months postpartum, most studies show that symptoms are more likely to be present in the first month followin delivery (Blauwet & Cooper, 2011). These symptoms include:

- Maternal dyspnea, cough, orthopnea (Veille, 1984)
- Paroxysmal nocturnal dyspnea and tachypnea (Brown & Bertolet, 1998), with most PPCM patients having NYHA class III or IV function (Bhakta, Biswas, & Banerjee, 2007)

- Pleuritic chest pain, palpitations and exercise intolerance (Hilfiker-Kleiner & Sliwa, 2014)
- Hemoptysis, chest pain, and abdominal pain documented in one third of cases (Lee & Cotton, 1989)
- Non-specific fatigue, malaise, and postural hypotension (Bhattacharyya, Basra, Sen, & Kar, 2012)

On the other hand, signs include:

- Lower extremity edema reported in more than half of PPCM cases (Lee & Cotton, 1989)
- Jugular venous distention (Brown & Bertolet, 1998)
- Tachycardia
- Third heart sound (S3) or gallop rhythm reported in in 92% of patients (Blauwet & Cooper, 2011; Sliwa, Fett, & Elkayem, 2006; Yamac, Bultmann, Sliwa, & Hilfiker-Kleiner, 2010)
- Mitral regurgitation murmur (Lee & Cotton, 1989)
- Displaced apical impulse in 72% of patients (Sliwa, Fett, & Elkayem, 2006)
- Pulmonary rales (Blauwet & Cooper, 2011)
- High incidence of thromboembolism (Abboud, Murad, Chen- Scarabelli, Saravolatz, & Scarabelli, 2007; Ibebuogu, Thornton, & Reed, 2007).
- Hepatomegaly and hepatojugular reflux; ascites and peripheral edema

It is nowadays agreed that PPCM is a "Diagnosis *of exclusion*" (Ford et al., 2000, page 1036), where other causes of cardiac disorders must be excluded first.

There are four main criteria for diagnosis as suggested by The National Heart, Lung, and Blood Institute (NHLBI), and are:

1. Development of PPCM in the last month of pregnancy or within five months after delivery
2. Absence of an identifiable cause of heart failure
3. Absence of recognizable heart disease before the last month of pregnancy
4. Echocardiographic diagnostic criteria of LV dysfunction

Demonstrable echocardiographic criteria for left ventricular systolic dysfunction include:

- Ejection fraction less than 45%
- End- diastolic dimension greater than 2.7 cm/m^2 body surface area
- Fractional shortening less than 30%

(Pearson, et al., 2000).

Although early presentation of PPCM is rare, it can still happen and physicians should be aware of that possibility (Elkayam, et al., 2005).The need to investigate this possibility by doing a thorough medical history of the exact onset of symptoms is mandatory to avoid delay in diagnosis with its devastating outcomes (Hilfiker-Kleiner & Sliwa, 2014). In fact, Goland et al found that diagnosis delay by one week can have major adverse effects, like death, heart transplantation, and defibrillator implantation, in 48% of the studied patients (Goland, et al., 2009).

As noted above, the diagnosis of PPCM is based on three clinical criteria: development of heart failure (HF) toward the end of pregnancy or in the months following delivery, absence of another identifiable cause of HF, and left ventricular (LV) systolic dysfunction with an LVEF < 45% (Hibbard, Lindheimer, & Lang, 1999; Sliwa K. , et al., 2010). The last criterion was added to prevent the inclusion of patients with disorders that mimic systolic HF (Hibbard, Lindheimer, & Lang, 1999; Lampert & Lang, 1995).Such disorders include accelerated hypertension (Podymow & August, 2007), diastolic dysfunction (Valensise, et al., 2001), systemic infection, pulmonary embolism, or complications of late pregnancy (eg. preeclampsia, placental infarction, or amniotic fluid embolus) (Kujovich, 2004), or severe complications of pregnancy-induced hypertension (eg. hemolysis syndrome, elevated liver enzymes, and low platelet count) (Weinstein, 1982).

Diagnostic tools/ Screening include the following:

1. *Echocardiography*

Echocardiography is the gold standard diagnostic tool for PPCM patients because it shows vital details about increased LV dimensions early in the disease process and in the progressive forms of it (Wiltin, DO, Mabie, & Sibai, 1996). Echocardiography should be performed with worsening or suspected new- onset heart failure during pregnancy. It is the safest type of screening as radiation should be avoided where possible (Class I, level C) (Howlet, et al., 2010). It usually shows left ventricular dilatation with apparent impairment of overall systolic performance. Absent clinical findings do not exclude the presence of the disease (Wiltin, Mabie, & Sibai, 1997). In PPCM patients, the diagnosis is made by

documenting reduced LVEF and by eliminating other possible causes of cardiac dysfunction. As discussed before, LVEF <45%, and/or fractional shortening < 30%, and end-diastolic dimension > 2.7cm/cm^2; Ejection fraction is the measurement of the end-diastolic volume pumped with each contraction (normal values > 55%); Fractional shortening is the percentage change in LV dimensions with each LV contraction (normal values in women: 27%- 45%); LV end- diastolic measurement is measured at end diastole, and corresponds to the largest cardiac dimension (normal values in women: 2.4-3.2 cm/cm) (Oh, Seward, & Tajik, 2006) . For better screening, combining echocardiography with cardiac magnetic resonance imaging (MRI) is ideal for diagnostic confirmation (Hilfiker-Kleiner & Sliwa, 2014).

2. *Cardiac magnetic resonance* (CMR)

Cardiac magnetic resonance may be used as a corresponding diagnostic tool for PPCM as it helps in identifying and understanding the mechanism involved, and provides essential clinical information (Carlin, Alfirevic, & Gyte, 2010). CMR is safe and radiation-free, and offers a global visualization of the myocardium. It can measure the global and segmental myocardial contraction, and can envision the characteristics of the myocardium, as well as be used as a guide in endomyocardial biopsies (Leurent, et al., 2009).

CMR can be used additionally as a systematic tool for diagnosis, prognosis and management because it is more accurate and specific than regular cardiac echocardiography, and shows specific details about ventricular size and contractile reserve that are very helpful to know in PPCM patients (Baruteau, et al., 2010). CMR is

particularly useful in identifying inflammatory and infiltrative conditions like in PPCM (McMurray, et al., 2012). Mouquet et al. (2008) challenged the idea of CMR being superior to echocardiography , and found no specific MRI characteristics that are more indicating than echocardiography in PPCM when assessing LV anatomy, systolic function and detection of myocardial fibrosis (Mouquet, et al., 2008). Kawano et al reported a PPCM case in which myocardial damage of the left ventricle was proven by delayed contrast enhancement with gadolinium (CMR contrast agent). Later on, the LV measure improved along with cardiac function after the patient was treated with classic heart failure treatment (Kawano, et al., 2007). In conclusion, CMR can be used either as a first line diagnosis tool when combined with echocardiography, or as a second line when used alone.

3. *Chest radiography (CXR)*

Chest radiography usually shows enlargement in the cardiac silhouette with evidence of pulmonary venous congestion and/ or interstitial edema (Wiltin, DO, Mabie, & Sibai, 1996). CXR helps as a prognosis predictor as persistent cardiomegaly on CXR is associated with 85% mortality (Ford, Barton, O'Brien, & Hollingsworth, 2000)

4. Cardiac biomarkers:

Unfortunately, there is not yet a reliable test to confirm the diagnosis. B-type natriuretic peptides have been used but they do not distinguish between different types of heart failure, and therefore, are specific for PPCM screening and diagnosis. Still plasma BNP or N-terminal pro-BNP (NT-proBNP) and plasma relaxin-2 are used for PPCM diagnosis. Affected women have significantly higher levels compared to healthy pregnant or post-partum women (Hilfiker-Kleiner & Sliwa, 2014; Forster, et al., 2008). Preliminary

results from recent studies suggest that microRNA-1464 (miR-146a) can be a potential biomarker in the future, yet to be confirmed in retrospective studies (Bachelier-Walenta, Hilfiker-Kleiner, & Sliwa, 2013). Nevertheless, a standardized biomarker is highly needed in order to differentiate PPCM, that carries high chance of complete recovery, from other types of cardiomyopathies, and to optimize the diagnosis, management, and risk stratifications for these young patients (Hilfiker-Kleiner & Sliwa, 2014).

Low levels of plasma aldosterone along with high levels of atrial natriuretic peptide were also concomitantly noted in some studies of women with PPCM, and were related to hypervolemia and alteration of the extracellular fluid volume related to heart failure in pregnancy (Adesanya, et al., 1991). Other cardiac biomarkers that are specific to myocytes damage like troponin T and the unspecific marker kinase can be used to detect cardiomyopathy in general, and to predict LV dysfunction and prognosis in PPCM patients (Hu, et al., 2007).

5. *Other blood tests*:

In order to rule out other medical problems, the following blood tests may be ordered: complete blood cell count with differential, creatinine, and urea levels, electrolytes levels, including magnesium and calcium, liver function tests, and levels of thyroid-stimulating hormone (Johnson-Coyle, Jensen, & Sobey, 2012).

6. *Right heart catherization (RHC)*

Right heart catherization is an accessory tool for the diagnosis for PPCM, and is normally avoided if the initial diagnosis is made, and if the patient responds to standard therapy (Lampert & Lang, 1995). RHC is used with combination with other non-invasive

techniques to help establish the right diagnosis (McMurray, et al., 2012). RHC is not generally needed for cardiac pressures as they can be assessed with physical examination and Doppler echocardiography (Kasper, et al., 1994). However, it can be more important in patients with abrupt decompensation requiring complete assessment and ongoing hemodynamic evaluation (Felker, et al., 2000; Philips & Warnes, 2004). When performed in decompensated patients, RHC generally shows increased right and left-sided filling pressures and decreased cardiac output (Marin-Neto, Maciel, Almeiden-Filho, & Amorim, 1991)

7. *Endomyocardial biopsy* (EMB)

EMB is shown to have an important role in the diagnosis process by showing inflammation, cell infiltration within the myocardium with areas of necrosis, hypertrophy and fibrosis (Sliwa, Fett, & Elkayem, 2006). However, it is not recommended as a standard protocol, but can be considered after two weeks of initiating main therapy (Phillips & Warnes, 2004). EMB is more clinically beneficial when done early (Midei, Feldman, Hutchins, & Baughman, 1990).

8. *Electrocardiogram* (ECG)

Electrocardiogram can show non-specific changes and include sinus tachycardia, and, occasionally, atrial fibrillation (Wiltin, DO, Mabie, & Sibai, 1996). Conduction defects and non-specific ST and T wave abnormalities, and voltage abnormalities are also noted. Q waves are randomly present in the anterior precordium. PR and QRS intervals may be prolonged (Ravikishore, Kaule, Sethi, & Khalilullah, 2001). An ECG is helpful in

identifying conditions in the differential diagnosis such as myocardial infarction and pulmonary embolism.

In summary, diagnosis of PPCM requires collecting information from the patient about history of the general and pregnancy related risk factors, assessment of signs and symptoms of heart failure, echocardiography and/ or MRI, 12 lead ECG, chest radiographs, levels of Troponin T and BNP, and occasionally, and in critical cases that are not responsive to standard treatment , right heart catherization and endomyocardial biopsy can be ordered to obtain more information about the disease process, stages and ways of aggressive management.

