PERIPARTUM CARDIomyOPATHY: A CHALLENGE FOR CARDIOLOGIST

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PERIPARTUM CARDIomyOPATHY: A CHALLENGE FOR CARDIOLOGIST (Abstract):
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 management of heart failure 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 for 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. Keywords: PERIPARTUM CARDIomyOPATHY, PROLACTIN, ECHOCARDIOGRAPHY, BROMOCRIPTINE, RIK OF RELAPSE.

DEFINITION, EPIDEMIOLOGY
In 1849, Ritchie was the first to establish a relationship between heart failure and puerperium. However, peripartum cardiomyopathy (PPCM) was recognized as a distinctive form of cardiomyopathy in 1937, when Gouley (cit. 1) described the clinical and pathological features of a severe heart failure associated with a dilated cardiomyopathy in the later months of pregnancy persisting after delivery. In 1965, Walsh (cit. 1) was the first to propose the specific period for the diagnosis, and highlighted that other conditions must be excluded. In 1971, Demakis et al. (2) defined the condition PPCM. The investigators established the 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 (3) (tab. 1).
In 2010, Heart Failure Association of the ESC Working Group on PPCM proposed a new definition: “an idiopathic car-
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diomyopathy 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% (1).

**TABLE I**

**Original definition of peripartum cardiomyopathy**

<table>
<thead>
<tr>
<th>Classic criteria (Demakis et al.) (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The development of heart failure in the last month of pregnancy or within the first 5 months postpartum</td>
</tr>
<tr>
<td>2. The absence of an identifiable cause for heart failure</td>
</tr>
<tr>
<td>3. The absence of recognizable heart disease prior to the last month of pregnancy</td>
</tr>
</tbody>
</table>

**Additional criterion (NHLBI & the Office of Rare Disease of NIH) (3)**

| 4. Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria (depressed ejection fraction or shortening fraction) |

Although the condition has been defined by several confusing names, PPCM is the preferred term because it highlights the overall chronological spectrum of the disease (4). 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 (5).

Good data about incidence are unavailable because so few population-based registries exist. Until recently, only small prospective studies were available to estimate the incidence of the disease (5-8). Only two large retrospective population-based studies have been conducted in USA with a reported incidence ranging between 1:3189 live births and 1:4025 live births (9, 10). The estimates are almost similar for Japan and Australia. PPCM is sporadic in Europe in the white women (11,12). The more recent data from the United States suggest the highest incidence in African-Americans (10). Outside the United States, the most comprehensive data came from the Peripartum Cardiomyopathy Project in Haiti, which estimated the incidence of PPCM as high as 1 case/299 live births (7). The data have been confirmed by Gentry (13), who noted an incidence of 1 case/1000 live births in South Africa. Although not clearly delineated, there are several suggested risk factors for the development and recurrence of PPCM (2, 3, 11, 14-19):

- african race appears to be the strongest 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 primigravida;
- twin pregnancies in 8-13% of cases compared with 1-2% rate noted among healthy women;
- gestational hypertension in 43% of cases, substantially higher than the 8% to 10% incidence in the overall pregnant population;
- the unique association with prolonged use of tocolytics for a period of at least four weeks;
- certain cultural practices such as consuming lake salt or rock salt known as “kanwa” or heating of the body on a clay bed with a fire beneath to keep warm;
- socio-economic level summarized in a stereotyped profile: “poor African female, with malnutrition and multiparity, making strenuous and sustained physical effort during pregnancy”.

ETIOLOGY AND PATHOGENESIS

Despite extensive research into its underlying etiology and pathogenesis, it is not clear exactly how PPCM occurs (17). 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 putative hypotheses, such as abnormal immune response to pregnancy, cytokine-mediated inflammation, increased myocyte apoptosis, abnormal response to hemodynamic stress, genetic susceptibility, malnutrition, increased adrenergic or vascular disease have been proposed, but, at the present time, two hypotheses are foremost: pregnancy associated hormonal changes, specifically the role of prolactin, and viral infection.

