

Peripartum cardiomyopathy: still unknown

The current state of knowledge

Kardiomiopatia połogowa – wciąż niepoznana. Aktualny stan wiedzy

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Abstract

Peripartum cardiomyopathy (PPCM) is defined as idiopathic cardiomyopathy which occurs at the end of pregnancy or in the first few months after delivery, with symptoms of heart failure (HF) secondary to left ventricular dysfunction, and at the same time there is no other cause for this condition. The pathomechanism of the disease has not yet been fully understood, but it is probably based on the interaction of complex factors. The clinical course of PPCM varies from life-threatening acute heart failure to mild symptoms resembling the symptoms typical of the perinatal period. In Europe, PPCM is a rare disease but there are areas of the world where it occurs in one in every 300 cases. The treatment of PPCM is similar to that of HF with reduced ejection fraction. However, it is important to exclude drugs with teratogenic effects during pregnancy. The inclusion of bromocriptine in PPCM therapy seems to be justified, and in some cases improves the prognosis.

Key words: peripartum cardiomyopathy, PPCM, heart failure, pregnancy, bromocriptine

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Introduction

The first reports of peripartum cardiomyopathy (PPCM) were presented in the mid-19th century when Virchow et al. [1] described a number of post-mortem examinations of women who had died during the perinatal period. At that time, the researchers did not know the cause of death, but they noticed that the patients had myocardial degeneration. It took several decades before Gouley et al. [1] associated the perinatal period with cardiomyopathy in 1937. In their study, seven cases of pregnant patients with acute heart failure (HF) were described, of whom four died. Dilated cardiomyopathy at a late stage of pregnancy was characteristic for each case, which persisted also after delivery. Post-mortem examinations of deceased patients showed

myocardial hypertrophy with areas of severe necrosis and fibrosis. In 1971, PPCM was named for the first time by Demakis and Rahimtooli [1, 2]. New criteria for PPCM have been developed in subsequent years thanks to the development of diagnostic techniques that include echocardiography and molecular biology, and the discovery of new biomarkers. This article presents the current state of knowledge regarding PPCM.

Definition of PPCM

The current definition of PPCM was created by the Heart Failure Association of the European Society of Cardiology in 2010. It is idiopathic cardiomyopathy, which manifests as HF secondary to left ventricular dysfunction without other

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Table 1. Major factors involved in the development of peripartum cardiomyopathy (PPCM)

Pathogenesis of PPCM	Brief description
Genetic/environmental factors	Epidemiological data on the increased incidence of PPCM in some areas and among selected ethnic groups, especially Africans or African-Americans [3]. Some studies suggest association with familial dilated cardiomyopathy [5, 6]
Infectious/autoimmune factors	Presence of the viral genome has been evidenced in cardiomyocytes of women with PPCM (31%) [7] Increase in the concentration of inflammatory markers is observed in PPCM: TNF- α , interferon γ , interleukin 6, CRP [8]
Factors related to angiogenesis	At the end of pregnancy, the placenta begins to secrete anti-angiogenic substances. In the case of impaired cardiac protective mechanisms against anti-angiogenic factors or an excess of these factors, subclinical dysfunction of cardiomyocytes may occur [8]
Factors related to prolactin	Physiologically, prolactin protects the endothelium and promotes angiogenesis; however, under increased oxidative stress caused by pregnancy, short form of prolactin may be generated that is toxic to cardiomyocytes [9]

TNF- α – tumor necrosis factor α ; CRP – C-reactive protein

causes. It occurs at the end of pregnancy or in the first few months after delivery. For a diagnosis of PPCM, the ejection fraction should be $\leq 45\%$, although there is no obligation to document the enlargement of the left ventricle dimension.

PPCM is a diagnosis of exclusion. In contrast to the previous definition from 2000, it does not take into account the exact time interval of the disease (previously it needed to occur between the final month of gestation and 5–6 months after delivery), or specific echocardiographic criteria (previously: lower ejection fraction $< 45\%$, and shortening fraction $< 30\%$ and enlargement end-diastolic dimension of the left ventricle cavity $> 2.7 \text{ cm/m}^2$ of the body surface). The current definition is less restrictive, thus reducing the chances of missing a patient with this disease [3, 4].

