Table 1 Definition/classification of peripartum cardiomyopathy

	Definition of PPCM
European Society of Cardiology on the classification of cardiomyopathies[49]	A non-familial, non-genetic form of dilated cardiomyopathy associated with pregnancy
AHA Scientific Statement on contemporary definitions and classifications of the cardiomyopathies[7]	A rare and dilated acquired primary cardiomyopathy associated LV dysfunction and heart failure
Workshop held by the National Heart Lung and Blood Institute and the Office of Rare Diseases[2]	The development of heart failure in the last month of pregnancy or within 5 months post-partum The absence of an identifiable cause of heart failure The absence of recognizable heart disease prior to the last month of pregnancy LV systolic dysfunction demonstrated by classical echocardiographic criteria. The latter may be characterized as an LV ejection fraction <45%, fractional shortening <30%, or both, with or without an LV end-diastolic dimension >2.7 cm/m^2 body surface area
Heart Failure Association of the European Society of Cardiology Working Group on PPCM 2010	PPCM is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%.

HF, heart failure; LV, left ventricular.

been found in the majority of women with PPCM.[26] Circulating auto-antibodies to every type of cardiac tissue were identified in all 10 cases screened by Lamparter *et al.*[27] Warraich *et al.* reported higher titres of antibodies (IgG and IgG subclasses) against cardiac myosin heavy chain in patients with PPCM compared with those with IDCM. Furthermore, these titres correlated with clinical presentation and with New York Heart Association (NYHA) functional class.[28] In addition, the potential role of microchimerism, due to the introduction of foetal cells of haematopoietic origin into the maternal circulation, has been raised.[29]

Whether or not these findings are causal in PPCM, or secondary to cardiac damage due to another mechanism, is not clear.

Genetic susceptibility to peripartum cardiomyopathy

Few data are available with which to formally evaluate any genetic contribution to susceptibility to PPCM and the studies that have been published are largely case reports rather than systematic studies. There are a number of reports in the literature of PPCM in women with mothers or sisters who had the same diagnosis. A widely cited study from the 1960s[30] identified 3 of 17 probands with PPCM who had a definite family history of the condition. Since that time, there have been several other carefully documented examples of two or three affected female first-degree relatives.[31–34] Frequently, uncertainty exists about whether such cases fulfil formal PPCM diagnostic criteria (i.e. absence of pre-existing heart disease) or whether, in contrast, the affected women have an inherited DCM that only became apparent during the haemodynamic stress of pregnancy. There have been reports of women with PPCM, who have male relatives affected by DCM, arguing that at least some familial cases are examples of DCM rather than a specific PPCM.[35] Recently, however, there have been two reports which more strongly support the suggestion that some cases of PPCM may in fact be part of familial DCM.[36,37] In one study from the Netherlands, van Spaendonck-Zwarts *et al.*[36] studied 90 families with familial DCM and investigated the presence of PPCM; in addition, they also examined PPCM patients and performed cardiac screening of their first-degree relatives. Their data suggest that a subset of PPCM is an initial manifestation of familial DCM and this was corroborated by the identification of a causative mutation in one family. In another study from the USA, Morales *et al.*[37] did similar observations in a large cohort study. These findings together may have important implications for cardiology screening in such families.

Nevertheless, the very high incidence in certain communities is suggestive of environmental risk factors,[38] although a common genetic founder mutation cannot be excluded. Studies in immigrant populations in the USA suggest an intermediate level of risk in African-Americans and a low incidence in Hispanics (more in keeping with changing environment than genetic origins).[9]

Within populations, there clearly remains scope for variable genetic susceptibility, just as there is with other forms of HF. Future research could evaluate both the common variants: common disease contribution to PPCM susceptibility and, potentially, analysis of uncommon larger-effect alleles (e.g. by re-sequencing). A number of candidate gene pathways would be promising targets, e.g. genetic variants in the JAK/STAT signalling cascade;[3] however, no associations have been detected to date.

On the basis of these results, general genetic testing is not recommended as a routine but is currently being done as part of research projects.

Clinical presentation and diagnosis

The clinical presentation of patients with PPCM is similar to those with other forms of systolic HF secondary to cardiomyopathy, but may be highly variable. Patients with only mild symptoms have been reported.[37] Early signs and symptoms of PPCM may often mimic normal physiological findings of pregnancy and include pedal oedema, dyspnoea on exertion, orthopnoea, paroxysmal

Table 2 Incidence of peripartum cardiomyopathy

Author	Year	Country	Case series or population based	Retrospective (R) or prospective (P)	Number with PPCM	Incidence	Mean age	Race	Definition of PPCM
Mielniczuk *et al.*[8]	1990–2002	USA	Population based	R	171	1990–2002: 1:3189; 2000–02: 1:2289	30	42% White; 32% African-American with PPCM	ICD 9 code 674.8 (plus least one of 514, 428, 425.4, 648.64) and then 2 reviewers of each potential case—PPCM if consensus
Brar *et al.*[9]	1996–2005	USA	Population based	R	60	Total (all races): 1:4025; 1:4075, Whites; 1:1421, African-Americans; 1:9861, Hispanics; 1:2675, Asians	33	NA	ICD 9 codes 428.0, 428.1, 428.4, 428.9, 425.4, and 425.9 and then case note review: (i) LVEF < 0.50 (ii) Framingham criteria for HF (iii) new symptoms of HF or initial echocardiographic diagnosis of left ventricular dysfunction occurred in the month before or in the 5 months after delivery
Fett *et al.*[5]	2000–2005	Haiti	Case series (single institution)	P	98	1:300	32	Afro-Caribbean	(i) CHF 1-month before to 5 months after delivery (ii) no pre-existing heart disease (iii) no other cause identified for CHF (iv) LVEF < 45% or FS < 30%
Chapa *et al.*[10]	1988–2001	USA	Case series (single institution)	P	32	1:1149	27	80% African American; 20% White	(i) FS < 30% (ii) LVEDD > 4.8 cm (iii) no other cause identified for CHF (iv) LVEF < 45% or FS < 30%
Desai *et al.*[11]	1986–1989	South Africa	Case series (single institution)	P	97	1:1000	29	Black Africans; except 1 Asian	Not stated; echocardiography performed—no results presented
Witlin *et al.*[12]	1986–1994	USA	Case series (single institution)	R	28	1:2406	NA	21 Black; 6 White; 1 Asian	(i) CHF 1 month before to 5 months after delivery (ii) no other cause identified for CHF (iii) absence of heart disease before the last month of pregnancy

Only studies recruiting after 1985 using echocardiography are included (except Mielniczuk—no echocardiography). Only studies including >25 patients after 1985 patients are included. NA, not available; LV, left ventricular; LVEF, left ventricular ejection fraction; EDD, end-diastolic diameter; NYHA, New York Heart Association.
[1]Date of publication.

nocturnal dyspnoea, and persistent cough. Additional symptoms experienced in PPCM include abdominal discomfort secondary to hepatic congestion, dizziness, praecordial pain, and palpitations, and, in the later stages, postural hypotension can occur. In many cases, women with PPCM and their doctors or midwives may believe that these symptoms are either due to gravidity or general tiredness, due to having given birth recently, and the associated lack of sleep. In addition, patients may be anaemic.