Pregnancy is a physiological state associated with enhanced oxidative stress. 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 in early postpartum (20). STAT3 is a cardiac tissue-specific DNA-binding protein which protects the heart from pregnancy-induced oxidative stress (21). The protein pathway is activated by full-length 23-kDa prolactin, a hormone with no adverse effects on the heart. Reduced levels of STAT3 lead to an unbalanced peri/postpartum oxidative stress, a potent stimulus for the activation of prolactin-cleaving protease cathepsin D in cardiomyocytes. The result is cleavage of the nursing hormone prolactin into an antiangiogenic, proapoptotic and proinflammatory 16-kDa subfragment, which also promotes ventricular dilatation and reducing of cardiac function. 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 (22,23). In explanted terminally failing hearts from PPCM patients, low STAT3 protein levels are displayed, suggesting the role of this signaling pathway in the pathogenesis (22). Prolactin production is not limited to pituitary gland, various other cell types, such as fibroblasts, being able to produce it. 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. 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 and significantly elevated pro-apoptotic serum markers (e.g. soluble death receptor sFas/Apo-1), indicative for enhanced oxidative stress, activated cathepsin D, and 16-kDa prolactin compared with pregnancy matched healthy controls (24). 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 (22) (fig. 1).
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 (25,26).

Fig. 1. Schematic mechanism for the development of PPCM (adapted from 24)

Myocarditis as a cause of PPCM in humans was first suggested by Gouley (cit. 1) in 1937. Since then, several investigators have supported this hypotheses. On the other hand, the prevalence of viruses detected in endomyocardial biopsies ranges from less than 10% to 78%, with a similar incidence in controls, suggesting no specific role for viral infection. It is worth noting that the molecular pathological study of endomyocardial biopsies 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%) (28). Another investigation suggests that viral infection increases the severity of myocardial damage in postpartum mice in comparison with non-pregnant control subjects (12). 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 (3). At the present time, no convincing data exist that myocarditis is the primary etiology of PPCM. Further studies using newer technologies such as PCR are needed to confirm a pathogenic role (17).

**DIAGNOSIS OF PERIPARTUM CARDIOMYOPATHY**

Patients with PPCM present with classical signs and symptoms of systolic heart failure due to other cardiomyopathies (28).
NYHA class III or IV functional status seems to be the most common initial presentation (6). Some case series describe unusual presentations such as acute cyanosis, multiple thromboembolic events or liver failure (16,28). A latent form of PPCM without overt clinical symptoms has been reported (29). The clinical diagnosis still represents a challenge because symptoms of early heart failure can appear in normal late pregnancy and after delivery. The diagnosis should be considered whenever women experience unexplained heart failure during the last month of pregnancy or within 5 months following delivery. It is important to note that 78% of PPCM cases develop heart failure symptoms in the first 4 months after delivery (30). Interestingly, Fett (31) reported clinically normal postpartum in women with asymptomatic echocardiographic systolic dysfunction, who either developed dilated cardiomyopathy or completely recovered LV function. 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. The rapid onset of heart failure symptoms in the peripartum period is another clue for diagnosis. Very recently, Fett (32) proposed a screening tool for early diagnosis (tab. II). A score ≥ 5 has always been associated with LV systolic dysfunction. A score > 4 suggests the need for further investigation, such as BNP and echocardiography. If the score is < 4 the patient should be monitored for BNP and C-reactive protein levels. If increased levels, echocardiography should be performed.

### TABLE II

**Self-test for early diagnosis of heart failure in PPCM**

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>Characteristics</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopnea (difficulty breathing when lying flat)</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Need to elevate head</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Need to elevate ≥ 45°</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea (shortness of breath on exertion)</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Climbing 8 or more steps</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Walking on level</td>
<td>2</td>
</tr>
<tr>
<td>Unexplained cough</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>At night</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Day and night</td>
<td>2</td>
</tr>
<tr>
<td>Swelling lower extremities</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Below knee</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Above and below knee</td>
<td>2</td>
</tr>
<tr>
<td>Excessive weight gain (during last month of pregnancy)</td>
<td>&lt; 2 pounds/week</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2-4 pounds/week</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt; 4 pounds per week</td>
<td>2</td>
</tr>
<tr>
<td>Palpitations (sensation of irregular heart beats)</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>When lying down at night</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Day and night, any position</td>
<td>2</td>
</tr>
</tbody>
</table>
The diagnostic work-up should focus on precise echocardiographic identification of new LV systolic dysfunction, peptide natriuretic measurement (3, 15), and ruling out other causes of heart failure. Additional investigations should be based on clinical suspicion. Blood tests, electrocardiogram, chest X-ray should be done in all patients, although none of these can help in screening or positive diagnosis. Echocardiography is the most widely used imaging method, which provides valuable, reproducible diagnostic and prognostic information. The technique is important to exclude other causes of heart failure and to monitor the evolution under treatment (1). In PPCM, cardiac MRI can be helpful at initial presentation to conduct further etiologic investigations (34). The interest for the technique is 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 (35) and for prognostic stratification (36). Fett (37) supports cardiac MRI for guiding the immunosuppressive therapy in the inflammatory forms of PPCM, as this option of treatment has successfully been tested in “myocarditis-like” PPCM. The Heart Failure Association of the ESSC Working Group on PPCM (1) recommends cardiac MRI to be performed at 6 and 12 months for a better assessment of cardiac functional changes. 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 (18, 33).