Pathogenesis

Probably there is a complex mechanism that causes PPCM, and therefore there is no other theory that can explain its development. The literature describes many factors involved in the development of the disease. Some of the more important ones are presented in Table 1 [3, 5–9]. This paper describes two pathomechanisms that seem to be the most important in PPCM [6].

Prolactin

Physiologically, prolactin with a mass of 23 kDa protects the endothelium and promotes angiogenesis. In the period of oxidative stress caused by pregnancy for example, a shorter form of 16 kDa with a strong cardiotoxic effect may be formed. STAT-3 is a protein responsible for the protection of the myocardium by the induction of antioxidant enzymes. The disruption of STAT-3 function leads to an intensification of oxidative stress and activation of several enzymes,

including cathepsin D which is responsible for the formation of a prolactin shorter form (16 kDa). It has been shown that in women with PPCM, the level of STAT-3 protein expression is reduced, and the production of 16 kDa prolactin is increased [9]. One of the new strategies for treating PPCM is based on this knowledge. It involves the addition to standard HF therapy of bromocriptine, a prolactin-inhibitor. Currently, the effects of therapy are satisfactory, and the 2018 guidelines of the European Society of Cardiology (ESC) assigned the class of recommendation IIa for bromocriptine treatment, with the reliability of data at level C [10].

sFLT1

At the beginning of pregnancy, the process of angiogenesis is increased. However, this tendency changes with the passage of time and especially in the perinatal period when the placenta begins to secrete anti-angiogenic substances. These include a soluble fms-like tyrosine kinase-1 (sFLT1) [11]. In a normal pregnancy, these are physiological processes and do not cause any complications. However, there may be subclinical dysfunction of cardiomyocytes in abnormal conditions of sFLT1 excess or when the mechanisms protecting the heart against antiangiogenic factors are compromised. PPCM patients have been shown to have a significantly elevated level of sFLT1. Moreover, multiple pregnancy and pre-eclampsia both increase the secretion of this antiangiogenic. This may explain why multiparous women with pre-eclampsia are more often diagnosed with PPCM [10]. An increase of the angiogenesis process by the administration of vascular endothelial growth factor (VEGF) has been proposed for PPCM treatment. Previous attempts were made only on mice, and the use of VEGF alone did not give the expected results. Only treatment with a combination of VEGF and bromocriptine turned out to be satisfactory [12].

Epidemiology

The prevalence of PPCM is characterised by significant geographical variations. In many areas, the actual number of cases is unknown and further research is needed. The highest density of recognised PPCMs has been recorded in Nigeria (1:100 cases) and Haiti (1:300 cases). For comparison, the disease affects 1:1,000–1,500 women in Germany, 1:1,000 in South Africa and 1:2,500–4,000 in the USA [3, 10]. From the cited data described in 2010 by Sliwa et al. [3], it is clear that African origins predispose to a more frequent occurrence of peripartum cardiomyopathy. The average age of PPCM incidence rate is 27–33 years, depending on the region. Indeed, compared to older publications, this average age has increased in recent publications [3]. In addition, there has also been an increased incidence of PPCM over recent years – from 1 in 4,350 women in 1990–1993 to 1 in 1,229 in 2000–2002. This increase may be attributable to several factors: the later age at which women are becoming pregnant, an increase in the number of multiple pregnancies, developing access to methods of assisted reproduction, and increased recognition of PPCM [13].

Clinical presentation

Difficulties associated with making the right diagnosis are related to the fact that the clinical picture of PPCM resembles the perceived symptoms typical of the final period of pregnancy or the effort associated with the birth itself. Often the symptoms do not have a high severity, which makes it difficult to make the right diagnosis [3].

The vast majority of patients develop symptoms in the first four months after delivery (78%), and only 9% show disease onset in the last month of pregnancy. The remaining 13% of cases refer to women diagnosed with PPCM earlier than one month before delivery or later than four months after delivery [3].

