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ORIGINAL RESEARCH ARTICLE

Peripartum cardiomyopathy in Iraq: initial registry-based data and 6 month outcomes

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Abstract

Aims This study aimed to evaluate the clinical characteristics, echocardiographic measurements, medical treatment, pregnancy outcomes, and the 6 month follow-up outcomes among patients with peripartum cardiomyopathy (PPCM) in Iraq.

Methods and results Data were collected prospectively at cardio-maternal clinic in Baghdad Heart Center, using case report form for the EORP-PPCM registry from January 2015 to November 2020. Six month follow-up was performed either by attendance of patients or by phone contact. A total of 64 PPCM patients were enrolled with a mean age of 32.1 ± 6.8 years. Diagnosis in 35 (54.7%) women was made in the post-partum period. There was a history of previous PPCM in 9 (14%), coexisting hypertension with the current pregnancy in 30 (51.7%), cholelithiasis in 5 (7.8%), and cancer in 3 (4.7%). Baseline mean left ventricular ejection fraction (LVEF) was 34.7 ± 8.1%, significantly higher than that reported globally (31 ± 10%) (*P*-value 0.011), and 26 (40.6%) of our patients had LVEF of ≤34%. Baseline mean global longitudinal strain (GLS) for 26 (40.6%) patients was −9.4 ± 4.1%. Baseline mean left ventricular end-diastolic and end-systolic dimensions were 61.2 ± 8.5 and 50.6 ± 10.2 mm, respectively. At 6 month follow-up, 11 (36.7%) women recovered their LVEF, lower than global data (46%) but higher than that in the Middle East (25%) with *P*-value 0.241 and 0.919, respectively. The mean LVEF was 44.5 ± 11.9%, and the mean GLS for 15 (23.4%) of patients was −13.4 ± 5.3%, including 5 (33.3%) with the range of −18.6% to −17%. Bromocriptine was the least used drug in 4 (8.2%) vs. globally reported (15%) (*P*-value 0.188). Thrombo-embolic events and maternal death were reported in 2 (4.1%) and 3 (4.7%) cases, respectively, within 6 months.

Conclusions Around half of our PPCM patients were diagnosed at post-partum period with impaired initial LVEF and GLS, and one-third had early LVEF recovery at 6 month follow-up, higher than that in the Middle East but lower than the globally reported figure in the EORP-PPCM registry. Limited use of bromocriptine might explain the later finding. The co-morbid diseases in our setting were hypertension and cholelithiasis. Interestingly, the comparable ratios of neonatal and maternal mortalities in our study to that of the EORP-PPCM registry were found less than the Middle East figures. Bromocriptine needs to be considered in Middle East countries, including Iraq, which may be the key to improving LVEF recovery and perhaps reducing maternal mortality.

Keywords Peripartum cardiomyopathy; Iraq; Mortality; Pregnancy

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Introduction

No clear and detailed data about peripartum cardiomyopathy (PPCM) are available in Iraq yet. Since 2015, Iraq has been enrolled in the international EURObservational Research Programme—Peripartum Cardiomyopathy (EORP-PPCM) registry, and accordingly, the first PPCM service, at the currently only available cardio-maternal clinic, in the country was established.[1] The clinic is presently at Baghdad Heart Center at Baghdad Teaching Hospital in the Medical City, the biggest referral governmental medical complex city in Iraq, located in the capital city, Baghdad. Patients with confirmed PPCM or who are undiagnosed are referred to the clinic from both urban and rural areas related to Baghdad and other cities in Iraq. In 2017, global data about the first 411 enrolled PPCM patients in the EORP-PPCM registry were published.[2] In

2018, PPCM patients' enrolment was closed in the EORP-PPCM registry; however, we continued enrolling patients using the EORP-PPCM case report form.

The aim of this study is to evaluate the clinical characteristics, echocardiographic measurements, medical treatment, and pregnancy and 6 month follow-up outcomes for patients with PPCM in Iraq. Recently published data from the EORP-PPCM registry disclosed the current clinical practice gap in the management of PPCM, including the limited use of bromocriptine and a higher maternal mortality rate in the Middle East.[3] Therefore, detailed and large studies of PPCM patients in this region, including Iraq, will be of high importance to assist in identifying malpractice and bridging gaps and to suggest ways of reducing mortality and optimizing PPCM patient outcome. Such studies should be beneficial not only to our region but also to other low-income and middle-income countries, encouraging them to raise the standard of PPCM quality of care. Moreover, results from different Middle East countries will be helpful in comparing variations within the same region and will be step towards upgrading the current improper clinical practice.

