Peripartum Cardiomyopathy: A Systematic Review

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1. Introduction

Peripartum cardiomyopathy (PPCM) is a rare but potentially life-threatening condition that occurs in previously healthy women during the last month of pregnancy and up to 5-6 months postpartum. The etiology and pathophysiology remain uncertain, although recent observations strongly suggest the specific role of prolactin cleavage secondary to unbalanced peri/postpartum oxidative stress. PPCM is a diagnosis of exclusion, as it shares many clinical characteristics with other forms of systolic heart failure secondary to cardiomyopathy. The heart failure management requires a multidisciplinary approach during pregnancy, considering the possible adverse effects on the fetus. After delivery, the treatment is in accordance with the current guidelines of heart failure. Some novel therapies, such as prolactin blockade, are proposed to either prevent or treat the patients with PPCM. A critical individual counseling concerning the risks of subsequent pregnancy must be considered. Because of its rare incidence, geographical differences, and heterogeneous presentation, PPCM continues to be incompletely characterized and understood. For all these reasons, PPCM remains a challenge in clinical practice, so future epidemiological trials and national registries are needed to learn more about the disease.

2. Historical perspective, definition, nomenclature

Peripartum cardiomyopathy has been described since the 19th century. In 1849, Ritchie was the first to establish a relationship between heart failure and puerperium (Ritchie, 1849). After 20 years, Virchow and Porak reported autopsy evidence of myocardial degeneration in females who died in the puerperium (Porak, 1880).
However, PPCM was not recognized as a distinctive form of cardiomyopathy until 1937, when Gouley et al. described the clinical and pathological features of seven pregnant women. The patients had severe or fatal heart failure associated with a dilated cardiomyopathy in the later months of pregnancy, which persisted after delivery, and autopsy findings of enlarged hearts with focal areas of fibrosis and necrosis, but no ischemic lesions. The authors remarked these features as atypical compared with those of other forms of myocardial failure and proposed that this heart failure was related to pregnancy and puerperium, directly or indirectly (Gouley et al., 1937). Since then, there were many reports on this form of cardiomyopathy. In 1965, Walsh et al. was the first to propose the specific

period for the diagnosis, and highlighted that other conditions, which may be revealed by pregnancy, labor or postpartum period, must be excluded (Walsh et al., 1965).

In 1971, Demakis et al. described the natural history of 27 pregnant females who presented with cardiomegaly and congestive heart failure and defined the condition *peripartum cardiomyopathy* (Demakis et al., 1971). The investigators established 3 original diagnostic criteria, which were subsequently confirmed by the National Heart Lung and Blood Institute [NHLBI] and the Office of Rare Diseases of the National Institutes of Health [NIH] Workshop, and completed with an echocardiographic criterion (Pearson et al., 2000). The new definition based on the presence of 4 criteria is summarized in Table 1.

Classic criteria (Demakis et al., 1971)
1. The development of heart failure in the last month of pregnancy or within the first 5 months postpartum
2. The absence of an identifiable cause for heart failure
3. The absence of recognizable heart disease prior to the last month of pregnancy
Additional criterion (NHLBI & the Office of Rare Disease of NIH, 1997)
4. Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria (depressed ejection fraction or shortening fraction)

Table 1. Original definition of peripartum cardiomyopathy

In 1999, Hibbard et al. proposed a more precise echocardiographic criterion that parallels those for detecting idiopathic dilated cardiomyopathy (Hibbard et al., 1999) (Table 2). The new definition has been widely accepted and has improved the diagnosis of both ventricular dysfunction and PPCM. The original definition states that PPCM must develop during the last month of pregnancy or within 5 months after delivery. However, several reports described females who presented with clear PPCM symptoms earlier during pregnancy (Alvarez, 2001; Brown, 1992; Forssell, 1994; Rizeq, 1994; Yahagi, 1994). In 2005, Elkayam et al. provided the largest retrospective database, challenging the classic criteria when they found that clinical course and outcome of females with pregnancy-associated cardiomyopathy diagnosed earlier than the last gestational month are similar to those of females with traditional PPCM. The authors concluded that these two conditions might represent a continuum of a spectrum of the same disease (Elkayam et al., 2005). Since then, several definitions have been proposed (Table 2).

In 2010, the experts considered the modification of the first criterion might be necessary. This definition specifically excludes females who develop cardiomyopathy early in their pregnancy and emphasizes that not all cases of PPCM present with LV dilation. In addition, it is recommended that other conditions which may be exacerbated and associated with heart failure in the puerperium, are excluded before the diagnosis of PPCM is considered. However, in clinical practice, it remains difficult to distinguish females with preexisting asymptomatic cardiomyopathy, progressing during pregnancy and labor, from actual PPCM females (Sliwa et al., 2010a).

Ever since the early descriptions of PPCM, the condition has been defined by several confusing names, such as post-partum heart failure, post-partum myocarditis, Meadow's syndrome, idiopathic myocardial degeneration associated with pregnancy, Zaria syndrome, toxic post-partum heart disease, or recently, postpartal heart disease, post-partum cardiomyopathy or peripartum cardiomyopathy.

Hibbard et al., 1999	NHLBI definition and a strict ecocardiographic criterion of left ventricular (LV) dysfunction: 1. ejection fraction < 45% or fractional shortening < 30% 2. end-diastolic dimension > 2.7cm/m²
American Heart Association [AHA] Scientific Statement on contemporary definitions and classifications of the cardiomyopathies (Maron et al., 2006)	A rare and dilated acquired primary cardiomyopathy associated with LV dysfunction and heart failure
European Society of Cardiology [ESC] on the classification of cardiomyopathies (Dickstein et al., 2008)	A non-familial, non-genetic form of dilated cardiomyopathy associated with pregnancy
Heart Failure Association of the ESC Working Group on PPCM (Sliwa et al., 2010a)	An idiopathic cardiomyopathy presenting with heart failure secondary to LV 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 LV may not be dilated but the ejection fraction is nearly always reduced below 45%

Table 2. Definitions of peripartum cardiomyopathy

Peripartum cardiomyopathy is the preferred term because it highlights the overall chronological spectrum of the disease (Abboud et al., 2007). Another accepted term is *pregnancy-associated cardiomyopathy* or *early peripartum cardiomyopathy*, used for those females with cardiomyopathy developing heart failure before the last month of pregnancy or at least five months after delivery (Ntobeko et al., 2009). These cases may be subclinical dilated cardiomyopathies presenting the first symptoms in early pregnancy, or viral myocarditis, both distinct entities from PPCM (Pyatt & Dubey, 2011).

3. Epidemiology

Good data about incidence are unavailable because so few population-based registries exist. Most studies have been performed in South Africa, Haiti, and USA, but PPCM was also reported in Caucasian, Japanese, Chinese, Indian, and Korean women. Until recently, only small prospective studies reporting the experience of single centers were available to estimate the incidence of the disease (Desai et al., 1995; Fett et al., 2002, 2005a; Pyatt & Dubey, 2011). Only two large retrospective population-based studies have been conducted in USA to identify cases of PPCM. Mielniczuk et al. reported an estimated incidence of 1:3189 live births, with a trend toward an increase over the study period (1 case/2289 live births for the years 2000-2002), probably related to increasing maternal age and rates of multiple births or to increasing recognition and diagnosis of the disease (Mielniczuk et al., 2006). The second study was performed by Brar et al., who reported an incidence of 1:4025 live births (Brar et al., 2007). The estimates are almost similar for Japan and Australia. PPCM is sporadic in Europe in the white women (Bahloul et al., 2009; Ramaraj & Sorell, 2009). The

estimated in-hospital mortality due to PPCM in USA is 1.36% in more recent reports, less than in older series, perhaps due in part to high utilization of modern heart failure therapy (Mielniczuk et al., 2006). These more recent data from the United States suggest a significant difference in the incidence between certain ethnic groups. The lowest observed incidence is reported in Hispanics and the highest in African-Americans (Brar et al., 2007). Outside the United States, the most comprehensive data come from the Peripartum Cardiomyopathy Project in Haiti, which estimates the incidence of PPCM as high as 1case/299 live births (Fett et al., 2005a). The data have been confirmed by Gentry et al., who noted an incidence of 1 case/1000 live births in South Africa (Gentry et al, 2010). In fact, in the absence of a multicentric trial, the incidence varies widely between African countries. For example, in Tunisia the reported incidence is very low unlike Nigeria where older studies have reported 1 case/100 live births (Bahloul et al., 2009).