The differential diagnosis of PPCM includes an array of pre-existing general/cardiac/ congenital disorders or emergent disorders that are more likely related to pregnancy due to the hemodynamic overload exerted on the body during this time. Some of these disorders include the following:

- Pre-existing cardiomyopathy including idiopathic dilated cardiomyopathy, familial dilated cardiomyopathy, or HIV/AIDS (which often presents without ventricular dilatation)
- Pre-existing acquired or congenital valvular heart disease (rheumatic disease, mitral stenosis, mitral regurgitation, aortic stenosis and aortic regurgitation) (Tsang, Bales, & Lang, 2014)
- Pre-existing undetected congenital heart diseases that are detected for the first time in pregnancy because of the increased hemodynamic stress. These diseases include

bicuspid valve, atrial septal defects, and patent ductus arteriosus (Tsang, Bales, & Lang, 2014)

- Diastolic heart failure due to hypertensive heart disease (Laghari, Khan, & Kazmi, 2014)
- Myocardial infarction : recent studies suggest an increase in risk of myocardial infarction during pregnancy (Roth & Elkayam, 2008)
- Aortic dissection, coronary embolus/ thrombosis secondary to myocardial infarction (Braverman, 2010)
- Coronary artery disease and coronary artery spasm (Howlet, et al., 2010)
- Pre-eclampsia, infections, thyroid dysfunction and toxins such as ethanol or cocaine (Howlet, et al., 2010)
- Aortic stenosis, thyrotoxicosis, preeclampsia (Carson, 2014)
- Hemorrhage, thromboembolism (amniotic fluid embolism and pulmonary embolism), and sepsis (Ray, Murphy, & Shutt, 2004).

D. Outcomes and prognosis

a. Maternal and fetal complications of PPCM

Serious maternal and fetal complications can evolve. Maternal complications include: 1) Thromboembolism: ventricular, apical and biventricular thrombi (Kim, Islam, Mondal, Mussell, & Rauchholz, 2011); 2) Arrhythmias: repetitive ventricular tachycardia (Gemici, Tezcan, Fak, & Oktay, 2004); 3) Hypoxia (Yamac, Bultmann, Sliwa, & Hilfiker-

Kleiner, 2010); 4) Progressive heart failure due to misdiagnosis due to misinterpretation of right heart catheterization, and considering hemodynamic results as normal physiological changes of pregnancy (Carson, 2014); 5) Inadequate treatment or testing because of exaggerated fear of harming the fetus (Albert, et al., 2010); and 6) Severe and long lasting morbidity and even death (Goland, et al., 2009).

Fetal complications include: 1) Fetal distress due to maternal hypoxia (Williams, Mozurkewich, Chilimigras, & Van de Van, 2008); 2) Distress due to placental hypo perfusion as a result of poor cardiac output, maternal hypovolemia due to excessive diuresis, or hypotension from aggressive afterload reduction (Carson, 2014); 3) Premature delivery reported in 25% of cases (Lee & Cotton, 1989); and 4) Increased rate of Caesarean deliveries by up to 40% (Shaikh, 2010)

b. Long term prognosis

PPCM Prognosis and outcomes are unpredictable and inconsistent, which is not the case in other types of cardiomyopathies and especially DCM (Warraich, et al., 2005). Some women recover fully even though they had severe LV dysfunction at presentation (Laghari, Khan, & Kazmi, 2014). Others deteriorate because of their rapid progression into severe cardiac failure, leading to sudden cardiac death due to rapid health deterioration in overall health while being on medical treatment (Nelson, Moorhead, Yost, & Whorton, 2012). Alternatively, women might die of heart failure complications like ventricular arrhythmias, thromboembolic events with biventricular thrombi (Kim, Islam, Mondal, Mussell, & Rauchholz, 2011), and sudden death (Phillips & Warnes, 2004; Pearson, et al.,

2000; Sliwa K. , et al., 2012).There is a high risk of relapse of PPCM with subsequent pregnancies (Johnson-Coyle, Jensen, & Sobey, 2012; Ramaraj & Sorelli, 2009).

It is important to mention that earlier studies were more suggestive of poor outcomes and higher mortality, while newer studies indicates better outcomes and lower mortality , which can be attributed to early diagnosis and management (Rasmusson, 2007). Some recent studies have demonstrated that the length of time required for recovery can vary, and can take 6 to 12 months. In a recent study done in Turkey, the length of time required for the left ventricular systolic function (LVSF) to recover in PPCM patients was found to exceed six months. However, a subgroup in the study achieved recovery within a year. Regardless of the time of recovery, the study showed that late deterioration can still happen after one year of full recovery, and that advanced remodeling and low LVEF were predictors of mortality and non-recovery (Biteker, Ilham, Biteker, Duman, & Bozkurt, 2012).

Predictors of recovery that were identified included LVEF and LVESD levels, with cut-off levels for LVEF of > 27% and LVESD of ≤ 5.5 cm (Duran, Günes, Duran, Biteker, & Özkan, 2008). Levels of 25% or less were determined to be associated with higher rates of relapse and heart transplantation (Habli, et al., 2008). Women with PPCM have decreased contractile reserves, and may respond poorly to hemodynamic stress despite evidence of full LVEF recovery on echocardiography (Lampert, et al., 1997). Other identified indicators of poor maternal outcomes and predictors of mortality are left ventricle end- diastolic dimension (LVDd) ≥ 48mm and/ or low fractional shortening (FS) ≤ 30% on echocardiography (Katsuragi, et al., 2012). This can be associated with 3-fold risk of poor

LV recovery (Chapa, Decara, Lang, & Hibbard, 2005), as well as prolonged QRS time (≥ 120 ms) (Duran, Günes, Duran, Biteker, & Özkan, 2008), and cardiomegaly that persists for 4-6 months after the initial diagnosis (Yancy, et al., 2013). Some other factor contributing to poor prognosis could be related to: low body mass index; low cholesterol (Bachelier-Walenta, Hilfiker-Kleiner, & Sliwa, 2013), race and ethnicity (Modi, et al., 2009), poverty , lack of access to appropriate heart failure therapy and quality obstetrical care (O'Connell, et al., 1986), and living in rural areas (where recovery rates are significantly lower compared to urban areas) (Fett J. , Christie, Carraway, & Murphy, 2005).

On the other hand, delayed recovery was mostly associated with delayed diagnosis (Amos, Jaber, & Russel, 2006),LV thrombus (Amos, Jaber, & Russel, 2006; Kim, Islam, Mondal, Mussell, & Rauchholz, 2011), higher NYHA functional class, black ethnicity (Gentry, et al., 2010), multiparity (Homans, 1985); and coexisting morbidity and low baseline LVEF at the time of diagnosis.(Fett J. , Christie, Carraway, & Murphy, 2005).

c. Subsequent pregnancy outcomes

Subsequent Pregnancy is highly discouraged in the literature in PPCM patients because of the considerable high risk for recurrence/relapse (McMurray, et al., 2012; Ruys, et al., 2014; Yancy, et al., 2013) which for example is 53% in Haitian women (Fett, Christie, & Murphy, 2006). Relapse has been attributed to the decreased contractile reserve masked by pregnancy in which hemodynamic workload increases by 30% to 40% (Fett, Fritose, & Welsh, 2010) , and low LVEF on diagnosis.

The outcome of subsequent pregnancy can unfortunately be deleterious on the fetus and the mother, leading to premature delivery and maternal cardiac dysfunction including regional contraction abnormality and wall akinesia (Habli, et al., 2008), decompensated heart failure and even sudden death (Nelson, Moorhead, Yost, & Whorton, 2012). Therefore, exercise stress echocardiography is suggested to estimate contractile reserve and wall abnormalities in order to eliminate unrecognized residual cardiac dysfunction that might be aggravated during pregnancy (Elkayam, et al., 2001).

E. Management

The management of PPCM is similar to standard treatment for other forms of heart failure (Sliwa K. , et al., 2012), with special consideration to the antepartum period in which certain medications should be avoided because of their teratogenic effects. The main approach should focus on reducing the preload/afterload and improving coronary blood flow to the affected heart muscle (Yancy, et al., 2013). Treatment varies depending on whether the heart failure in PPCM is compensated or decompensated.

a. Compensated heart failure

As is the case in chronic heart failure, the management of compensated heart failure of PPCM centers on lifestyle management and drug therapy. No published guidelines were found that address PPCM management specifically. The discussed management guidelines are adapted from the most recent American Heart Association (AHA), European Society of Cardiology (ESC), and the Canadian Cardiovascular Society (CCS) on heart failure, in addition to publications on women with PPCM.

i. Diet and lifestyle

Sodium and fluid restriction are vital in maintaining volume status. Low- sodium diet with a limit of 2g sodium per day, and fluid restriction of 2L/ day are recommended. Exercise namely light daily activity when tolerated (eg, walking) should be encouraged in stable patients, Episodes of bed rest may be necessary to reduce cardiac workload that is already exaggerated by pregnancy and heart failure together. Alcohol intake should be avoided because of its depressant effect on the myocardium (Johnson-Coyle, Jensen, & Sobey, 2012; Phillips & Warnes, 2004; Selle, Renger, Labidi, & Hilfiker- kleiner, 2009; Ruys, et al., 2014; Yancy, et al., 2013)

ii. Pharmacological management

The section below reviews the main drugs used during the antepartum period in PPCM, including beta blockers, anti-arrhythmics, vasodilators, Digoxin, diuretics and anticoagulation therapy. It is important to mention that several commonly used cardiac medications, such as ACE inhibitors, angiotensin-receptor blockers (ARBs), aldosterone antagonists and warfarin, are teratogenic. Their use should be avoided or, in the case of warfarin, restricted to certain stages of the pregnancy (Class I, Level C) (Albert, et al., 2010). Adherence to multipharmacotherapy has been otherwise shown to be effective in HF management (Peters-Klimm, Müller-Tasch, Remppis, Szecsenyi, & Schellberg, 2008), and has been used widely adopted in large medical centers (Albert, et al., 2010; Howlet, et al., 2010; Jessup & Brozena, 2003).

ACEI and ARBs, which constitute the main treatment of heart failure, are teratogenic and should be avoided in the antepartum period (Hoes, et al., 2014). During the antepartum period, beta blockers (beta blocker is a vital standard therapy of chronic systolic ventricular dysfunction with LVEF ≤ 40%) (Strong Evidence, High-Quality Evidence) (Mckelvie, et al., 2013; McMurray, et al., 2012) . The use of one of the three beta-blockers that are shown to reduce mortality (bisoprolol, carvedilol, and sustained- release metoprolol) is recommended for all patients with persistent HF, unless contraindicated, to reduce mortality and morbidity (Yancy, et al., 2013). Clinical trials have demonstrated survival advantage and improvement on the clinical and the hemodynamic levels with both: selective and non- selective agents (Lechat, et al., 1998). However, beta blockers can have possible side effects on the fetus like low birth weight, hypoglycemia, and bradycardia. Thus, neonatal monitoring is required post delivery (Hoes, et al., 2014). Commonly used drugs include Carvedilol (starting dose 3.125mg twice daily, target dose 25mg twice daily) and Extended –release Metoprolol (starting dose 0.125 mg daily, target dose 0.25 mg daily).

Arrhythmias should be treated aggressively, especially if they are symptomatic. Atrial fibrillation is the most common arrhythmia in PPCM (Bhattacharyya, Basra, Sen, & Kar, 2012), and ventricular arrhythmia: repetitive monomorphic ventricular tachycardia is noted also and discussed in case reports (Gemici, Tezcan, Fak, & Oktay, 2004). Patients with atrial fibrillation should maintain a controlled ventricular rate at rest and at exercise (< 100 beats/ minute), and restoration of sinus rhythm when possible (Strong Recommendation; Moderate- Quality Evidence) (Mckelvie, et al., 2013).