Typical symptoms include shortness of breath, swelling of the lower limbs, orthopnoea, fatigue, chest pain, reduced exercise tolerance, and heart palpitations. In the study of Patel et al. [14] from 2015, 19 Swedish patients were chosen (according to the ESC criteria from 2010) to determine the most common symptoms of PPCM. All subjects reported more than one symptom. The most common complaints were: dyspnoea (18 out of 19), fluid retention (15 out of 19), excessive fatigue (14 out of 19), and a persistent cough (eight out of 19). The study also looked at mental symptoms: 11 out of 19 women reported at least one of the following symptoms: feelings of unavoidable death (seven), panic attacks (five), anxiety (five) or fear (fear) [14].

Table 2. Selected biomarkers for peripartum cardiomyopathy (adapted from [8, 18, 19])

Biomarker's name	Level in PPCM
micro-RNA 146	Increased
Endothelial cells and monocyte microparticles	Increased circulating levels in the blood
sFLT1	Increased in late pregnancy and rapid decrease after delivery (the threshold values are difficult to define)
Inflammatory proteins: CRP, TNF- α , interferon γ , interleukin 6	Increased
Prolactin 16 kDa	Increased
Catepsin D	Increased
Relaxin 2	Decreased (the threshold values are difficult to define)
Oxidized LDL	Increased
TGF- β_1	Decreased

PPCM – peripartum cardiomyopathy; sFLT1 – soluble fms-like tyrosine kinase-1; CRP – C-reactive protein; TNF- α – tumor necrosis factor α ; LDL – low-density lipoprotein; TGF- β_1 – transforming growth factor β_1

Diagnosis of PPCM

A diagnosis of PPCM is based on the exclusion of other HF causes [15]. The disease should be suspected in all peripartum women with symptoms of HF or those who have a delay in returning to their pre-pregnancy baseline [16]. Two key studies that must be performed when PPCM is suspected are echocardiography and N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP). Further testing for PPCM is necessary if the left ventricular ejection fraction (LVEF) is $\leq 45\%$ or the level of natriuretic peptides is increased [12]. The useful tests include chest radiograph (this can show enlargement of the heart, low blood circulation and pleural effusion), and ECG (left ventricular overload, non-specific changes in ST segments, prolonged QT interval or large QRS complexes). MRI may be performed as an addition to echocardiography [17] and a myocardial biopsy in suspected HF with infectious aetiology [16].

In addition, newly discovered biomarkers appear to be promising in women suffering from PPCM and could be helpful in the differential diagnosis. Selected ones are presented in Table 2 [8, 18, 19].

Treatment

According to the latest guidelines of the European Cardiac Society (ESC) from 2018, the treatment of PPCM does not

Table 3. Selected drugs used in peripartum cardiomyopathy (adapted from [15, 16])

Class of drugs	Non-proprietary name	Comment
ACEI	Captopril	Contraindicated during pregnancy (risk of kidney damage, malformations and hypotension in the fetus)
	Enalapril	
	Ramipril	There is no data on the risk during pregnancy
Sartans	Candesartan	Contraindicated during pregnancy and breast-feeding
	Valsartan	
Potassium-sparing diuretics	Spironolactone	Contraindicated during pregnancy and breast-feeding (possible antiandrogenic effects in the fetus)
	Eplerenon	Negative effects have not been fully understood (category B according to the FDA classification)
Beta-blockers	Extended-release metoprolol	Low risk of bradycardia and respiratory failure in the newborn
	Carvedilol	Cardioselective drugs preferred during pregnancy
	Atenolol	Risk of low birth weight and fetal bradycardia if administered in II or III trimester
Vasodilators	Hydralazine	In combination with nitrates as a safe alternative to ACEIs/ /sartans during pregnancy
	Nitroglycerin	Risk of hypotension
Diuretics	Hydrochlorothiazide	Risk of reduced placental blood flow. Use only in patients with signs of congestion in the pulmonary circulation
	Furosemide	Use only in patients with signs of congestion in the pulmonary circulation
Inotropes	Digoxin	Consider in patients with low EF. Keep in mind the risk of toxicity when used in high doses
	Dobutamine	Insufficient evidence for safe use during pregnancy
	Milrinone	
Anticoagulants	Warfarin	Risk of abnormal development of the bones of the nose, limbs, joint cartilage, as well as the risk of ear, eye and central nervous system anomalies
	Low-molecular-weight heparin	Use in patients treated with bromocriptine. Implement treatment if EF < 35%
Prolactin inhibitors	Bromocriptine	Increased thromboembolic risk; recommendation class IIa, level of evidence C Dosing schedule: 2.5 mg twice daily for 2 weeks, and then 2.5 mg once daily for 6 weeks
Heart rate lowering agents	Ivabradine	Use in patients with high heart rate Contraindicated during pregnancy and breast-feeding
ARNI	Sacubitril/valsartan	Contraindicated during pregnancy and breast-feeding