On the basis of several reports series of PPCM, varying genetic pools and diverse environmental factors have been proposed as risk factors in different areas. Although not clearly delineated, there are several suggested risk factors for development and recurrence of PPCM (Bahloul et al., 2009; Demakis et al., 1971; Fett et al., 2005a; Fisher et al., 2008; Murali & Baldisseri, 2005; Moioli et al., 2010; Nkoua et al., 1991; Ntusi & Mayosi, 2009; Pearson et al., 2000; Sliwa 2006a, 2006b):

- African race – appears to be the strongest risk factor, possibly due to a greater incidence of arterial hypertension in this group. Brar et al. reported the incidence of PPCM in African-American women to be 2.9-fold higher than in whites, and 7-fold than in Hispanics (Brar et al., 2007). Recently, Elkayam has shown that PPCM in USA is not limited to African women (Elkayam et al., 2005). It remains unclear whether race represents an independent risk factor.
- advanced maternal age – the disease generally occurs over the age of 30 years;
- multiparity – 71% of cases occur after ≥ 3 pregnancies compared with 8% in primigravidas (Demakis, 1971, as cited in Ntusi, 2009);
- twin pregnancies – which are observed in 8-13% of cases compared with 1-2% rate noted among healthy women;
- gestational hypertension – with an incidence of approximately 43%, substantially higher than the 8% to 10% incidence in the overall pregnant population. It is important to note that pregnancy-related hypertensive disorders should be considered as distinct entities from PPCM, and not included in the spectrum of PPCM. The complete recovery of LV function in pregnancy-related hypertensive disorders is the rule, whereas persistent cardiac dysfunction is frequent in PPCM patients.
- prolonged use of tocolytics refers to the use of terbutaline, salbutamol, ritodrine, isoxsuprine, magnesium sulfate etc for a period of at least four weeks (Bassett, 1985 as cited in Ntusi, 2009). The association with left ventricular dysfunction seems to be unique to pregnancy, as the same drugs do not determine similar complications in non-pregnant patients, even at high doses.
- certain cultural practices performed during the puerperium which are frequently related with high incidence of PPCM, such as consuming lake salt or rock salt known as "kanwa" (to promote the flow of breast milk), or heating of the body on a clay bed with a fire beneath to keep warm (Moioli et al., 2010; Murali & Baldisseri, 2005);
- socio-economic level is discussed as a risk factor, and can be summarized in a stereotyped profile: "poor African female, with malnutrition and multiparity, making strenuous and sustained physical effort during pregnancy" (Bahloul et al., 2009).

> **Main concerns**
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> *What is the true incidence?* Physicians still do not know how often PPCM occurs. Despite being a rare disease in many geographic areas of the world, PPCM remains an important cause of morbidity and mortality in pregnant females.
> *Who is at risk?* There are several cardiac factors that may play a causative role. Regardless of the documented risk factor, the association with PPCM is not clearly explained.
>
> **Implications for research**
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> Collaborative, multicenter, prospective, population-based, well-conducted trials are required for adequate diagnosis of this condition.

4. Etiology and pathogenesis

Despite extensive research into its underlying etiology and pathogenesis, it is not clear exactly how PPCM occurs (Ntusi et al., 2009).

Previously, PPCM was generally considered a form of idiopathic dilated cardiomyopathy that was unmasked by the hemodynamic stress of pregnancy (Cunningham et al., 1986). In this case, one would expect PPCM to present during the second trimester coincident with the maximum hemodynamic load of pregnancy. However, it more commonly presents later in pregnancy or postpartum. Moreover, 30% of patients with PPCM experience complete recovery, with partial recovery in many cases, in contrast to rare recovery in idiopathic dilated cardiomyopathy (Fett et al., 2002). Finally, epidemiological data show that PPCM is diagnosed in young women during the peripartum period, whereas idiopathic dilated cardiomyopathy is more common in older patients (Pearson et al., 2000). Although the two conditions have similar clinical presentations and hemodynamic features, there are also significant differences in histological characteristics.

It is now accepted that PPCM is a distinct entity, rather than a clinically silent underlying cardiomyopathy exacerbated by the hemodynamic changes during pregnancy (Robson et al., 1989).

The pathogenetic mechanisms of PPCM have been difficult to study as its incidence is too low to allow meaningful evaluations, and the suitable animal models to study the disease are rare. Several hypotheses have been proposed (Figure 1), but at the present time, two hypotheses are foremost: pregnancy associated hormonal changes, specifically the role of prolactin, and viral infection.

4.1 Excessive prolactin production

Pregnancy is a physiological state associated with enhanced oxidative stress related to high metabolic turnover and elevated tissue oxygen requirements. In order to protect the heart, an efficient antioxidant defense mechanism counteracts the oxidative stress. The total antioxidant capacity increases in the last trimester with a peak early postpartum (Toescu et al., 2002).

Prolactin has been suggested as a potential mechanism in the development of PPCM (Kothari, 1997). Experimental data in a mouse model of PPCM demonstrates the activation of STAT3 pathway by 23-kDa prolactin to be necessary (Hilfiker-Kleiner et al., 2007a). STAT3 is a cardiac tissue-specific DNA-binding protein, activator of transcription-3 that promotes myocardial angiogenesis and cardiomyocyte hypertrophy. In addition,

STAT3 protects the heart from pregnancy-induced oxidative stress in part by up-regulation of a powerful reactive oxygen species, scavenging mitochondrial enzyme named manganese superoxide dismutase (MnSOD) (Negoro et al., 2001). Reduced levels of STAT3 lead to an unbalanced peri/postpartum oxidative stress, a potent stimulus for the activation of prolactin-cleaving protease catehpsin D in cardiomyocytes. The result is cleavage of the nursing hormone prolactin into an antiangiogenic, proapoptotic, and proinflammatory 16-kDa subfragment (Roberg & Ollinger, 1998). Interestingly, prolactin is a hormone with opposing cardiovascular effects, depending on the circulating form. The full-length 23-kDa prolactin had no adverse effects on the heart (Hilfiker-Kleiner et al., 2007a). In contrast, high expression of 16-kDa fragment destroys the cardiac microvasculature, reduces in vivo cardiac function, promotes ventricular dilatation. The same fragment inhibits vascular endothelial growth factor-induced proliferation of endothelial cells and migration, induces apoptosis, dissociation of capillary structures, impairs nitric oxide-mediated vasorelaxation, and cardiomyocyte function (Hilfiker-Kleiner et al., 2008). Prolactin production is not limited to pituitary gland, various other cell types, such as fibroblasts, being able to produce it (Nagafuchi et al., 1999). PPCM is often associated with a high degree of cardiac fibrosis mediated by locally produced prolactin, which enhances the circulating pituitary 16-kDa prolactin damaging cardiac effects.
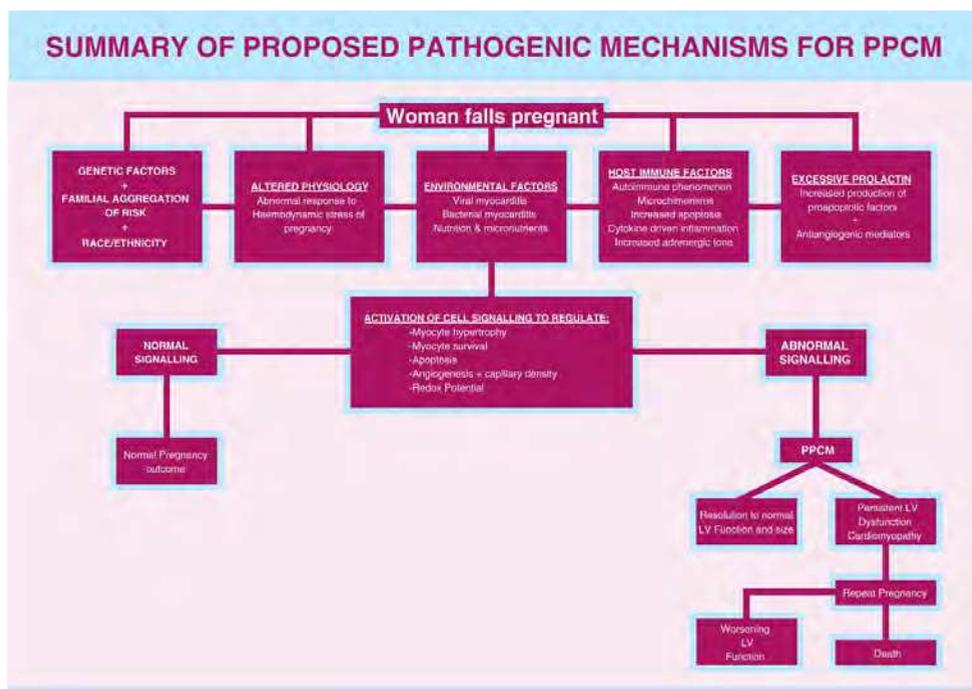

Fig. 1. Summary of proposed pathogenic mechanisms for PPCM (from Ntusi, N.B.A. & Mayosi, B.M. Aetiology and risk factors of peripartum cardiomyopathy: A systematic review. *Int J Cardiol*, Vol.131, No.2 (Jan 2009), pp. 168-179, with permission from Elsevier)