In the majority of patients, symptoms develop in the first 4 months after delivery (78%). Only 9% of patients present in the last month of pregnancy. Thirteen per cent present either prior to 1 month before delivery, or more than 4 months post-partum.[39] In at least some countries, patients often present later than 5 months post-partum as their symptoms are not initially attributed to HF (K.S., South Africa, personal experience). Such patients have not been included in any studies to date as they do not meet current criteria for a diagnosis of PPCM. It is also possible that some women who present later in life with DCM have previously unrecognized PPCM.

The most frequent initial presentation is with NYHA functional class III or IV symptoms,[11] but this may vary from NYHA I to IV symptoms. Some patients may present with complex ventricular arrhythmias or cardiac arrest.[40]

Only one study has reported physical signs in PPCM. Of 97 South African patients, 72% had a displaced apical impulse, 92% a third heart sound, and 43% mitral regurgitation.[11]

Left ventricular thrombosis is not uncommon in PPCM patients with an LVEF < 35%.[31,41] Peripheral embolic episodes, including cerebral embolism, with serious neurological consequences, coronary and mesenteric embolism, have been reported.[42,43] Haemoptysis and pleuritic chest pain may be presenting symptoms of pulmonary embolism.

Prospective registries are needed to accurately quantify the risk of systemic and venous thrombo-embolism.

Investigation of peripartum cardiomyopathy

As PPCM is a diagnosis of exclusion, all patients should have a thorough investigation to identify any alternative aetiology of HF (*Figure 1*). Both cardiac and non-cardiac causes of symptoms should be considered.

Electrocardiogram

An electrocardiogram (ECG) should be performed in all patients with suspected PPCM as it can help distinguish PPCM from other causes of symptoms. Two studies investigated the prevalence of ECG abnormalities in PPCM.[11,40] In 97 South Africans with PPCM, 66% had voltage criteria consistent with LV hypertrophy and 96% ST-T wave abnormalities. On presentation, the ECG of PPCM patients in HF is seldom normal. However, studies with larger sample sizes are needed.

Patients with PPCM are as susceptible to arrhythmias as those with other cardiomyopathies, particularly if LV systolic dysfunction becomes chronic.[44]

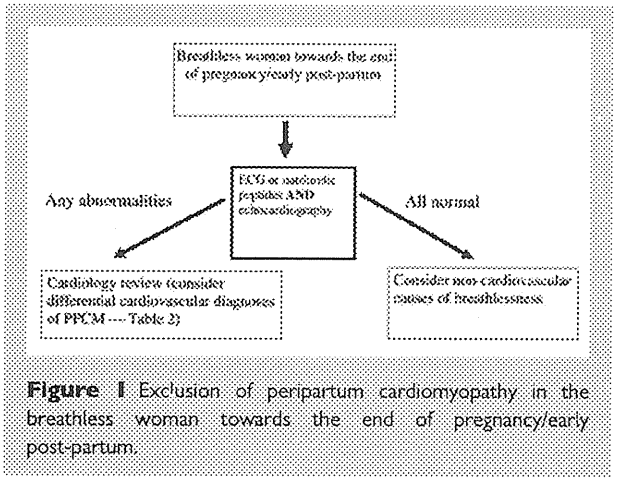

Figure 1 Exclusion of peripartum cardiomyopathy in the breathless woman towards the end of pregnancy/early post-partum.

B-type natriuretic peptide

As a result of elevated LV end-diastolic pressure due to systolic dysfunction, patients with PPCM commonly have an increased plasma concentration of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP).[19] Of 38 patients with PPCM, all had abnormal NT-proBNP plasma levels (mean 1727.2 fmol/mL) when compared with 21 healthy mothers post-partum (mean 339.5 fmol/mL), $P < 0.0001$.

Cardiac imaging

Cardiac imaging is indicated in any peripartum woman with symptoms and signs suggestive of cardiac failure in order to establish the diagnosis and, if PPCM is present, to obtain prognostic information.

Not all patients present with LV dilatation,[2] but a LV end-diastolic diameter >60 mm predicts poor recovery of LV function (as does a LVEF < 30 %).[10,44,45] Imaging is also important in ruling out LV thrombus, particularly where the LVEF is severely depressed.[41] Imaging should be carried out as quickly as possible. Although echocardiography is the most widely available imaging modality, magnetic resonance imaging (MRI) allows more accurate measurement of chamber volumes and ventricular function than echocardiography[46] and also has a higher sensitivity for the detection of LV thrombus.[47] In addition, specific MRI techniques, such as measurement of late enhancement following administration of gadolinium, provide critical information in the differential diagnosis of myocarditis. The European Society of Radiology recommends that gadolinium should be avoided until after delivery, unless absolutely necessary. Breast feeding does not need to be interrupted after administration of gadolinium.[48]

Echocardiography should be repeated before patient discharge and at 6 weeks, 6 months, and annually to evaluate the efficacy of medical treatment. If available, cardiac MRI can also be repeated at 6 months and 1 year to get a more accurate assessment of changes in cardiac function.

Peripartum cardiomyopathy is a diagnosis of exclusion with a large differential diagnosis (*Table 3*). Confusion may arise when cardiac changes accompany pregnancy-induced hypertension (pre-eclampsia). The inclusion of patients with this complication in both the index and prior pregnancies has probably contributed to the discrepancy between studies in the reported characteristics of