Ventricular arrhythmia should be treated aggressively and promptly. The use of class I and class II antiarrhythmics is not recommended because they are poorly tolerated and have proarrhythmic side effects. Quinidine and Procainamide are safe to use in pregnancy and are used as first line antiarrhythmics in pregnancy (Joglar & Page, 1999). Cardiac defibrillation or cardioversion is a choice in symptomatic patients (Jessup & Brozena, 2003). Transesophageal echocardiography is required before the cardioversion to rule out left atrial thrombus.

For supraventricular arrhythmias, β- Adrenergic blockers are often the drug of choice (Murali & Baldisseri, 2005). Class III (Amiodarone) and class IV (Verapamil) agents are to be avoided because of their side effects on the fetus: fetal hypothyroidism, premature delivery, fetal bradycardia, and hypotension (Howlet, et al., 2010). However, calcium channel blockers such as diltiazem and class III anti- arrhythmic agents such sotalol and Amiodarone may be sometimes needed in an arrhythmia that is not responding to the standard therapy. Calcium channel blockers are negative inotropic agents and can lead to cardiac decompensation in stable patients, and so they should not be used for long time. Sotalol also has many systemic side effects and should be used with extreme caution and for the shortest time possible (Murali & Baldisseri, 2005).

Digoxin slows ventricular rhythm in heart failure patients and helps regulate atrial fibrillation rhythm by increasing parasympathetic tone (Rahimtoola, 2004). Digoxin is recommended for patients with NYHA class II and III symptoms (Murali & Baldisseri, 2005). Recent studies suggest that adding Digoxin as an adjunct therapy to Carvedilol has a

superior effects than giving Digoxin or Carvedilol alone (Khand, et al., 2003). The starting dose is 0.125 mg daily, target dose 0.25 mg daily) and serum levels must be monitored.

In terms of vasodilators, combining hydralazine and isosorbide have been shown to reduce mortality and improve symptoms in patients with moderate to severe systolic dysfunction and an LVEF < 35% (Class I, level B) (McMurray, et al., 2012; Mckelvie, et al., 2013). Their combination is recommended in patients who can't tolerate ACE /ARBs, especially and this intolerance is manifested by angioedema, severe hypotension, hyperkalemia, and renal dysfunction (Strong Recommendation, Low- Quality Evidence) (Mckelvie, et al., 2013; Yancy, et al., 2013). The starting dose is 10 mg 3 times a day, titrated up to a target dose of 40 mg 3 times a day. Isosorbide dinitrate, when used alone, is prescribed at 30-40 mg daily three to four times, and the dose must be given in intervals to allow at least a-14 hour, drug- free interval to avoid drug's tolerance.

Thiazide diuretic (used with caution), for instance Hydrochlorothiazide (12.5- 50 mg daily) can also be used and loop diuretics may be considered with caution

Anticoagulation is a must in PPCM (Yancy, et al., 2013) due to the hypercoaguble state induced by pregnancy itself plus the additional risk imposed by the disorder such as dilatation of the heart and turbulent blood flow (Midei, Feldman, Hutchins, & Baughman, 1990). Low-molecular- weight heparin is given if ejection fraction < 35%. Warfarin is the drug of choice in the postpartum.

During the postpartum period, the recommendations for using beta blockers are the same as during the antepartum period. In addition, Angiotensin-converting enzyme (ACE)

inhibitors are recommended for all patients with symptomatic heart failure and LVEF ≤ 40% unless contraindicated (Class I, level A) (Howlet, et al., 2010; McMurray, et al., 2012). ACEI treatment is shown to improve ventricular function and patient well-being. Large key randomized controlled trials (CRTs) (CONSENSUS and SOLVD- Treatment) have shown reduction in mortality, irrespective of NYHA class, and reduction in symptoms, hospitalization, and progression of heart failure (Brown & Vaughen, 1998; Dickstein, et al., 2008). The recommended drugs and doses include:

- Captopril (starting dose 6.25-12.5 mg 3tiems daily, target dose 25-50 mg 3 times daily)
- Enalapril (starting dose 1.25- 2.5 mg 2 times daily, target dose 10 mg 2 times daily)
- Ramipril (starting dose 1.25-2.5 mg 2 times daily, target dose 5 mg 2 times daily)
- Lisinopril (starting dose 2.5-5mg daily, target dose 25-40 mg daily)

Considerations should be given to lower starting dosages for pharmacotherapy in certain ethnic groups (i.e., Chinese and Japanese patients frequently are administered a lower starting dose of ACE inhibitors or beta blockers). Target doses remains identical to guideline recommendations (Howlet, et al., 2010). If the ACE inhibitor is not tolerated, Angiotensin-receptor blockers (are used, such as Candesartan (starting dose 2mg daily, target dose 32 mg daily) Valsartan (starting dose 40mg twice daily, target dose 160mg twice daily).

In case women are intolerant of ACE and angiotensin- receptor blockers, nitrates or hydralazine are considered. In terms of diuretics, a loop diuretic such as Furosemide IV or oral dosing considerations should be made on the basis of creatinine clearance. If the glomerular filtration rate is > 60 mL/min per 1.73 m^2 furosemide 20-40mg is prescribed every 12-24 hours. If the glomerular filtration rate is < 60 Ml/min per 1.73 m^2 furosemide 20-80 mg every 12- 24 hours is used. Moreover, Spironolactone has been shown to reduce all-cause mortality, hospitalizations, and heart failure symptoms in patients with NYHA class II- IV and LVEF less than 35% when used concomitantly with beta-blockers and ACE inhibitor, provided creatinine levels are > 30ml/ min and potassium levels are < 5.0mEq /Dl (class I, LOE A) (Yancy, et al., 2013). In addition to spironolactone (starting dose 12.5 mg daily, target dose 25- 50 mg daily),Eplerenone can be used (starting dose 12.5 mg daily, target dose 25- 50 mg daily)

In addition to the above, the following vasodilators may be used in the post-partum period: Hydralazine (starting dose 37.5 mg 3 to 4 times a day, target dose 40 mg 3 times daily); Isorbide dinitrate (starting dose 20 mg 3 times daily, target dose 40 mg 3 times daily)

For anticoagulation, Warfarin **is prescribed** if EF is < 35%, to prevent thromboembolic complications that are high in pregnancy due higher concentrations of coagulation factors and fibrinogen (Ramaraj & Sorelli, 2009). This risk can persist for up to six weeks post-delivery (Lampert & Lang, 1995)Kim, et al., 2011; Shimamoto, et al., 2008). Anticoagulation should be initiated according to the American College of Chest physicians Evidence-based Clinical Practice Guidelines (8th Edition) 2008 (Geerts, et al.,

2008) (Class I, Level C). Warfarin should not be prescribed antepartum as it should be monitored closely (Murali & Baldisseri, 2005).

b. Decompensated heart failure

Pregnant women who are acutely decompensated should be managed according to the most up-to-date guidelines for acute decompensated HF and should be referred to a tertiary center with known expertise in HF and PPCM management, including invasive hemodynamic monitoring and advanced mechanical circulatory support and transplantation (Class I, level C) (Mckelvie, et al., 2013). In decompensated heart failure, management begins with the airway breathing circulation (ABC) assessment, as women with impending conditions need prompt intervention and mechanical ventilation (Williams, Mozurkewich, Chilimigras, & Van de Van, 2008). Women with acute heart failure need to be started on positive inotropic agents like dobutamine and milrinone that are allowed in pregnancy (Ramaraj & Sorelli, 2009). The management described below is based in part on Jessup et al, Heart Failure Society of America, Carlin et al, and Canadian Cardiovascular Society Guidelines, Gevaert et al) (Albert, et al., 2010; Carlin, Alfirevic, & Gyte, 2010; Gardetto, et al., 2008; Gevaert, et al., 2011; Howlett, et al., 2010; Jessup, et al., 2009).

The ABC management involves intubating the patient early enough when in distress to avoid increased breathing workload, and to prevent breathing complications, provision of .supplemental oxygen, maintaining continuous pulse oximetry to monitor SaO_2, regular measurement of arterial blood gases (every 4-6h) until breathing is stable,

and initiation of cardiac and blood pressure monitoring through arterial and central venous pressure monitoring.

In addition in antepartum women, fetal monitoring must be done (Hilfiker-Kleiner & Sliwa, 2014).

i. Pharmacological management

Intravenous loop diuretic is the first line treatment but caution is advised in antepartum women. Furosemide is often used, with dosing considerations made based on creatinine clearance. If glomerular filtration rate is > 60 Ml/min per 1.73 m^2: furosemide 20- 40 mg IV every 12- 24 h can be administered. If glomerular filtration rate is < 60 mL/min per 1.73 m^2, furosemide 20-80 mg IV every 12- 24 h is given. In severe fluid overload, consideration is made of furosemide infusion or ultrafiltration

Vasodilators are indicated in patients with worsening heart failure and difficult to manage pulmonary congestion in the setting of preserved blood pressure. They can be used with close monitoring and include the following:

- Nitroglycerin infusion 5-10 mg μg/kg per minute
- Nitroprusside 0.1-5 μg/kg per minute, use with caution in antepartum women. Nitroprusside is not recommended except in the setting of acute need for significant afterload reduction where all other interventions have been insufficient, due to the risk of fetal cyanide toxicity.

When decompensation is associated with hypotension, persistent pulmonary edema and/or evidence of organ hyoperfusion, inotropic support with dopamine, dobutamine and milrinone should be considered based on the clinical scenario. The doses are as follows.

- Milrinone 0.125- 0.5 μg/ kg per minute.
- Dobutamine 2.5-10 μg/kg per minute.

  Other considerations for drug therapy include avoiding β-blockers in the acute phase, as they can decrease perfusion.

Heparin sodium, alone or with oral warfarin (Coumadin) therapy is also recommended. Every effort should be made to develop an oral medical regimen that can maintain symptomatic improvement and reduce subsequent worsening of clinical status

During the acute phase, oxygenation must be monitored with arterial blood gases every 4-6 h until the patient's condition is stable. Endomyocardial biopsy is considered and if viral myocarditis is ruled in, immunosuppressive medications (e.g., azathioprine, corticosteroids) are considered.

ii. Non pharmacologic therapies

If no improvement is noted clinically with the above management**,** cardiac magnetic resonance imaging is considered and an endomyocardial biopsy to detect viral myocarditis is done if not previously performed. If a woman remains refractory to therapy, other possibilities include Bromocriptine or cabergoline administration for suppression of

prolactin production. Finally, assist devices like intra-aortic balloon pump, extra corporeal membrane oxygenator (ECMO), left ventricular assisted devices (LVAD), extracorporeal oxygenation, and transplantation are considered. Intra-aortic balloon pump (IABP) is a safe and effective bridge to recovery or as a bridge to LVAD and transplantation. ECMO provides a temporary support as a bridge to LVAD, while LVADs provides a safe bridge to transplant (Gevaert, et al., 2011). Below is an overview of the assist devices and their recommendations for use in PPCM.