There is more evidence linking findings from experimental models to human PPCM. Patients with acute PPCM have increased serum levels of oxidized low-density lipoprotein indicative for enhanced oxidative stress, activated cathepsin D, and 16-kDa prolactin compared with pregnancy matched healthy controls (Hilfiker-Kleiner et al., 2007a). It is therefore likely that activation of this cascade plays a key functional role in human PPCM. PPCM patients have also significantly elevated pro-apoptotic serum markers (e.g. soluble death receptor sFas/Apo-1) with predictive power of impaired functional status and mortality (Sliwa et al., 2006b). In explanted terminally failing hearts from PPCM patients, low STAT3 protein levels are displayed, suggesting the role of this signaling pathway in the pathogenesis (Hilfiker-Kleiner et al., 2007a) (Figure 2).
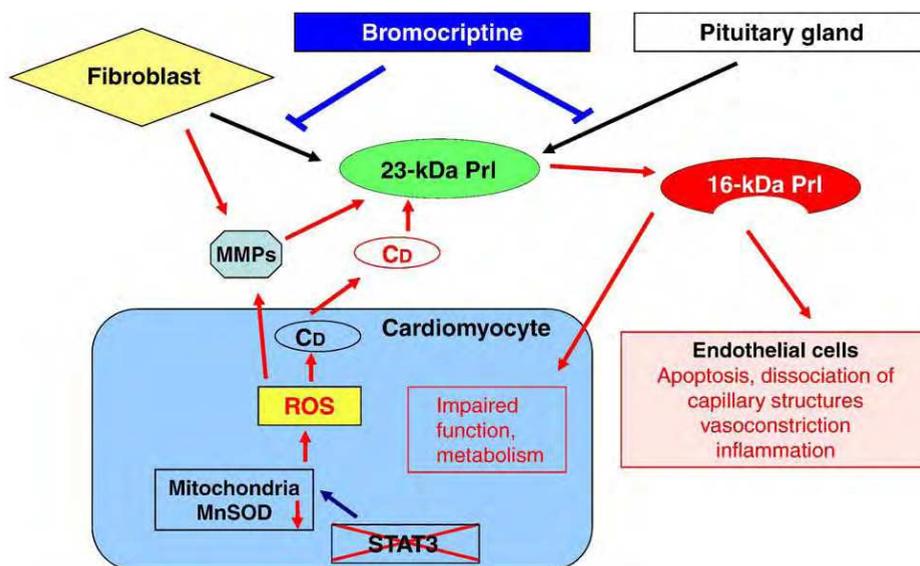

Fig. 2. Schematic mechanism for the development of PPCM (from Hilfiker-Kleiner, D., Sliwa, K. & Drexler, H. (2008). Peripartum Cardiomyopathy: Recent Insights in its Pathophysiology. *Trends Cardiovasc Med,* Vol.18, No.5 (July 2008), pp. 173–179; with permission from Elsevier)

Consistent with the idea of prolactin involvement, blockade by bromocriptine, a dopamine D2 receptor agonist, was tested. Bromocriptine eliminates the substrate for the generation of 16-kDa prolactin, and prevents the onset of disease in the mouse model of PPCM (Hilfiker-Kleiner et al., 2007a) (Figure 2). Several reports suggest that bromocriptine may have beneficial effects when added to the standard therapy of heart failure in women with acute onset of PPCM (Habedank et al., 2008; Hilfiker-Kleiner et al., 2007b; Sliwa et al., 2010b). However, at present, bromocriptine is not recommended until results of ongoing controlled randomized trials will provide information for the actual benefit of this therapy concept in patients with PPCM.

4.2 Viral myocarditis

The relationship between pregnancy and viral myocarditis was established in 1968 in pregnant mice (Farber & Glasgow, 1970). Myocarditis as a cause of PPCM in humans was

first suggested by Gouley et al., who corroborated infection with enlarged hearts with focal areas of fibrosis and necrosis (Gouley et al., 1937). Since then, several investigators have suggested myocarditis as a cause of PPCM (Cenac, 2003 as cited in Ntusi, 2009; Melvin, 1982; O'Connell, 1986). The prevalence of viruses detected in endomyocardial biopsies varies considerably between the different studies, ranging from less than 10% (Rizeq et al., 1994) to 78% (Midei et al., 1990), with a similar incidence in controls, suggesting no specific role for viral infection in the etiology of PPCM. It is worth noting that the molecular pathological study of endomyocardial biopsies within a cohort with PPCM found a high prevalence of viral genomes (parvovirus B19, human cytomegalovirus and herpes virus 6, Epstein-Barr virus) as well as inflammatory changes consistent with myocarditis (30.7%) (Bultmann et al., 2005). Other investigation suggests that viral infection increases the severity of myocardial damage in postpartum mice in comparison with non-pregnant control subjects (Lyden & Huber, 1984, as cited in Ramaraj & Sorrell, 2009). It is possible that the postviral immune response to be directed inappropriately against native cardiac tissue proteins leading to LV systolic dysfunction in the presence of the characteristic hemodynamic changes during pregnancy. Given the imunosuppressed state of pregnancy, it is logical that pregnant women are more susceptible to infection or viral reactivation (Pearson et al., 2000). At the present time, the exact role of viral infection or reactivation is far from conclusive. No convincing data exist that myocarditis is the primary etiology of PPCM. Further studies using newer technologies such as PCR are needed for detecting actively replicating viruses and myocardial viral load in PPCM (Ntusi et al, 2009) and confirming a pathogenic role.

4.3 Other putative hypotheses
4.3.1 Abnormal immune response to pregnancy

Abnormal immune response to pregnancy is another potential mechanism, probably generated by the decreased immunity during pregnancy (Cruz et al., 2010). The abnormal immune response may be produced after previous exposure immunization from prior pregnancy, or previous exposure to paternal major histocompatibility antigens. A local tissue inflammatory response is induced, followed by releasing of cytokines and a nonspecific innocent bystander myotoxicity and myocarditis (Pearson et al., 2000). Circulating auto-antibodies to selected cardiac tissue proteins were reported by several studies in more than 50% of PPCM patients (Sliwa, 2000, 2006a; Sundstrom, 2002, as cited in Cruz, 2010). Auto-antibodies are associated with increased levels of cytokines (tumor necrosis factor-α, interleukin-6, soluble Fas receptors), and are correlated with dilation of LV and systolic dysfunction (Sliwa et al., 2006b). The circulating auto-antibodies are formed against proteins released after delivery (e.g. actin, myosin), when the degeneration of the uterus occurs, and may cross-react with "target-proteins" found in the maternal myocardium (Freedman, 2004; Jahns, R., 2004). It was reported that in all patients with PPCM, irrespective of geographic location, auto-antibodies against cardiac myosin are non-selectively increased immunoglobulins G (class G and subclasses G1, G2, G3) (Warraich et al., 2005). Other studies have reported the phenomenon called chimerism, when fetal cells of hematopoietic origin reside in maternal serum, but remain undetected because of the weak immunogenicity of paternal haploytpe or maternal altered immunity (Ansari, 2002, as cited in Ramaraj & Sorrell, 2009). If fetal cells lodge in maternal myocardium during pregnancy, it is possible to be recognized as non-self while postpartum immune recovery, and an

abnormal immune response is triggered (Pearson et al., 2000). At the present time, it is unclear if all these data contribute directly to myocardial injury in PPCM, or should be considered as a consequence of the disease.

4.3.2 Citokine-mediated inflammation

Citokine-mediated inflammation is a basic pathophysiological mechanism in heart failure. The vasodepressor pro-inflammatory cytokines, like tumor necrosis factor-α, interleukin-6 and 1, interpheron-γ, expressed at high concentrations result in LV systolic dysfunction and remodeling, fetal gene expression, and cardiomyopathy. Increased levels of the same cytokines, and of hs-C-reactive protein have been reported in the serum of patients with PPCM (Fett, 2004; Sliwa, 2006b). It is still unclear if a true causal link between cytokines and PPCM does exist. If cytokines are involved in the pathogenesis of PPCM, these would prove useful targets for immunomodulatory therapy.

4.3.3 Increased myocyte apoptosis

Increased myocyte apoptosis represents an imbalance between cellular elimination and cellular regeneration. Experimental data suggest that terminally differentiated cardiac myocytes undergo apoptosis as the final common pathway in many cardiomyopathies (Narula, 2000; Wencker, 2003). Transgenic mice develop PPCM when cardiac-specific α-subunit of Gq is over-expressed (Hayakawa, 2003, as cited in Hilfiker-Kleiner, 2008). The Gq subunit is discussed to be responsible for coupling several cell surface receptors to intracellular signaling pathways involved in cardiomyocyte hypertrophy and apoptosis.

The inhibition of caspases, the proteases that mediate apoptosis, has been demonstrated to improve LV systolic function and reduce the mortality in pregnant Gαq mice. Recently, the proapoptotic gene Nix or Bnip3 have been demonstrated to play a key role in peripartum cardiac apoptosis and heart failure (Diwan, 2008, as cited in Hilfiker-Kleiner, 2008). Thus, experimental models, as well as indirect evidence in humans (increased plasma levels of key-proteins like Fas and Fas ligand), provides evidence for a role of apoptosis (Sliwa et al., 2006a). On the other side, the role of cardiomyocyte loss as a general key mechanism seems unlikely, since complete recovery of cardiac function has been observed in PPCM patients. Further studies are needed to evaluate the prevalence and exact role of apoptosis in PPCM patients, as well as the therapeutic value to prevent cardiomyopathy decompensation.

4.3.4 Abnormal response to hemodynamic stress

Abnormal response to hemodynamic stress is a hypothesis that suggests the exaggerated decrease in systolic function of LV in the presence of the cardiovascular changes in pregnancy (Ntusi et al., 2009). The normal hemodynamic changes during pregnancy result in a physiological transient and reversible hypertrophy and enlargement of the LV to meet the needs of the fetus and mother (Geva, 1997, as cited in Ntusi, 2009). These changes normally maintain up to 2-3 weeks postpartum and may persist until the 12th week after delivery. In patients with PPCM, LV anatomy may return to normal, but the contractile reserve is persistently decreased when assessed by dobutamine stress echocardiography (Lampert et al., 1997). Until now, there are no convincing data to support this hypothesis.

