ORIGINAL ARTICLE

Peripartum cardiomyopathy: Frequency and predictors and indicators of clinical outcome

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Abstract

Objective: To determine frequency and prognostic factors of peripartum cardiomyopathy.

Methods: The prospective cohort study was conducted from April 2012 to September 2013 at Civil Hospital, Karachi. Cases were collected in the first year, and were then followed up for six months. On clinical and transthoracic 2-D M Mode echocardiography, cases of prepartum peripartum cardiomyopathy were detected. After necessary lab tests, cardiac opinion and treatment, pregnancy was terminated using caesarean section. At complete clinical recovery, the subjects were discharged to be followed up in cardiac and gynaecology clinics with current echocardiograph at 3rd and 6th month. SPSS 15 was used for data analysis.

Results: Out of 5742 deliveries, 22(0.38%) were cases of prepartum peripartum cardiomyopathy; the frequency being 3.8/1000 births. At 6-month follow-up, 14 (63.63%) cases recovered and 6(27.3%) did not. Two (9%) cases expired on 2nd and 16th day of delivery. On baseline or diagnostic echo, left ventricular ejection fraction and fractional shortening were statistically significant predictors of clinical outcome ($p<0.05$ each). Ejection fraction and fractional shortening were strong predictors of clinical outcome ($p<0.05$ each).During follow-up, left ventricular ejection fraction, fractional shortening, left ventricular internal dimension at diastole, and left ventricular internal dimension at systole (LVISd) were statistically significant indicators of clinical outcome ($p<0.05$ each).

Conclusion: Baseline and follow-up echo was the best tool for prognosis. Baseline left ventricular ejection fraction and fractional shortening were significant predictors of clinical outcome.

Keywords: Systolic heart failure, Ejection fraction, Echocardiography, predictor, Fractional shortening, Left ventricular internal diameter at diastole. (JPMA 66: 1517; 2016)

Introduction

Cardiovascular diseases affect 4% of pregnancies in western industrialised countries and the trend is increasing.[1] Even in the absence of pre-existing cardiovascular disease, pregnancy complications such as hypertensive complications i.e. gestational hypertension, and more severe forms of preeclampsia, HELLP syndrome (the haemolysis, elevated liver enzyme levels, and low platelet levels) and peripartum cardiomyopathy (PPCM) may induce cardiovascular disease.[2,3]

PPCM is an uncommon disorder associated with pregnancy in which heart dilates and weakens, leading to symptoms of heart failure (HF). PPCM may be difficult to diagnose because symptoms mimic those of pregnancy. Affected women may recover normal heart function; stabilise on medicines, or progress to severe HF requiring mechanical support or heart transplantation. Even when the heart recovers, another pregnancy may be associated with a risk of recurrent HF.[4]

PPCM is diagnosed when HF develops in the last month of pregnancy or within 5 months of delivery; heart pumping function is reduced, with an ejection fraction (EF) less than 45% (typically measured by an Echo); no other cause of HF with reduced EF can be found.[4]

PPCM is rare in the United States (US), Canada and Europe, with an estimated case rate of 1 per 2500-4000 births.[3] In some countries, PPCM is much more common e.g. 1 in 1000 live-births in South Africa and up to 1 in 300 live-births in Haiti.[5]

The underlying cause of PPCM has not been clearly defined. Heart biopsies performed in women with PPCM have shown inflammation in 10%-75% of cases. This may be attributable to a prior viral illness or abnormal immune response, although there is no evidence that antiviral or immunosuppressive medication improves outcome. Other potential causes include nutritional deficiencies and defective antioxidant defences. Genetics may also play a role in the tendency to develop PPCM.[4]

The evaluation of PPCM includes general/physical examination, lab tests, markers of cardiac injury such as

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troponin, electrocardiography (ECG) (heart tracing) to assess heart rate and rhythm to rule out heart attack, and echocardiography (Echo) (heart ultrasound) to assess the size and function of heart. The primary measure of heart function is the left ventricular ejection fraction (LVEF). This is the percentage of blood ejected from the heart with each beat, and normally ranges between 50% and 70%.[4] Management includes medications to stabilise heart function, to improve blood flow to vital organs and to reduce fluid overload.

