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Peripartum women with dyspnea in the emergency department

Is it peripartum cardiomyopathy?

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Abstract

Peripartum cardiomyopathy (PPCM) is life-threatening and its diagnosis is a challenge. We highlight the clinical characteristics and bio-markers of PPCM and the proper differential diagnosis of peripartum dyspnea to aim to make an early diagnosis available.

We analyzed 262 peripartum patients with dyspnea, and summed up the final diagnosis. The clinical data of the control group and the PPCM group as well as before and after the treatment of the PPCM group were compared.

In total, 147 (56%) of the perinatal patients were physiologic dyspnea of pregnancy; only 11 (4%) patients met the PPCM diagnostic criteria. Compared with the basic baseline characteristics between the PPCM group and control group, patients with PPCM had a higher heart rate, and the white blood cell, high-sensitivity C-reactive protein (hs-CRP), and B-type natriuretic peptide (BNP) levels were markedly elevated, whereas PaO_2 and left ventricular ejection fraction (LVEF) were lower. The heart rate, CRP and BNP levels were lower at the follow-up compared with the pretreatment. Patients who were followed up showed significant improvements in the LVEF and New York Heart Association function class.

We standardized the symptoms of dyspnea for calculating, and analyzed the diagnostic efficacy of laboratory indicators. The research highlighted that the use of echocardiography and disease-specific bio-markers may aid in the diagnosis and management.

Abbreviations: ALB = albumin, BNP = B-type natriuretic peptide, CK-MB = creatinine kinase-MB isoenzyme, ED = emergency department, FC = function class, hs-CRP = high-sensitivity C-reactive protein, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, PPCM = peripartum cardiomyopathy, TNI = cardiac troponin I, WBC = white blood cell.

Keywords: bio-marker, diagnosis, peripartum cardiomyopathy

1. Introduction

Dyspnea is a very frequent presentation of peripartum women with complaints in the emergency department (ED). The symptom during the normal pregnancy may be associating with many diseases, which implies a long list of possibilities, even some rare fatal complications of pregnancy, such as peripartum cardiomyopathy (PPCM). PPCM is a potentially life-threatening dilated cardiomyopathy of an uncertain origin that can occur in pregnant or postpartum women with no preexisting heart disease. Overall, the PPCM diagnosis is commonly delayed until patients experience major symptoms or adverse events including ventricular arrhythmias and venous or arterial emboli.[1] PPCM is a diagnostic challenge to the emergency physician. Therefore, we highlight the clinical characteristics and specific bio-markers of PPCM and the proper differential diagnosis of peripartum dyspnea from a single medical center, in an attempt to make an early diagnosis available in the future.

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2. Materials and methods

2.1. Patient population

This clinical trial was designed as a retrospective observational study. From October 2009 to October 2016, we analyzed 262 peripartum patients (from prenatal 3 months to postpartum 5 months) with dyspnea hospitalized in our ED. It is a comprehensive tertiary hospital in Tianjin, China, and our ED provides services for approximately 130,000 emergency visits each year. Consent was obtained from all participants. Ultimately, some causes of dyspnea, such as malignancy, severe liver and kidney dysfunction, poisoning, and chest trauma, had to be excluded.

For control group, the 11 patients were random selected from 147 patients who were eventually diagnosed with physiologic dyspnea of pregnancy.

2.2. Clinical data collection

For those who met the inclusion criteria, an investigation of epidemiology and the lifestyles of patients were inquired about in great detail.

2.3. Laboratory tests

For the patients, a routine physical examination was performed, and blood samples were collected to measure the complete blood counts, electrolytes, hepatic and renal function, arterial blood gas analysis, high-sensitivity C-reactive protein (hs-CRP), cardiac troponin I (TNI), creatinine kinase-MB isoenzyme (CK-MB), and B-type natriuretic peptide (BNP). The test for TNI, CK-MB, and BNP was used with the Alere Triage MeterPro by fluorescence immunoassay. At the same time, electrocardiography, echocar-

diography, and chest X-ray (obtaining permission from patients) were also conducted within 24 hours after admission. Studies of 2-dimensional Doppler echocardiography were carried out with a ViViD7 cardiac ultrasound unit as well as a 2.5-MHz sensor (GE, Erie, PA). Acute views of Simpson biplane method were used to measure the left ventricular ejection fraction (LVEF).