4.3.5 Genetic susceptibility

Genetic susceptibilitywas first suggested in the 1960s (Pierce at al., 1963). Since that time, several other documented cases with familial clustering of PPCM, as well as familial reports with familial PPCM and idiopathic dilated cardiomyopathy have been published, suggesting the contribution of genetics (Sliwa et al., 2010a). It is not clearly documented whether these cases meet the criterion of absence of an identifiable cause of heart failure, or whether an inherited idiopathic dilated cardiomyopathy becomes symptomatic because of the hemodynamic changes during pregnancy and after delivery. Also, the very high incidence in certain geographic regions or communities is strongly suggestive for environmental factors role. A genetic mutation cannot be excluded, but genetic testing is not usually performed in PPCM. Secondly, experimental studies have reported a genetic susceptibility to viral myocarditis in animals deficient in transforming growth factor-β, as well as the potential role of the defective STATE3 gene, or gene polymorphism of MnSOD (Hilfiker-Kleiner, 2008; Horwitz, 2007; Kim, 2005; Kühl 2005b; Lang 2008). Recently, van Spaendonck-Zwarts et al. investigated the occurrence of PPCM in 90 families with idiopathic dilated cardiomyopathy. The authors suggested that a subset of PPCM could be an initial manifestation of the disease, when a mutation in the gene encoding cardiac troponin C was identified (van Spaendonck-Zwarts et al., 2010). In another study from the USA, Morales et al. confirmed PPCM in 5 cases with gene mutations. The involved genes encoded myosin heavy chain 7 (MYH7), sodium channel, voltage-gated, type V, α-subunit (SCN5A), and presenilin 2 (PSEN2) in 3 cases with familial disease and myosin heavy chain 6 (MYH6), cardiac troponin T2 (TNNT2) in 2 with sporadic disease (Morales et al., 2010). Both reports have important implications, suggesting the necessity for the cardiologic screening in first-degree family members of PPCM patients without recovery of LV function and dimensions. In addition, reproductive risk counseling about PPCM or pregnancy-associated cardiomyopathy is appropriate for first-degree family members of patients with idiopathic dilated cardiomyopathy in the context of a genetic evaluation (Hershberger et al., 2009).

4.3.6 Malnutrition

Malnutrition was thought to be involved because of increased incidence of PPCM in communities with low socio-economic level (Hull, 1937, as cited in Ntusi, 2009; Walsh, 1965). For example, selenium deficiency has been reported in Sahel region of Africa (Cenac et al., 1992) but not in Haiti, and excessive consumption of salt in Nigeria (Ntusi et al., 2009). However, malnutrition it is not a key factor because many cases of PPCM are reported in well-nourished cohorts.

4.3.7 Abnormal hormonal regulation

Abnormal hormonal regulation although proposed in the 1930s, cannot be affirmed (Musser, 1938, as cited in Ntusi, 2009). Estrogens and relaxin were believed to play a role in PPCM, due to the cardiovascular effects, but no convincing evidence has been documented.

4.3.8 Increased adrenergic tone

Increased adrenergic tone secondary to physical or emotional stress has been proposed to cause "myocardial stunning" and transient cardiac dysfunction, fluid overload, decreased colloid osmotic pressure (Wittstein et al., 2005). Considering the evidence for the role of β1-

adrenergic receptor antibodies, it is possible to contribute to cardiac muscle dysfunction (Jahns R., 2004; Freedman, 2004).

4.3.9 Vascular disease

Vascular disease with subsequent myocardial ischemia has also been suggested, but morphology and function of coronary arteries were unaffected in PPCM patients (Koide, 1972; Lampert, 1995, as cited in Cruz, 2010).

4.3.10 Other possible mechanisms

Other possible mechanisms postulate the role of cardiac nitric oxide synthase, cardiac dystrophin, immature dendritic cells, toll-like receptors etc (Ramaraj & Sorell, 2009).

Main concern

What causes PPCM? Contributing factors and specific mechanisms remain unclear. Although various hypotheses have been proposed, so far no cause has been clearly identified. It is likely that PPCM is a heterogenous disorder, with a multifactorial etiology and complex biopathological processes.

Implications for research

Further studies are needed to elucidate this difficult condition. "The challenge will be to devise a study with sufficient power to give valid results" (Fett, 2010).

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5. Diagnosis

5.1 Clinical presentation

Patients with PPCM present with classical signs and symptoms of systolic heart failure due to other cardiomyopathies. The most common symptoms are dyspnea and fatigue (90%), tachycardia (62%), and peripheral edema (60%) (Elkayam et al., 2005). Other symptoms like persistent nocturnal dry cough, orthopnea, paroxysmal nocturnal dyspnea are frequently reported (Moioli et al., 2010). NYHA class III or IV functional status seem to be the most common initial presentation (Desai et al., 1995). Other non-specific signs and symptoms include dizziness, non-specific praecordial pain (50%), abdominal discomfort, palpitations, most frequently due to tachycardia or supraventricular tachiarryhtmias (Bertrand, 1977; de Beus, 2003; Weinblatt, 1995). Complex ventricular arrhythmias and cardiac arrest have also been reported (Diao et al., 2004). Some case series describe unusual presentations such as acute cyanosis (Cole et al., 2001), multiple thromboembolic events (Carlson et al., 2000) or liver failure (Fussell et al., 2005). Systemic and pulmonary embolic episodes are found during the clinical course of PPCM more frequently than in patients with other forms of cardiomyopathy (Bennani, 2003; Box, 2004; Helms & Kittner, 2005; Jha, 2005; Lasinska-Kowara, 2001). Sudden dyspnea, pleuritic pain, and hemoptysis suggest an episode of pulmonary embolism.

Regarding the physical signs in PPCM, a high incidence of the third heart sound (92%) and displaced apical impulse (72%) are reported (Desai et al., 1996). New murmurs consistent with mitral and tricuspid regurgitation are present in almost 50% of PPCM patients (Fadouach et al., 1994). Sinus tachycardia is the rule of cardiac exam. In the later stages, signs of pulmonary hypertension, including a loud or split second heart sound

and pulmonary crackles, are common. Elevated jugular venous pressure and hepatomegaly associated with edema are present as signs of congestive heart failure. Blood pressure may be normal or increased (when gestational hypertension is associated). In the later stages, postural hypotension can occur (Sliwa et al., 2010a). A latent form of PPCM without overt clinical symptoms has been reported (Elkayam et al., 2005).

The clinical diagnosis still represents a challenge because symptoms of early heart failure such as dyspnea, fatigue, palpitations, pedal edema, can appear in normal late pregnancy and after delivery. Therefore, in many cases, patients and their physicians may consider the symptoms to be normal.

There are some important clues for making the diagnosis. Clinical exam remains essential because a persistent sinus tachycardia, third heart sound, basal pulmonary crackles, and elevated jugular venous pressure are abnormal for pregnancy state and heart failure may be considered. Secondly, the diagnosis should be considered whenever women experience unexplained heart failure symptoms and signs during the last month of pregnancy or within 5 months following delivery, in accordance with PPCM definition. It is important to note that 78% of PPCM cases develop heart failure symptoms in the first 4 months after delivery, and only 9% of patients present in the last month of pregnancy (Lampert et al., 1995). It is possible that some patients to present later in postpartum because their symptoms are not initially recognized as heart failure (Sliwa et al., 2010a). Interestingly, Fett et al. reported clinically normal postpartum in Haitian women with asymptomatic echocardiographic systolic dysfunction, who either developed dilated cardiomyopathy or completely recovered LV function (Fett et al., 2005b). These cases may represent a latent phase of PPCM before the development of dilated cardiomyopathy later in life or subclinical dilated cardiomyopathy presenting in early pregnancy or a viral myocarditis, distinct conditions from true PPCM (Fett, 2008; Pyatt &Dubey, 2011). Thirdly, the rapid onset of heart failure symptoms in the peripartum period may also distinguish this clinical entity and requires further investigations.

In conclusion, there are no specific criteria for differentiating symptoms of early heart failure from normal late pregnancy, so it is imperative to maintain a high index of suspicion in conjunction with timing of symptoms to identify the patients with PPCM.

5.2 Investigation of peripartum cardiomyopathy

Blood tests should be done in all patients, although none of these can help in screening or positive diagnosis of PPCM. Initial laboratory assessment should include complete blood count and biochemical parameters. The thyroid function, a septic screen, and viral serology should also be performed in order to exclude other causes of cardiomyopathy and heart failure (Pyatt &Dubey, 2011). Molecular markers of an inflammatory process are found in most of the patients. It was reported that 90% of the patients with PPCM had high levels of plasma C-reactive protein, positively related with LV dimensions and inversely with LV ejection fraction (Fett, 2005a; Sliwa, 2006b). Cardiac markers, such as troponin T determined early after the onset of PPCM, are suggested to have prognostic significance. Only B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), commonly increased in patients with PPCM, are recommended by the Heart Failure Association of the ESC Working Group on PPCM to be determined (Sliwa et al., 2010a). Measurement of natriuretic peptides can be also helpful for risk stratification and

volume status assessment. Increased levels in pregnancy have been related with systolic dysfunction, increased LV filling pressures and LV hypertrophy, acute myocardial infarction (Hameed, 2009; Garrison, 2005).