Early improvement in EF in the first 6 months predicts a good outcome. Some women will have slow, gradual improvement in EF stretching over years. After full recovery of heart function, which is defined as EF $\geq$ 50%, decision to stop medication is controversial. Most physicians, however, agree that Angiotensin Converting Enzyme (ACE) inhibitors and beta (β) blockers should be continued for at least 1 year after EF normalisation.[4]

The risk of subsequent pregnancy depends on the recovery of heart function after the diagnosis of PPCM. For women with persistently reduced EF, there is substantial risk of recurrent HF and even death.[4]

The current study was planned to investigate the frequency of PPCM and predictors and indicators of clinical outcome.

Since PPCM remains a major cause of maternal morbidity and mortality, identification of the predictors and indicators of clinical outcome can help to select cases at risk for sudden cardiac death, and determination of the risk of recurrent HF in subsequent pregnancy. The current study was planned to investigate the frequency of PPCM, and predictors and indicators of clinical outcome.

Patients and Methods

The prospective cohort study was conducted over one-and-a-half years from April 2012 to September 2013 at Civil Hospital, Karachi. Cases were collected using non-probability purposive sampling in the first year, and were then followed up for six months. All cases fulfilling criteria of PPCM were included while cases of ischaemic heart disease, valvular heart disease and heart failure secondary to anaemia were excluded. Clinical evaluation was made through history and examination. LVEF assessment was done on standard transthoracic Doppler 2-D M Mode Echo. Echo at 3rd and 6th month postpartum was done to evaluate recovery status. Doppler parameters of advanced remodelling were measured according to American Society of Echocardiography Guidelines.[6]

Recovery was defined as resolution of HF symptoms and signs and normalization of left ventricular systolic function (LVSF) (EF $\geq$ 50%) and persistent left ventricular dysfunction (PLVD) (EF<50%) at 6 month postpartum.

Data was analysed using SPSS 15. Continuous variables were expressed as mean ± standard deviation (SD) and were compared between groups by two-tailed Student t test. Fisher exact (X^2) test was used for comparison of categorical variables. For all analysis $p<0.05$ was considered significant.

The study protocol was approved by the institutional review board and informed consent was taken from each patient. Literature has shown 62.5%[7] cases of PPCM to have recovered in a tertiary care centre. In order to calculate the sample size 62.5% proportion was taken to determine the sample size both in exposed and non-exposed groups for PPCM. The level of significance was 5% and confidence interval (CI) 95% with a power of study of 80%. The final sample size was calculated using method described by Kelsey et al method in observational epidemiology.[8]

Results

Out of 5742 deliveries, 22(0.38%) were cases of PPCM; the frequency being 3.8/1000 births. Age, parity and medical condition was noted for each patient (Table-1). Two (9.1%) cases expired on the 1st & 16th postnatal day. Of the survivors, 14(63.3%) recovered and 6 (27.3 %) were left with PLVD at 6-month follow-up.

Table-1: General characteristics.

Characteristic	N	%
Age (Years)		
20	2	9.1
25	4	18.2
26	4	18.2
30	12	54.5
Parity		
Primi	8	36.4
Second	6	27.3
Multipara	8	36.4
Foetus number		
Singleton	20	90.9
Twins	2	9.1
Associated morbidities		
Severe hypertension	12	54.5
Pre-eclampsia	2	9.1
Jaundice	2	9.1
Mild hypertension	6	27.3
Recovered/ not recovered		
Recovered	14	63.6
Not recovered	8	36.4

Table-2: Serial echo of recovered and not recovered cases.

Characteristic	Recovered (n=14)		Not recovered(n=8)		t-test	P- value
At Diagnosis	**Mean**	**SD**	**Mean**	**SD**		
LVIDd	56.2857	4.42769	59.0000	2.36643	-1.403	0.178
LVISd	36.7143	5.19509	36.6667	7.60701	0.016	0.987
EF	44.7143	2.26779	29.6667	8.01665	6.641	<0.001
FS	23.1429	3.69734	17.6667	2.25093	3.341	0.004
After 3 Months						
LVIDd	41.8571	5.77604	53.3333	4.58984	-4.298	<0.001
LVISd	27.1429	4.75325	33.6667	3.72380	-2.977	0.008
EF	57.1429	3.77964	43.3333	2.58199	8.113	<0.001
FS	25.2857	1.72888	18.3333	1.36626	8.708	<0.001
After 6 Months						
LVIDd	41.4286	5.28735	52.0000	4.47214	-4.270	<0.001
LVISd	26.7143	4.69744	32.6667	2.73252	-2.874	0.010
EF	58.5714	3.63137	45.0000	0.00000	9.012	<0.001
FS	26.1429	1.29241	19.3333	2.06559	9.024	<0.001