Red — drugs contraindicated during pregnancy, blue — there are no data indicating fetal toxicity; ACEI — angiotensin-converting enzyme inhibitors; ARNI — angiotensin receptor neprilysin inhibitors; EF — ejection fraction; FDA — Food and Drug Administration

deviate from the recommendations used in acute HF, cardiogenic shock, or chronic HF of a different aetiology. It is important to exclude drugs that may have a harmful effect on the developing foetus or those that are contraindicated during breastfeeding [angiotensin-converting enzyme inhibitors (ACEI), sartans, angiotensin receptor neprilysin inhibitor (ARNI), potassium-sparing diuretics, warfarin, and ivabradine] [15]. Selected contraindicated medications are

presented in Table 3 [15, 16]. A pregnant woman with PPCM should be under the combined care of a cardiologist and an obstetrician, and possible complications for the foetus should be observed in ultrasound [3].

Pregnancy in a patient with cardiovascular disease is always at high risk of complications. Therefore, it is necessary to inform the patient that the frequency of ultrasonography of the foetus will be different from the standard procedure

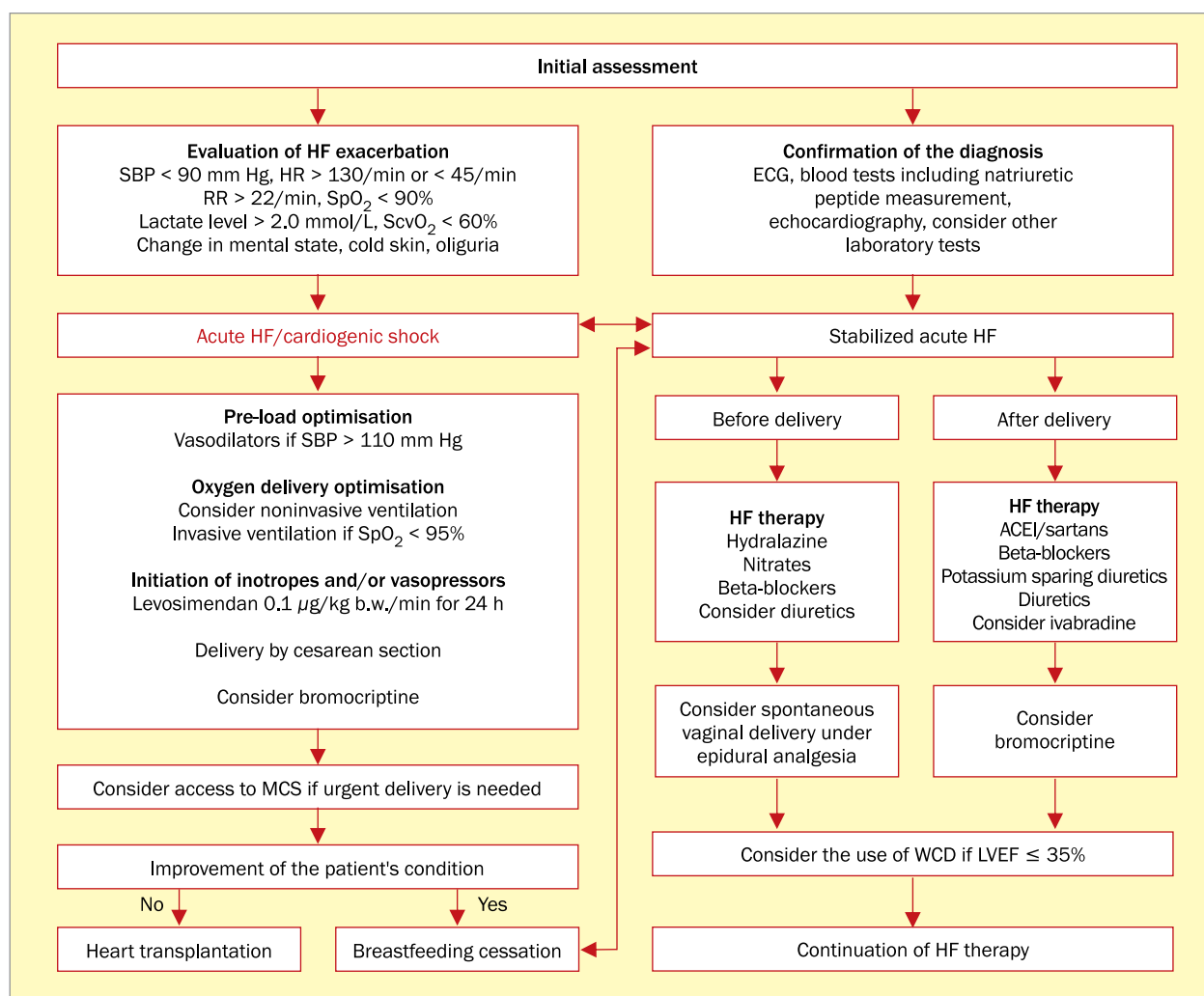


Figure 1. Algorithm for the management of peripartum cardiomyopathy (PPCM) (adapted from [15]); SBP – systolic blood pressure; HR – heart rate; RR – respiratory rate; SpO₂ – arterial blood oxygen saturation; ScvO₂ – central venous oxygen saturation; MCS – mechanical circulatory support; ECG – electrocardiography; HF – heart failure; ACEI – angiotensin-converting enzyme inhibitors; WCD – wearable cardioverter-defibrillator; LVEF – left ventricular ejection fraction