Genetic testing is not recommended as a routine, but only for research purposes (Sliwa et al., 2010a).

Electrocardiogram is seldom normal in patients with heart failure caused by PPCM, but it is mostly non-specific. Sinus rhythm or sinus tachycardia are usually present, atrial fibrillation or ventricular tachycardia may occur, particularly if LV systolic dysfunction becomes chronic (Diao, 2004; Duran, 2008). An intraventricular block pattern or prolonged PR and QRS are seldom reported. LV hypertrophy pattern, Q waves in the anteroseptal leads, ST-T abnormalities largely vary in incidence between studies (Brown, 1998; O'Connell, 1986, as cited in Moioli, 2010). Negative T waves can be of ischemic origin in 50% of cases (Bertrand, 1975, as cited in Bahloul, 2009).

Chest X-ray should be part of the initial assessment of all patients with PPCM and clinical heart failure. Radiological findings can be cardiomegaly, pulmonary congestion/edema, and pleural effusion.

Echocardiography is the most widely used imaging method, which provides valuable, reproducible diagnostic and prognostic information. The technique is not diagnostic for PPCM, but is important to exclude other causes of heart failure. Hibbard et al. proposed precise echocardiographic criteria that should be applied (**Table 2**). Several studies highlighted the strong relation between LV end-diastolic diameter > 60 mm, or ejection fraction < 30% and the recovery of LV function (Duran, 2008; Elkayam, 2005). Another important finding may be the presence of LV thrombus, particularly when LV function is severely depressed. It is important to note that LV dilatation is not always present (Kane, 2001; Sliwa, 2000). It is strongly recommended to monitor the evolution under treatment before patient's discharge, at 6 weeks, 6 months, and annually (Sliwa et al., 2010a).

Cardiac magnetic resonance imaging (MRI) is widely used in other forms of cardiomyopathy for assessment of cardiac structure and function as a reference technique. Also it has a high ability to detect myocardial fibrosis as a consequence of myocarditis, using delayed contrast enhancement technique with gadolinium. In PPCM, cardiac MRI provides more accurate quantification of chamber volumes and ventricular function, and is more sensitive in detecting LV thrombus than echocardiography (Mouquet, 2008; Srichai, 2006). At the present time, there are four case series with PPCM assessed by cardiac MRI (Caballero-Borrego, 2008; Kawano, 2008; Leurent, 2009; Mouquet, 2008). In only two of these studies the technique revealed myocardial inflammation. Baruteau et al. consider that all these MRI results are not in contradiction, but underline the complex pathogenesis of PPCM. Cardiac MRI can distinguish two forms of PPCM, inflammatory and non-inflammatory, according to the presence or absence of late gadolinium enhancement. Therefore, cardiac MRI can be helpful at initial presentation to conduct further etiologic investigations (Baruteau et al., 2010). The interest for the technique is also suggested by the ability to differentiate PPCM from other forms of cardiomyopathy, like Tako-Tsubo or ischemic cardiomyopathy. The technique might be a useful method for guiding biopsy to the abnormal area (Leurent et al., 2009), and for prognostic stratification (Kawano et al., 2008). In his comment, Fett supports cardiac MRI for PPCM which is not responding to conventional therapy as long as late gadolinium enhancement is more likely to be present in these cases (Fett, 2009). In other words, cardiac MRI could guide the immunosuppressive therapy in the inflammatory forms

of PPCM, as this option of treatment has successfully been tested in "myocarditis-like" PPCM (Ntusi et al., 2009). Further larger prospective studies are needed to evaluate these findings, and the real diagnostic contribution of MRI in PPCM. The Heart Failure Association of the ESSC Working Group on PPCM recommends cardiac MRI to be performed at 6 and 12 months for a better assessment of cardiac functional changes (Sliwa et al., 2010a). It remains the problem of using gadolinium during pregnancy, not recommended by the European Society of Radiology until after delivery, unless absolutely necessary (Webb et al., 2005).

Invasive evaluation including cardiac catheterization and coronary angiography are not routinely indicated, as no specific findings are present, and coronary arteries are usually normal in PPCM.

Endomyocardial biopsy is not routinely recommended in PPCM for multiple reasons. Its role is controversial because a specific microscopic pattern for PPCM does not exist, even though a "myocarditis-like" form is frequently found (Fett, 2006a; Zimmermann, 2005). In addition, the technique is not widely available, is invasive, and has a relatively high complication rate.

Considering all these data, PPCM should be suspected whenever the patient experiences symptoms and signs of heart failure during peripartum period. A careful history and physical exam should be performed to identify heart failure due to other cardiac or non-cardiac entities. The differential diagnosis of PPCM should include all the pre-existing clinical conditions, either unrecognized, such as congenital heart disease, or unmasked by pregnancy, such as sporadic and familial idiopathic dilated cardiomyopathies, HIV/AIDS cardiomyopathy, valvular heart disease, particularly rheumatic mitral valve disease. Other non-cardiac conditions (collagen vascular disease, sexually transmitted disease, thyroid disorders) and precipitating factors (current use of alcohol, tobacco, illicit drugs, sodium intake, other therapies) may be also considered. A useful clue for diagnosis is the onset of symptoms, most frequently in postpartum for PPCM unlike the other clinical conditions, which usually present by the 2nd trimester. Pregnancy-associated myocardial infarction, venous thromboembolism, hypertensive heart disease must be also included in the diagnostic approach. Timely diagnosis of PPCM is critical for best outcomes of survival and recovery. Very recently, Fett proposed a screening tool for early diagnosis of PPCM. The test is a focused medical history for PPCM screening, looking for the most common early signs and symptoms of heart failure during last month of pregnancy (Fett, 2011). The author proposes 6 clinical categories, easy to quantify, which are included in a self-scoring system (Table 3). A score ≥ 5 has always been associated with LV systolic dysfunction. A score > 4 suggests the need for further investigation. In this case, a blood BNP test and an echocardiography are recommended. If the score is < 4 the patient should be monitored for BNP and C-reactive protein levels. If increased levels, echocardiography should be performed. The author emphasizes that this test is not diagnostic for PPCM, but encourages an expanded use, because it may be a useful tool for early recognition of the new onset heart failure.

In conclusion, the diagnostic work-up should focus on precise echocardiographic identification of new LV systolic dysfunction, peptide natriuretic measurement (Murali, 2005; Pearson, 2000), and ruling out other causes of heart failure. Additional investigations should be based on clinical suspicion. PPCM remains a *diagnosis of exclusion*. Early detection is critically important to the patient with PPCM, because delayed diagnosis may be associated with increased morbidity and mortality (Fett, 2008; Fussell, 2005; Pearson, 2000; Sliwa, 2006a).

Sign/symptom	Characterstics	Scoring
Orthopnea (difficulty breathing when lying flat)	None Need to elevate head Need to elevate $\geq 45^0$	0 1 2
Dyspnea (shortness of breath on exertion)	None Climbing 8 or more steps Walking on level	0 1 2
Unexplained cough	None At night Day and night	0 1 2
Swelling lower extremities	None Below knee Above and below knee	0 1 2
Excessive weight gain (during last month of pregnancy)	< 2 pounds/week 2-4 pounds/week > 4 pounds per week	0 1 2
Palpitations (sensation of irregular heart beats)	None When lying down at night Day and night, any position	0 1 2

Table 3. Self-test for early diagnosis of heart failure in PPCM (adapted from Fett JD, 2011).

Main concerns

How to optimize the diagnosis? Early involvement of a cardiologist is needed for a timely diagnosis. The rapid onset of heart failure symptoms in the peripartum period may distinguish this difficult entity, only if other causes of cardiomyopathy are excluded. A screening clinical self-test for early recognition of PPCM is now proposed. Cardiac MRI is also suggested to have a great diagnostic and prognostic potential.

What's next in PPCM investigation?

A multicentre registry systematically using these tools may be considered for a better diagnostic approach.

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6. Management of peripartum cardiomyopathy

When considering treatment during the peripartum period, a multidisciplinary approach is needed. Involvement of a maternal-fetal medical team, including a cardiologist, obstetrician, anesthetist, intensivist, and neonatologist is imperative as earliest as possible after the diagnosis. The type of monitoring and care should be individualized to minimize maternal and fetal morbidity and mortality.

6.1 General management of peripartum cardiomyopathy

The medical treatment is generally similar to that for other forms of non-ischemic dilated cardiomyopathy, with some possible exceptions because of the risks of certain drugs on the fetus and newborn. The aims of medical treatment should be to reduce cardiac afterload and preload, while increasing myocardial contractility, to prevent complications, particularly thromboembolism, cardiac arrhythmia, progressive heart failure, and to improve long-term prognosis. Current therapeutic options consist of conventional supportive treatment for acute and chronic heart failure.