2.4. Diagnostic criteria

In 1971, Demakis was the first to propose PPCM diagnostic criteria, which refer to heart failure for 6 months, starting from the last month before laboring to the fifth month after giving birth.[2] Currently, most scholars use the 2010 redefinition of PPCM proposed by the Heart Failure Association of the European Society of Cardiology:[3] PPCM is an idiopathic cardiomyopathy conferred with heart failure secondary to left ventricular (LV) systolic dysfunction near the end of a pregnancy or during the months following the delivery, where no other cause of heart failure can be found; it is a diagnosis of exclusion, with the LVEF almost always reduced to below 45% but not consistently associated with LV dilatation. Other disease diagnoses comply with Goldman Cecil Medicine, 24th edition.

2.5. Improvement standard

We classified the patients with PPCM into improved provided that LVEF according to the echocardiography was elevated to 10 absolute units or in the event that the New York Heart Association (NYHA) classification increased by one class. We categorized patients as not improved provided that these patients exhibited any of the parameters, for instance LVEF $< 35\%$, did not raise the LVEF by 10 absolute units, stayed at an NYHA class III/IV or had been dead. Complete recovery was determined when arriving at a 55% LVEF level as well as NYHA classes I to II.

2.6. Analysis of data

SPSS 14.0 for windows was used to analyze the data. The patient population was described by measuring outright quantity and the percentum. Data were demonstrated as average ± standard deviation for continuous variables. Variable analysis was later adopted to compare the 2 groups' mean values. The rates between the 2 groups were tested by Chi-squared. If the P-value $<$ .05, we considered it is statistically important.

3. Results

3.1. Classification of diseases

In total, 262 patients complaining of dyspnea were recruited to our study; 147 (56%) of them were eventually diagnosed with physiologic dyspnea of pregnancy, 33 (13%) patients had respiratory tract infections, 26 (10%) patients had asthma, 17 (6%) patients had severe anemia (below 70 g/L), and only 11 (4%) patients met the PPCM diagnostic criteria. The primary causes of patients with perinatal dyspnea are shown in Figure 1.

3.2. Comparison of the clinical data between the PPCM group and the control group

The average age of the 11 patients with PPCM was 24.2 (range 19–39) years. Two patients had a second child, and the rest were in their first pregnancy. All 11 patients were experiencing the first onset. Six of them were affected during the first month after giving birth, 4 of them presented with symptoms within 2 to 3 months after delivery, and the last one had the disease within 4 to 5 months after delivery; however, no cases were found before the prepartum period (Fig. 2). The New York Heart Association (NYHA) function classes (FC) II, III, and IV were discovered in 3 (27%), 6 (55%), and 2 (18%) patients, respectively.

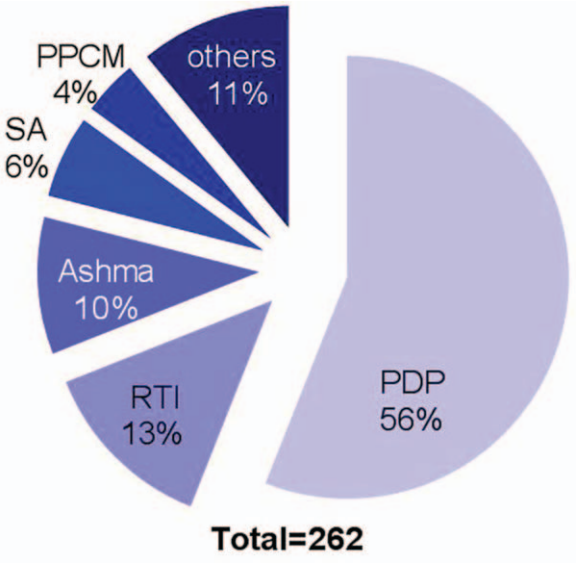

Figure 1. Etiology of dyspnea in 262 patients during the perinatal period. PDP = physiologic dyspnea of pregnancy, PPCM = peripartum cardiomyopathy, RTI = respiratory tract infection, SA = severe anemia.