for an uncomplicated pregnancy. Until the 28th week of pregnancy, the test should be performed once a month for patients in New York Heart Association (NYHA) class I and II and every two weeks or more often for those in NYHA class III and IV. After the 28th week of pregnancy, the examination should take place every week until delivery [20].

In case of acute severe HF, one should bear in mind the need for premature termination of pregnancy with access to a mechanical circulatory support system (MCS) and the implementation of lung maturation accelerating treatment in the foetus beyond the 23rd week of pregnancy + 5 days [15]. Furthermore, the inclusion of intensive acute HF treatment is obligatory.

The principles of PPCM treatment are presented in Figure 1 [15], including the period before and after delivery.

In addition to the standard procedure, it is also worth paying attention to the possibility of bromocriptine inclusion for the treatment of PPCM. According to the 2018 ESC guidelines, the addition of bromocriptine to standard HF therapy favourably affects left ventricular function and improves prognosis in women with a severe PPCM course [15]. For an uncomplicated PPCM, a dose of 2.5 mg per day is recommended for at least a week. Patients with ejection fraction < 25% and/or cardiogenic shock may be considered for a therapy of 2.5 mg twice daily for two weeks, followed by 2.5 mg once daily for six weeks. When treating with bromocriptine, it is important to remember about anticoagulation (prophylactic doses of low molecular weight heparin) [15]. Studies have shown very good treatment effects: in a six-month follow-up, total recovery

Table 4. Summary of the most important data from the papers cited in this article