The IABP countrepulsation provides mechanical afterload reduction and improves coronary blood flow (Phillips & Warnes, 2004). IABP devices are safe to apply in antepartum in the acutely decompensated patients and easily installed at the patient's bedside, and have few side effects for the young population (Gevaert, et al., 2011). The most common side effect is femoral thromboembolism of the femoral artery requiring thrombectomy. Patients need to be anticoagulated on unfracationned heparin (UFH) (Gevaert, et al., 2011).

PPCM patients who are refractory to inotropic support, but have the chance to recover should be put on ECMO (Mckelvie, et al., 2013). ECMO should be considered in patients as a viable option for the treatment and management of acute cardiogenic shock as a bridge to recovery or to LVAD or transplantation (Gevaert, et al., 2011). ECMO can be only used for a short time due to plasma leakage and decreased gas exchange leading to hemolysis and thromoemolism. However, new ECMO machines have combined circuit technology to reduce patient's complications (Palanzo, et al., 2009)

LVADs have promising outcomes in PPCM patients and their bridging to transplantation (Tandler, Schmid, Weyand, & Scheld, 1997). Successful cases of LVAD's with recovery within nine months of LVAD implantation and return of LVFE to normal with regain of full systolic function three years has been noted (Oseorom, de Jonge, Kirkels, Klopping, & Lahpor, 2008). In Lebanon, a reported case of postpartum cardiomyopathy with severe cardiogenic shock was treated urgently and successfully with the implantation of LVAD, and the patient fully recovered her LV normal function shortly after the implantation (Hamdan, et al., 2013). HeartMate and Novacor are the two devices approved for use by the US Food and Drug Administration for use as a bridge to transplantation. Major complications of LVAD therapy are thromboembolism and infection (Phillips & Warnes, 2004).

Cardiac resynchronization therapy (CRT) is indicated in case of ventricular dys-synchrony, that is manifested by a QRS duration > 130 milliseconds on ECG (Murali & Baldisseri, 2005), and in patients with NYHA III and ambulatory NIHA IV with left bundle brunch block (Strong Recommendation, High Quality Evidence) (Mckelvie, et al., 2013). Mouquet et al (2012) found that PPCM patients, who are refractory to conventional therapy, can show rapid and significant recovery (Mouquet, et al., 2012). A recent meta-analysis study found that women respond better than men respond to CRT, and will have reduced rate of death. However, women are under-referred to CRT (Narasimha & Curtis, 2014). CRT is also considered as a bridge therapy to transplantation (Moss, et al., 2009).

Transplantation should be considered as a last choice in patients whose symptoms are refractory to all the available therapies, and before reaching end organ failure, to

improve chances of surviving with improved quality of life (Selle, Renger, Labidi, & Hilfiker- kleiner, 2009). Contraindications include recent history of neoplasm, systemic infection, and poor psychosocial profile (Phillips & Warnes, 2004). Heart transplantation outcome has been reported as promising with survival rate and complications similar to other groups (Rickenbacher, Rizeq, Hunt, Billingham, & Fowler, 1994). Yet, some other studies showed higher than expected rates of rejection and infection in PPCM patients compared to other heart transplantation recipients (Keogh, et al., 1994). Other reported complications of heart transplantation in PPCM patients are: maternal death, graft dysfunction, uncontrolled hypertension, and stress. Because of lifelong immunosuppressants, women face miscarriage, viral infection and premature births (Morini, et al., 1998). However, successful pregnancy is possible after transplantation provided that the patient has regular follow up and undergoes immunosuppressant's adjustment during pregnancy (Cowan, Davison, Doria, Moritz, & Armenti, 2012)

c. Emerging therapies

A number of new therapies are being studied as alternative strategies for the treatment of PPPCM and are reviewed below.

A. Intravenous immune globulin (IVIG):

The administration of IVIG at early presentation of PPCM demonstrated distinct improvement in LVEF in a small retrospective study (Bozkurt, et al., 1999). However, a larger randomized prospective study of patients with recent –onset dilated cardiomyopathy (DCM) failed to show any beneficial effects of the patients studied (McNamara, et al.,

2001). This inconsistency in results can be due to the differences in mechanisms between PPCM and DCM. Based on the fact that PPCM is related to impairment in the regulatory immune mechanism, IVIG should be considered in PPCM patients without contraindication (Phillips & Warnes, 2004).

B. Bromocriptine

Bromocriptine is an old drug that has been used for a long time to inhibit prolactin in women who do not want to breastfeed, and is currently being tested and scrutinized for the great results shown on PPCM patients (Yamac, Bultmann, Sliwa, & Hilfiker-Kleiner, 2010). Due to its promising results, Bromocriptine can be the innovative future drug for PPCM patients. Experimental data suggest a causal role of the 16kDa prolactin for the development of PPCM in mice, which was prevented by the administration of bromocriptine before the onset of the disease. Bromocriptine similarly prevented the recurrence of PPCM in humans in a small pilot study (Hilfiker-Kleiner, et al., 2007).

Bromocriptine has been found to be beneficial when added to standard heart failure therapy by improving LVEF and clinical outcomes in women with acute severe PPCM (Jahns, Stein, Hilfiker-Kleiner, Pieske, & Emons, 2008; Sliwa K. , et al., 2010). More studies are nevertheless needed for the combination of bromocriptine and conventional HF therapy. A study is currently being launched in Germany to examine the benefits of the combination of standard HF therapy with bromocriptine (Hilfiker-kleiner, 2012). Side effects mentioned in some case reports include myocardial infarction due to thromboembolism in postpartum women (Box, Hanak, & Arciniegas, 2004). Therefore,

patients who are taking bromocriptine are strongly recommended to be on low-dose heparin (Selle, Renger, Labidi, & Hilfiker- kleiner, 2009).

C. Cabergoline

Cabergoline is a new long- acting dopamine receptor agonist that is very effective and well tolerated in the treatment with pathological hyperprolactenemia. This theory was supported by Verhelst et al. in a large-scale retrospective study in which the majority of patients (86%), who showed bromocriptine intolerance, had their prolactin normalized after taking cabergoline (Verhelst, et al., 1999). Cabergoline administration in a PPCM patient was first given in 2008, and the patient showed great improvement by promptly dropping her prolactin levels and by recovering her LVEF function rapidly from 26% to 47% (de Jong, Rietveld, van Lochem, & Bouma, 2009).

D. Pentoxyfilline

Pentoxyfilline is a xanthine –derived inhibitor of the production of tumor necrosis factor-α (TNF-α) (Phillips & Warnes, 2004). It has been shown to be elevated in heart failure patients along with other inflammatory cytokines, and has been associated with ventricular remodeling and heart failure progression (Bradham, Bozkurt, Gunasinghe, Mann, & Spinale, 2002) . Sliwa et al. showed promising outcomes in women with PPCM who improved with the addition of pentoxifylline to their regular heart failure regimen (400 mg orally three times daily) (Sliwa, et al., 2002). Therefore, additional studies in PPCM patients with elevated serum levels of TNF-α will be beneficial to explore their therapeutic options in the future.

E. Selenium

Selenium is a trace element that has been shown to act as an antioxidant (Rayman, 2000). Low levels of selenium have been detected in PPCM patients (Cenac, et al., 1992; Levander & Beck, 1999), which may predispose the heart to injury from viral infection (Mehta, Mehata, Khan, NY, & NE, 2001). However, the role of selenium in PPCM is controversial, and was shown to be efficacious in some population, but not in others. Studies in women with PPCM in the Sahelian area of Niger demonstrated low levels of selenium, therefore suggesting that selenium deficiency might play a role in the PPCM mechanism in that geographic area (Cenac, Simonov, Moretto, & Djibo, 1992). On the other hand, women with PPCM studied in a Haitian hospital didn't show selenium deficiency, and no relationship between the two has been established (Fett, Sunstrom, & Combs, 2002). Selenium supplementation can be added to PPCM patients who are known to have poor nutrition and coexistent parasitic illnesses. Normal levels of selenium are > 70 ng/ml, and oral supplements are safe during pregnancy and lactation at a dose of 100- 200 μg/d (Phillips & Warnes, 2004).

d. Delivery management and anesthetic considerations

PPCM patients need close follow ups during pregnancy preferably by a multidisciplinary team to assure safe delivery with the least complications possible. If diagnosis is made peripartum, anesthesiology and neonatology should be involved, and the patient might be transferred to a high- risk perinatal center (Sliwa K. , et al., 2010). Urgent and early delivery with consideration of C-section can be indicated in patients requiring hospitalization for worsening heart failure accompanied by symptomatic left ventricular

dysfunction. Combined spinal- epidural techniques can be considered as an acceptable anesthetic alternative technique that helps reduce preload, afterload and cardiac output fluctuations (Shnaider, et al., 2001). In cases of severe hemodynamic instability during pregnancy, ending pregnancy can be the ultimate choice as a lifesaving procedure, and to enable the mother to proceed with aggressive HF treatment

In stable patients with good pain control, spontaneous vaginal delivery is possible and preferable in order to avoid hemodynamic instability. A Cc-section carries a slightly increased risk of thromboembolism or hemorrhagic complications as it is associated with larger blood loss. PPCM patients may experience hemodynamic instability postpartum and especially in the first 48 to 72 hours after delivery because of an increase in afterload and fluids shifts. Therefore, patients need to be closely monitored for this indicated period. (Carlin, Alfirevic, & Gyte, 2010; Hoes, et al., 2014; Phillips & Warnes, 2004).

e. Patient's education and follow-up

Patient education and follow up are vital in PPCM patients to help them recognize signs and symptoms of potential complications, and to avoid and prevent relapses as much as possible. Patients are advised to read about their disorder to have a better understanding of the possible deterioration in their overall health. They also need to understand how to maintain a stable level by following healthy lifestyle tips and by avoiding extra stress on the overloaded heart muscle. Patients follow up and education is summarized below:

- Obstetrical-gynecological nurses should be aware and familiar with PPCM risk factors, and should screen suspicious cases as soon as possible after obtaining a

thorough medical history. Although it is not possible to prevent PPCM, it is possible to catch it early and prevent its devastating outcomes.

- Awareness campaigns/ teaching sessions can be held with pregnant women early in their pregnancies to inform them about this rare but life- threatening disease. The emphasis should be put on the regular follow up especially in the last trimester where PPCM initiates mostly. An individual patient profile can be created, in which risk factors can be highlighted to screen patients and follow them up. For example, patients who have a high PPCM profile will be scrutinized closely, and sent for further assessment.
- Regular medical office visits depending on the clinical status. For those who are having medication titration, weekly to biweekly visits may be necessary based on how they are responding to their medications. Patients who do not need to be on medical therapy in case of stable or fully recovered LVEF should be reevaluated if they have new cardiac concerns or complaints.
- Diet management, weight and diuresis teaching: salt and fluid restriction(1.5 l / 24h and 2g of sodium is recommended for hyponatremia setting and volume overload to decrease pulmonary congestion
- Nurses must teach patients about medications and their side effects.
- Smoking cessation should be strongly advised
- Abstinence from alcohol is recommended
- Patients with known familial dilated cardiomyopathy and/ or PPCM should be sent for routine genetic testing as these women have poorer prognosis than women who

don't have a genetic predisposition (Hilfiker-Kleiner & Sliwa, 2014). First degree-relatives not known to be affected should undergo serial echocardiographic screening with assessment of LV function and size (Yancy, et al., 2013).