Finally, the results of our study should be useful when considered along with other results from the Middle East and developing countries for strengthening other available evidence concerned with the use of bromocriptine, particularly when compared, later on, with the global results as a retrospective case–control study focusing on the association between the use of bromocriptine and maternal mortality.

Methods

Study design

Data were collected prospectively at the cardio-maternal clinic in Baghdad Heart Center/Medical City, from January 2015 until November 2020, using the case report form of the EORP-PPCM registry. Such form was used as the patient's medical record file at the clinic. Assessment of signs and symptoms of heart failure was performed by a senior consultant cardiologist. Baseline and follow-up data of the patients with a known PPCM, including treatment, were collected and documented initially by a cardiology clinical pharmacist along with the findings of a clinical examination, which had already been performed by a senior consultant cardiologist. Electrocardiogram (ECG) and echocardiography are performed and saved with the results within the case report form for each patient, and the collected data are re-evaluated by the senior consultant cardiologist during the heart team members meeting, during which a management plan for each patient is discussed. The data of the first 41 patients registered in the EORP-PPCM registry were rechecked by the remote monitor of the PPCM registry, as well as by the EORP-PPCM staff who monitor electronic data registration. Echocardiographic measurements for all patients were collected using GE Vivid E9 with an XDclear™ machine. The study was conducted according to the Declaration of Helsinki, and ethical approval was obtained. PPCM patients were enrolled according to the inclusion criteria of the EORP-PPCM registry: (i) peripartum state [no precise time windows were mandated as per the 2010 European Society of Cardiology (ESC) Position Statement]; (ii) signs and/or symptoms of heart failure; (iii) left ventricular ejection fraction (LVEF) $\leq$45%; and (iv) exclusion of other causes of heart failure.[3] Six month follow-up was performed either by attendance of the patients at the cardio-maternal clinic using ECG and echocardiograph or by using telemedicine particularly during the COVID-19 era.

Statistical analysis

Categorical variables were presented as numbers and percentages and compared using χ^2 test, whereas continuous variables were presented using mean and standard deviation and compared using Student's *t*-test. A *P*-value of <0.05 was considered statistically significant. The statistical analysis was performed using Excel for Mac, Version 15.13.3, and SigmaPlot Version 14.5 (Systat Software, Inc., San Jose, CA, USA).

Results

Baseline characteristics

The total number of patients with confirmed PPCM was 64, with a mean age of 32.1 ± 6.8 years. History of PPCM was documented in 9 (14%) patients, and hypertension during the current pregnancy was found in 30 (51.7%) patients. Other co-morbid diseases were cholelithiasis in 5 (7.8%), as well as hypothyroidism, asthma, thrombo-embolism, and cancer, each accounting for 3 (4.7%), as shown in *Table 1*.

Clinical variables, echocardiogram, and electrocardiogram measurements

Mean LVEF was 34.7 ± 8.1%, and 26 (40.6%) of patients had LVEF $\leq$ 34%. The mean global longitudinal strain (GLS) for 26 (40.6%) patients was -9.4 ± 4.1%, and mitral regurgitation was found in 30 (46.9%) patients. ECG showed left bundle branch block and left ventricular hypertrophy in 5 (9.6%) and 7 (13.5%) patients, respectively (*Table 2*).

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Table 1 Baseline characteristics of Iraqi patients with peripartum cardiomyopathy

Age (years)	*n*		64
	Mean ± SD		32.1 ± 6.8
Education	*n* (%)	Primary	33/56 (58.9)
		Secondary	13/56 (23.2)
		High school	5/56 (8.9)
		College	5/56 (8.9)
Parity	*n* (%)	Para 0	12/61 (19.7)
		Para ≥1	49/61 (80.3)
Hypertension during current pregnancy	*n* (%)		30/58 (51.7)
History of previous PPCM (subsequent pregnancy)	*n* (%)		9/64 (14)
Co-morbid	*n* (%)	Cholelithiasis	5/64 (7.8)
		Hypothyroidism	3/64 (4.7)
		Asthma	3/64 (4.7)
		Thrombo-embolism	3/64 (4.7)
Cancer	*n* (%)	Previous history of HL	2/64 (3.1)
		Tongue cancer after PPCM	1/64 (1.7)
Time of diagnosis	*n* (%)	Prepartum	29/64 (45.3)
		Post-partum	35/64 (54.7)
Mode of delivery	Prepartum, *n* (%)	CS	14/22 (63.6)
		NVD	8/22 (36.4)
	Post-partum, *n* (%)	CS	19/34 (55.9)
		NVD	15/34 (44.1)

CS, caesarean section; HL, Hodgkin's lymphoma; NVD, normal vaginal delivery; PPCM, peripartum cardiomyopathy; SD, standard deviation.

