ORIGINAL ARTICLE:

Peripartum cardiomyopathy and its relationship with preeclampsia

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ABSTRACT

Objectives: To know the characteristic of PPCM in RSUD Dr. Soetomo Hospital Surabaya and to know the relationship between PPCM and PE.
Materials and Methods: This was a case control study. Data was obtained from medical record of 2843 patients within 2014-2015, divided into 2 groups, 19 patients with PPCM in a case group, and 2824 patients in control group. The statistical analysis used was Fisher exact test.
Results: Peripartum cardiomyopathy patients were older compared to control group (32.21 ± 6.83 y.o vs 29.26 ± 6.45 y.o). The incidence of PPCM in our study was about 1 per 149 live births. Most cases were diagnosed antepartum (52.63%), and about 84.2% PPCM cases were also complicating with preeclampsia. The statistical analysis revealed that there was increase risk of PPCM if the pregnant women complicates PE during pregnancy, with Odds Ratio (OR) 20.679, p<0.05. The most common perinatal outcomes was Small for Gestational Age (SGA) babies (81.8%), whereas case fatality rate (CFR) in maternal was 15.7%.
Conclusion: Although diagnosis of PPCM is still an exclusion diagnosis, we have to pay more attention to pregnant women complicating with preeclampsia, since preeclampsia can increase the risk of PPCM.

Keywords: Peripartum cardiomyopathy; preeclampsia; SGA babies; pregnancy

ABSTRAK

Tujuan: Untuk mengetahui karakteristik PPCM di RSUD Dr. Soetomo Surabaya dan untuk mengetahui hubungan PPCM dengan PE.
Bahan dan Metode: Ini adalah studi kasus kontrol. Data diperoleh dari rekam medis sebanyak 2.843 pasien selama periode 2014-2015 yang terbagi menjadi 2 kelompok, kelompok kasus 19 pasien PPCM, dan kelompok kontrol 2.824 pasien. Analisis statistik yang digunakan adalah uji Fisher.
Hasil: Pasien kardiomiopati peripartum berusia lebih tua dibandingkan kelompok kontrol (32,21 ± 6,83 y.o vs 29,26 ± 6,45 y.o). Insiden PPCM dalam penelitian kami adalah sekitar 1 per 149 kelahiran hidup. Sebagian besar kasus terdiagnosis antepartum (52,63%), dan sekitar 84,2% kasus PPCM juga mengalami komplikasi preeklamsia. Hasil analisis statistik menunjukkan bahwa terdapat peningkatan risiko PPCM jika ibu hamil mengalami komplikasi PE selama kehamilan, dengan Odds Ratio (OR) 20.679, p <0,05. Outcome perinatal yang paling umum adalah bayi Small for Gestational Age (SGA) (81,8%), sedangkan case fatality rate (CFR) pada ibu adalah 15,7%.
Simpulan: Walaupun diagnosis PPCM masih merupakan diagnosis eksklusi, namun kita harus lebih memperhatikan ibu hamil yang mengalami komplikasi preeklamsia, karena preeklamsia dapat meningkatkan risiko PPCM.

Kata kunci: kardiomiopati peripartum; preeklamsia; bayi SGA; kehamilan

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INTRODUCTION

Peripartum cardiomyopathy is a rare but life-threatening condition that occurs during the peripartum period in previously healthy women, without preexisting heart disease. The diagnosis criteria proposed by National Heart Lung and Blood Institute and Office of Rare Disease Workshop (2000) was the development of cardiac failure in the last month of pregnancy or within 5 months of delivery, the absence of an identifiable cause for the cardiac failure, the absence of recognizable heart disease prior to the last month of pregnancy, left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria, ejection fraction less than 45%, fractional shortening less than 30% or both, and end-diastolic dimension more than 2.7 cm/m2.[1]