- Discussion about future pregnancies should happen as early as possible in the follow-up phase due to the high risk of relapse among PPCM patients. Women should be frankly told about the rationale of avoiding future pregnancies due to the increased risk of LV dysfunction as PPCM is likely to reoccur, carrying higher risk for complications and even death. Additionally, these patients should be informed about the unfavorable fetal outcomes and potential complications such as the high chance of having a premature delivery and therapeutic abortion (McMurray, et al., 2012; Yancy, et al., 2013)
- Appropriate referrals for contraception or sterilization should be made afterwards. Patients with heart failure should avoid hormonal contraception due to the increased associated risk of thrombosis, fluid retention and arrhythmias (especially ectopies). They should consider instead non-hormonal contraception like non-hormonal IUD with the choice of a low-dose +progestogen only oral agent if patients prefer hormonal contraception (Sedlak, Bairey Merz, Shufelt, Gregory, & Hamilton, 2012).

CHAPTER III

CLINICAL PATHWAY FOR PPCM PATIENTS

In this chapter, a clinical pathway for PPCM patients is proposed, which includes initial assessment and screening, treatment strategies, risk stratification, and care strategies. The first step includes assessing women for risk factors of PPCM in the third trimester. Second, the diagnostic criteria discussed in chapter II are used to identify related signs and symptoms. Once the diagnosis is confirmed treatment strategies are planned based on whether the presentation is compensated or decompensated hearty failure. The assessment sheet below can be used to document assessment findings.

A. Screening /Risk stratification sheet for PPCM patients

First and last name ——— ———
Date of birth — — ———
Gestation weeks ——— ———
Gravida ——— / Para ——— / Abortus ———
Attending GYN/ OB ——————
Reason for referral ——————————

Patient's label

PPCM screening for risk factors

General

- ☐ Genetic predisposition:
  - ☐ African race
  - ☐ History of familial PPCM
  - ☐ History of familial DCM
- ☐ History of hypertension
- ☐ Diabetes
- ☐ Obesity
- ☐ Smoking
- ☐ Alcohol abuse
- ☐ Cocaine abuse
- ☐ Advanced maternal age
- ☐ Low selenium levels

Pregnancy –related

- ☐ Gestational hypertension
- ☐ Twin pregnancy
- ☐ Multiparity
- ☐ Teenage pregnancy
- ☐ Prolonged tocolytic therapy
  - ☐ Terbutaline
  - ☐ Salbutamol
  - ☐ Ritodrine
  - ☐ Isoxsuprine
  - ☐ Magnesium sulfate
- ☐ Gestational hypertension
- ☐ Cultural practices and lifestyle
  - ☐ Excessive consumption of rock salt
  - ☐ Body heating in hot clay beds

Signs and symptoms

□ Dyspnea	□ Lower extremities edema
□ Cough	□ Jugular venous distention
□ Orthopnea	□ Tachycardia
□ Paroxysmal nocturnal dyspnea	□ S3 or gallop rhythm
□ Fatigue	□ Mitral regurgitation
□ Malaise	□ Displaced apical impulse
□ Postural hypotension	□ Pulmonary rales
	□ Thromboembolism
	□ Hepatomegaly
	□ Hepatojugular reflex
	□ Ascites
	□ Peripheral edema

- □ ***Low suspicion index for PPCM***
  - □ consider alternative diagnosis
- □ ***High suspicion index for PPCM***→ send patient for :
  - □ Echocardiography
  - □ Cardiac magnetic resonance
  - □ Or both

****If PPCM is confirmed on echocardiography and/or cardiac magnetic resonance, consider proceeding with the following tests:***

- □ Electrocardiogram
- □ Pro-BNP (NT-pro-BNP)
- □ Troponin-T
- □ Plasma relaxin-2
- □ oxLDL
- □ IFN-*y*
- □ Prolactin
- □ sFlt-1/ PIGF ratio
- □ sFLt-1/ VEGF ratio
- □ Chest radiograph

- Complete blood cell count with differential
- Magnesium
- Calcium
- Liver function test
- Thyroid stimulating hormone

- Genetic screening / family pedigrees if history of familial PPCM and/or DCM

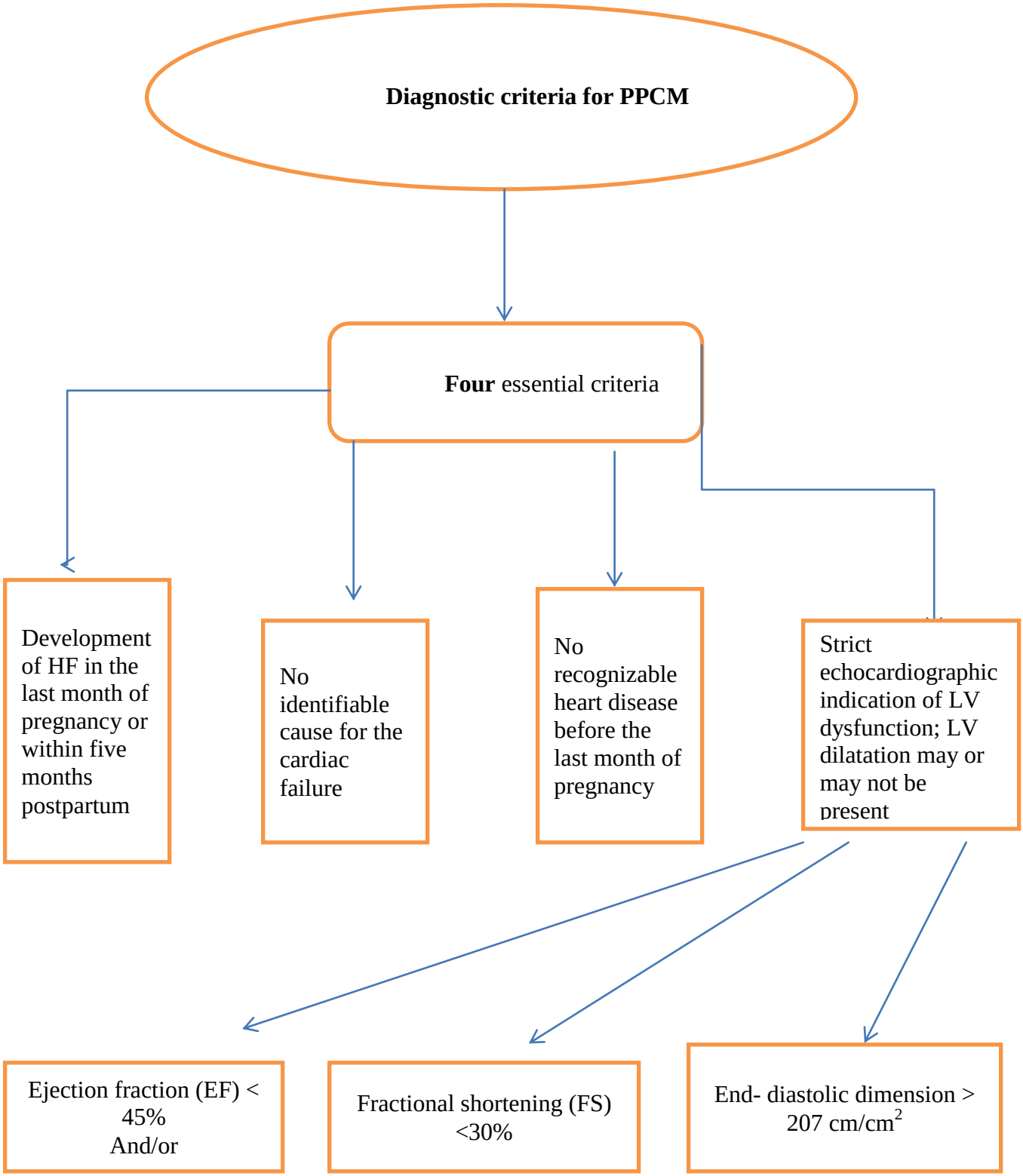
Consider the following based on case-by-case status:

- HF team referral
- Endomyocardial biopsy (EMB) *if patient is deteriorating/ not responding to standard HF therapy*
- High-risk pregnancy centre referral in antepartum
- Perinatologist referral in antepartum
- Family meeting with the multidisciplinary team
- Psychology referral when needed

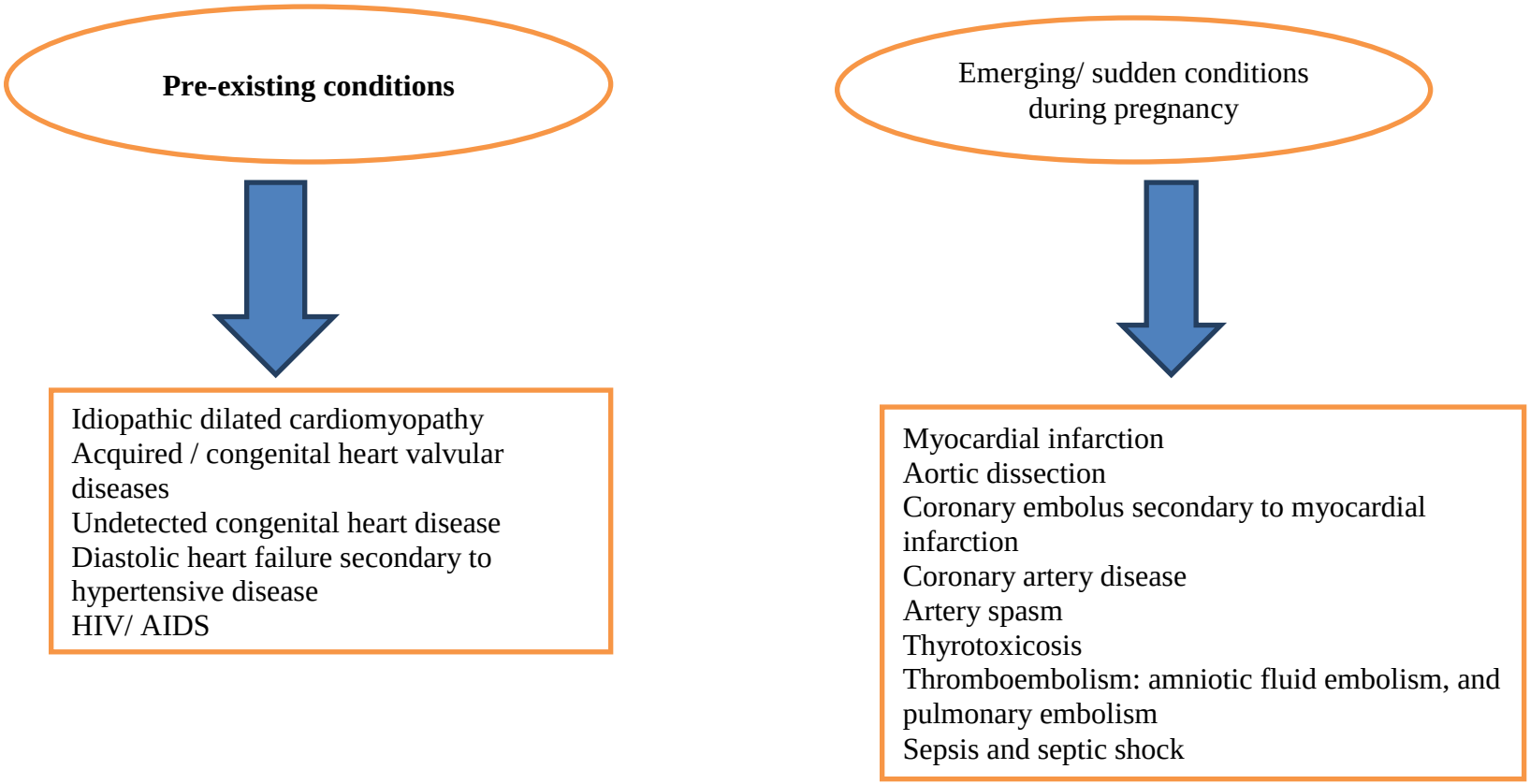
Gravida= total number of pregnancies, regardless of whether these pregnancies were carried to term; Para= number of viable (>20 weeks) births; Abortus= number of pregnancies that were lost for any reason, including abortion and miscarriages /PPCM= Peripartum Cardiomyopathy; DCM= Dilated Cardiomyopathy; GYN= Gynecologist; OB= Obstetrician; NT-proBNP= N-terminal pro-brain natriuretic peptide; plasma relaxin 2= PPCM patients have lower levels of relaxin; oxLDL=Oxidized Low-Density Lipoprotein; IFN-y= Interferon-y; sFLt-1= anti-angiogenic factor released in higher amounts in preeclamptic placentas; PIGF= Placenta Growth Factor; VEGF= Vascular Endothelial Growth Factor/ sFLt-1/PIGF and sFLt-1/ VEGF ratios are found to be significantly low in PPCM patients; HF= heart failure.
Baseline NT-proBNP and the failure to decrease oxLDL, IFN-Y, and prolactin are associated with poor outcome in PPCM as most studies indicate; therefore they play a role in the pathophysiology and for risk stratification of PPCM patients.