Table 2 Baseline clinical variables, electrocardiogram, and echocardiogram measurements in Iraqi patients with peripartum cardiomyopathy

Vital signs		
SBP (mmHg)	*n*	59
	Mean ± SD	123.5 ± 23.8
DBP (mmHg)	*n*	59
	Mean ± SD	81.2 ± 16
HR (b.p.m.)	*n*	61
	Mean ± SD	100.2 ± 21.7
ECG		
LBBB	*n* (%)	5/52 (9.6)
LVH	*n* (%)	7/52 (13.5)
Atrial fibrillation	*n* (%)	2/52 (3.85)
Echocardiogram		
LVEF%	*n*	64
	Mean ± SD	34.7 ± 8.1
LVEF ≤ 34%	*n* (%)	26/64 (40.6%)
GLS%	*n*	26
	Mean ± SD	−9.4 ± 4.1
LVEDD (mm)	*n*	60
	Mean ± SD	61.2 ± 8.5
LVESD (mm)	*n*	55
	Mean ± SD	50.6 ± 10.2
Mitral regurgitation	*n* (%)	30/64 (46.9)
Left ventricular thrombus	*n* (%)	1/64 (1.7)

DBP, diastolic blood pressure; ECG, electrocardiogram; GLS, global longitudinal strain; HR, heart rate; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; SD, standard deviation.

Medications over 6 months

Among 49 (76.6%) patients with a documented medication profile over the first 6 months, beta-blockers (including bisoprolol, carvedilol, and metoprolol succinate) were prescribed for 45 (91.8%) patients. Angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and angiotensin receptor-neprilysin inhibitor (ARNI) were used in 36 (73.5%), spironolactone in 20 (40.8%), anticoagulant in 11 (22.45%), digoxin in 4 (8.2%), and bromocriptine in 4 (8.2%) (*Figure 1*).

Pregnancy outcomes

Caesarean section was the most common mode of delivery, performed for 33 (51.6%) patients. Out of 64 pregnant patients enrolled in this series, there were 48 (75%) live deliveries, including six twins and one triplet, making a total of 56 alive babies, from whom 4 (4.1%) neonates were lost. The mean birth weight for the live-born babies was 2.5 ± 0.8 kg, and of note, among them, there were 24 (44.4%) including two of the dead neonates, whose birth weight was less than 2.5 kg (*Figure 2*).

Six month outcomes

At 6 months, LVEF was measured for 30 (46.9%) patients, LVEF recovered in 11 (36.7%), mean LVEF was 44.5 ± 11.9%, and mean GLS for 15 (23.4%) patients was −13.4 ± 5.3%, with 5 (33.3%) of them ranging between −18.6% and −17%. Maternal mortality within 6 months after diagnosis was reported in 3 (4.7%) patients due to sudden cardiac death, torsade de pointes, or heart failure. Among 9 (14.1%) cases with previous history of PPCM, 6 (66.7%) patients were alive and 3 (33.3%) patients missed follow-up. Two out of 49 (4.1%) patients had thrombo-embolic events (*Table 3*).

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Figure 1 Patient drug profile during the first 6 months among Iraqi patients with peripartum cardiomyopathy. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist.