The incidence of peripartum cardiomyopathy varies widely, 1:1.149 to 1:4.350 live births in US,[2] 1:1.000 live births in South Africa, 1 in 299 in Haiti, 1:837 in Pakistan,[3], and 1:20.000 in Japan.[4]. The reported mortality rates were quite high, range between 18% and 56%.[1] PPCM accounts for 5% of heart transplants in U.S. women,[5] and as many as 25% of women with PPCM in developing countries die within 5 years,[6] with an associated infant mortality rate as high as 50-70%.[7]

Multiparity, advanced maternal age, multiple gestation, obesity, preeclampsia, gestational hypertension, black race, and obesity are known to be risk factors for PPCM.[2,3,8] The etiology of PPCM is still unknown, but many potential causes have been proposed. These include viral myocarditis, abnormal immune response to pregnancy, abnormal response to increase hemodynamic burden of pregnancy, hormonal abnormalities, malnutrition, inflammation, and apoptosis.[9-12] Beside the unknown etiology, the other challenging issues was recognizing and differentiating the clinical presentations of PPCM that were similar to normal physiological changes of pregnancy. Many women in the last month of pregnancy experience dyspnea, fatigue, pedal edema, and symptoms identical to early congestive heart failure.[1] Peripartum cardiomyopathy may, therefore, go unrecognized, leading to underestimation of incidence.

Diagnosis of peripartum cardiomyopathy was made with exclusion, and confirmed by standard echocardiography assessment of left ventricular systolic dysfunction. The echocardiography examination was not a regular examination to be performed, especially in developing countries, like Indonesia. On the other hand, data from Dr. Soetomo Hospital in the last 3 years was showing that the most leading cause of MMR has been shifting. Preeclampsia and then followed by heart disease have become the most common cause of MMR in Indonesia respectively. Since preeclampsia is known to be one of the risk factors of PPCM, the prevalence of PPCM could be increasing too in Indonesia. This study was enrolled to know the magnitude of the preeclampsia existing together with PPCM.

MATERIALS AND METHODS

This study was a retrospective case control study using medical record in Dr. Soetomo Hospital Surabaya between 2014-2015. The total sampling included 2.843 patients, whether pregnant or post partum patients came to Obstetric and Cardiology wards. We divided patients into 2 groups, PPCM and non-PPCM.

The diagnosis of PPCM was made upon recommendations from the National Heart, Lung, and Blood Institute and the Office of Rare Disease of the National Institutes of Health Workshop on Peripartum Cardiomyopathy,[1] unless the onset of the disease, since there was an early onset of PPCM reported in many studies. Each of group then classified based on whether preeclampsia comorbidity did exist or not. Diagnosis of preeclampsia was defined as Blood Pressure (BP) > 160/110 mmHg, with or without existence of proteinuria (severe feature). Statistical analyses were performed with the use of Chi square test using the SPSS statistical package program.

RESULTS AND DISCUSSION

A total of 2843 patients between 2014-2015, there are 19 patients in PPCM group, and the incidence of PPCM was 0.66% (1 in 149 live births). The mean age of case and control group was (32.21 ± 6.83 vs 29.28 ± 6.46, $p<0.05$). Obesity was higher in PPCM group, compared to control group (21.1% vs 11.4%, p 0.264). Preeclampsia was even higher in PPCM group, compared to control group (84.2% vs 20.5%, $p<0.05$). Either the gravidity or parity between case and control group were not significantly different. The mean gravidity was (2.2 ± 1.549 vs 2.21 ± 1.253, p=0.766), meanwhile the mean parity were (1.32 ± 1.56 vs 1.05 ± 1.1, p=0.726) for case and control group respectively. These results are summarized in (Table 1).

PPCM Group

Among 19 patients diagnosed with PPCM, about 10 patients (52.63%) presented in antepartum period, and the others 9 patients (47.37%) presented in post partum period. The peak of cases presented PPCM is within 32-36 weeks gestational age of pregnancy whereas in post partum period, the peak happens within the first 7 days of post partum (Figure 1)