The clinical data of the patients arriving at the ED and of the control group are listed in Table 1. Only 1 patient (9%) had high blood pressure. The general characteristics of the study group and the control group were not statistically significant with respect to age, proportion of cesarean sections, body mass index, diastolic blood pressure, body temperature, systolic blood pressure, and multi-delivery. The initial heart rate of the patients with PPCM was faster than that of the control group (Table 1).

In comparison with the control group, white blood cell (WBC), CRP, and BNP in the patients with PPCM were higher, whereas the PaO_2 and LVEF was lower (Table 1). The alanine aminotransferase in the patient group was lower compared to the control one, but there was no practical clinical significance.

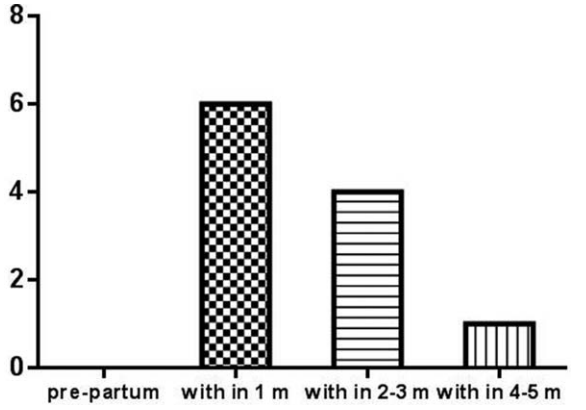

Figure 2. Patients with peripartum cardiomyopathy presenting with symptoms.

Table 1

Comparison of the basic baseline characteristics between the peripartum cardiomyopathy group and the control group.

Clinical data	Patients (n = 11)	Control (n = 11)	P
Age, y	24.2±4.2	23.6±3.8	.364
Cesarean section	3 (27.3)	4 (36.4)	.213
BMI, kg/m^2	24.8±6.2	24.3±5.1	.551
Systolic blood pressure, mm Hg	116±11.9	113±13.4	.432
Diastolic blood pressure, mm Hg	70.9±9.7	68±12.3	.291
Heart rate, beat per minute	104.6±21.2	85.5±10.8	.038
Body temperature, °C	36.6±0.3	36.4±0.6	.433
Multi-delivery	2	1	.511
Total WBC, 10^9/L	11.5±1.17	9.3±1.41	.001
Hemoglobin, g/L	9.7±0.7	10.0±0.8	.394
CRP, mg/L	38.8±12.8	11.8±8.9	<.001
ALB, g/L	34.1±4.2	36.5±6.5	.330
ALT, U/L	32.4±11.3	41.4±16.9	.165
Cr, μmol/L	90.7±11.4	84.3±14.7	.265
BNP, pg/mL	710.6±285.4	102.2±42.7	<.001
CK-MB, ng/mL	3.4±1.5	2.3±1.2	.063
TNI, ng/mL	0.37±0.030	0.10±0.10	.075
PaO_2, mm Hg	65.5±9.7	87.9±7.0	<.001
LVEF, %	32.4±6.1	56.8±5.2	<.001

ALB = albumin, BNP = B-type natriuretic peptide, CK-MB = creatinine kinase-MB isoenzyme, CRP = C-reactive protein, LVEF = left ventricular ejection fraction, TNI = cardiac troponin I, WBC = white blood cell.

Furthermore, there was no significant difference in hemoglobin, albumin (ALB), creatinine, CK-MB, and TNI between the 2 groups (Table 1).

3.3. Clinical results

The patients with PPCM all got standard therapy for cardiac failure. The average time in the hospital was 8.6±5.8 days. No death happened during their hospital stay. Symptoms of cardiac failure as well as PPCM indications noticeably increased in each patient when they left the hospital.

3.4. Follow-up

Each patient was tracked at the outpatient clinic for 2 to 4 weeks after discharge. The clinical data were made a comparison between first presentation in ED at the base line and follow-up after 2 to4 weeks of standard treatment, which can be seen in Table 2. The heart rate, CRP, and BNP levels were lower at the follow-up compared with the pretreatment. Patients who were followed up showed significant improvements in the LVEF and NYHA FC (Table 2). However, normalization of the LVEF (EF ≥ 50%) was only observed in 7 (64%) patients.

Table 2

Clinical variables and the left ventricular function at the baseline and follow-up of patients.

