

ORIGINAL ARTICLE

The rationale and design of the national peripartum cardiomyopathy registries in Turkey: The ARTEMIS-I and ARTEMIS-II studies

Türkiye'deki peripartum kardiyomiyopati kayıt çalışmalarının temeli ve tasarımı: ARTEMIS-I ve ARTEMIS-II çalışmaları

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ABSTRACT

Objective: Peripartum cardiomyopathy (PPCM) is left ventricular (LV) systolic dysfunction with an ejection fraction of $\leq 45\%$ occurring in the later stages of pregnancy or soon after delivery. Although various risk factors have been identified, the exact cause of the disease is unknown. Unlike most countries in the European region, Turkey has yet to determine the current PPCM burden. A registry for this purpose does not exist. To close this gap, the A RegisTry of pEripartuM cardlomyopathy in Turkish patientS (ARTEMIS-I and ARTEMIS-II), was planned and endorsed by the Turkish Society of Cardiology. The aim of this manuscript is to describe the rationale and design of the ARTEMIS-I and ARTEMIS-II registries.

Methods: ARTEMIS was designed to be the nationwide PPCM registry of Turkey, with the goal of identifying problems and opportunities while improving quality and consistency in the medical care of PPCM patients. A second goal is to determine the clinical characteristics pertinent to patients in this region. The ARTEMIS registry will consist of 2 arms. All secondary and tertiary cardiology centers have been electronically invited to participate in ARTEMIS-I, which will be conducted to assess the current standard of care and outcome measures. Centers will be asked to enroll PPCM patients admitted to their clinic in last 5 years retrospectively. Eligibility criteria will consist of pregnant or early postpartum woman without a previous history of heart failure (HF) or known pathology associated with HF, LV ejection fraction $\leq 45\%$, and exclusion of other causes of LV systolic dysfunction. ARTEMIS-II will consist of the prospective enrollment of patients.

Conclusion: The nationwide PPCM registries, ARTEMIS-I and ARTEMIS-II, are designed to determine the current status of medical care, provide insights into nature of the disease, and suggest solutions on how to improve care and outcomes in these patients.

ÖZET

Amaç: Peripartum kardiyomiyopati (PPKM) gebeliğin ilerleyen safhalarında ya da lohusalığın ilk aylarında gelişen ve sol ventrikül (SoLV) ejeksiyon fraksiyonunun $\leq 45\%$ olduğu SoLV sistolik işlev bozukluğudur. Birçok farklı risk faktörü belirlenmiş olmakla birlikte hastalığın kesin nedeni bilinmemektedir. Bu boşluğu doldurmak amacıyla, Türk Kardiyoloji Derneği desteğiyle, Türk PPKM kayıt çalışmaları ARTEMIS-I ve ARTEMIS-II planlanmıştır. Bu yazı ARTEMIS-I ve II çalışmalarının temel ve tasarımını tanımlamayı amaçlamaktadır.

Yöntemler: ARTEMIS çalışmasında PPKM hastalarının tıbbi bakımında yaşanan sorunlar tespit edilirken aynı zamanda bu hastalığın bakımında kalite ve tutarlılığın iyileştirilmesi amacıyla, Türkiye'nin ulusal PPKM kayıt çalışması olarak tasarlandı. Bölgedeki hastalara özgü klinik karakteristiklerin saptanması da ek olarak amaçlandı. ARTEMIS kayıt çalışmasının iki koldan oluşması planlanmaktadır. ARTEMIS-I'de mevcut bakım standartlarının ve sonlanım ölçütlerinin değerlendirilmesi amacıyla ikinci ve üçüncü basamak bütün kardiyoloji merkezleri elektronik olarak çalışmaya davet edilecektir. Bu merkezlerden, son 5 yılda başvuran tüm PPKM hastalarını geriye dönük olarak dahil etmeleri istenecektir. Uygunluk kriterleri: gebe veya yeni doğum yapmış kadın olması, daha önceden bilinen kalp yetersizliği (KY) veya KY ile ilişkilendirilmiş bilinen patolojisi olmaması, SoLV ejeksiyon fraksiyonunun $\leq 45\%$ olması, SoLV sistolik işlev bozukluğunun diğer nedenlerinin dışlanmasından oluşacaktır. ARTEMIS-II'de ise hastaların ileriye dönük olarak çalışmaya dahil edilmesi amaçlanmıştır.

Sonuç: Ulusal PPKM kayıt çalışmaları ARTEMIS-I ve ARTEMIS-II, tıbbi bakımın mevcut durumunu belirlemek, hastalığın doğasına ilişkin içgörüyü sağlamak ve bu hastaların bakımının ve sonlanımlarının iyileştirilmesine yönelik çözümler geliştirmek amacıyla tasarlanmıştır.