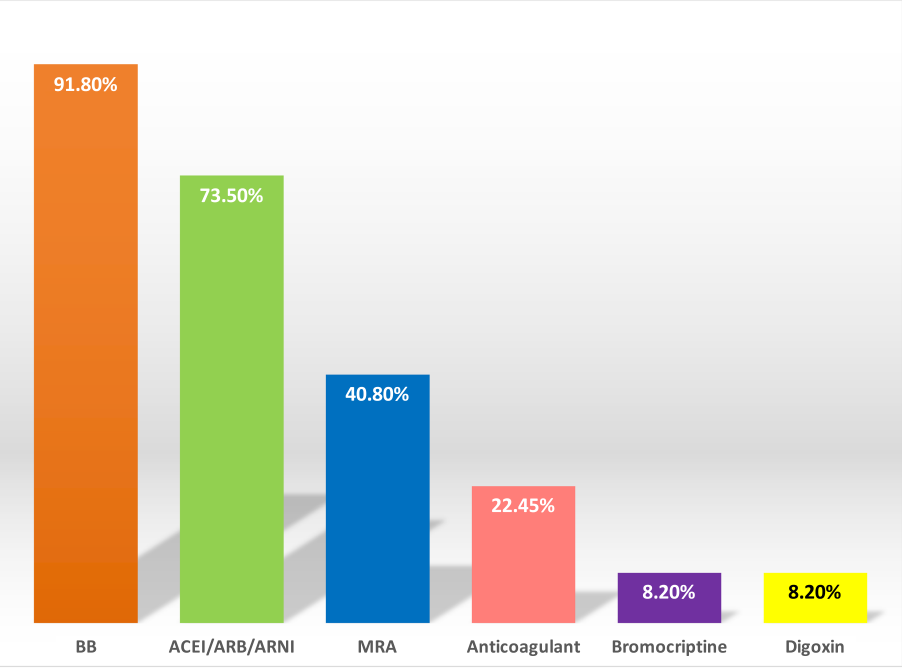
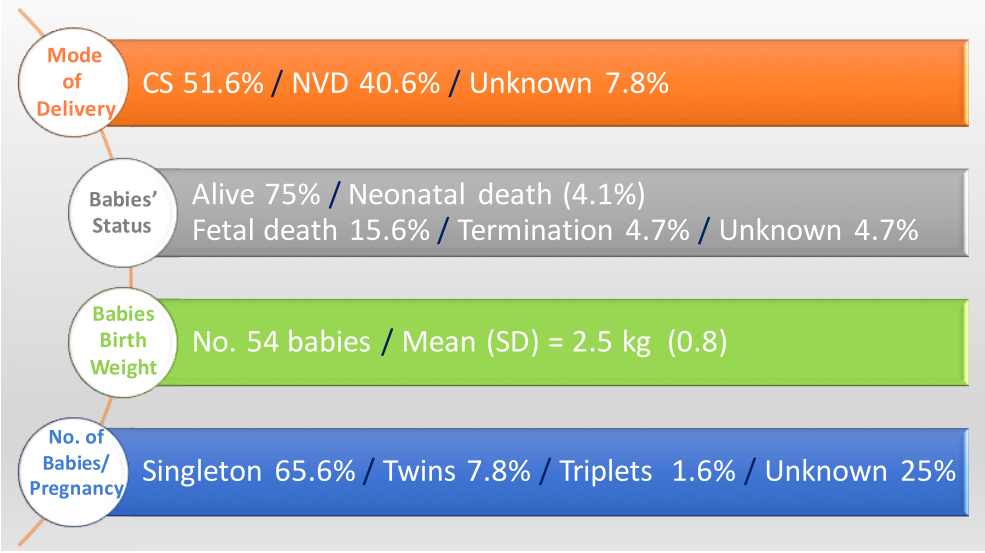


Figure 2 Pregnancy outcomes among 64 Iraqi patients with peripartum cardiomyopathy. CS, caesarean section; NVD, normal vaginal delivery; SD, standard deviation.



Discussion

To our knowledge, this is the first detailed, registry-based, and prospectively collected data about PPCM in Iraq, with more than half of the patients diagnosed in the post-partum period, some of whom had a previous history of PPCM (subsequent pregnancy). Although the subsequent pregnancy in patients with PPCM is associated with a 12% mortality rate, still there are some patients with unplanned pregnancy who refuse an abortion.[4] Hypertension was the most common co-morbid

Table 3 Six month follow-up outcomes in Iraqi patients with peripartum cardiomyopathy

Echo		
LVEF%	*n* (%)	30/64 (46.9)
	Mean ± SD	44.5 ± 11.9
LVEF ≥ 50%	*n* (%)	11/30 (36.7)
GLS%	*n*	15
	Mean ± SD	−13.4 ± 5.3
GLS ≤ −17%	*n* (%)	5/15 (33.3)
LVEDD (mm)	*n*	28
	Mean ± SD	59.1 ± 8.7
LVEDD ≥ 60 mm	*n* (%)	14/28 (50)
LVESD (mm)	*n*	26
	Mean ± SD	46.3 ± 10.4
Thrombo-embolic events		
DVT	*n* (%)	2/49 (4.1)
Maternal mortality		
Death	*n* (%)	3/64 (4.7)