**MANAGEMENT OF PERIPARTUM CARDIOMYOPATHY**

When considering treatment during the peripartum period, a multidisciplinary approach is needed. Involvement of a cardiologist, obstetrician, anesthetist, intensivist, and neonatologist is imperative as earliest as possible after the diagnosis. The medical treatment is generally similar to that for other forms of non-ischemic dilated cardiomyopathy, with some general 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 (38). Novel therapies are emerging, but the available data are inconsistent and limited. Some studies suggested that immunosuppressive drugs might be helpful in patients with active biopsy proven lymphocytic myocarditis, only after active viral infection is excluded (1). At 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 and β blockers 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. Sliwa et al. (39) reported a significant improvement of LV function > 10%, and end-diastolic dimensions, a reduction in mortality rate, and greater increase in functional status. Considering the observations that strongly suggest prolactin
cleavage as a specific mechanism for the development of PPCM, specific inhibition of its secretion with bromocriptine is promising. Several case reports demonstrated recovery of LV function after treatment with bromocriptine (25,40,41). Very recently, Sliwa (42) 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). Analyzing these data together, Fett (43) remarked that important details of studies design must be corrected for appropriate results. 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. 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 (5).

In addition to the treatment of heart failure, an obstetrical plan for close monitoring must be developed when PPCM is diagnosed during pregnancy. A collaborative approach is essential to optimal care. Serial clinical assessments should be scheduled during late pregnancy. Antenatal testing, such as non-stress test and amniotic fluid index, or biophysical profile, baseline ultrasound scan for fetus is also recommended (44). 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 (15).Breastfeeding should be avoided in PCCM, although several drugs have been tested and are safe.

**PROGNOSIS AND PREGNANCY OUTCOME**

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. However, a subset of women, despite using an optimal medical treatment, follows a rapid and irreversible course, associated with persistent LV dysfunction, severe heart failure, or premature death. Analyzing the long-term prognosis, Duran (45) concluded that 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 ≥ 120 ms was a predictor for mortality. Recently, Baruteau (34) discussed the potential significance of cardiac MRI in prognostic stratification. Elevated C-reactive protein and Fas/APO-1 were also reported to be related to decreased LV function and mortality (42). These perspectives remain to be evaluated by further studies.

Follow-up of patients with PPCM is similar with that for other forms of cardiomyopathy and LV systolic dysfunction. Considering that the recovery interval is not restricted to the first 6-12 months post-partum, it is strongly recommended to continue treatment and follow-up for a long period of time to achieve best results (37). An echocardiogram should be repeated at about every 6-12 months until recovery is
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confirmed, or a plateau is reached (1). Dobutamine stress echocardiography may be performed to assess the potential for LV function recovery, by measuring the inotropic contractile reserve (46). The technique is useful especially when LV systolic function is normal, and the contractile reserve remains decreased.

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. 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 (1);
- 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, pregnancy can be completed in almost all cases (5).

In postpartum period, it is imperative to give contraceptive counseling and educate the patients about the existing alternatives. The combined oral contraceptives, containing estrogens and progestins are contraindicated, as estrogens increase the thromboembolic risk. 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 (1).

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 woman who experienced PPCM to be considered at risk, and to be closely monitored by the medical team, in a high-risk obstetrical center.

REFERENCES