Authors	Follow-up period, country	No. of patients with PPCM	Mean age at diagnosis	EF/NYHA	Recoveries	Recurrences	Deaths (%)	Other	Complications
Sliwa et al. [23]	Start on March 31, 2016 43 countries	411	30.07	LVEF: 32.2% NYHA I-II: 31.2% NYHA III: 36.6% NYHA IV: 32.2%	n/a	n/a	2.4% Heart failure: 60% stroke: 10% sudden cardiac death: 30%	PM: 0.7%; ICD: 1.2%; CRT: 0.2%; VAD: 2.0%	Heart failure at 1 month after diagnosis: 86.9% Hemorrhagic stroke: 0.7% Ischemic stroke: 1.0% Deep-vein thrombosis: 1.5% Pulmonary embolism: 2.4% Upper limb arterial thromboembolism: 1.0% Lower limb arterial thromboembolism: 0.2% Prematurely terminated pregnancy: 8.8%
Hilfiker-Kleiner et al. [24]	2005–2015 Germany, Scotland, South Africa	34	27 ± 7% with LVEF < 50% 29 ± 5% with LVEF > 50%	31 ± 7%	18/34	16/34	2.9% 25% due to recurrence during the next pregnancy	-	Postpartum hemorrhage: 22.9% Chronic HF with LVEF < 35%: 1.83% MCS: 3.28%
Ersbøll et al. [25]	2005–2014 Denmark	61	31.7 ± 6.3	26.7 ± 9.0%	32/61	n/a	3.8%	-	MCS and heart transplantation: 3.28% MCS and death: 1.64%
Perveen et al. [26]	2012–2013 Pakistan	22	27.4	44.7 ± 2.3% in recovered patients (LVEF > 50%) 29.7 ± 8.0% in non-recovered patients (LVEF < 50%)	14/22	n/a	9.1%	-	n/a
Wu et al. [27]	1997–2011 Taiwan	925	30.4 ± 5.7	n/a	n/a	n/a	Cardiac deaths: 3.3% overall mortality: 7.8% MACE: 7.0%	Heart catheterization: 8.1%; IABP: 0.8%; ECMO: 4.1%	Heart transplantation: 0.5% Cerebrovascular accident: 0.4% Myocardial infarction: 0.1% Rehospitalization due to HF: 3.6% Dialysis resumption: 0.2%
McNamara et al. [28]	2009–2013 USA	100	30 ± 6	LVEF: 0.35 ± 0.10% NYHA I: 12% NYHA II: 46% NYHA III: 25% NYHA IV: 17%	72%	n/a	4.4%	-	At 12 months, out of 91 women: LVAD: 4 patients, of whom 2 died and 1 required heart transplantation
Kolte et al. [29]	2004–2011 USA	34 219	30.3 ± 7.0	n/a	n/a	n/a	1.3% – in-hospital mortality	-	Cardiac arrest: 2.1% Heart transplantation: 0.5% MCS: 1.5%
Kamiya et al. [30]	2007–2008 Japan	102	32.7	31.6 ± 12.0%	63%	n/a	4%	LVAS [LVAD?]: 2%	Acute pulmonary edema: 1.8% Thromboembolic disease: 6.6% Cardiogenic shock: 2.6% Pulmonary edema: 0.9% Acute HF: 0.9%
Pillarsetti et al. [31]	1999–2012 USA	100	30 ± 6.5	28 ± 9% NYHA I: 30% NYHA II: 17% NYHA III: 45% NYHA IV: 8%	42%	35 became pregnant again and 11% of them died	11%	VAD: 1% ICD: 13% including 2 CRT-D	Sudden cardiac arrest: 0.9% Exacerbation of chronic HF: 0.9% Preterm delivery: 40% Heart transplantation: 2%

PPCM – peripartum cardiomyopathy; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; n/a – not available; MACE – major adverse cardiac events; PM – pacemaker; ICD – implantable cardioverter-defibrillator; CRT – cardiac resynchronization therapy; VAD – ventricular assist device; MCS – mechanical circulatory support; IABP – intra-aortic balloon pump; ECMO – extra corporeal membrane oxygenation; ESC – European Society of Cardiology; HF – heart failure; LVAD – left ventricular assist device; CRT-D – cardiac resynchronization therapy with a defibrillator

was found in 60% of cases, with 0% mortality. Patients did not require a transplant or the use of cardiac devices [21].

Prophylaxis and further management

Contraception

Patients who have been diagnosed with PPCM are of childbearing age. The associated risk of PPCM recurrence, especially in the absence of ejection fraction parameters normalisation, makes it necessary to implement an effective and relatively safe method of contraception [3].

According to the 2018 European Society of Cardiology (ESC) guidelines [15], ethinyl oestradiol drugs are contraindicated in patients with PPCM due to the high risk of thromboembolic complications. Sliwa et al. described the possible consequences [3]. In their opinion, oral two-component agents combining oestrogen and progesterone derivatives are not a good method due to the adverse thromboembolic profile. Gestagens are an alternative to these measures. It is believed that they have little effect on the risk of thromboembolism in the case of subcutaneous implants and injections, and pose no thromboembolic risk in oral form and in intrauterine devices. The safety profile and high efficacy of levonorgestrel available in the form of an intrauterine system and a subcutaneous implant are particularly appreciated [15].