Table 1. Characteristic of women included in case and control group

	Case	Control	p
Mean age (years)	32.21 ± 6.83	29.28 ± 6.46	0.046
10-19 yo	1 (5.3%)	657 (23.3%)	
20-34 yo	10 (52.6%)	1994 (70.6%)	0.196
≥ 35 yo	8 (42.1%)	173 (6.1%)	
Obesity	4 (21.1%)	323 (11.4%)	0.264
Preeclampsia	16 (84.2%)	579 (20.5%)	<0.0001
Gravidity	2.2 ± 1.549 (1-6, n=10)	2.21 ± 1.253 (1-12, n=2698)	0.766
Parity	1.32 ± 1.56 (0-5)	1.05 ± 1.10 (0-9)	0.726
Rate of CS %	100% (n=10)	44.9%	

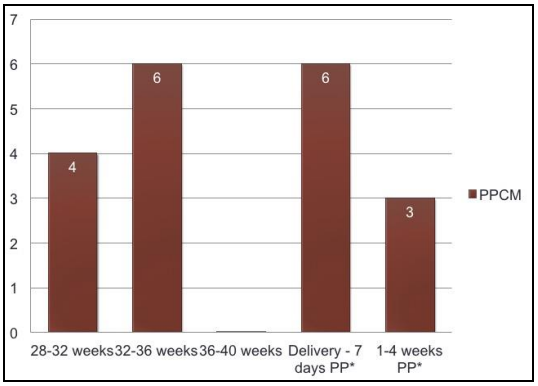

Figure 1. Time to diagnosis of PPCM in 19 patients

Patients came with heart failure presentation, and PPCM confirmed echocardiography, was showing a broad spectrum of severity. About 74% patients presented with DCFC III-IV, and the rest, 26% presented with DCFC I-II (Figure 2). Left Ventricular Ejection Fraction (LVEF) at the time of diagnosis ranged between 15-44%, with the mean Ejection Fraction (EF) was 36.63 ± 7.2%. Most of patients (68%) presented with PPCM, the EF ranged between 35-44% (Figure 3).

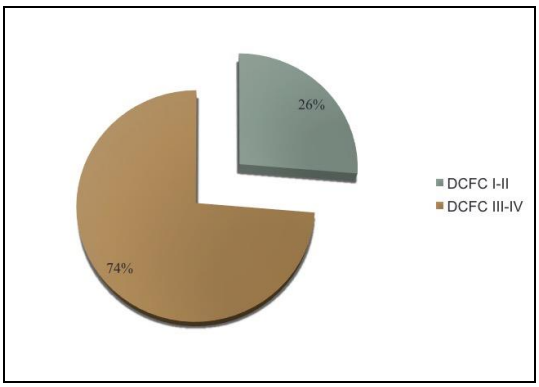

Figure 2. Severity of heart failure in PPCM patients

A total of 10 patients presented PPCM within ante partum period, there are 6 cases (60%) that managed directly to do termination, 1 case (10%) that managed to do termination after lung maturation, and we had 3 cases (30%) that managed conservatively due to earlier gestational age of pregnancy and improvement of the clinical presentation of PPCM (Figure 4). All of the patients were performed Caesarean Section (CS) delivery to terminate the pregnancy (100%, n=10). Meanwhile the CS rate of all patients presented with PPCM was 94.7% (18 of 19 cases), and 1 delivery was done with vacuum extraction in the secondary hospital (Figure 5). Moreover, undiagnosed PPCM in the referral hospital made 53% of PPCM patients had not received contraception methods yet.