Clinical data	Baseline	Follow-up	P
Systolic blood pressure, mm Hg	116±11.9	111±7.2	.24
Heart rate, beats per minute	104.6±21.2	83.6±11.1	.002
CRP, mg/L	38.8±12.8	10.0±9.9	<.001
BNP, pg/mL	710.6±285.4	168.6±104.2	<.001
LVEF, %	32.4±6.1	49.1±5.0	<.001
NYHA	FCs I II3, FCs III IV8	FCs I II10, FCs III IV1	.008

BNP = B-type natriuretic peptide, CRP = C-reactive protein, FC = function class, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association.

4. Discussion

The PPCM is a unique dilated cardiomyopathy, whose origin is unknown. It is featured by heart failure development on account of marked LV systolic dysfunction. It happens to previously healthy women during the last pregnant month and the fifth month after giving birth.[4] The authentic PPCM occurrence is still a problem and differentiates broadly, for example, in Haiti, the live birth is 1/299,[5] in South Africa, the rate is 1/1000[6] and in the United States, it is approximately 1/2289–4000.[7] The PPCM incidence in China is not clear. Complicated and changeable clinical manifestations are often confused with the symptoms during normal pregnancy, and thus the incidence may be higher than reported. In recent years, due to the thorough understanding of the disease and improved diagnosis technology, there has been a significantly increased trend in PPCM.[7]

The pathogenesis of PPCM may be induced by multi-fetal pregnancy, advanced maternal age and so on[8]; however, none of them is definite. Past studies have revealed that the causes of PPCM included viral myocarditis,[9] immunologic injury,[10] hemodynamic stress of pregnancy,[11] apoptosis and inflammation,[12] oxidative stress–prolactin axis,[13] and genetic factors.[14] However, no single factor has been identified as the underlying cause of the disease.

It has been reported that there were nearly 80% patients with PPCM associated with first pregnancy and there were more than 60% patients with postpartum symptoms.[15–18] These may be related to race, economic conditions, geographical area, and sample size.

In this study, the rate of hypertension (9%) was similar to those in South Africa (2%)[15] and Haiti (4%)[5] and was significantly different from other reported values of 25% to 45% among Caucasian, Nigerian, and Japanese patients.[19] Differences in race, lifestyle, geographical area, sample size, and medical standards might be involved in these findings. The results also do not support the causative presumption between hypertension and the development of PPCM.

Patients present with dyspnea due to a variety of diseases. Physiologic dyspnea is an extremely common phenomenon during normal pregnancy, affecting up to 60% of healthy women during exercise and 20% of women at rest,[20] compared with 56% in our study. In comparison, only 11 (4%) patients had PPCM in 262 cases. If all the patients who have difficulty in breathing are included, the proportion of PPCM will be lower. This disease is rare and constitutes <1% of all cardiovascular events related to pregnancy,[21] but PPCM could be linked with vital and continuous complications, such as severe heart failure, cardiopulmonary arrest secondary to heart failure, cardiac shock, arrhythmias, thromboembolic complications, and even death.[22]

Even so, a study has shown continual diagnosis delays before the recognition of PPCM in 48% of patients.[1] A critical reason is most likely associated with the resemblance between clinical performance of PPCM and concomitant pregnant symptoms.[23] Meanwhile, in many cases, low levels of consciousness as well as failing to routinely consider a cardiac cause for demonstrating signs have obviously associated with late diagnosis.[1] Furthermore, unexpectedly, some cases of PPCM are asymptomatic, which causes the diagnosis to be delayed or, in mild cases, even completely missed.[24] Since PPCM is a diagnosis of exclusion an

Table 3

The application value of bio-markers analyzed in patients with PPCM.

Bio-marker	The application value for PPCM
CRP	possibly reflects the presence of a low-grade chronic inflammatory process in PPCM[12,27]
BNP (N-terminal pro-BNP)	it is not the cause of PPCM but rather a marker of the severity of heart failure process[31]
16 kDa Prolactin	pathophysiologic factor of PPCM, high technical effort for measurement,diagnostic accuracy needs to be evaluated[13,34,35]
cathepsin D	the enzyme generates the 16 kDa prolactin, activity elevated in plasma of patients with PPCM, diagnostic accuracy needs to be further evaluated[13,34,35]
miR-146a	a direct target of the 16 kDa prolactin, high technical effort for measurement,diagnostic accuracy needs to be evaluated[34]
ADMA	an endogenous inhibitor of nitric oxide synthase, marker for endothelial dysfunction and cardiovascular risk, diagnostic accuracy needs to be evaluated[34]