The next algorithms display: diagnostic criteria, differential diagnosis, initial screening, management, and complications.

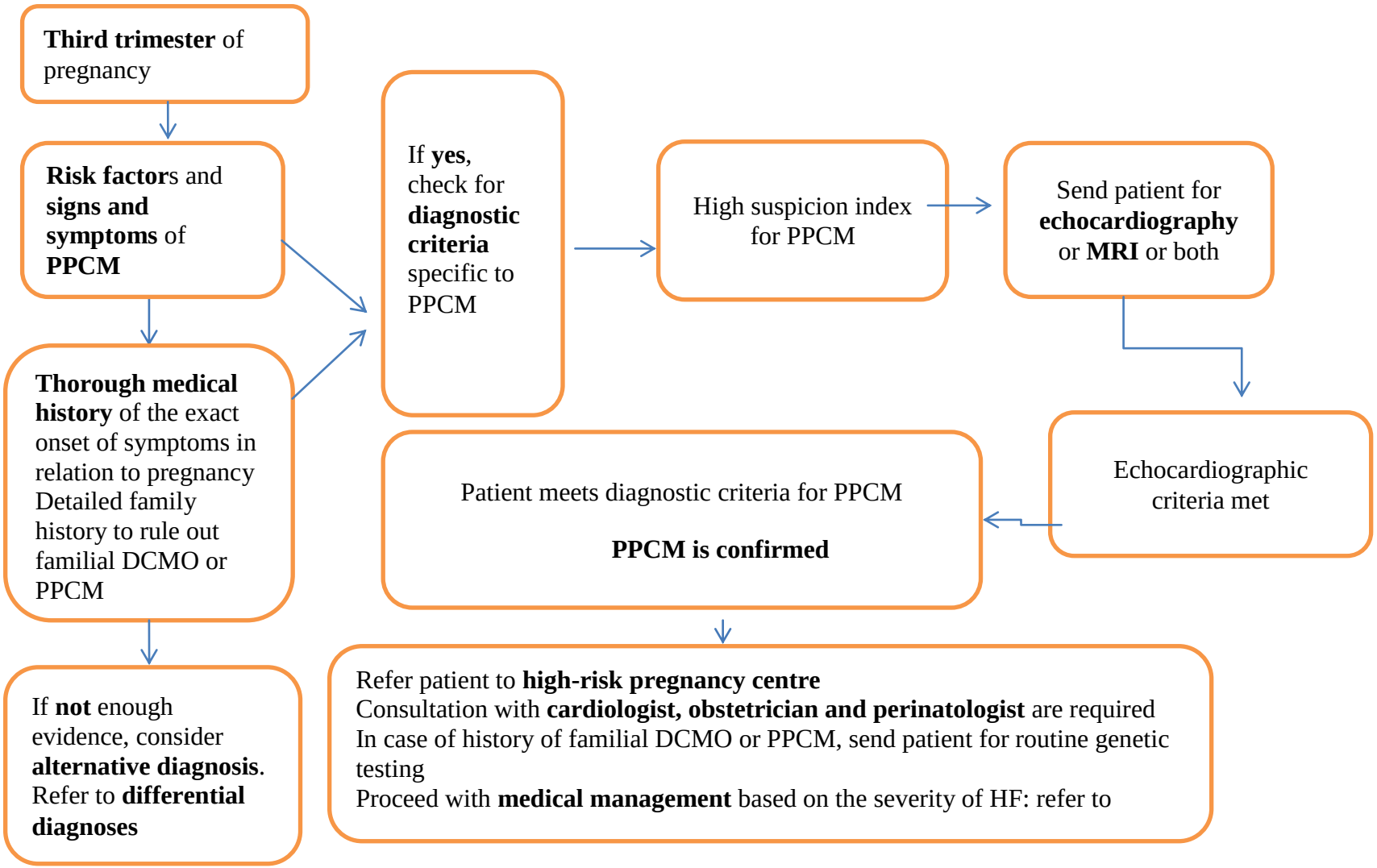
B. Diagnostic Criteria for peripartum cardiomyopathy