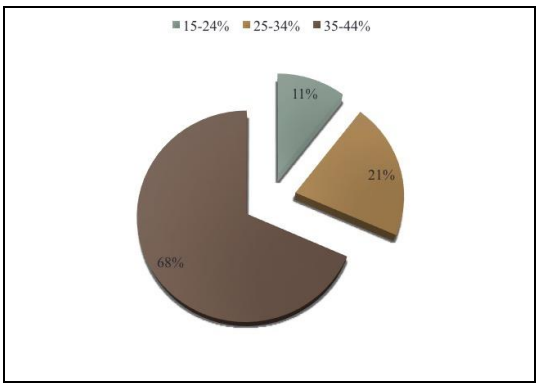

Figure 3. Ejection fraction of PPCM patients

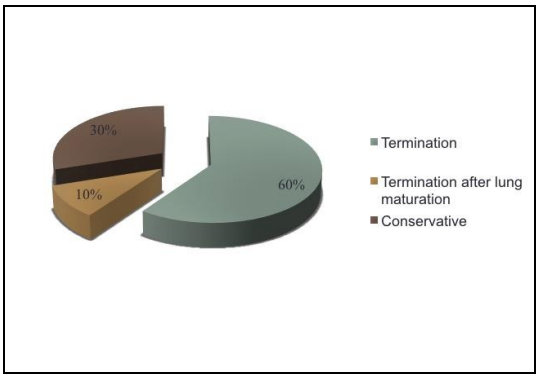

Figure 4. Management of the pregnant women diagnosed with PPCM.

Among 10 patients referred to the hospital during antepartum period, the indications of CS were due to fetal indication in 7 patients, and due to lung edema in 3 patients. Fetal distress, abnormal NST, and severe oligohydramnion were the indications recorded in this study (Figure 6).

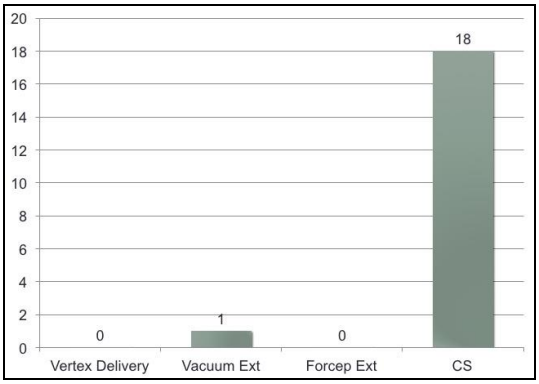

Figure 5. Mode of delivery patients diagnosed with PPCM

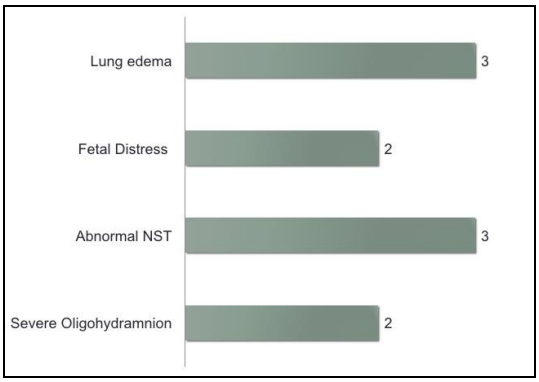

Figure 6. Indication of CS in pregnanct women diagnosed with PPCM

We observed the outcome of baby from PPCM mother. Most of babies were born preterm, with weight less than 2500 g (Figure 7), and there were 81.8% IUGR babies born from mothers diagnosed with PPCM within antepartum period. But there is no perinatal mortality rate during hospitalization. While, baby weight deliver-Sed from PPCM women diagnosed during postpartum were bigger. The distributions of baby weight were more than 2000 gram (Figure 8).

Complications of PPCM reported from these patients consist of cardiology and non-cardiology complication. Cardiology events complicated PPCM patients were lung edema (14 patients), cardiogenic shock (3 patients), cardiac arrest (1 patients), emboly stroke (1 patient), and atrial fibrillation (1 patient) (Figure 9). Non-cardiologic complications were happened during hospitalization, such as pneumonia (5 patients), acute kidney injury (AKI) and septic condition (4 patients), and multiple organ dysfunction syndrome (MODS) and encephalopathy (2 patients) (Figure 10).