6.1.1 Management of acute heart failure

The principles of treatment in PPCM are no different than those applying to acute heart failure from other etiologies (Dickstein et al., 2008). A careful bedside clinical assessment may be helpful to identify the hemodynamic profile. Acute heart failure is usually manifested by worsening pulmonary congestion to pulmonary edema and hypoxemia, peripheral congestion with large weight gain, or low output status indicated by signs of hypoperfusion. All patients should be hospitalized and closely monitored.

Oxygen therapy should be promptly administered in order to relieve symptoms, while achieving an arterial oxygen saturation of ≥ 95%. Non-invasive ventilation with a positive end-expiratory pressure of 5-7.5 cm H_2O should be used when necessary. Extracorporeal membrane oxygenation to treat severe pulmonary edema shortly after delivery has been reported to be useful (Yang et al., 2007).

Patients with significant volume overload but adequate perfusion are treated with *intravenous diuretics*, with an initial bolus of furosemide 20-40 mg i.v. Particular potential adverse effects of diuretics were reported during pregnancy, such as pancreatitis, decreased carbohydrate tolerance (Lindheimer & Katz, 1973) bleeding, and hyponatremia in newborns (Ferrero et al., 2003).

Intravenous nitrates may be added when diuretics are inadequate in controlling symptoms. Nitroglycerin starting at 10-20 up to 200 μg/min is safe when systolic blood pressure is > 110 mmHg. Nitroprusside may be used in certain cases, but theoretically, accumulation of its catabolites thiocyanate and cyanide may be harmful to the fetus (Egan et al., 2009). Nesiritide is insufficiently studied in human pregnancy (Cruz et al., 2010).

Inotropic agents can be used without unnecessary delay in patients with low output status or those with persistent congestion despite diuretic and/or vasodilatator therapy. Dobutamine or levosimendan are strongly recommended when needed. Small studies with levosimendan suggest persistent hemodynamic improvement attributable to production of an active long half-life metabolite (OR-1896), and no safety concern, but breast-feeding should be avoided (Benezet-Mazuecos & de la Hera, 2008; De Luca, 2006).

Mechanical ventricular support and cardiac transplantation are needed in patients dependent on inotropic agents, or intra-aortic balloon pump counterpulsation, despite optimal medical strategy. Surgical support with ventricular assist devices may be considered in appropriately selected patients as a bridge to recovery or to cardiac transplantation. Heart Failure Association of the ESC Working Group on PPCM recommends an individualized discussion between experts in such cases, as the optimal strategy in PPCM is not known (Sliwa et al., 2010a). If the type of ventricular assist devices is discussed, two prosthetic ventricles - BiVADs and CardioWest TAH, depending on body surface area, heart size and presence of multiorgan failure were proposed (Zimmerman et al., 2010). Complications may occur with ventricular assist devices, such as a high incidence of thrombotic events (Potapov et al., 2008). Recovery of myocardial function can occur in approximately 15% of patients with PPCM on ventricular assist device support (Murali et al., 2005). If the clinical improvement does not occur, cardiac transplantation should be considered. Since 1987, when Aravot et al. reported their first experience (Aravot, 1987, as cited in Abboud, 2007), several case series were treated by heart transplantation with mixed results. In 1994, Keogh et al. demonstrated no difference in survival rates for cardiac transplantation in women with dilated cardiomyopathy, irrespective of etiology, but higher rates of early rejection in PPCM were noted (Keogh, 1994, as cited in Zimmerman, 2010). Other authors supported the

hypothesis of an overactive immunological response in "myocarditis-like" PPCM, which predisposes to recurrent severe rejection, and subsequent development of fatal transplant-associated complications. A recent prospective study demonstrated that survival and freedom from cardiac allograft vasculopathy in PPCM was similar to that of women with other indications for heart transplantation (Rasmusson et al., 2007). At the present time, based on available data, 0-11% PPCM patients undergo heart transplantation, with a similar outcome compared with other etiologies of heart failure (Sliwa et al., 2010a). Generally, heart transplantation in PPCM is associated with survival rates similar to that in patients with idiopathic dilated cardiomyopathy (88% at 2 years, and 78% at 5 years) (Murali et al., 2005).Very recently, a long term survey on 8 patients with PPCM (mean post-transplant survival 7.1 years) has shown that cardiac transplantation alone can be a successful option (Zimmerman et al., 2010).

6.1.2 Management of stable heart failure

There are no clinical trials to support any particular treatment regimen for PPCM. After delivery, the patient should be treated according to the current guidelines for heart failure (Pearson, 2000; Sliwa, 2010a). During pregnancy and lactation, the management approach must consider the welfare of the fetus along with that of the mother, so several restrictions to these guidelines will be applied.

Dietary restrictions and lifestyle changes are essential and complementary to pharmacological therapy. Fluid restriction to ≤ 2 liters per day and salt restriction (2-4 g per day) are advisable for volume overload control, particularly when NYHA class III and IV symptoms occur. Daily monitoring for edema and weight loss is clinically useful (Oakley et al., 2003). Smoking and alcohol cessation is strongly recommended. Strict bed rest was the standard in the past, still not recommended, except the patients with severe symptoms. Regular modest exercise may be resumed after relief of symptoms (Pyatt &Dubey, 2011; Sliwa 2006a). Since many of pharmacological agents are secreted in the breast milk, breast-feeding is not advised in patients with PPCM (Sliwa et al., 2010a).

Diuretics should be used cautiously because of decreasing placental perfusion with aggressive administration (Egan, 2007; Sliwa 2006a). After delivery, diuretics are safe to reduce preload, and relieve symptoms of pulmonary congestion and volume overload (Amos, 2006; Oakley, 2003). Loop diuretics, such as furosemide, are most frequently used and safer during hospitalization. Thiazide diuretics may be added, if loop diuretics are insufficient, or used in mild cases (Oakley, 2003; Sliwa 2010a). Possible increase of risk of births defects or fetal thrombocytopenia, were reported (Cruz et al., 2010). On experimental studies, spironolactone is reported to have antiandrogenic effects during late pregnancy, but it can be safely added in postpartum period (Pyatt &Dubey, 2011). Eplerenone should be also avoided during pregnancy, as its effects on human fetus are insufficiently studied (Muldowney et al., 2009).

Angiotensin-converting enzyme inhibitors (ACEI) and *angiotensin-II receptor blockers* (ARB) are contraindicated, because of severe fetal toxicity in the 2nd and 3nd trimester of pregnancy, particularly on kidney, resulting in oligohydramnios, fetal renal failure, and neonatal death, but also hypocalvaria, limb contractions, hypoplastic lungs (Cruz et al., 2010). After delivery, or in postpartum onset PPCM, ACEI and ARB are efficient agents to reduce the afterload, and are strongly recommended, as it has been demonstrated to improve survival in all patients with systolic heart failure. It is also recommended the patient counseling

about the teratogenic potential of these drugs, with a recurrent pregnancy (Cruz et al., 2010). Some of ACEI, such as captopril and enalapril, are safe during breast-feeding (Ghuman et al., 2009).

Hydralazine and long-acting nitrates are considered safe and useful to reduce preload. The combination can replace ACEI/ARB during pregnancy, or if there is drug intolerance, and may be added to standard therapy in symptomatic patients (Moioli et al., 2010). The agents are reported to be especially effective and further increase survival among African-American patients with NYAH II and III class heart failure (Hunt et al., 2009). The combination is also compatible with breast-feeding.

β-blockers have not been tested in PPCM, but have been safely used in pregnancy-induced hypertension. *β1-selective blockers* are preferred, as *β2*-blockade is theoretically reported to have anti-tocolytic effect (Ghuman et al., 2009). The benefit of these drugs to maternal survival usually outweighs the potential risk to the fetus and newborn. The risks consist of growth retardation, resulting in low-birth-weight newborns, hypoglicemia and bradycardia. Therefore, care should be given when these drugs are used in late pregnancy. β-blockers are recommended for all patients with PPCM, unless contraindicated, as these drugs improve symptoms, ejection fraction, and long term prognosis, reduce the risk of arrhythmia and sudden death. Because transient worsening of heart failure may appear with initiation of therapy, patients should be stable, with minimal evidence of volume overload, and doses should be titrated cautiously. Although carvedilol has been shown to improve overall survival in dilated cardiomyopathy, no safety information related to its use during pregnancy are available. Therefore, use of metoprolol is preferred under careful monitoring, as the drug is also compatible with breast-feeding (Abboud, 2007; Cruz, 2010).

Antiarrhythmic drugs, although well tolerated, should be used only in the acute setting, because their safety for fetus cannot be guaranteed. β-blockers are often adequate for treating supraventricular arrhythmias, also in chronic use. Sotalol or amiodarone may be needed, but, considering their systemic side effects during chronic use, are not recommended. Calcium channel blockers, because of their negative inotrop effects, are also not recommended. Ventricular arrhythmias may be frequently life-threatening, and should be managed aggressively. Class I and class II antiarrhythmic agents are not recommended, because the drugs are poorly tolerated and have proarrhythmic effect. Digoxin is safe during pregnancy, even if it crosses the placental barrier. Careful monitoring of serum levels is recommended, because of the narrow therapeutic-to-toxic window. A digoxinemia of ≤ 1-1.2 ng/dl and early use of the drug in symptomatic women with ACEI/ARB contraindications are recommended (Cruz et al., 2010). Digoxin is also secreted in breast milk, but no adverse effect has been described in newborns (Moioli et al., 2010). In appropriate patients, electrical cardioversion may be necessary, after transesophageal echocardiography rules out the presence of a left atrial thrombus.