LVIDd: Left ventricular internal dimension at diastole
LVISd: Left ventricular internal dimension at systole
EF: Ejection fraction
FS: Fractional shortening.

Table-3: Serial Echo comparisons.

Characteristic	Differences at Diagnosis and 3 months			Differences at Diagnosis and 6 months		
	Mean Differences	**Paired t-test**	**P-value**	**Mean Differences**	**Pairedt-test**	**P-value**
LVIDd	11.80000	6.631	<0.001	-12.50000	-7.453	<0.001
LVISd	7.60000	4.254	<0.001	-8.20000	-4.608	<0.001
EF	-12.80000	-11.852	<0.001	-14.30000	-11.573	<0.001
FS	-1.70000	-2.087	0.051	-2.60000	-4.859	<0.001

LVIDd: Left ventricular internal dimension at diastole
LVISd: Left ventricular internal dimension at systole
EF: Ejection fraction
FS: Fractional shortening.

Using echocardiography status at 3rd and 6th month follow-up, findings comparing recovered and non-recovered cases were compared (Tables-2 and 3).

Baseline EF $\leq$35% was associated with poor prognosis in 6(27.3%) cases.

Baseline fractional shortening (FS) $\leq$ 20% was associated with poor prognosis in 4(18.2%) cases.

Discussion

PPCM is a rare form of idiopathic primary myocardial disease associated with pregnant state. Multiple mechanisms have been postulated, but it remains a diagnosis of exclusion.

Frequency of prepartum cases of PPCM in this study was 3.8/1000 births. There is very little literature available from Asian countries. In South India its reported incidence is 1 case/1374 live-births.[9] It is common in African Americans (43.9%) compared to white (40.8%), Hispanic (8.7%) and Asians (2.7%).[10] In Nigeria, the incidence is very high (1 case/102 births).[11] This high incidence may have an association with the local Hausa custom of eating Kenwa a dry local salt for 40 days after delivery. This incidence includes all pre and postpartum cases. We studied only prepartum cases. Postpartum cases were referred to the Cardiology department. In one study of 10-year period, out of 45 cases 14 (31.1%) were presented during pregnancy,[12] out of 16 cases of a study, only 5(22%)[13] were prepartum and 12 (28.6%) out of 42 cases of PPCM in another study.[14] Incidence of prepartum cases is less compared to postpartum cases. It has been documented that incidence of PPCM is 78% in postpartum period, 9% in

the last month of pregnancy and 13% either prior to last month of pregnancy and more than 4 months postpartum.[15] Definition of timing for this reason is very strict and all cases with HF and fulfilling criteria for PPCM in 2nd & 3rd trimester should also be included.

We found increasing age, multiparity and hypertension as strong risk factors for PPCM, which is also seen in other studies.[4,16] Multiparity can cause a stepwise cumulative insult to cardiac function.[17] A few studies found young age, primigravida prone to developing PPCM, but failed to establish the reason for high prevalence in them.[13] In South Asian population, preponderance of PPCM towards a young age could be due to earlier age of marriage. In India, frequency of PPCM in >30 years is 28.8% and in multigravida 44.4%.[12] One study found that 67% women with PPCM were multiparous.[17] PPCM is therefore more likely to occur in women over the age of 30 years who are pregnant and have had prior pregnancies, but it also can occur in young women pregnant with their first child. In this study >90% had coexisting hypertension. A recent epidemiology report from North Carolina shows that out of 79 cases of PPCM, 51 (65%) had some form of hypertension.[18] It has been documented in one study that prevalence of pre-eclampsia is 4 times in patients of PPCM compared to the general population.[17] Hypertension and preeclampsia accentuates the first hit of late gestational circulating cardiotoxic and other angiogenic factors that increase the likelihood of triggering frank PPCM.[17] Pre-eclampsia has often been cited as an independent risk factor for the development of PPCM. The current study demonstrates that hypertensive disorder of pregnancy, pre-eclampsia, multiparity and increasing age are strong risk factors for the development of PPCM.