Table 3 Differential cardiovascular diagnoses of peripartum cardiomyopathy

	Distinguishing features	Diagnosis/investigation
Pre-existing idiopathic dilated cardiomyopathy (IDC) unmasked by pregnancy	PPCM most commonly presents post-partum, whereas IDC (unmasked by pregnancy) usually presents by the 2nd trimester IDC usually presents during pregnancy with larger cardiac dimensions than PPCM	History, ECG, BNP, echocardiography
Pre-existing familial dilated cardiomyopathy (FDC) unmasked by pregnancy	PPCM most commonly presents post-partum, whereas FDC usually presents by 2nd trimester Positive family history in FDC FDC usually presents during pregnancy with larger cardiac dimensions than PPCM	History, ECG, BNP, echocardiography, genetic testing, family screening
HIV/AIDS cardiomyopathy	HIV cardiomyopathy presents often with non-dilated ventricles	HIV test
Pre-existing valvular heart disease unmasked by pregnancy	Rheumatic mitral valve disease is often unmasked by pregnancy PPCM most commonly presents post-partum whereas valvular heart disease usually presents by 2nd trimester	History, examination, ECG, echocardiography
Hypertensive heart disease	Exclude pre-existing severe hypertension in those presenting before delivery	
Pre-existing unrecognized congenital heart disease	Previously unrecognized congenital heart disease often has associated pulmonary hypertension PPCM most commonly presents post-partum, whereas congenital heart disease usually presents by 2nd trimester	History, ECG, echocardiography
Pregnancy-associated myocardial infarction	History (but can present atypically)	History, ECG, cardiac enzymes, coronary angiography, echocardiography
Pulmonary embolus	History	Medical history, ECG, D-dimers; consider echocardiography, ventilation/perfusion scan, CT pulmonary angiogram

ECG, echocardiogram; HIV, human immunodeficiency virus; BNP, B-type natriuretic peptide.

patients with PPCM and in the timing of presentation. Studies with greater proportions of patients with pre-eclampsia (and of patients with more severe pre-eclampsia) report a far greater frequency of PPCM cases presenting in the last month of pregnancy.[45] In contrast, studies that have attempted to minimize the inclusion of patients with pre-eclampsia (or which only include patients with milder hypertension) show a clear post-partum peak in the presentation of PPCM, most commonly 2–62 days after delivery.[5,14,44]

Management

Management of acute heart failure in peripartum cardiomyopathy

Initial management

The principles of managing acute HF due to PPCM are no different than those applying to acute HF arising from any other cause and are summarized in the recent ESC/ESICM guidelines.[49] Briefly, rapid treatment is essential, especially when the patient has pulmonary oedema and/or hypoxaemia. Oxygen should be administered in order to achieve an arterial oxygen saturation of $\geq$95%, using, where necessary, non-invasive ventilation with a positive end-expiratory pressure of 5–7.5 cm H_2O. Intravenous (i.v.) diuretics should be given when there is congestion and volume overload, with an initial bolus of furosemide 20–40 mg i.v. recommended. Intravenous nitrate is recommended (e.g. nitroglycerine starting at 10–20 up to 200 μg/min) in patients with a systolic blood pressure (SBP) >110 mmHg and may be used with caution in patients with SBP between 90 and 110 mmHg.

Inotropic agents should be considered in patients with a low output state, indicated by signs of hypoperfusion (cold, clammy skin, vasoconstriction, acidosis, renal impairment, liver dysfunction, and impaired mentation) and those with congestion which persists despite administration of vasodilators and/or diuretics. When needed, inotropic agents (dobutamine and levosimendan) should be administered without unnecessary delay and withdrawn as soon as adequate organ perfusion is restored and/or congestion reduced.

Mechanical ventricular support and cardiac transplantation

If a patient is dependent on inotropes or intra-aortic balloon pump counterpulsation, despite optimal medical therapy, implantation of a mechanical assist device or cardiac transplantation should be considered. Since the prognosis in PPCM is different from DCM with a significant proportion of patients normalizing their LV function within the first 6 months post-partum,[50] an LV-assisted device (LVAD) may be considered before listing the patient for cardiac transplantation, although the optimum strategy is not known and discussion

between experts on a case-by-case basis may be helpful. However, implantation of LVAD should certainly be considered as a rescue measure in a life-threatening situation ('bridge to transplantation').

Left ventricular-assisted devices have improved mechanically and experience with their use has increased greatly in recent years, with a large number of LVADs implanted in Europe as either a 'bridge to transplantation' or as 'destination therapy'.[51] Nevertheless, complications related to their use remain high[52] and thrombotic complications may occur more often in patients with PPCM than in others because PPCM is a pro-thrombotic condition. Size of device also remains a limiting factor as not all fully implantable devices will fit into a small woman.

After clinical improvement of the patient and recovery of cardiac function, weaning from the device may be attempted. Since no data are available specifically for PPCM, the criteria developed for DCM should be used.[53] If weaning cannot be attempted, or is not successful, transplantation should be considered.

Published data show that between 0 and 11% of patients with PPCM undergo heart transplantation (*Table 4*). So far, the two largest published series each included just eight patients.[54] Both reported similar outcomes in women with PPCM compared with patients with HF due to other causes.

International registries could greatly increase knowledge of both the use of cardiac transplantation and LVADs in PPCM.

Management of stable heart failure in peripartum cardiomyopathy

Drug therapy

After delivery, PPCM should be treated in accordance with the current ESC guidelines for HF.[49]

During pregnancy, the following restrictions to these guidelines apply.

Angiotensin-converting enzyme-inhibitors and angiotensin-II receptor blockers. Angiotensin-converting enzyme (ACE)-inhibitors and angiotensin-II receptor blocker (ARB) are contraindicated because of serious renal and other foetal toxicity (I-C).[55,56]

Hydralazine and long-acting nitrates. It is believed that this combination can be used safely, instead of ACE-inhibitors/ARBs, in patients with PPCM.[57]

β-Blockers. These have not been shown to have teratogenic effects.[58] β-1-selective drugs are preferred because β-2 receptor blockade can, theoretically, have an anti-tocolytic action.

Diuretics. Diuretics should be used sparingly as they can cause decreased placental blood flow.[13,59] Furosemide and hydrochlorothiazide are most frequently used.

Aldosterone antagonists. Spironolactone is thought to have anti-androgenic effects in the first trimester.[60] Because the effects of eplerenone on the human foetus are uncertain, it should also be avoided during pregnancy.

Antithrombotic therapy. Fetotoxicity of warfarin needs to be considered in all patients with PPCM and LVEF <35%. Unfractionated or low-molecular-weight heparin can be used. Fetotoxicity of warfarin needs to be considered.

Cardiac resynchronization therapy and implantable cardioverters/defibrillators

Peripartum cardiomyopathy patients are not specifically discussed in the section on implanting implantable cardioverters/defibrillators (ICDs) and cardiac resynchronization therapy (CRT) in the 2008 ESC guidelines. Decisions about both the necessity and the timing of ICD and CRT implantation in these patients are extremely difficult and require careful consideration of the pros and cons in the context of the natural history of PPCM. The obvious issues are the cost and potential complications of implanting a device in a patient who may not need it for long because of subsequent recovery of ventricular function. However, if a patient with PPCM has persistently severe LV dysfunction 6 months following presentation, despite optimal medical therapy, many clinicians would advise implantation of an ICD (combined with CRT if the patients also has NYHA functional class III or IV symptoms and a QRS duration >120 ms).