Antithrombotic therapy is recommended as pregnancy and puerperium are prothrombotic states. In addition, LV dysfunction (particularly ejection fraction < 35%), severely dilated cavities, and mural thrombus, history of venous thromboembolism and atrial fibrillation are associated with an increased risk of thromboembolic events. A recent study of 182 women with PPCM demonstrated an incidence of 2.2% for thromboembolic complications (Goland et al., 2009). VKA antagonists are contraindicated prior to delivery, because of their risk of fetal and neonatal cerebral hemorrhage, and central nervous system anomalies for warfarin. Heparins are considered necessary and preferred, as they do not cross the placental barrier,

and are found in breast milk in significant amount. Low-weight molecular heparins are preferred, as they have a lower risk of premature maternal osteoporosis and thrombocytopenia. Also, low-weight heparins have a short half-life, so they can be discontinued at least 12 hours prior to delivery, to prevent maternal hemorrhage, and resumed 12-24 hours after delivery. Currently, low-weight heparins are safely used in weight-adjusted doses. A strictly adaptation using anti-Xa monitoring is necessary in women at extremes of body weight, or with renal disease. Fondaparinux cannot be used during pregnancy, as there are no consistent data. In 5-7 days postpartum, heparin can be replaced with VKA antagonists, even to breast-feeding mothers (Torbicki et al., 2008).

Cardiac resynchronization therapy and implantable cardioverter/defibrillators have individualized indication, otherwise very difficult to decide in the context of the natural history of PPCM and lack of specific data. The main concern is the usefulness of such methods in patients who may not need them, if ventricular function will recover. For this reason, the indication is advisable when LV ejection fraction < 35% persists after 6 months following presentation. Patients with recurrent symptomatic ventricular arrhythmias may be candidates for an implantable defibrillator. If NYHA III and IV heart failure symptoms and a QRS duration > 120 ms are present, cardiac resynchronization may be required (Sliwa et al., 2010a).

Novel therapies are emerging, but the available data are inconsistent and limited.

Immune modulatory therapy in PPCM is not clear, although an immune pathogenesis has been postulated. The beneficial effects of intravenous immunoglobulin therapy have been inconsistently demonstrated by several studies. Likewise, immunosuppressive drugs, such as azathioprine, cyclosporine or steroids, have shown mixed results. For all these reasons, a multicenter prospective clinical trial in PPCM is needed to support use of such agents. Some studies suggested that immunosuppressive drugs might be helpful in patients with active biopsy proven lymphocytic myocarditis, only after active viral infection is excluded (Sliwa, 2006a; Zimmerman, 2005). Also, recent studies demonstrate the role of cardiotrophic viruses in some cases of idiopathic dilated cardiomyopathy (Kűhl, 2005a, 2005b), but only one study had demonstrated viral genomic material in endomyocardial biopsy from patients with PPCM (Bultmann et al., 2005). At the present time, the role of immunosuppressive therapy in women with negative biopsies remains unknown. It is important to note that current therapies with ACEI, ARB (Godsel et al., 2003), and β blockers (Pauschinger et al., 2005) may have an additional effect on controlling the overactive immune system in PPCM. Also, immunomodulatory therapy acting on inflammatory cytokine TNF-α may be beneficial. Pentoxifyline, a xanthine agent known to inhibit the production of TNF-α and to prevent apoptosis, has been studied in PPCM. In a prospective study of 59 women with PPCM, 30 treated with pentoxifyline 400 mg three times a day in addition to standard therapy of heart failure, a significant improvement of LV function > 10%, and end-diastolic dimensions, a reduction of mortality rate, and greater increase in functional status, compared with the control group were found (Sliwa et al., 2002).

Bromocriptine therapy

Considering the observations that strongly suggest prolactin cleavage as a specific mechanism for the development of PPCM, specific inhibition of its secretion with bromocriptine, a dopamine D2 receptor agonist, is promising. Thus, bromocriptine might represent a novel specific therapeutic approach to either prevent or treat patients with acute PPCM (Hilfiker-Kleiner et al., 2008). Several case reports demonstrated recovery of LV

function after treatment with bromocriptine (Elkayam & Goland, 2010; Habedank, 2008; Hilfiker-Kleiner, 2007b; Jahns, B.G., 2008; Meyer, 2010). Very recently, Sliwa et al. reported the results of a prospective, single-center, randomized, proof-of-concept pilot study of women with newly diagnosed PPCM receiving standard therapy with or without bromocriptine for 8 weeks. The addition of bromocriptine appeared to significantly improve LV function (27% at baseline, to 58% at 6 months, p=0.012), and a composite clinical outcome (Sliwa et al., 2010b). Analyzing these data together, Fett remarked that important details of studies design must be corrected for appropriate results. The author proposes some essential conditions to conduct further trials. Patients included in such trials may be best to have serum cathepsin-D activation, positive test for serum 16-kDa prolactin, and very important, to accept lactation suppression while assuring alternative newborn nutrition (Fett, 2010). Also, Fett suggests that bromocriptine treatment should be limited to those patients with LV ejection fraction < 35%, because of poor prognosis with standard therapy in this category. Concerning the safety of bromocriptine in early postpartum women, there are several reports of myocardial infarction (Hopp et al., 1996), while adding adequate anticoagulant therapy, thromboembolism is not reported in such patients (Meyer, 2010; Sliwa, 2010b). Secondly, there are many reports on myocardial infarction in early postpartum independent from bromocriptine administration (Hilfiker-Kleiner et al., 2008).

The results of these studies may represent breakthroughs in the understanding of PPCM pathogenesis, and in the development of a new specific therapy for this clinical entity. But, at the present time, a large, prospective, multicenter, randomized trial is needed to allow bromocriptine extensive use. Such a trial is on-going in Haiti and South Africa (Pyatt & Dubey, 2011).

Other proposed therapies are based on the potential of several agents, such as calcium channel antagonists, statins, interferon-β, monoclonal antibodies, or methods (immunoadsorbtion, apheresis) to influence pro-inflammatory cytokines in acute myocarditis (Ramaraj & Sorrell, 2009).

Main concern

How to treat better? The current medical strategies are not always safe enough for maternal prognostic. There is no clear evidence for the beneficial effect of standard therapy on the recovery of cardiac function in patients with PPCM. As the cause of PPCM is still unknown, no specific therapy has been established to treat this condition.

Implications for research

As the excessive prolactin hypothesis seems to be specific for PPCM, a specific therapeutic intervention using bromocriptine should be tested in an extensive, controlled manner.

6.2 Specific management of peripartum cardiomyopathy

In addition to treatment of heart failure, an obstetrical plan for close monitoring must be developed when PPCM is diagnosed during pregnancy. A collaborative approach, including the obstetrician, cardiologist, anesthesiologist, and neonatologist is essential to optimal care. Serial clinical assessment should be scheduled during late pregnancy. Antenatal testing, such as non-stress test and amniotic fluid index, or biophysical profile is also recommended (Cruz et al., 2010). A baseline ultrasound scan is best to be performed during pregnancy for monitoring the fetus (Sliwa et al, 2010a). If patient is stable, responsive

to medical therapy, the pregnancy should be allowed to go to term. The medical team should discuss the delivery mode, primarily considering the mother's benefit. Spontaneous vaginal delivery is preferred in stable women with healthy fetus. For patients with newly diagnosed PPCM before delivery, labor should be induced, or a cesarean section must be planned if mothers are critically ill, or LV function is deteriorating rapidly, or with obstetrical indication (Murali, 2005). After delivery, strict maintenance of fluid status is recommended, using diuretic therapy to prevent volume overload, as fluids are resorbed into the intravascular space (Cruz et al., 2010). Continuous invasive maternal monitoring, including an arterial line and pulmonary catheter, for adequate assessment of patient's hemodynamic status and guide management, as well as continuous fetal cardiotocography are strongly recommended (de Beus et al., 2003). Antenatal medication may be administered, except heparin which should be discontinued at least 12 hours prior to delivery, and resumed 12-24 hours after delivery, with obstetrician and anesthesiologist's permission. Continuous analgesia and anesthesia are needed to minimize further cardiac stress and pain relief, and should be performed with careful specialized monitoring. Epidural analgesia is preferred during labor, as it stabilizes cardiac output through a sympathectomy-induced afterload reduction (Sliwa et al., 2010a). Continuous spinal anesthesia, with epidural analgesia are recommended for cesarean section, as the hemodynamic stability may be more easily maintained (Murali et al., 2005). If general anesthesia is required, drugs with myocardial depressant effect should be avoided, and induction and maintenance with a high-dose opioid technique is preferred. The second stage of labor can cause maximum hemodynamic and oxidative cardiac stress, so these periods must be shortened using a vacuum device or low forceps. A single dose of intramuscular oxytocin can optimally manage the third stage of labor; ergometrine is forbidden (Oakley et al., 2003).Breastfeeding should be avoided in patients with PPCM, although several drugs have been tested and are safe.