DVT, deep vein thrombosis; GLS, global longitudinal strain; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; SD, standard deviation.

disease, followed by cholelithiasis. There was a significant association between gallstone disease and heart failure, and cholelithiasis was reported in 58.6% of patients with heart failure vs. 38% in the general population.[5,6] The association between cardiovascular disease and cholelithiasis may be related to shared risk factors, which include obesity, physical inactivity, and hypertension.[7] Other co-morbid disease among the studied patients was cancer, and of note, recently published data reported that the risk of cancer both before and after diagnosis with PPCM was 9-fold and 16-fold greater, respectively, compared with age-matched women without PPCM.[8] Baseline mean LVEF was comparable with that in the Middle East (35 ± 9%) but significantly higher than the findings in the EORP-PPCM registry (31 ± 10%) (*P*-value 0.011).[3,9] Mean left ventricular end-diastolic and systolic diameters in our cohort approximate those in patients from the Middle East 62 ± 8 and 51 ± 9 mm, respectively, although they were higher than those in other regions, such as Asia-Pacific 55 ± 6 and 46 ± 7 mm, respectively, as shown in the EORP-PPCM registry.[3] Low mean GLS was found among the patients. Data about the role of GLS in PPCM are controversial, with recent evidence showing an association between baseline impaired GLS and poor subsequent clinical outcomes, including death and unrecovered LVEF, while impaired GLS is considered a more sensitive marker for persistent left ventricular dysfunction, even after normalization of LVEF values.[10–12] Regarding the treatment strategy for PPCM, the most commonly prescribed anti-failure agent in Iraq was beta-blocker, higher than that reported in the global (81%) and Middle East (75%) registries, *P*-value 0.059 and 0.02, respectively.[3,9] This might be explained by the significantly lower mean of the heart rate among PPCM patients in the Middle East registry group (79.7 ± 10.8), compared with that recorded in Iraq (*P*-value <0.001).[9] However, in the global registry, the heart rate was 100 ± 22, comparable with that in Iraq (*P*-value <0.997).[3] In both global and Middle East patients, the most commonly prescribed drug group was ACEI/ARB in 85% and 86% of cases, respectively, while ACEI/ARB/ARNI was the second most commonly group prescribed in Iraq, an issue that may be related to the lower mean systolic and diastolic blood pressure readings among PPCM patients in Iraq compared with that in the Middle East, 125.5 ± 28.8 and 83.4 ± 21 mmHg, respectively.[3,9] Anticoagulant use was significantly higher in Iraq compared with its use in the global registry (16%) (*P*-value <0.024). Notably, the use of anticoagulant in our study was not used for PPCM severity *per se* but was rather prescribed in a prophylactic dose concomitantly with bromocriptine or in a therapeutic dose for atrial fibrillation or thrombo-embolic event.[3] Bromocriptine was the least used drug in our setting, lower than the globally reported figure of 15% (*P*-value <0.188).[3] Data about using bromocriptine in the Middle East were available from the EORP-PPCM registry, whereas such data were lacking from the Middle East cohort study.[3,9] Thus, the Middle East was the region least using bromocriptine for the management of PPCM patients despite the recommendation of the Heart Failure Association of the ESC Study Group on PPCM, as well as the new recommendation in the 2018 ESC guidelines, which emphasized the use of bromocriptine post-delivery in PPCM patients with different severity of LVEF, due to its beneficial effect on the cessation of lactation, enhancement of LVEF recovery, and reduction in mortality.[3,13,14] The reason for the limited use of bromocriptine in the Middle East registry was not clear. In Iraq, some cardiologists avoid prescribing bromocriptine for PPCM patients for a number of reasons, including the cost issue related to the use of concomitant prophylactic anticoagulant, the possibility of the patient missing a follow-up, the mother's wish to continue breastfeeding, symptomatic hypotension that might necessitate the cessation of the drug, or the level of evidence (Class IIb) in the guidelines.[14] Data from the EORP-PPCM registry revealed that prescribing guideline-directed medical therapy for heart failure was similar globally, including in Iraq, something that may be explained by the impact of the enrolment in the PPCM registry and by following the updated ESC guidelines for the management of cardiovascular disease during pregnancy.[3,14] Pregnancy outcomes showed caesarean section as the most common mode of delivery, whether the patients were diagnosed with PPCM in the post-partum or prepartum period. Unlike global data in the EORP-PPCM registry, in which normal vaginal delivery was the main mode among those diagnosed in their post-partum period compared with those diagnosed in the prepartum period (caesarean section was 46% vs. 59%, and normal vaginal delivery was 53% vs. 33%).[3] The same thing was noticed in the Middle East registry (caesarean section was 47% vs. 59%, and normal vaginal delivery was 52% vs. 22%).[3] According to the United Nations estimation in 2017, neonatal mortality in Iraq was 17 per 1000.[15] Interestingly, while the neonatal mortality in the current study was comparable with that of the