International registries should be structured in a way to include PPCM as a specific diagnosis and thereby to provide information for the future.

New therapeutic strategies

As indicated earlier, bromocriptine may be a novel disease-specific treatment for PPCM.[16] Several case reports have suggested that the addition of bromocriptine to standard therapy for HF may be beneficial in patients with acute onset of PPCM.[16,17,31,61] In addition, a proof-of-concept randomized pilot study of patients with newly diagnosed PPCM presenting within 4 weeks of delivery also showed promising results.[18] Patients receiving bromocriptine 2.5 mg twice daily for 2 weeks, followed by 2.5 mg daily for 4 weeks, displayed greater recovery of LVEF (27% at baseline to 58% at 6 months, $P = 0.012$) compared with patients assigned to standard care (27% at baseline to 36% at 6 months, NS). One patient in the bromocriptine-treated group died compared with four patients in the placebo group.

Bromocriptine has been used for more than 20 years in postpartum women to stop lactation. The use in this period has been associated with several reports of myocardial infarction.[62] Because of these, anti-coagulation therapy is strongly encouraged in PPCM patients with a low LVEF in general and in those taking bromocriptine in particular. Furthermore, with adequate anti-coagulation therapy, thrombo-embolism in all PPCM patients treated with bromocriptine has not been observed.[18,31] However, the data available are limited.

The safety of bromocriptine was also examined in a survey of more than 1400 women who took the drug primarily during the first few weeks of pregnancy. No evidence of increased rates of abortion or congenital malformation was reported.[63]

Before this treatment can be recommended as a routine strategy, there is a need for a larger randomized trial, although some physicians currently add bromocriptine to conventional therapy on an individual basis.

Timing and mode of delivery

Women who present with PPCM during pregnancy require joint cardiac and obstetric care. Possible adverse effects on the foetus must be considered when prescribing drugs. A baseline ultrasound scan is important for subsequent monitoring of foetal growth and well-being.

Timing and mode of delivery in PPCM are important issues currently not addressed by randomized trials or large cohort studies.

Table 4 Prognosis of peripartum cardiomyopathy

Author	Year	Country	Study type	n	Age (mean)	Mortality (mean follow-up)	LV function	Transplantation and VAD	Predictors of mortality
Population-based studies									
Mielniczuk *et al.*[8]	1990–2002	USA	Retrospective, population based	171	30	1.36% in-hospital, 2.05% 'long term'	NA	NA	NA
Brar *et al.*[9]	1996–2005	USA	Retrospective, population based	60	34	3.3% (4.7 years)	NA	0%	NA
Case series									
Sliwa *et al.*[24]	2005–08[a]	South Africa	Prospective, single centre	80, 100% African descent	30	10% (6 months), 28% (2 years)	Mean LVEF: baseline 30%, 24 months 51%	NA	NA
Sliwa *et al.*[14]	2003–05	South Africa	Prospective, single centre	100, 100% African descent	32	15% (6 months)	Mean LVEF: baseline 26%, 24 months 43%, 23% normal LV function after 6 months	NA	Fas/Apo-1 and NYHA functional class independent predictors of mortality
Fett *et al.*[5]	2000–05	Haiti	Prospective, single centre	98, 100% African descent	32	15% (2.2 years)	28% normal ventricular function after 2.2 years	NA	LVEDD and LVEF at presentation not predictive of mortality
Fett *et al.*[72]	1994–2001	Haiti	Prospective + retrospective, single centre	47	32	14% (time period not available)	NA	NA	NA
Duran *et al.*[44]	1995–2007	Turkey	Prospective + retrospective, single centre	33	33	30% (47 months)	24% of patients recovered completely, 39% were left with persistent LV dysfunction	6%	QRS > 120 ms — 1
Modi *et al.*[73]	1992–2003	USA	Single centre, retrospective	44 patients, 39 African-American	NA	15.9%	LV function returned to normal in 35%	NA	LVEF did not predict mortality
Sliwa *et al.*[41]	1996–97	South Africa	Single centre, prospective	29	29	27.6% (6 months)	Mean LVEF: baseline 27%, 6 months 43%	NA	NA
Desai *et al.*[11]	1986–89	South Africa	Single centre, retrospective	99	29	14% (time period not available)	NA	NA	NA
Felker *et al.*[75]	1983–98	USA	Single centre (those referred for cardiac biopsy)	51	29	6% (5 years)	NA	7%	NA
Chapa *et al.*[10]	1988–2001	USA	Single centre, retrospective	32	27	9.6% (time period not available)	59% persistent LV dysfunction (46 months)	6.5%	NA

Witlin et al.[12]	1986–94	USA	Single centre, prospective	28; 21 black, 6 white, 1 Asian	NA	18% (time period not available)	64% persistent LV dysfunction	11%	18%	
Carvalho et al.[76]	1982–88	Brazil	Single centre, prospective	19	26	16% (21 months)	NA	NA		Increased LVEDD and late onset of symptoms
Survey										
Elkayam et al.[77]	2005; 1997–98	USA	Survey (2% response rate)	100; 19% African descent; 67% White	31	9% (2 years)	LV function returned to normal in 54%	4%	NA	

Only studies including >25 patients after 1985 are included. NA, not available; LV, left ventricular; LVEF, left ventricular ejection fraction; EDD, end-diastolic diameter; NYHA, New York Heart Association; ECG, echocardiogram.
[a]Date of publication.

Unless there is deterioration in the maternal or foetal condition, there is no need for early delivery.[64] Urgent delivery, irrespective of gestation, may need to be considered in women presenting or remaining in advanced HF with haemodynamic instability.[65] A team (comprising a cardiologist, obstetrician, anaesthesiologist, neonatologist, and intensive care physician) should discuss the planned mode and conduct of delivery in each case, taking into account the woman's or couples wishes. The primary consideration should be maternal cardiovascular benefit.[64] In general, spontaneous vaginal birth is preferable in women whose cardiac condition is well controlled with an apparently healthy foetus.[64,66] Planned Caesarean section is preferred for women who are critically ill and in need of inotropic therapy or mechanical support.[65] Cardiovascular challenges during labour and delivery include supine hypotension, increased cardiac output, blood loss, and administration of i.v. fluids.[67]

Labour is best conducted in a high care area where there is experience in managing pregnancies with cardiac disease. Principles of management are similar to those for women with other cardiac disease in pregnancy.[68,69] Continuous invasive haemodynamic monitoring is recommended,[70] with continuous urinary catheter drainage. Care must be taken to prevent fluid overload and pulmonary oedema from i.v. infusions. Antenatal oral medications are continued, but heparin should not be given after contractions have started.