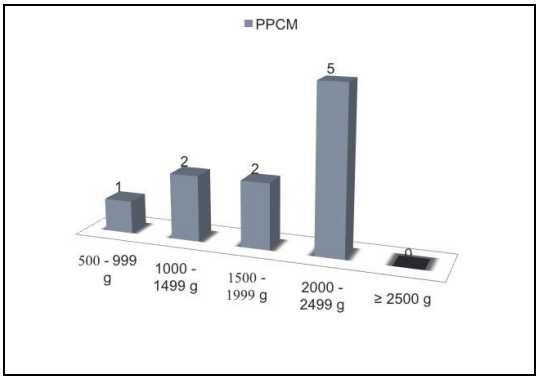

Figure 7. Distribution of baby weight delivered from PPCM women diagnosed antepartum

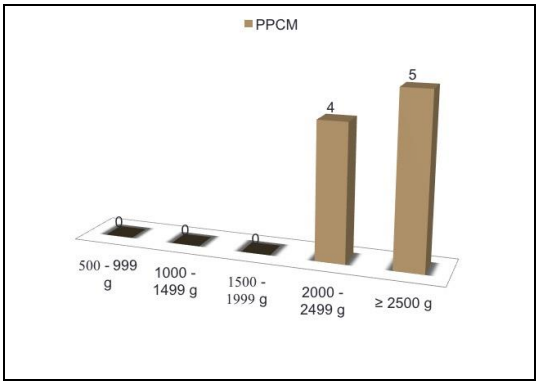

Figure 8. Distribution of baby weight delivered from PPCM women diagnosed postpartum

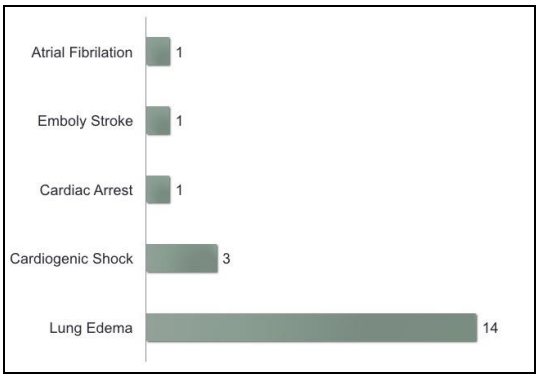

Figure 9. Distribution of cardiology fvent in PPCM patients

Most of patients (68%) need ventilator during hospital-ization. Duration of ventilator needs was about 1-3 days in almost 60% patients. Mean of ventilator usage was 3.54 ± 2.69 days. Meanwhile, the mean of length of stay was 12.16 ± 7.335 days. The Case fatality rate of PPCM patients in Dr Soetomo Hospital was 15.7%, there were 16% patients died after hospitalized in intensive care

unit. Based on chi-square statistical test there was significant difference between severe preeclampsia and PPCM (p<0.0001), with odd ratio (OR) 20.679 95% CI [6.005-71.210].

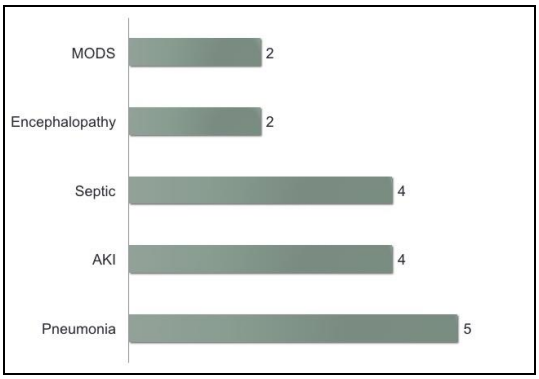

Figure 10. Non-cardiologic complication of PPCM patients

DISCUSSION

Clinical profile of PPCM

The present study provides the first database on patients with PPCM in Indonesia, especially in Surabaya. In our study we found 84.2% patients with preeclampsia in PPCM patients. Previous studies in Japan revealed that the incidence of hypertensive disease was 41% in PPCM patients,[8] whereas study in US by Elkayam et al found similar rates, 43%,[4] or study by Mode et al reported 46%.[13] Several reasons like ethnicity and life style might attribute to this discrepancy. The overall incidence of PPCM in this study was quite high, 1 in 149 live births. There was a possibility that our study was held in a tertiary hospital, which only severe cases referred from the referral hospital. Moreover, limited echocardiographic examination in primary and secondary hospital and low socioeconomic family might limit access to advanced medical care and make several cases of PPCM remained undiagnosed until the patients died.