ADMA = asymmetric dimethylarginine, BNP = B-type natriuretic peptide, CRP = C-reactive protein, PPCM = peripartum cardiomyopathy.

accurate medical history, appropriate diagnostic tools are important to identify alternative etiologies of heart failure.[25]

However, timely and accurate diagnosis is not without a clue to follow; as previously reported, the mean hs-CRP in control patients of the same postpartum period with diagnosed patients with PPCM varied somewhat from patients with PPCM.[26] Similarly, in our study, an elevated plasma concentration of hs-CRP was observed in patients with PPCM, and these results possibly reflected the existence of a mild chronic inflammatory process because of the emission of endotoxin or endotoxin-like materials and the following pro-inflammatory cytokines discharge, which might matter in PPCM development[12,27] (Table 3).

Levels of BNP or N-terminal pro-BNP do not fluctuate during normal pregnancy or in the postpartum period[28,29] and are only mildly increased in women with preeclampsia.[30] However, an earlier BNP measure may be helpful in PPCM diagnosis. In PPCM, the BNP levels are significantly high because of the increased LV end-diastolic pressure caused by systolic dysfunction[31] (Table 3). The same results were found in our study as well as for hs-CRP.

The advance of total CK and CK-MB is precisely relevant to delivery type, labor duration, mother parity, as well as birth weight,[32] but may not help for PPCM detection. Furthermore, there was no remarkable improvement in the patients with PPCM contrasted with the control group in our study.

During the first assessment, the serum concentration of troponin might be useful in patients with a substantial myocardial insult at the time of the diagnosis; nonetheless, a rise in troponin during acute stage of PPCM, with no myocardial infarct, may happen.[33] An elevated TNI in the PPCM group was also observed in our research but turned out to be statistically insignificant, which was probably related to the sample number being insufficient. In a recent paper, a rise in the serum concentration of cathepsin D, miR-146a, as well as asymmetric dimethylarginine (ADMA) was found in patients with PPCM in comparison with postpartum controls, supporting the pathophysiologic aspect of 16 kDa prolactin for PPCM[34] (Table 3).

In early diagnosis and risk stratification, peripartum women crucially need bio-markers specific for PPCM. The high morbidity of raised BNP or N-terminal pro-BNP, activated cathepsin D, and 16 kDa prolactin may be useful for determining a disease-specific bio-marker profile[35] (Table 3).

Differing from the ECG findings' lack of specificity, echocardiography is the foundation in diagnosing PPCM. It is paramount for determining the decreased LVEF and assessing LV dilatation or thrombi presence.[3] PPCM was a global cardiac dilation with restrictive pattern of LV diastolic function.[36] In addition, as a tool for predicting the prognosis, when PPCM followed by serious systolic heart dysfunction (LVEF $< 30\%$), chances for malignant arrhythmia and sudden cardiac death (SCD) increase.[37] Consequently, lots of patients with PPCM undergo the early improvement of systolic functions, and it is essential to perform a subsequent LVEF echocardiogram within 2 to 4 weeks after being diagnosed, which can help to confirm the progress and adjust the drug dosage.[37] This view has also been verified in our article (Table 2). The ensuing tracking with an echocardiogram at routine periods (at the time of discharge, 6 weeks, 6 months, as well as annually) should be put in place to inspect the disease development.[3]

The differential diagnosis of PPCM is extensive; respiratory tract infections, asthma, pulmonary edema, pulmonary thromboembolism, valve disease, preeclampsia, and severe anemia should be considered. No explicit criteria exist for distinguishing the signs of heart failure from those of normal to late pregnancy, and thus a mechanism for quantifying the harshness of various symptoms that has been proposed and validated is needed urgently.[38] In this investigation, a traceable study of 47 patients with PPCM, all who scored 4 or higher were found to have LV systolic dysfunction (Table 4).[38]

To aid in early detection, this metric is used to assist patients and clinicians in differentiating normal pregnancy and postpartum signs and symptoms. It also works as a useful reminder to initiate the workup, including CRP, BNP or N-terminal pro-BNP, activated cathepsin D, etc, to facilitate the diagnosis and an echocardiogram to resolve the ejection fraction. A configurable

Table 4

Self-test for the early diagnosis of peripartum cardiomyopathy.