The foetus is monitored with continuous cardiotocography. The left lateral position has been suggested to ensure adequate venous return from the inferior vena cava,[66,71] but a sitting-up position may be needed for women in cardiac failure. For analgesia and anaesthesia, an experienced anaesthesiologist should be consulted. Epidural analgesia is preferred during labour as it stabilizes cardiac output.[69] For Caesarean section, continuous spinal anaesthesia and combined spinal and epidural anaesthesia have been recommended.[64] The second stage of labour is a time of increased exertion and strong contractions and prolonged bearing down efforts must be discouraged. Where spontaneous delivery cannot be achieved rapidly, low forceps or vacuum-assisted delivery will reduce exertion and shorten the second stage.[64,67] The third stage of labour can be managed actively, using a single dose of intramuscular oxytocin. Ergometrine is contraindicated.[68] After delivery, auto-transfusion of blood from the lower limbs and contracted uterus may significantly increase pre-load. A single i.v. dose of furosemide is commonly given at this stage. If used, anticoagulants should be restarted in consultation with the obstetrician and anaesthesiologist when post-partum bleeding has stopped and the epidural or spinal catheter has been removed.

Breastfeeding

On the basis of the postulated negative effects of prolactin subfragments described above, breastfeeding is not advised in patients with suspected PPCM, even if this practice is not fully evidence-based. Several ACE-inhibitors (captopril, enalapril, and quinapril) have been adequately tested and can be used in breastfeeding women.[58]

Prognosis

Disappointingly, there are no European studies of the prognosis of PPCM in any population. The worldwide data that are available

suggest that the prognosis of PPCM appears to vary geographically (*Table 4*).[5,8–12,14,24,44,45,72–76] It had been thought that mortality was lowest in the USA. However, a recent study by Modi *et al.*[73] reported recovery of LV function and survival rates of PPCM patients in the USA similar to those reported from Haiti and South Africa. No population-based studies have been performed in the USA. In South Africa, case series have demonstrated that mortality rates have slowly improved over time but 6-month and 2-year mortality rates remain at 10 and 28%, respectively. Single-centre studies in Brazil and Haiti report mortality rates of 14–16% within 6 months. In Turkey, a single tertiary centre reported a mortality rate of 30% over 4-year follow-up.

The proportion of patients in whom LV systolic function returns to normal is more consistent in case series in the USA, Haiti, and Turkey at 23–41%.

Factors that independently predict mortality are not clear.[18] Candidates for further study are NYHA class, LVEF, QRS duration, and late onset of symptoms.

Subsequent pregnancies, counselling, and contraception

Family-planning counselling is very important as women with PPCM are usually in the middle of family building. Only a few studies have reported on subsequent pregnancies of women with a history of PPCM.

In a retrospective investigation, Elkayam *et al.*[77] studied 44 women with PPCM and a subsequent pregnancy and found that LVEF increased after the index pregnancy but decreased again during the subsequent pregnancy, irrespective of earlier values. Development of HF symptoms was more frequent in the group where LEVF had not normalized before the subsequent pregnancy (44 vs. 21%). In addition, three of the women with a persistently low LVEF entering the subsequent pregnancy died, whereas none with normalized LVEF died. There was no perinatal mortality. In a retrospective study, Habli *et al.* compared 70 patients with PPCM, where 21 had a successful subsequent pregnancy, 16 terminated the pregnancy, and the remaining 33 had no subsequent pregnancy. Ejection fraction at diagnosis was higher in those who had a successful subsequent pregnancy, but had no relation to worsening clinical symptoms, which developed in nearly one-third of these patients.[78]

Because of the sparse knowledge in this field, it is difficult to give individual counselling, but with a LVEF of <25% at diagnosis or where the LEVF has not normalized, the patient should be advised against a subsequent pregnancy. All patients should be informed that pregnancy can have a negative effect on cardiac function and development of HF and death may occur.

Women with PPCM need careful counselling about contraception because, as indicated above, they have a high risk of relapse in subsequent pregnancies and terminating pregnancy may not prevent the onset of PPCM.

Intrauterine devices (copper and progestogen-releasing IUDs) are very effective and long-lasting forms of contraception which do not increase the risk of thrombo-embolism. Combined hormonal contraceptives contain oestrogens and progestins (synthetic forms of progesterone) and should be avoided. Oestrogens increase the risk of thrombo-embolism and should be avoided, but intramuscular, subcutaneous, and subdermal forms of progesterone-only contraception appear to be safe.[79] Barrier methods of contraception are not recommended because of their high failure rate. Sterilization options can be considered and include vasectomy, tubal ligation, and insertion of intratubal stents. Because of the psychological impact, women should be counselled carefully and educated about the effective alternatives. In addition, anaesthetic risk must be considered in women with persisting severe LV dysfunction.

Conclusion and way forward

Peripartum cardiomyopathy remains a difficult condition to both diagnose and treat. Prior definitions, emphasizing strict time windows and echocardiographic cut-offs for diagnosis, have probably led to women with the condition being overlooked or misdiagnosed. The rarity of the condition and lack of awareness of it among physicians and nurses/midwives often leads to late diagnosis and treatment. National and international registries, with systematic, prospective collection of data, are needed to better document the incidence, modes of presentation, current treatment practices, complications, and prognosis (including recovery) of PPCM. Multicentre studies are also required to improve the understanding of the pathogenic mechanisms of PPCM, including potential genetic and life-style aspects.

With the recent discovery of an oxidative stress–cathepsin D–16-kDa prolactin cascade in experimental and human PPCM, a specific pathophysiological hypothesis for PPCM has emerged, which may provide the rational basis for a specific therapeutic intervention. This intervention, bromocriptine, which is a drug that blocks the release of prolactin, and which has been used for many years in women in order to stop lactation (or a related compound), should now be tested in a number of prospective randomized controlled trials in women with PPCM.