It should be remembered that the right form of contraception is the key to prevent the recurrence of PPCM. It is necessary to present a patient with possible ways of preventing another pregnancy. During the choice of optimal contraceptive therapy, we are obliged to take into account both the medical indications and the comfort in use for the woman.

Breastfeeding

In a case of diagnosed PPCM, breastfeeding cessation should be considered. Persistent high levels of prolactin during lactation may adversely affect the course of the disease and prognosis of the patient. Therefore, patients with significant left ventricular systolic dysfunction should not breastfeed and should be considered for bromocriptine. An exception to the above recommendation is a situation where a small impairment of left ventricular systolic function coexists with poor access to modified milk and unfavourable environmental conditions. In these circumstances, sustaining breastfeeding seems to be justified [22].

Follow-up

It is recommended that echocardiography should be performed every six months until LVEF returns > 50%. In women

with restored left ventricular function, which remain stable after HF medication reduction, an annual follow-up visit is recommended for the next 10 years [22].

Prognosis

Although the clinical course of PPCM may vary considerably, the general prognosis of patients after normal treatment is good. About 50% of women have a full recovery (defined as LVEF > 55% and NYHA class I), while 35–40% improve (defined as an increase of LVEF by more than 10% and improvement of at least one NYHA class) [12]. Based on the literature, mortality varies between 2% in Germany and 12.6% in South Africa 1–6 months after delivery. The mortality rate between six and 12 months after childbirth ranges from 4% to 14%; for women of African descent it is 12–14%. Subsequently, in the range of 1–5 years, mortality in a population of 182 women in the United States was 7% at the time of the follow-up examination in the 19th month. For African-American patients, this rate was higher and in the second year of the study, the mortality rate was 28% in South Africa, 16% in the USA and 15% in Haiti. Between the second and the fifth year, these values varied significantly depending on the region, and ranged from 0–6%, in France and the United States, to 15–30% in China, Brazil, Turkey, South Africa and the Philippines. There is little data available for a prognosis of more than five years. In this period, mortality is 7–16% in India and 8.3% in Malaysia [8].

In addition, there have as yet been no publications on the long-term prognosis for patients after heart transplantation and with an implanted left ventricle assist device (LVAD). Table 4 summarises the most important information from work on PPCM [23–31].

Conclusions

In recent years, the awareness about PPCM has risen, and a growing interest was sparked by recent publications. Although data on the extent of disease prevalence in most parts of the world is lacking, and many issues remains unexplained, in recent years a number of findings have been made that have contributed to improved PPCM diagnosis and treatment. New biomarkers have been proposed, new underlying mechanisms contributing to its onset have been discovered, and bromocriptine treatment has been introduced. It has been documented that bromocriptine in PPCM therapy is beneficial, although more research is needed on the use of this medicine.

Streszczenie

Kardiomiopatię połogową (PPCM) definiuje się jako idiopatyczną kardiomiopatię, która występuje pod koniec ciąży lub w pierwszych kilku miesiącach po porodzie z objawami niewydolności serca (HF) wtórnie do zaburzeń czynności lewej komory i jednocześnie nie stwierdza się żadnej innej przyczyny tego stanu. Patomechanizm choroby nie został w pełni poznany, natomiast prawdopodobnie opiera się na działaniu złożonych czynników. Przebieg kliniczny PPCM jest zróżnicowany: od zagrażającej życiu ostrej HF po łagodne objawy naśladujące dolegliwości charakterystyczne dla okresu okołoporodowego. W Europie PPCM jest dość rzadką chorobą, natomiast są rejony, gdzie występuje z częstością 1/300 przypadków (Haiti). Leczenie PPCM jest podobne jak dla HF z obniżoną frakcją wyrzutową, jednak ważne jest wykluczenie leków o działaniu teratogennym w trakcie trwania ciąży. Włączanie bromokryptyny do terapii PPCM wydaje się zasadne i w niektórych przypadkach poprawia rokowanie.

Słowa kluczowe: kardiomiopatia połogowa, PPCM, niewydolność serca, ciąża, bromokryptyna

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