EORP-PPCM registry (5%) (*P*-value 0.635), it was found less than the Middle East rate of 9% (*P*-value 0.207).[3] At 6 month follow-up, most of PPCM patients who had a previous history of PPCM were alive. The rate of LVEF recovery was higher than that registered in the Middle East (25%) but lower comparing with that in the global group data of 46%, with *P*-value 0.241 and 0.919, respectively. The latter finding may be explained by the low baseline LVEF and GLS, higher baseline left ventricular end-diastolic diameter among our patients, limited use of bromocriptine, and multiparity.[3] Such details are in line with the available data concerned with the predictors of delayed LVEF recovery showing that left ventricular end-diastolic dimension $\geq$60 mm, multiparity, LV thrombus, and initial LVEF $<$ 34% are predictors for delayed LVEF recovery, while use of bromocriptine is an independent predictor of early recovery.[3,10–12,16–20] Furthermore, post-partum diagnosis of PPCM is a predictor of early LVEF recovery.[21] Of note, the 6 month maternal mortality rate was comparable with the European rate of 4% but less than the Middle East group rate of 10% and that was mostly attributed to the setting up of the new services for PPCM patients in Iraq that raised the standard of care for such patients leading to a reduction in the mortality rate.[1,3] Loss of follow-up at 6 months in most of our patients could be due to lack of experience in registration, as the EORP-PPCM registry was the first international registry in cardiology enrolling Iraq. However, patient follow-up was improved by using telemedicine, inviting the patient's family in the first patient heart team interview to increase their confidence with the care of the heart team, and by introducing new PPCM patients to previous patients in order to share their experiences regarding their condition and outcomes.[1]

In summary, the current study showed for the first time in our setting the clinical pattern and outcomes of PPCM patients in Iraq, and it highlighted newly documented data about the presence of cholelithiasis among our patients. Such information needs to be studied in the future with more details as a possible predictor for early or late LVEF recovery. This study also disclosed the essential and vital role of the EORP-PPCM registry and its case report form, which provided the initiative to establish the first PPCM service in Iraq, along with the collection of a thoughtful database and lessons that may be beneficial for both developed and developing countries. More importantly, our data showed that maternal and neonatal mortalities at 6 month follow-up were lower than that in the Middle East report, with higher rate of LVEF recovery. Thus, other countries in this region, in addition to other low-income and middle-income countries, may benefit from our PPCM service experience as a template for improving their clinical practice, such as by placing an emphasis on following the updated ESC guidelines in the management of PPCM patients and by including a cardiology clinical pharmacist in the heart clinic team. Although the set-up of a special service for PPCM in Iraq and the presence of expert heart team members, along with using guideline-directed medical therapy of heart failure for managing PPCM patients, had improved our results leading to less maternal as well as neonatal mortality compared with the Middle East group, early LVEF recovery was still lower than that reported globally. The reason behind that might be strongly related to the limited use of bromocriptine in our setting, and thus, our data can be used, together with similar global data, in a retrospective case–control study to strengthen the evidence regarding the important role of bromocriptine for early LVEF recovery. Consequently, this may upgrade the recommendation of bromocriptine in the management of PPCM.

Limitation

Global longitudinal strain was not performed for all patients because it was not available at the beginning of the study.

Conclusions

The current registry-based study data revealed that about half of our PPCM patients were diagnosed at the post-partum period with impaired initial LVEF and GLS, and one-third had early LVEF recovery at 6 month follow-up, higher than that in the Middle East but lower than the globally reported figure in the EORP-PPCM registry. Limited use of bromocriptine might be a cause. The most common coexisting diseases in our setting was hypertension, followed by cholelithiasis. Interestingly, we reported a neonatal and maternal mortality ratio comparable with that of the EORP-PPCM registry and less than the Middle East figures. Finally, bromocriptine needs to be considered in the Middle East countries, including Iraq, as a key for improving LVEF recovery and perhaps reducing maternal mortality.

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Conflict of interest

None declared.

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