The mean age of patients presented with PPCM was older than patients without PPCM. The mean age was 32.21 ± 6.83 years old. Previous study in Pakistan reported similar result, whose mean age was 30.94 ± 6.63 years,[3] in Haiti the mean age was 31.8 years,[15] South Africa was 31.6 years.[6] Calculation of the mean age of PPCM patients in studies held in 4 countries was more than 30 years old. This could be one of predictors that women aged more than 30 years old should be managed as high-risk pregnancies. Others risk factor of PPCM in this study reported same result.[2,3,4,8,14] Advanced age, multi parity, preeclampsia, and obesity were higher in PPCM group.

Some mechanisms of pathogenesis of PPCM have been proposed. Besides familial and genetic predisposition, prolactin and its cleaved products have been described as a trigger factor to present PPCM. The nursing hormone prolactin is among the prominent hormone in the peripartum phase, released from the pituitary gland into circulation during lactation. Prolactin can exert opposing effects on angiogenesis depending on the proteolytic process. Full-length 23kDa form as a potential proangiogenic, and 16kDa derivative as an antiangiogenic.[16] The 16kDa prolactin could lead an impairment of metabolic activity of cardiomyocytes,[17] and leading to PPCM. Since prolactin is released in a massive amount within peripartum period, PPCM is also presented during peripartum, whose incidence was higher during postpartum compared antepartum.[4,8,17]

The time of diagnosis of PPCM in our study revealed a different result from previous studies. Incidence in antepartum period was higher, about 52.63%. Higher incidence of preeclampsia might be one of a brief explanation that affects the onset of the disease presented, since preeclampsia manifested earlier (> 20 weeks of gestational weeks). Our study found that preeclampsia could increase the incidence of PPCM with OR 20.679 95%CI [6.005-71.210], (p<0.0001). The OR value in our study was quite similar with the previous study by Gunderson et al,[14] OR 20,8 (10.9-39.5) for preeclampsia and eclampsia cases. Preeclampsia is known to release high quantities of antiangiogenic produced by placenta, called Soluble Fms-Like Tyrosine kinase-1 (sFLT-1), which could antagonize the expression of Vascular Endothelial Growth Factor (VEGF). Similar mechanism correlated with antiangiogenic factors between these 2 diseases might accelerate the onset of PPCM.

According to the clinical presentation of PPCM, our study found 26% PPCM patients, presented mild to moderate symptoms of heart failure (DCFC I-II). This result was consistent with the literature that described the wide range of symptoms that could overlap with normal physiologic changes of pregnancy, and become under diagnosed in some cases.

Managing PPCM patients presented within antepartum period has been a big dilemma to Obstetricians, especially in Indonesia. The accessibility of Neonatal Intensive Care Unit (NICU), the capability to treat premature babies, and social factors (advanced maternal age or expected pregnancy) have become our consideration to terminate the pregnancy. Data from our center in 2015 showed perinatal mortality rate was very high,

reached 50% in babies weighted less than 1500 gram. Our study showed that we are still doing a conservative management for the pregnancy in some mild cases of PPCM. There were 4 cases that had been managed conservatively for days to give lung maturation before planned to do termination. Unless there is deterioration in the maternal or fetal condition, there is no need for early delivery.[10] Our study demonstrated 7 of 10 patients were decided to perform delivery due to fetal compromised, meanwhile 3 of 10 patients performed termination of pregnancy due to worsening of maternal condition. All pregnant women who complicated by PPCM were decided to perform Cesarean delivery (100%). If we combined all patients referred post partum and presented PPCM, the CS-rate was still high, 18 of 19 patients underwent cesarean delivery (94.7%). This number was contrast with others studies reported. Gunderson et al concluded that CS was more common among women who developed PPCM compared to non-PPCM (45.5% vs 19.7%).[14]

Another highlight from our study was the newborn outcome. Among 10 pregnant women presented PPCM were all preterm pregnancies. and all of babies delivered were having low birth weight (<2500 g). Surprisingly, 81.8% babies born were experienced Intrauterine Growth Restriction (IUGR). This adverse fetal outcome was directly related to the maternal cardiac status and associated obstetric complications like preeclampsia.[14]

As an Obstetrician, future pregnancy in women with PPCM needs to be considered. There is a concern that the next pregnancy may be associated with an increased risk of recurrence of cardiomyopathy. Previous study by Elkayam et al.[19] demonstrated that in women who have had PPCM, subsequent pregnancies may be associated with deleterious fetal and maternal outcomes, not only in women with persistent left ventricular dysfunction after the initial diagnosis of PPCM, but also in women whose left ventricular function returned to normal after the initial pregnancy complicated by PPCM.