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分担研究報告書

バソインヒビンと心血管障害

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要旨

周産期心筋症（PPCM）の原因が、授乳ホルモンであるプロラクチンがカテプシン D（CathD）によって酵素切断を受けた異型プロラクチン（バソインヒビン：Vi）であるという報告がある。

この報告を受け我々は、PPCM 及び PPCM と合併率 40%である妊娠高血圧症候群（PIH）患者において、vi 量と CathD 活性を測定した。その結果、健常者と比べ PPCM では有意に Vi 値が高く、PIH においても有意ではないが高い傾向を示した。CathD 活性は PIH、PPCM ともに健常者よりも高い傾向を示した。

A. 背景

プロラクチンとは

プロラクチン（Prolactin：PRL）とは分子量約 23kDa の下垂体前葉ホルモンであり、泌乳促進作用がその名の由来である。構造と機能の類似性から成長ホルモン（Growth hormone：GH）、胎盤性ラクトゲン（Placental lactogen：PL）と同一のファミリーであると考えられている。ヒトでは 199、マウスでは 197 のアミノ酸からなり、構造的には 3 つの S-S 結合と、4 つのαヘリックスを特徴とする。主に脳下垂体前葉のラクトトロフで合成、分泌される。

PRL 分泌は隆起下垂体路ドーパミン（DA）作動性神経が正中隆起で放出する高濃度の DA によって通常抑制されている。ラクトトロフ上のドーパミン D2 レセプター（D2R）に DA が結合することで、PRL の放出が制御されている。また、PRL はプロテアーゼ切断、リン酸化、糖付加を受けた異型 PRL や下垂体以外の末梢組織から発現している異所性 PRL が知られている。これらの機能は本来の PRL と異なり、そのため PRL の機能は 300 種にも及ぶと言われ、その一つに血管新生作用が挙げられる。

血管新生は胎児や発育中には盛んに行われているが、大人になると創傷治癒、女性性周期に伴う子宮内膜の周期的な肥厚、妊娠中の胎盤増殖や子宮内膜肥厚などに限定されている。PRL はホルモンの性質上、妊娠時の胎盤や胎児における血管新生と血液循環コントロールに寄与していると考えられる。

バソインヒビンとは

PRLがプロテアーゼにより11kDa～18kDaに切断されたN末端側異型は血管新生を阻害する。前述したGH/PRLファミリーに属する3ホルモンも、同様にN末端側から2/3以上を含む形で切断を受けると抗血管新生作用をもつペプチドとなる（Figure.A）。これらの抗血管新生作用をもつペプチドはその作用からバソインヒビン（Vasoinhibin：Vi）と名付けられた。

Viの生理作用の研究と共に、Viを産生するプロテアーゼの研究が進んでいる。カテプシンD（Cathepsin D：CathD）はリソソーム性アスパラギン酸プロテアーゼであり、多くの組織に偏在している。このCathDは酸性条件下でヒトPRLを約11、15、16.5、17kDaのViへと切断することが明らかとなっている（Figure.B）。マトリクスメタロプロテアーゼ（Matrix metalloproteinase：MMP）は細胞外マトリックスであるコラーゲンやプロテオグリカン等を分解することで知られている。MMPファミリーの中でもMMP-1, 2, 3, 8, 9, 13はPRLをViへと切断することが分明らかとなっている。一方GH、PLはスブチリシン（Subtilisin）、キモトリプシン（Chymotrypsin）、プラスミン（Plasmin）、トロンビン（Thrombin）によってViとなる。

ViはPRLRに対する結合能をもつが、その結合力は弱くPRLと同様のシグナル伝達は起こらないと考えられている。PRLRとは異なる受容体が存在することが示唆されているが発見には至っていない。現在判明しているViの作用は血管内皮細胞に対して、アポトーシス誘導、細胞増殖抑制、血管拡張抑制、細胞遊走抑制をすることである。

これらPRL-Viがもたらす拮抗した血管新生作用が崩壊することで、疾病が引き起こされる可能性が示されている。糖尿病性網膜症は糖尿病の合併症の一つであり、視野狭窄や視力の低下、失明を招く疾患である。この網膜症は眼底の血管から脆弱な毛細血管が新生することで、網膜の圧迫や硝子体内への出血を起こす。この患者血中ではVi濃度が低いことが示された。この糖尿病性網膜症のようにPRL-Viの均整崩壊によって疾患が引き起こされる例があり、PRLの分泌が昂進する周産期の妊娠関連疾患にViが関与する可能性が考えられている。

周産期心筋症とは

周産期心筋症（Peripartum cardiomyopathy：PPCM）とは、心疾患の既往がなかった女性が、妊娠、出産を契機に心不全を発症する妊娠関連疾患である。心不全に見られる全身浮腫や呼吸困難を主な病態とし、心臓の形態は拡張型心筋症に似て左心室の肥大、拡張を示す。

PPCMの発症原因は不明であるが、ウイルス感染説、異常免疫反応説、妊娠に伴う循環負荷への反応説が挙げられてきた。そして、2007年にHilfiker-kleinerらによってPPCMの発症にPRLが関与する可能性が示された（Hilfiker-Kleiner, D., K. A *Cell,* 128, 589-600. 2007）。

彼女らは、PPCM モデルマウス（心筋の Stat3 ノックアウトマウス）において、心筋内酸化ストレスが上昇し、CathD も産生されていることを示した。そして CathD が血中の PRL を切断し、Vi が心筋細胞の代謝障害や血管内皮細胞のアポトーシスを引き起こしていることを同定した。さらに、このマウスにブロモクリプチンを投与すると心筋症を発症しないこと、実際の周産期心筋症患者の血清中にも Vi が出現していることもあわせて報告した（Figure.C)。さらにアデノウイルスにより Vi を心筋特異的に過剰発現させても周産期心筋症を発症する事を明らかにした。本来の PRL は心筋細胞において、酸化ストレスを減少させ、STAT3 を活性化する。その結果、血管新生と心臓増大によりむしろ周産期心筋症から保護している。このことからも、血管新生における PRL と Vi の相反する作用は、血管新生バランスを維持するための正と負のシグナルにより臨機応変に対応していると言える。

妊娠高血圧症候群とは

そしてもう一つ、Vi との関連が示唆されている疾病に、妊娠高血圧症候群がある。この妊娠高血圧症候群は国立循環器病研究センターの神谷らの報告によると、周産期心筋症との合併率 38% と非常に高い。PRL と妊娠高血圧腎症の関連は 30 年以上前から研究されており、近年には、妊娠高血圧腎症患者尿中 PRL 濃度が健常妊娠者と比較して高く、重度になるにつれて PRL 濃度が上昇する事や、重症妊娠高血圧腎症患者尿中から Vi が検出されたという報告がある。また、妊娠高血圧腎症患者血清中や羊水からも Vi が検出され、その羊水は血管内皮細胞増殖因子（VEGF）による内皮細胞増殖を阻害したという報告もある。さらに、Masumoto らは岡山大学病院において 4 人の重症な妊娠高血圧症の胎盤において、Vi を検出している（Masumoto, A. *Acta Medica Okayama,* 64, 249-255. 2010)。これらの結果は、低酸素濃度により酸性環境になってしまった妊娠高血圧症患者の胎盤において、Cath D による PRL 切断が起こることを示唆しているのかも知れない。