We received and managed undelivered PPCM cases. Following initial treatment of HF with a team of cardiology, all of them underwent Echo to confirm the diagnosis and to obtain prognostic information. As previous reports showed, most women with PPCM completely recover in terms of heart size and function usually within 6 months of delivery[15] and if cardiac dysfunction persists beyond 6 months it is an indication of irreversible damage and is indicator of worse prognosis.[19] On this basis, we followed the cases for 6 month postpartum. Serial Echo at presentation, at 3 month and at 6 month postpartum were carried out. In this study those cases that had baseline or diagnostic EF of $\leq$ 35% did not recover fully at 6 month follow-up. Baseline EF of $\leq$ 35% was associated with PLVD at the last follow-up Echo. Therefore, baseline or diagnostic EF and FS were strong predictors of recovery, and baseline EF 35% or above was associated with high chances of recovery. In many studies LVEF is a significant predictor of prognosis.[3,15,20,21] One study concluded that in PPCM 5/6 major adverse events (like death, transplantation or PLVD) occurred in those with baseline EF <0.03(30%) and left ventricular internal dimension at diastole (LVIDd) $\geq$ 6.0cm.[22] In one local study, high baseline EF was associated with good outcome.[16] Women with severe LVSD at presentation have poor outcome. However, one study did not find baseline EF statistically significant in relation to prognosis.[23] In this study, baseline FS of $\leq$ 20% was also associated with poor prognosis. In one study, risk of PLVD was 3-fold with baseline FS $\leq$ 20% and LVIDd6.0 cm or more.[24] Follow-up Echo at 3 and 6 months can also help to monitor status of recovery by improving parameters of remodelling. In this study we found EF, FS and LVIDd were good indicators for recovery at 3 and 6-month follow-up. We did not find LVIDd as strong predictor of clinical outcome. A few studies found it to be a good predictor of prognosis if baseline LVIDd was $\leq$ 6.0cm.[24] The cases that expired in this study had baseline EF 35%, FS <20% and LVIDd < 6.0cm and only one case that had baseline LVIDd 6.0 cm did not recover at 6-month follow-up.

The recovery rate in this study was 63.3% at 6-month postpartum follow-up. In other studies, it was around 54%.[15,25] In one study, recovery rate was 47.2% with high mortality rate of 23.8%.[14] In one large study of 123 cases at a mean follow-up of 2 years, mortality rate was 10%.[25] In our study mortality rate was 9.1%. In one study mortality rate was 6%.[13] In a study carried out in Turkey, mortality rate over 4-year follow-up was 30%.[21] These studies suggested that outcome of PPCM had improved, with survival rates as high as 90-95% with contemporary medical and device therapy. Timely critical care instituted under supervision of cardiologist can favourably change outcome. Early improvement in EF, FS, LVIDd and left ventricular internal dimension at systole (LVISd) (i.e, within the first 3-6 months) indicates good outcome.

In terms of limitations, it's the single-centre hospital-based nature of the study can be cited. At the time of discharge one Echo should also have been performed to determine recovery status.

Because of the probability of either delayed recovery or deterioration of LVSF in PPCM, long-term follow-up is needed not only in non-recovered cases, but also in cases with full recovery. We therefore recommend that cardiac resynchronisation therapy (CRT) or implantable cardioverter defibrillator (ICD) shall be used in non-recovered cases to prevent sudden death during 3-6 month follow-up while assessing Echo LVSF improvement. In spite of beneficial effect of the prolactin blocker

bromocriptin in patients with acute PPCM, the European medical agency has recommended restricted use for adverse effect on blood pressure and thrombosis.[26] Also, heart transplantation is associated with excellent post-transplantation survival and shall be considered.

Conclusion

Baseline and follow-up Echo was the best tool for prognosis. Baseline LVEF and FS were significant predictors of clinical outcome. EF, FS, LVIDd and LVISd were strong indicaters of recovery. Aggressive medical and obstetrical management is crucial for good prognosis.

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