CONCLUSION

Our study demonstrated more than half of women who their pregnancy complicated by PPCM (53%) had not decided their contraception method. This phenomenon could cause bigger problem in the future that we need our concerns to consider the magnitude of this disease, and not to underestimate preeclampsia itself.

REFERENCES

1. Pearson GD, Veille JC, Rahimtoola S, et al. (2000). Peripartum cardiomyopathy. National, Heart, Lung, and Blood Institude and Office of Rare Disease (National Institutes of Health) Workshop Recommendations and Review. Am Med Association. 2000;283(9):1184-88.
2. Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States. J Am Coll Cardiol. 2011;58(7):659-70.
3. Shah I., Shahzeb, Shah ST, et al. Peripartum cardiomyopathy: risk factors, hospital course and prognosis; experiences at lady reading hospital Peshawar. Pak Heart J. 2012;45(02):108-15.
4. Elkayam U, Akhter MW, Singh H, et al. Pregnancy associated cardiomyopathy. Clinical characteristics and a comparison between early and late presentation. Circulation. 2005;111:2050-5.
5. US Department of Health and Human Services. Available at: http://optn.transplant.hrsa.gov/latestData/rptData.asp. Accessed September 9, 2017
6. Sliwa K, Skudicky D, Bergemann A, et al. Peripartum cardiomyopathy: analysis of clinical outcome, left ventricular function, plasma levels of cytokines and Fas/APO-1. J Am Coll Cardiol. 2000;35:701–5.
7. Clark SJ, Kahn K, Houle B, et al. Young children's probability of dying before and after their mother's death: a rural South African population- based surveillance study. PLoS Med. 2013;10:e1001409.
8. Kamiya CA, Kitakaze M, Ishibashi-Ueda H, et al.. Different characteristic of peripartum cardiomyopathy between patients complicated with and without hypertensive disorders. Circulation J. 2011;75:1975-81.
9. Ntusi NB, Mayosi BM. Aetiology and risk factors of peripartum cardiomyopathy: A system-atic review. Int J of Cardiol. 2009;131:168-79.
10. Sliwa K, Hilfiker-Kleiner D., Petrie M., et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working group on peripartum cardiomyopathy. Eur J Heart Fail. 2010;12:767-78.
11. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. Lancet. 2006;368:687-93.
12. Abboud J, Murad Y, Chen-Scarabelli C, et al. Peripartum cardiomyopathy: A comprehen-sive review. Int J of Cardiol. 2007;118: 295-303
13. Modi KA, Illum S, Jariatul K, et al. Poor outcome of indigent patients with peripartum cardiomyopathy in the United States. Am J Obstet Gynecol. 2009;201:171e1 – e5
14. Gunderson EP, Croen LA, Chiang V, et al. Epidemiology of peripartum cardiomyopathy: Incidence, predictors, and outcomes. Am Coll Obs Gyn. 2011;1118(3): 583-591

15. Fett JD, Christie LG, Carraway RD, Murphy JG. Five-year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Proceed 2005; 80: 1602–06?
16. Lkhider M, Castino R, Bouguyon, E, et al. Cathepsin D released by lactating rat mammary epithelial cells is involved in prolactin cleavage under physiological conditions. J. Cell Sci. 2004;117:5155–64.
17. Hilfiker-Kleiner D, Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. Nat Rev Cardiol. 2014;11:364-70.
18. Elkayam U, Tummala PP, Rao K, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyop- athy. N Engl J Med. 2001;344:1567–71.