Symptoms	0 point	1 point	2 points
Orthopnea	None	Need to elevate the head	Need to elevate by 45° or more
Dyspnea	None	Climbing 8 or more steps	Walking on level
Unexplained cough	None	At night	Day and night
Lower extremity swelling	None	Below the knee	Above and below the knee
Excessive weight gain during the last month of pregnancy	Under 2 pounds per week	2–4 pounds per week	Over 4 pounds per week
Palpitations	None	When lying down at night	Day and night, any position

The presence of 4 or more points should prompt an additional investigation. The data are taken from Fett (2011).[38]

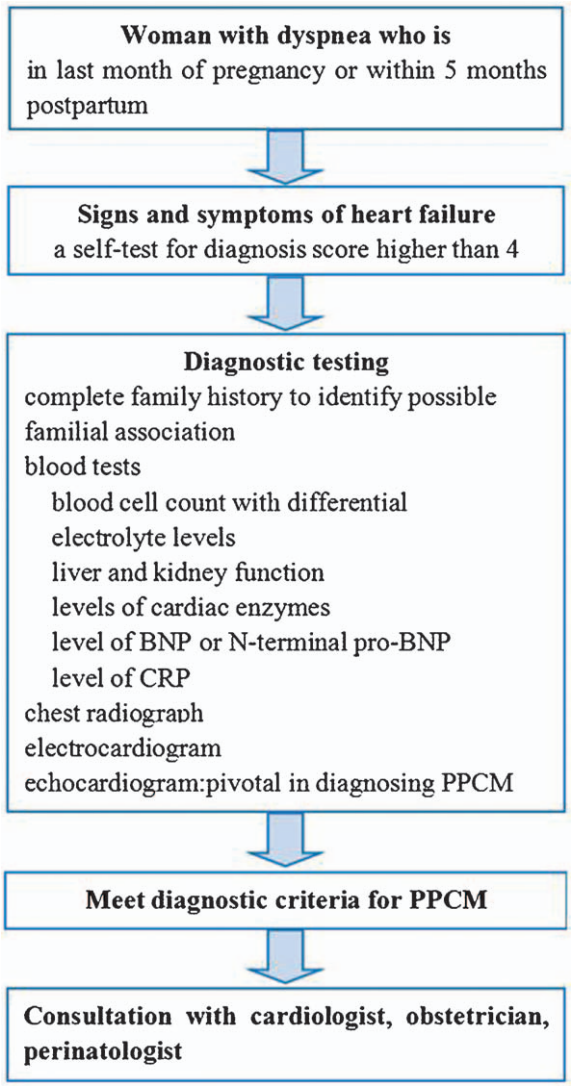

Figure 3. The diagnosis process of peripartum cardiomyopathy. BNP = B-type natriuretic peptide, CRP = C-reactive protein, PPCM = peripartum cardiomyopathy.

diagnosis process based on the protocol for diagnosing PPCM based on the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) is offered in Figure 3, which gives a better basis for the early evaluation and identification PPCM.

The limitations of this study are that the sample size was relatively small and the patient outcomes were only studied during the hospitalization and shortly after the discharge period. Although all patients remained in good health, it has not been identified the survival rate of this PPCM population in the long term. Our study projects a future direction in which the usage of bio-markers and risk prediction models to increase screening has the potential to improve the prognosis through an earlier diagnosis.

5. Conclusion

The PPCM is a disease with unknown etiology that confers significant risks for morbidity and mortality. In this single-center study, 56% of well-documented patients complaining of shortness of breath had physiologic dyspnea, compared with 4% meeting the criteria of PPCM. Patients with PPCM had a higher heart rate, and the WBC, hs-CRP, and BNP levels were markedly elevated in the patients compared with the controls, whereas the PaO_2 and LVEF values were lower. Patients who were followed up showed significant improvements in the LVEF and NYHA FC. Use of echocardiography and disease-specific bio-markers may aid in the diagnosis and management. Raising awareness of the disease and a precise assessment of the risk factors in pregnant women are keys to facilitate the early detection of PPCM.

Author contributions

Investigation: Weiwei Wang.
Project administration: Yu Wang.

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