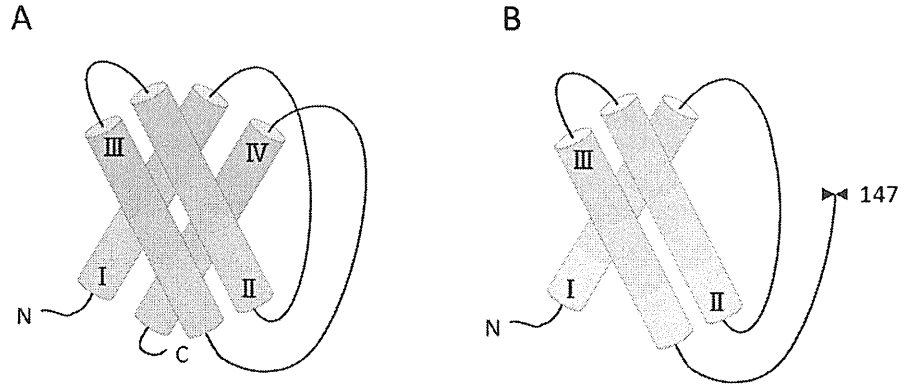

Figure.A PRL、Viの構造模式図
A:未切断PRL
B:Vi

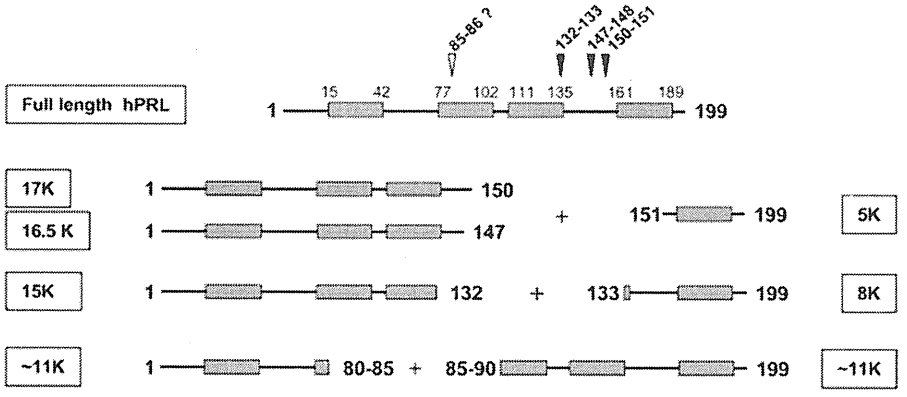

Figure.B ウシCathDによるヒトPRLの切断部位
引用: Piwnica, D., Touraine, P., Struman, I., Tabruyn, S., Bolbach, G., Clapp, C., Martial, J.A., Kelly, P.A., and Goffin, V. (2004). Cathepsin D processes human prolactin into multiple 16K-like N-terminal fragments: Study of their antiangiogenic properties and physiological relevance. Molecular Endocrinology *18*, 2522-2542.

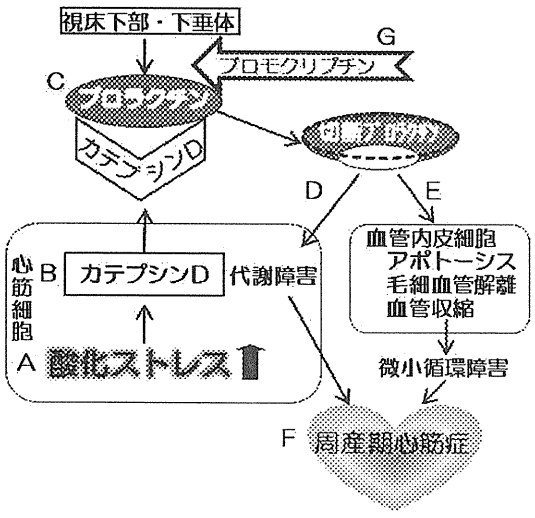

Figure.C 周産期心筋症
発症メカニズム仮説

A) 妊娠に伴い心臓血管形成機能が亢進するが、一部の妊婦では酸化ストレスが増加

B) 酸化ストレス増加に伴いプロラクチンを切断するカテプシンD発現と活性が上昇

C) カテプシンDによりプロラクチンが切断プロラクチンへ変化

D) 切断プロラクチンにより酸化ストレスと活性化カテプシンDの影響が加速

E) 切断プロラクチンが内皮細胞のアポトーシスや毛細血管の解離、心筋細胞内の代謝障害を誘導

F) 心臓機能不全発症

G) ブロモクリプチン投与でプロラクチン発現を抑制すると心機能が改善

B.目的

本研究はPPCMおよびPIH患者血中からVi、CathDを検出することで症状との関連性を見出し、治療の一助とすることを目的とする。

妊娠関連疾患は、妊娠による体調の変化と捉えられ、患者自身が症状を自覚することは少ない。PPCM、PIHは症状を早期に発見して治療を行うことが肝要であるが、発症を予見するような因子は見つかっていない。PPCM患者血中からViが検出されたこと、PIH患者の羊水、尿からViが検出されたことからViが両疾患を予見するリスクファクターと成り得る可能性を模索した。

C.材料と方法

検体

全ての検体は国立循環器病研究センター倫理委員会の承認を受けて採取された。採血、常温静置後、遠心分離することで血清を、EDTA含有真空採血管で採血することで血漿を調整し、-20℃で冷凍保存した。健常妊娠者（Control）とPIHの患者については出産前（産前1日～42日：平均15日）、出産直後（産後1～11日：平均4日）、出産1ヶ月後（産後20～51日、平均33日）の3点で採血した。PPCM患者はおよそ出産2週後にPPCMと診断された時点、診断2週間後（出産1ヶ月後、診断後7～22日：平均15日）、3ヶ月後（診断後66～134日：平均97日）、半年後（診断後150～192日：平均172日）、1年後（診断後356日～410日：平均381日）の時点で採血を行った。また、PPCM患者は症状改善を目的として、PRL分泌抑制剤である、D2R拮抗剤を処置検体を含む。症例数は、Control 12例、PIH 9例、PPCM 10例（うち6例PRL抑制処置）である。

Vi量測定

昨年度、当研究室ではヒト血中からのVi検出法を確立した。本法は、PRL抗体で免疫沈降し、キャピラリー電気泳動により微量なViを検出するものである。本研究では波形グラフで検出されたViの定量化を行った。詳細を以下に示す。

Vi量測定：免疫沈降(Immunoprecipitation：IP)

血清250μlをAlbumin/IgG Removal Kit (Calbiochem, Germany)により前処理の後、Protein G-Agarose (Roche, Switzerland) 50μlと4℃16時間インキュベートしIgGを除去した。ヒトPRL抗体であるanti-hPRL-IC-5, CYTO (National Hormone & Peptide Program, USA)を用いてProtein G-Agaroseキットのプロトコル通りにIPを行った。