7. Prognosis

7.1 Predictive factors and follow–up

Very few studies have been done to assess the long-term survival and recovery outcomes in PPCM. Although PPCM is a form of dilated cardiomyopathy, a characteristic feature is that a higher rate of spontaneous recovery of LV function occurs. A subset of women with PPCM, despite using an optimal medical treatment, follows a rapid and irreversible course, associated with persistent LV dysfunction, severe heart failure, or premature death.

Whitehead et al. reported that in USA 30-50% of patients return to normal within 6 months post partum (Whitehead et al., 2003), while a single centre prospective study, conducted in South Africa, described only a 23% recovering rate of LV function, despite optimal therapy with ACEI and β blockers (Sliwa et al., 2006b). The same author reported a 32% 6-month mortality rate in case series from South Africa (Sliwa et al., 2000). In another study, in Haitian women, with a mean follow-up period of 5 years, the rate of recovery was 31.5%, while mortality rate was 15 %. An important finding of this study was that the recovery to normal LV function can occur later, after 2-3 years after diagnosis, so it is not limited to the first 6-12 months (Fett et al., 2005a). A recent study describes similar rates of LV function recovery and survival in women from USA, Haiti, and South Africa, probably related to improvements in medical therapy, and to the aggressive use of cardioverters in the non-American studied population (Modi et al., 2009). Analyzing *the predictive factors* for long-

term prognostic, Duran et al. concluded NYHA functional class, QRS duration, and LV parameters at the time of diagnosis were important predictors. Initial cut-off values of ≤ 5.5 cm for LV end-systolic diameter, and > 27% for LV ejection fraction were identified to predict complete recovery of LV function, while QRS duration on electrocardiogram ≥ 120 ms was a predictor for mortality (Duran et al., 2008). Reviewing 182 patients with PPCM for major adverse events and death, Goland et al. also demonstrated that in all cases there was a strong relation with severe LV dysfunction, non-Caucasian race, and a delayed diagnosis (Goland et al., 2009). These findings complete previous observations about the relation between the severity and persistence of LV dysfunction and the incidence of morbidity and mortality. A LV ejection fraction > 30% at the time of diagnosis might be a predictor for recovery (Elkayam et al., 2005). LV end-diastolic diameter ≥ 6 cm and fractional shortening ≤ 20% are proposed as risks factors for long-term prognosis, as are correlated with a more than threefold higher risk of progressing to persistent LV dysfunction later on (Chapa, 2005; Wittin, 1997). Recently, Baruteau et al. discussed the potential significance of cardiac MRI in prognostic stratification, by assessing LV size, function, and contractile reserve, as well as prognostic MRI factors identified in myocarditis for "myocarditis-like" forms of PPCM (end-diastolic volume, septal localization, and total amount of late gadolinium enhancement at initial time) (Baruteau et al., 2010). Other authors propose immunological mediators and markers of apoptosis to predict outcome. Elevated C-reactive protein and Fas/APO-1 were reported to be related to decreased LV function and mortality (Sliwa et al., 2006b). These perspectives remain to be evaluated by further studies.

In summary, the prognosis varies according to geographical region, and probably, the most important predictor remains the recovery of LV systolic function.

Follow-up of patients with PPCM is similar with that for other forms of cardiomyopathy and LV systolic dysfunction. Patients should be monitored regularly to assess clinical course, complications, LV systolic dysfunction and dimensions, and the response to treatment. Considering that the recovery interval is not restricted to the first 6-12 months postpartum, it is strongly recommended to continue treatment and follow-up for a long period of time to achieve best results (Fett, 2009). However, the optimal period remains unknown. At the present time, echocardiography is the most important tool for serial assessment. In the first several weeks after diagnosis, an echocardiogram should be performed to assess the level of LV function. After that, it should be repeated at about every 6-12 months until recovery is confirmed, or a plateau is reached (Sliwa et al., 2006a). Dobutamine stress echocardiography may be performed to assess the potential for LV function recovery, by measuring the inotropic contractile reserve (Dorbala et al., 2005). The technique is useful especially when LV systolic function is normal, and the contractile reserve remains decreased (Lampert et al., 1997).

7.2 Subsequent pregnancies, risk of relapse

One of the most important issues in PPCM is the safety of subsequent pregnancies. Even after the full recovery of LV function, the risk of relapse might be present.

In Haitian women, Fett et al. described a rate of recurrence of 53% with subsequent pregnancy. In a retrospective study in USA, it was observed that subsequent pregnancy was associated with the recurrence of heart failure, regardless the previous LV function. However, in women who had a normal LV function, the rate of heart failure was 21% compared with 44% in women who had altered function. Also, all deaths occurred in the last group. Furthermore, recovery of LV function was more frequent in patient with an

ejection fraction > 30% at diagnosis of disease (Elkayam et al., 2001). Another retrospective study confirmed a better prognosis for subsequent pregnancy in women who had a higher ejection fraction at diagnosis. However, no relation between ejection fraction and worsening clinical symptoms was found in 29% of patients. Also, a baseline ejection fraction of ≤ 25% at index pregnancy was associated with a higher rate of cardiac transplant (Habli et al., 2008). According to these data, it is especially important to provide the most appropriate information about a potential relapse with subsequent pregnancy. LV systolic function seems to be the key prognostic factor when counseling women with PPCM about the further risks. Individual planning might be done after an echocardiogram was performed:

- if LV ejection fraction is < 25% at diagnosis or incompletely recovered, the advice should be against further pregnancy (Sliwa et al., 2010a);
- even if LV function is normal, the patients ought to have stress-echocardiography:
  • women with an abnormal LV inotropic response to dobutamine have a moderate risk of relapse and pregnancy is not recommended;
  • women with complete recovery on both echocardiography and dobutamine stress test can be informed about the low rate of complications. In this group, despite a 35% rate of risk of recurrence, pregnancy can be completed in almost all cases (Pyatt & Durbey, 2011).

In postpartum period, it is imperative to give contraceptive counseling and educate the patients about the existent alternatives. Women who had PPCM should avoid pregnancy, best until LV function has recovered. The combined oral contraceptives, containing estrogens and progestins are contraindicated, as estrogens increase the thromboembolic risk. Progesterone contraception alone is permitted (Thorne et al., 2006). Barrier methods are not recommended as they have a high rate of failure. Intrauterine systems are the most efficient and safe methods of contraception. Sterilization methods, including vasectomy, tubal ligation, and insertion of intratubal stents may be considered (Sliwa et al., 2010a).

At the present time, no protocols for decision-making when counseling women with PPCM about risks of subsequent pregnancies are established. For this reason, it is advisable that every women who experienced PPCM, to be considered at risk, and to be closely monitored by the medical team, in a high-risk obstetrical center.

Main concern

What is the course and prognosis of the disease? With the sparse knowledge in this field, the individual outcome is difficult to predict.

Implications for research

Novel diagnostic strategies, based on improved understanding of pathophysiology and molecular basis of PPCM, should be developed to enhance both diagnostic and prognostic utility. Collecting data from the children born to affected women should be an important priority.

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8. Conclusions and future directions

Since its original description, peripartum cardiomyopathy remains a challenge for both diagnosis and treatment. Although several advances have been made to further the knowledge, the condition is still considered a cardiomyopathy of unknown cause. In terms

of future research, a better understanding of its molecular basis and fundamental underlying mechanisms, including potential genetic contribution and life-style aspects, is needed. From a clinical perspective, the ability to identify patients at risk to develop the disease is mandatory. Despite current definition, PPCM can remain undiagnosed until it's too late, as some important issues, such as, its rarity in developed countries, the heterogenity of studied populations, and the lack of adherence to diagnostic guidelines, are not resolved. Collaborative, multicentre prospective, well-conducted, population-based trials are required for the development of national and international health policies on prevention, early diagnosis and management, and standard therapeutic control. The Peripartum Cardiomyopathy Netwotk is a NIH-funded North America ongoing trial conducted in order to address some of unresolved issues, as long as the Haitian PPCM Registry is the only existing population-based registry in the world (Fett, 2005a, 2010). Novel diagnostic strategies and biomarkers are potential candidates that should be validated in large clinical trials. Cardiac MRI and prolactin production might provide valuable diagnostic and prognostic information. Also, it would be ideal to have some specific therapeutic strategies. The most realistic candidate seems to be bromocriptine, although potential new treatments, including immune-modulatory therapy, apheresis, and antiviral agents might have a decisive role. Considering all these data, it is important for clinicians to be aware of this condition, so that unnecessary delays in diagnosis can be avoided, and appropriate therapy can be prescribed in a timely fashion. With current technology, clinicians and researchers are now connected, and new bases for multidisciplinary collaboration might be developed.

9. References

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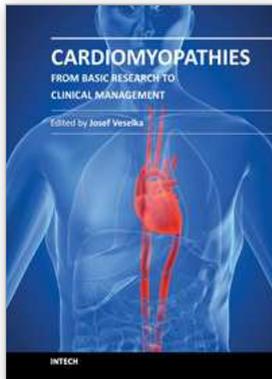
Cardiomyopathies - From Basic Research to Clinical Management
Edited by Prof. Josef Veselka

Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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