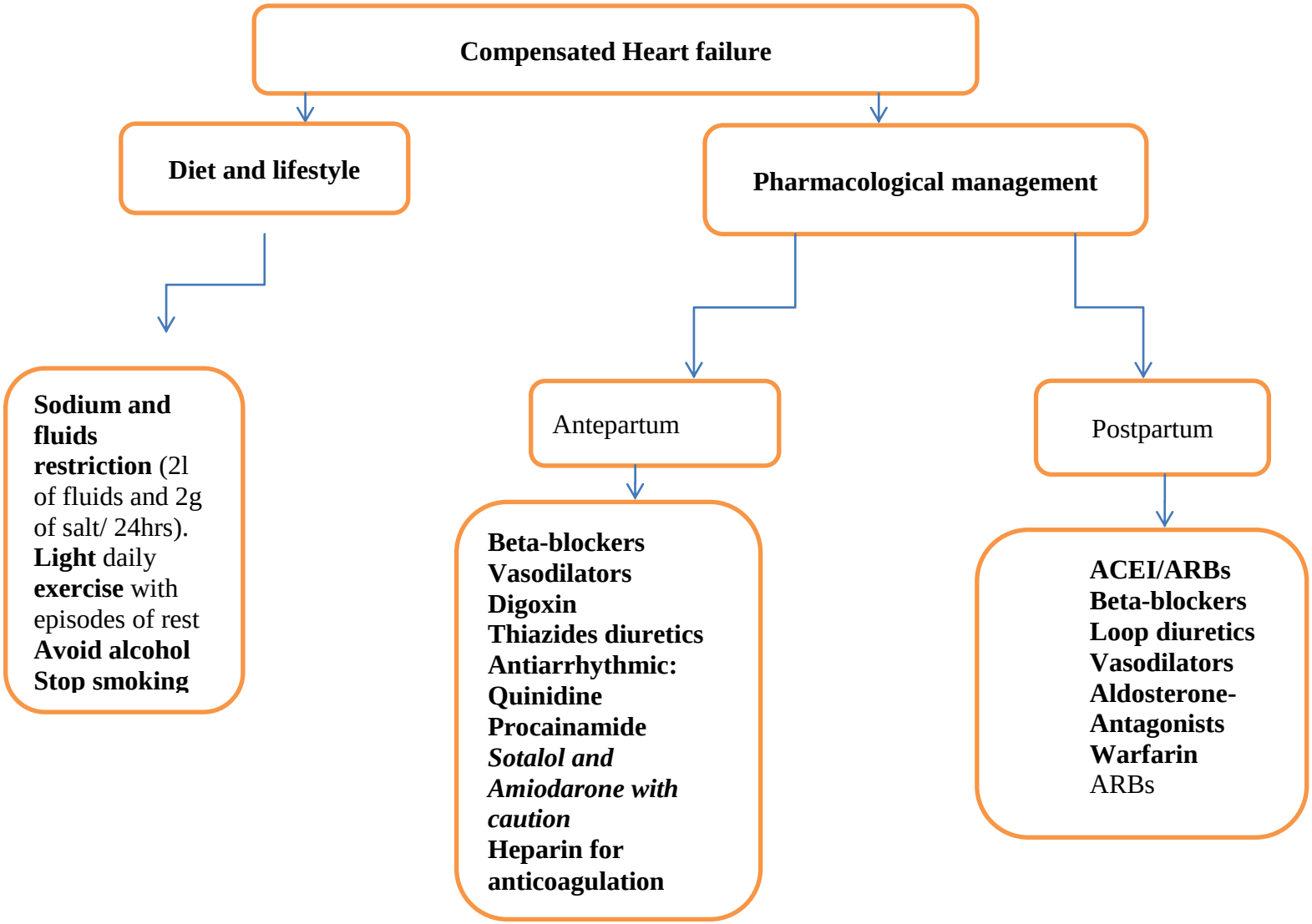
C. Differential Diagnoses



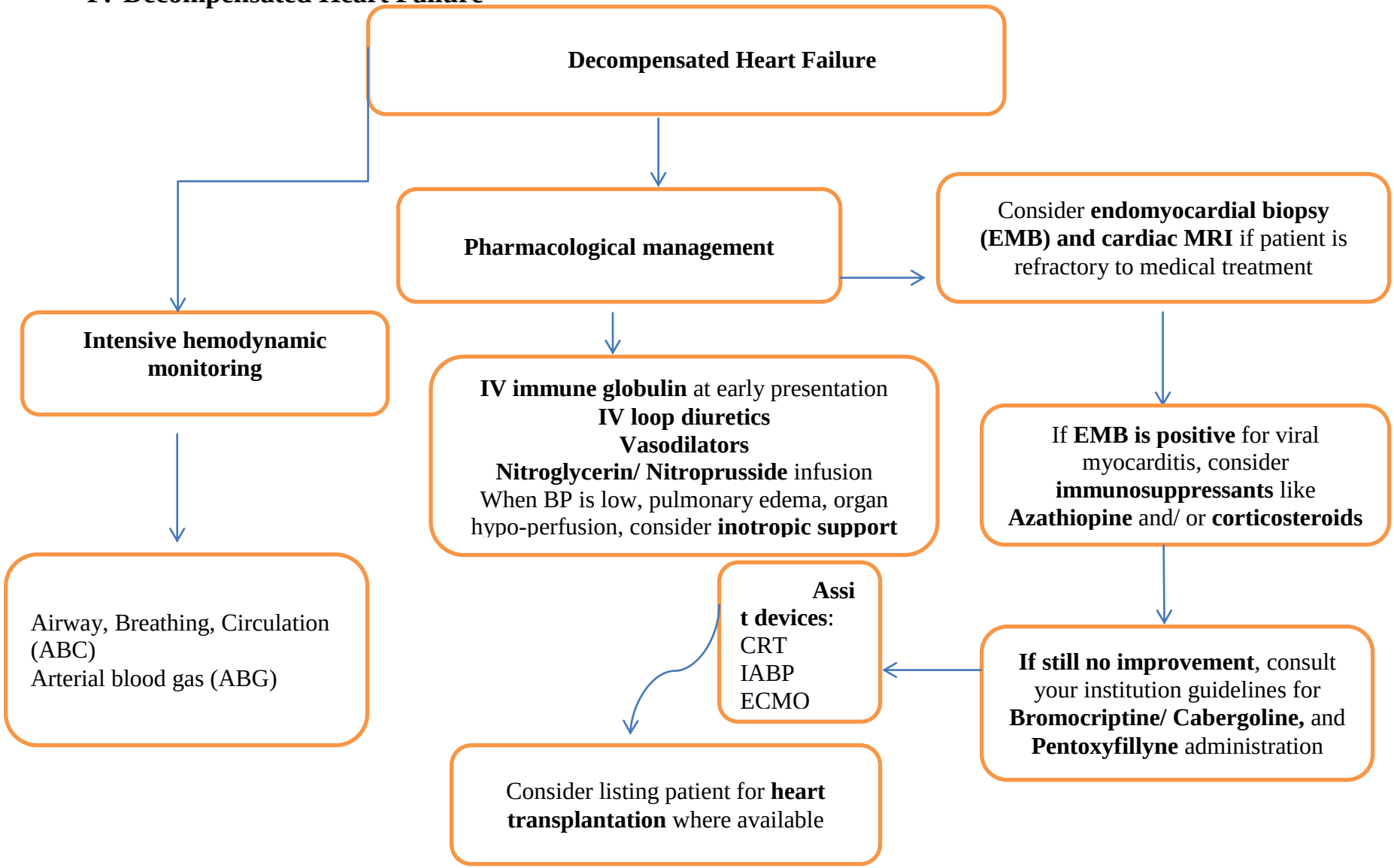
D. Initial Screening



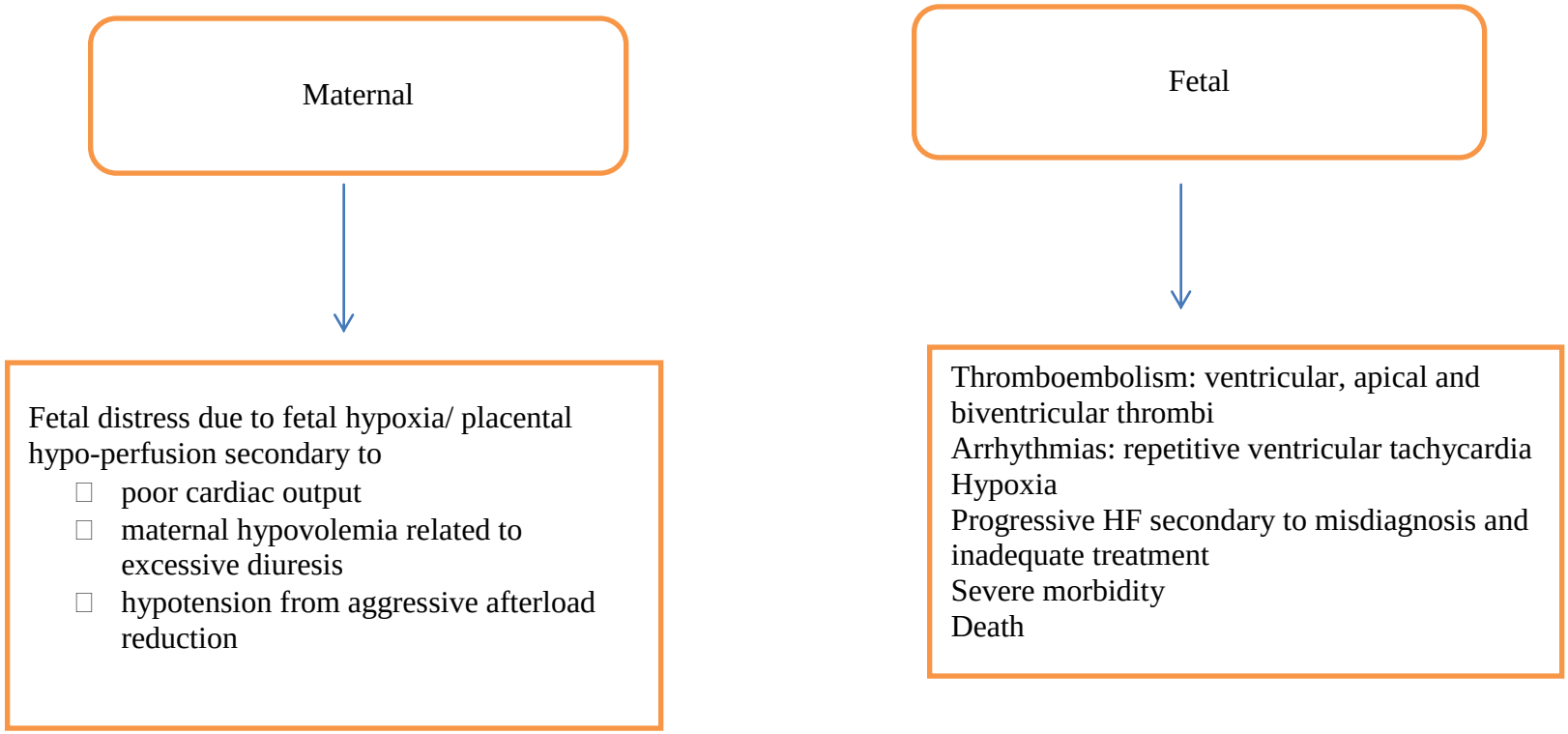
E. Management: Compensated Heart Failure



F. Decompensated Heart Failure



G. Monitor for Complications



CHAPTER IV

PROTOCOL IMPLEMENTATION AND EVALUATION

A. Implementation of the Pathway

A clinical pathway is a tool that summarizes the best evidence recommendations and most up-to-date clinical guidelines in accessible format for care and management by the multidisciplinary health team in hospital settings. Since clinical pathways implementation improves outcomes in prevention, screening, patient's care, and management, it is imperative to have them available and activated by advanced practice nurses to help standardize and optimize patient care and resource use.

The goal for the pathway is to be initially implemented on PPCM patients at AUBMC. It will go through various stages before its final approval. Many units will be involved in the implementation's process: maternity, step-down units, ICU, CCU, and obstetrical/ gynecological/ perinatal/ high risk pregnancy centers and cardiology outpatient clinics. Accordingly, cardiologists, obstetricians, gynecologists, perinatologist, emergency physicians, and family physicians will be consulted and asked to share their knowledge and participate in the implementation process. Obtaining support from these specialties is extremely important, as they are the main users of this protocol and the key to access to medical units. The opinion of an HF cardiologist was solicited for this pathway.

Since PPCM is an uncommon disorder, and its complexity is not seen very often in clinical practice, it is important to educate the staff in different specialty areas about its pregnancy-like symptoms, and how it can be caught early in the disease's course. A multidisciplinary team will be chosen based on their expertise and specialty, to obtain agreement about the process of implementation, quality and outcomes of care to be monitored. The team, to which the proposed pathway will be referred, will hence include an obstetrician/ gynecology physician, heart failure /cardiology physician, emergency physician, cardiology and obstetrical clinical nurse specialist, clinical pharmacist, clinical educator for the concerned units, and registered nurse representative from both the coronary care unit and remote telemetry unit where patients with PPCM are admitted, and the initiator of the pathway. The team will evaluate and discuss the pathway proposed and adjust its content accordingly. A proposal about the pathway and its benefit will be presented to the education committee and administration for approval. After securing administrative approval, an implementation plan will be established.

B. Educational Methods

The next phase in the protocol's implementation would include involving nurses from the different units that are likely to have PPCM patients, including outpatient clinics. A series of teaching sessions will be conducted to provide a general overview, benefits, and details of the pathway with the collaboration of the Clinical and Professional Development Center (CPDC) personnel. Not only will nurses be educated regarding the pathway components, but also medical interns and residents. Group sessions will be held in the CPDC once weekly for two months in order to allow enough time for all nurses to attend

and benefit from the information. A pre-test will be developed and administered to participant nurses to measure and evaluate their previous knowledge, and a post-test will be performed to verify that nurses will reach an appropriate knowledge acquisition. In terms of teaching delivery tools, power point presentations will be used to demonstrate the pathway. In addition, case studies and open discussions will be utilized to confirm proper grasp of the pathway and its implementation.

C. Pathway Evaluation and Feedback

The next phase will be piloting the clinical pathway. Due to the low frequency of PPCM, five patients will be only enrolled in the pilot study during a period of four months. Meanwhile, physicians will monitor and document the findings in the clinical pathway on patients with suspected diagnosis of PPCM. The management plan will be followed according to the pathway steps and in case of non-implementation; justification of variance in management shall be documented. Members of the multidisciplinary team will follow up closely the execution of the pathway steps integrated in the management plan of PPCM patients. Feedback will be collected by the members of the multidisciplinary team and later discussed during pre-set meetings. Feedback will be obtained from the end-users regarding encountered challenges, feasibility of the pathway, and any recommendations or suggestions for protocol amelioration. During the period of implementation of the clinical pathway, both during the pilot phase and later on, adherence will be measured periodically, and modifications will be made based on the collected feedback.

With the aim to assess the impact of following the clinical pathway on patients' outcomes, baseline data should be collected on PPCM patients admitted prior of the pathway implementation. The collected data should include quality indicators and diagnosis criteria relevant to this patient population. A database will be developed that includes elements identified by the European Society of Cardiology/ Working Group on Peripartum Cardiomyopathy (Sliwa K. , et al., 2012). For the pre-implementation data collection, retrospective data can be collected (to avoid delay initiation of the pathway) about patients admitted with PPCM in the past three years on the following: risk factors; diagnosis criteria, signs and symptoms; fetal and maternal complications including the incidence of thromboembolism in this specific population; treatments used: pharmacological, emerging therapy, bridging alternatives, their success and any complications; length of stay, anticoagulation therapy and INR upon discharge; number of re-hospitalizations. Then one year after the pathway is initiated, these data will be collected prospectively again, in addition to patient quality of life using a simple measure like the one item asking patients to rate their currently perceived health on a 5 point Likert scale, and the specialty of the health care provider (HF specialist or not) or whether a HF specialist was consulted and why. In addition, documentation of discharge patient education needs to be monitored. Patients need to be taught how to manage HF diet at home, signs and symptoms they should report to their health care provider, as well as the importance of following the medication regimen and INR checking if applicable. Appendix B shows drugs safety in the peripartum period and lactation. The above data or measures will be collected after a year period to be able to measure the quality of performance and patient outcomes.

Baseline data along with the after pathway implementation data will be compared and findings will be used for further recommendations and adjustment. An analysis of variances from pathway implementation will be performed to identify the difficulties/ gaps happening in the delivery of care process, and determine if the pathway requires immediate revision. The proposed pathway will be regularly reviewed, amended and updated according to international published practice guidelines about PPCM. The cardiology and obstetrical clinical nurse specialist (CNS) will coordinate efforts into the evaluation and implementation processes and monitor the data collection. Then they can undertake the data analysis and reporting of results to be presented to the cardiology/ obstetrical team.