Vi量測定：タンパク質の分子量と量の測定

IPサンプル中のタンパク質の分子量と量の測定にはAgilent Protein 80 Kit (Agilent Technologies, USA)を用いた。本実験の結果は波形グラフからなる電気泳動図により示し、ピークが検出された時間を横軸にとり、縦軸に検出された蛍光量(Fluorescence unit：FU)を表示した。

Vi 量測定：ピークの検出と数値化

検出された波形グラフを表計算ソフト Excel によって処理し、Vi の定量化を行った。数値処理に際し、操作の簡便化のために Visual Basic Editor によってプログラミングを行った。

CathD 活性測定

SensoLyte520 Cathepsin D Activity AssayKit（AnaSpec, USA）を用いて測定を行った。キットの原理は、サンプルに CathD 特異的な基質を加え、その分解量を測定するものである。基質の分解によって発される蛍光をマルチラベルカウンターで測定し、検量線から分解した基質の量を算出した。測定はトリプリケートで行い、測定された基質分解量を、inter assay 間で常に測定した健常非妊娠女性を基準として数値（%）を示した。この測定法は Hilfiker-Kleiner らの方法に準じている。

血液、尿検査

症状との関連性を調べるために株式会社エスアールエルに血液検査、尿検査を依頼した。測定項目は PRL、脳性ナトリウム利尿ペプチド（Brain Natriuretic Peptide：BNP）、総タンパク量(Total Protein：TP)、アルブミン(Albumin：Alb)、総タンパク質（Total protein：TP)、クレアチニン（Creatinine：Cre)、ドーパミン(Dopamine：DA)、ノルアドレナリン(Noradrenaline：NA)、アドレナリン(Adrenaline：A)である。BNP は心不全の病態把握に用いられる利尿ペプチドである。Alb は浸透圧の維持や不溶性部室の血液輸送に関わるが、腎不全や全身性浮腫では血清中量が減少する。TP は腎不全、肝機能障害を示す。Cre は ATP 生成のためにクレアチンから作り出される代謝産物である。筋肉で生成された Cre は腎糸球体から濾過され、ほとんど再吸収されることなく尿中に排泄されるため、腎臓での濾過機能の指標となる。DA、NA、A らカテコールアミンは心不全、腎不全で高値をしめす（Table1-1)。

心エコー

これら検査に加えて、NYHA 分類による心不全の程度評価を行い、PPCM 患者に限り心エコーによる心機能の評価を行った。心エコーの結果は左室拡張末期径（LVEDD)、左室収縮末期径（LVESD)、左室短縮率（FS)、左室駆出率（EF）で示した（Table1-2,3)。

検体情報

検体取得時の患者情報を記載した。項目は、年齢、経過日数、身長、体重、喫煙歴の有無、妊娠歴（G：妊娠、P：出産)、分娩方法、分娩時妊娠週数、出生児体重、授乳方法（母乳、ミルク、混合)、内服薬である。

統計解析

群ごとの数値は平均値±標準誤差で示し、有意差検定には t-検定を用いた。Vi および CathD 活性と各検査項目との相関は、正規分布を仮定したピアソンの積率相関係数（r）で示し、相関係数

検定表により有意差を求めた。検定に際して使用

した相関係数検定表を Table1-4 に示す。

略称	血中	尿中
PRL	100～300ng/ml (妊娠時)	-
BNP	～18.4 pg/ml	-
Alb	4.0～5.0 g/dL	-
TP	6.5～8.3 g/dL	-
Cre	0.47～0.79 mg/dL	0.40～1.50 g/day
A	～100 pg/ml	3.4～26.9 μg/day
NA	100～450 pg/ml	48.6～168.4 μg/day
DA	～20 pg/ml	365.0～961.5 μg/day

Table1-1：検査項目と基準値

NYHA 分類	
Ⅰ度	心疾患があるが、身体活動に制約がないもの
Ⅱ度	身体活動に軽度の制約があるもの
Ⅲ度	身体活動が高度に制限されるもの
Ⅳ度	安静時においても症状の出るもの

Table1-2：NYHA 分類

	略称	正常値
左室拡張末期径	LVEDD	35～50mm
左室収縮末期径	LVESD	30～42mm
左室駆出率	EF	27～50%
左室内径短縮率	FS	55～80%

Table1-3：心エコー検査項目と正常値

sample size	significance level		
n	0.10	0.05	0.01
3	0.988	0.997	1.000
4	0.900	0.950	0.990
5	0.805	0.878	0.959
6	0.729	0.811	0.917
7	0.669	0.754	0.875
8	0.621	0.707	0.834
9	0.582	0.666	0.798

Table1-4：相関係数検定表

D.結果

患者別測定結果

Control、PIH、PPCMの症例ごとに、代表3例の測定結果を示した（Figure.1-1-1～9）。

Vi測定

症例、採血時期ごとのVi測定値を示す。検体中から、約11kDa、14kDa、16kDa、18kDaのViを検出した。Controlでは14kDaのViが検出されたが、16kDaのViが検出された例は少数だった。一方PPCMでは全ての検体から16kDaのViが検出された（Figure.1-6）。その内、およそ16kDaのViに限り数値化を行った。PIHでは出産前と出産後1ヶ月でControlよりもViが高い傾向にあった（Figure.1-2A）。PPCMにおいては、採血時期が近いPPCM診断時をControlの出産後と比較し、PPCM診断2週間後をControl出産1ヶ月後と比較した。その結果、PPCMでは両時期ともにControlよりも有意に高いVi測定値を示した（Figure.1-2B）。また、PPCMでは診断3ヶ月後、半年後、1年後においてもVi値が高い傾向にあった（Figure.1-4A）。加えて、PRL抑制処置を施したPPCMでは、未処置のPPCMと比べてViの低下が見られたが、Controlよりは高い傾向にあった（Figure.1-5）。

CathD活性

症例、採血時期ごとのCathD活性平均値を示す。PIHでは、出産前、出産後、出産1ヶ月後を通してControlよりもCathD活性が高い傾向にあった（Figure.1-3A）。PPCMでは診断時、診断2週後においてControlよりも有意に高いCathD活性を示した（Figure.1-3B）。

Viと測定因子の相関

測定因子の中で、Vi値と有意な相関関係にあった因子を示した。PPCM診断時において、Vi値とFS（左室内径短縮率）が有意な負の相関関係を示した（Figure.1-7）。

CathD活性と測定因子の相関

測定因子の中で、CathD活性と有意な相関関係にあった因子を示した。PIH出産前において、収縮期血圧（$r = 0.763, p < 0.05$）、血中BNP（$r = 0.813, p < 0.01$）、新鮮尿中A（$r = 0.666, p < 0.05$）、新鮮尿中NA（$r = 0.621, p < 0.10$）がそれぞれ有意な相関を示した（Figure.1-8）。