The development and implementation of a clinical pathway requires a multidisciplinary effort. The management of PPCM requires a strict follow-up post discharge for medical management and anticoagulation and for evaluation of symptoms recurrence. During hospitalization, patients should be educated about HF symptoms and management based on whether they have compensated or decompensated HF. The development of a patient information guide will provide better understanding of the patients about their current condition and raise their awareness. Thus, patients can be offered the Arabic pamphlet developed with this project, which can help patients better understand the condition. The CNS has a key role in ensuring evidence based practice is implemented and patient outcomes are improved. He/she must keep up to date with the literature on PPCM so that novel treatments or new evidence are integrated in the clinical pathway.

APPENDICES

A. Differentiation table between normal pregnancy, severe eclampsia and PPCM

Normal pregnancy	Severe preeclampsia (PIH)	PPCM
Fatigue	Fatigue	Fatigue
Dyspnea	Respiratory distress due to capillary leak Paroxysmal nocturnal dyspnea	(crackles on auscultation)
Weight gain Peripheral edema	Weight gain Generalized edema Hypertension (> 160/110 mm Hg) Cough Proteinuria (> 5 g/dL) Distended neck veins Headache, Chest pain Blurred vision Pulmonary edema Hyperreflexia, clonus, leading to seizures Hepatic tenderness 2nd subscapular hematoma HELLP syndrome Impaired coagulation Decreased creatinine clearance Increased uric acid Low to normal cardiac filling pressures High SVR Low, normal, or high CO	Weight gain Peripheral edema Cough Proteinuria (> 5 g/dL) Distended neck veins Headache Chest pain Blurred vision Pulmonary edema Seizures Abdominal tenderness 2nd venous engorgement Thromboembolism New murmur Palpitations EF< 45% End-diastolic dimension > 2.7 cm/m2 BSA Fractional shortening < 30%

Comparison of Normal pregnancy, Severe Preeclampsia, and PPCM Table

Not all signs, symptoms, and diagnostic features may be present. Severe preeclampsia can develop after 20 weeks' gestation. PPCM can develop in the last month of pregnancy or within 5 months after delivery and lacks an identifiable cause of heart failure or recognized heart disease before the last month of pregnancy. Peripheral edema no longer part of diagnostic criteria, although often present.

Abbreviations: PPCM, peripartum cardiomyopathy; HELLP, hemolysis, elevated liver enzymes, and low platelet count; EF, ejection fraction; BSA, body surface area; SVR, systemic vascular resistance; CO, cardiac output; LVH, left ventricular hypertrophy

Adapted from Selle et al (Selle, Renger, Labidi, & Hilfiker- kleiner, 2009), Cunningham, Rivera &Spence (Cunningham, Rivera, & Spence, 2011)

B. Safety of Drugs during pregnancy

Drug Name	Class during pregnancy	Class During Lactation
Hydrochlorothiazide	B	AAP- compatible
Furosemide	C	Continue feeding
Lisinopril	D	Discontinue feeding
Losartan	D	Discontinue feeding
Hydralazine	C	AAP-compatible
Nitroglycerin	C	Unknown/ caution
Nitroprusside	C	Unknown
Dopamine	C	Unknown
Dobutamine	C	Unknown
Milrinone	C	Unknown/ caution
Epinephrine	C	Unknown
Norepinephrine	C	Unknown
Digoxin	C	AAP-compatible
Metoprolol	C	AAP-compatible
Carvedilol	C	Discontinue feeding
Amlodipine	C	Not recommended
Quinidine	C	Continue feeding
Procainamide	X	AAP-compatible
Warfarin	B	AAP-compatible
Enoxaparin	C	Caution
Intravenous immunoglobulin	C	Unknown
Pentoxifylline	B	Discontinue feeding
Bromocriptine		Discontinue feeding

Abbreviations: AAP: American Academy of Pediatrics

Class B: Animal reproduction studies have failed to show a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women; or animal studies have shown

an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

Class C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in human beings, but potential benefits may warrant use of the drug in pregnant women despite risks.

Class D: Positive evidence of human fetal risk has been shown y adverse-reaction data from investigational or marketing experience or studies in human beings, but potential benefits

May warrant use of the drug in pregnant women despite risks.

Class X: Studies in animals or human beings have shown fetal abnormalities or there is positive evidence of human fetal risk on the basis of adverse-reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Adapted from (Bhattacharyya, Basra, Sen, & Kar, 2012)

C. An Arabic pamphlet on PPCM for the Lebanese/ Arab population

إعتلال عَضلة القَلب المُصاحب للحَمْل و للولادة

القلب هو عضلة لا إرادية, تَضُخُّ دماً في الأوعية الدموية لكل أعضاء الجسم , و ذلك من خلال انقباضات متكررة و متناسقة مع بعضها البعض. عضلة الفلب هي الجزء الاساسي في عمل القلب , و أيّ عُطل فيها يؤدّي إلى اختلال وظائف هذه العضلة , و التسبب بقصور في تأدية مهامها الانقباضية, و توزيع الدم في الشرايين لتغذية الاعضاء الاساسية في الجسم البشري. الاختلال الحادّ و المفاجىء في عضلة القلب يؤدّي الى تدهور سريع في الوضع الصحّي للأشخاص, و قد يتسبب بتعقيدات جدّية تؤدي لمشاكل جسيمة قد تؤدي للوفاة.

هذا الاعتلال قد يحدث عند النساء الحوامل , و يُمكن تعريفه بأنه إعتلال لعضلة القلب من النوع التوسعي الغير معروف الأسباب , و الذي يحدث ما بين الشهر الأخير في الحمل و الشهر الخامس بعد الولادة.

يُعتبر هذا الاختلال نادراً. و لكن نسبه مرتفعة في العرق الإفريقي بشكل خاص حيث تصل نسية حدوثه الى واحدة لكل مئة حالة مسجلة في هذه الأماكن (خصوصا بعض القبائل في نيجيريا و وسط إفريقيا) حيث يتم استعمال ملح الطعام بكميات كبيرة , مع استخدام المواقد تحت الاسرّة

المصنوعة من الطّين , و ذلك يؤدي الى توسيع الأوعية الدموية, مع زيادة شرب الماء, و الذي بدوره يؤدي إلى هبوط في عضلة القلب.

العوارض

كمثل أعراض هبوط القلب عموما, و بسبب تغييرات فيزيولوجية و هرمونية , معظم العوارض تتجلّى كالآتي:

- ضيق في التنفس ٩١% من الحالات, ما يستدعي من المريضة استخدام أكثر من وسادة وقت النّوم
- تسارع في دقّات القلب
- ارهاق شديد, غثيان, و دوخة
- سُعال جاف
- آلام في الصدرو في البطن
- ارتفاع في ضغط الدّم
- تورّم في الساقين

العوامل التي تُساعد على حدوث المرض

ليس للمرض مسبب واحد أو معروف يمكن التأكد منه كسبب لحدوث هذه الحالة النادرة و المُحيّرة, و لكن ثمّة عدة عوامل مجتمعة , و التي جاء ذكرها في دراسات عديدة, و أهمها: تقدم سن المرأة, الحمل المتكرّر , الأصول الإفريقية للمرأة, سوء التغذية, حمل التوائم , ارتفاع الضغط خلال

الحمل, تسمم الحمل, وجود حالات قصور تمددي لعضلة القلب في العائلة او مصاحبة للحمل (عند الأم و الأخوات و الخالات), و كذلك استعمال بعض العقاقير المانعة للإجهاض.

الفُحوصات التشخيصية

- فُحوصات دم للتأكد من مَهمام الأعضاء الأساسية كالقلب و الكبد و الكلي, و التي تتأثر سَلبا بهبوط عضلة القلب.
- دراسة غازات الدّم
- الأشعة الصوتية للقلب لمعرفة مدى الضرر على عضلة القلب و الصمّامات , و قدرة القلب على ضخّ كمّية دم مناسبة لتغذية الأعضاء الرئيسية الأخرى.
- عند اللزوم , أخذ خزعة من عضلة القلب المُصابة من خلال إجراء قسطرة قلبية(تمييل) لاستثناء حدوث التهاب فيروسي في عضلة القلب , و إذا ما تأكد حدوثه, يتم معالجته بالعقاقير اللازمة.
- فحوصات تكميلية لاستبعاد أمراض قلبية أُخرى.

العلاج

العلاج مُشابه لعلاج قُصور عضلة القلب ذي الأسباب المختلفة, و لكن مع مُراعاة حالة الحمل و استبعاد الأدوية المُضرّة بالجنين. مُعظم هذه الادوية هي مُدرّات بول, و مُنشّطات لعضلة القلب, و قد يحتاج بعضها لمُسيّلات للدم لتجنب حدوث جلطات و ذلك بسبب حُدوث خلل في آلة القلب الكهربائية, و تردّي عضلة القلب و عَجزها عن ضخّ كميّات دم تتناسب مع حاجة الجسم , ما

يَجعل الدم يتخثّرليتسبب بحدوث جلطات قد تودي بحياة المريض . بعض الأدوية , و التي تمت تجربتها حديثاُ, و التي تعمل على إيقاف إفراز هرمون البرولاكتين, أَثبتت فعاليّة عالية في بعض الحالات, و بدأ استخدامها في مراكز مهمة من العالم. أيضا العقاقير البيولوجية و المُضادّة للمناعة, و الكورتيزون في حالات إلتهاب عَضلة القلب الفيروسي, و ذلك بعد التأكد من خلال إجراء فحص الخزعة لعضلة القلب.

مصير الأم و الطفل

أَثبتت الدراسات الحديثة أنّ حالة إعتلال عضلة القلب المُصاحب للحَمل و الولادة قد تكون حالة قابلة للانعكاس و التعافي , و الرجوع بعضلة القلب الى قُدرتها الطبيعية ما قبل الحمل (تقريبا في ٥٠% من الحالات). المهم إكتشاف الحالة مُبكرآ, و مُعالجتها و مُتابعتها من فَريق مُتخَصّص بأمراض قُصور عَضلة القلب, و أَمراض التوليد و الولادات المُعقدة و القَيصرية, و من أَخصائيي البَنج اذا ما لَزم الأمر. المتابعة الطبية مهمة للغاية من خلال الزيارات الطبية المنتظمة للطبيب المختص بقصور عضلة القلب, و إجراء الصورة الصوتية للقلب و الفُحوصات المِخبرية اللازمة. بسيي تشابه عوارض اعتلال عضلة القلب المصاحبة للحمل و الولادة بعوارض الحمل ذاتها, قد يتأخر التشخيص الصحيح أحيانا.

فُرص تكرار المرض

فرص تكرار المرض في حمل لاحق واردة , وهي نسبة عالية تصل ل ٣٠% في بعض الحالات.

لا يُنصح بتكرار الحمل خصوصا اذا كانت عضلة القلب لم تستعد حالتها الطبيعية من دون أي قصور تردّدي و حتى في حال تحسّن عضلة القلب, تُنصح السيدة باستشارة طبيب القلب المتابع بسبب فُرص إعادة حدوث المرض في الحمل اللاحق.

الخُلاصة

إعتلال عضلة القلب المُصاحبة للحمل و الولادة هي حالة نادرة, و لكنّها قد تَتَسَبَب بالوفاة إذا لم يتم اكتشافتها مُبكراً و تدارك عواقبها قبل أن تستفحل و تتسبب بضرر فادح و نهائي لعضلة القلب.

بعد الإصابة الأولى يجب أن يتم باستشارة طبيب و إشراف طبي متخصصفي حال التخطيط لأي حمل لاحق

المتابعة المستمرة مع الطبيب المختص ضرورية جدا لمراقبة نشاط و قوة عضلة القلب و للتأكد من فعالية الادوية المعطاة .

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