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Peripartum cardiomyopathy (PPCM) is the development of heart failure (HF) during the late stages of pregnancy or early puerperium in a previously asymptomatic woman, provided that alternative causes of myocardial dysfunction are excluded. Left ventricular (LV) ejection fraction is often reduced to well below 45%.^[1] Mortality rates of up to 1 in 10 cases and recurrence rates up to half have been reported. There is a substantial risk of residual LV dysfunction, and pregnancy is deemed World Health Organization Grade IV, hence contraindicated, in these cases, due to a dismal prognosis.^[2]

There is considerable variation of PPCM frequency in different populations. While the estimated incidence in the USA is roughly 1 in 3189 live births, incidences up to 1 in 300 live births have been reported.^[3,4]

Considering the scarce data on this condition, a PPCM working group of the Heart Failure Association of the European Society of Cardiology (ESC) started collecting data with a standardized survey questionnaire under the EURObservational Research Programme. This registry had the goal of defining demographic and clinical characteristics, as well as outcome data for 1000 women all around the world. Turkey was represented by only a few patients in this cohort.^[5] While the EURObservational survey is looking into comparable characteristics of PPCM patients from all around the world, another registry program, also endorsed by ESC, has been designed to enroll patients prospectively.^[6] Recently published initial results of this registry revealed a significantly high rate of embolic events in the overall cohort, a significantly increased frequency of HF at 1 year following the first episode, and significant differences between EU and non-EU countries with respect to several parameters.^[7]

A Registry of pEripartuM cardiomyopathy in Turkish patients (ARTEMIS) program was designed to be a conjoint PPCM registry for Turkey, planned under the umbrella of the worldwide PPCM registry, and was endorsed and sponsored by the Turkish Society of Cardiology. The aim of this manuscript is to define the rationale and design of the ARTEMIS-I and

Abbreviations:

ARTEMIS	A Registry of pEripartuM cardiomyopathy in Turkish patients
HF	Heart failure
ICD	International Classification of Diseases
IRB	Institutional review board
LV	Left ventricular
PPCM	Peripartum cardiomyopathy
QOL	Quality of life

ARTEMIS-II studies, which are, respectively, the retrospective and prospective arms of ARTEMIS.

METHODS

The main goal of the ARTEMIS studies is to evaluate the current standard of care and clinical properties of PPCM patients in Turkey. Women older than 18 years of age, presenting with HF with a LV ejection fraction $\leq 45\%$ during the last months of pregnancy or first 6 months of puerperium will be enrolled, if alternative causes of LV systolic dysfunction are ruled out.^[8] The diagnostic criteria of PPCM are summarized in Table 1.

ARTEMIS-I, is a retrospective, national, multi-center, observational study, which was designed to provide insight into the clinical status of women with PPCM in Turkey. The primary objective is to identify the real-life clinical characteristics of PPCM, including the demographic and possible etiological and prognostic factors. Additionally, defining the short- and long-term outcomes, management, and diagnostic work-up are among the objectives of ARTEMIS-I. The inclusion criteria include age ≥ 18 years, diagnosis of PPCM (unexplained HF symptoms developed toward the end of pregnancy or in the first 6 months of the postpartum period with an ejection fraction $< 45\%$ documented with echocardiography). Patients with any other known cardiac pathology will be excluded. The study will enroll all PPCM patients admitted to participating centers within the last 5 years. All cardiology centers have been invited to participate in the ARTEMIS-I study by electronic letter. An invitation was also presented on the website of the Turkish Society of Cardiology. Several sociodemographic, clinical parameters of the mother and the newborn, as well as laboratory and imaging results, pharmacotherapy during initial diagnosis, and follow-up will be col-

Table 1. Definition of PPCM by HFA of the ESC

- Idiopathic cardiomyopathy
- Presenting with heart failure secondary to left ventricular systolic dysfunction with a LVEF of less than 45%
- Towards the end of pregnancy or in the months following delivery
- Where no other cause of heart failure is found

ESC: European Society of Cardiology; HFA: Heart Failure Association; LVEF: Left ventricular ejection fraction; PPCM: Peripartum cardiomyopathy.

Table 2. Data to be collected in the ARTEMIS registry

Demographic information	Diagnostic criteria	Risk factors	Other past medical history	Accompanying CVD	Obstetric history	Family history	Information regarding the pregnancy during which PPCM developed
Date of visit	Age >18 years old	Gestational DM	Cerebrovascular accident	ASCVD	Gravida	Multiple pregnancy	Presenting symptoms
Date of birth	Unexplained heart failure in the last month of pregnancy or in the first 6 months of lactation	Gestational HTN	HPL	MI	Para	CV risk factors	Rank of the pregnancy during which PPCM developed
Level of education	Chronic HTN	Chronic HTN	Renal disease	Coronary revascularization	Abortus	HF/CMP and the relationship and age in whom these complications developed	DOD
Economic status	DM and type of DM	DM and type of DM	Pulmonary disease	Severe primary valvular disease	D/C and the indication	Week and stage of the pregnancy during which symptoms appeared and PPCM developed	Week and stage of the pregnancy during which symptoms appeared and PPCM developed
Type of hospital admission (inpatient vs outpatient)	LVEF less than 45%	Tobacco exposure	Other significant disease not mentioned in the list	Severe secondary valvular disease and DOD for these diseases	CV or non-CV complications in previous pregnancies	Last menstruation	Last menstruation
	Other cardiac pathology	Alcohol exposure			ICD/CR implantation	CV risk factors	CV risk factors
	Other cardiac pathology that could explain the clinical picture	HIV/AIDS			Multiple birth	Alcohol use	Alcohol use
		Connective tissue disease			History of labor induction in previous pregnancies	HIV	HIV
					Surgical or interventional treatment for these diseases	Connective tissue disorder	Connective tissue disorder
					Other CVD not mentioned in the list and DOD	Cerebrovascular disease	Cerebrovascular disease
						Pulmonary disease	Pulmonary disease
					Total duration of breastfeeding in previous pregnancies	Induction of labor	Induction of labor
					HF during pregnancy or lactation	Total duration of breastfeeding during the pregnancy during which PPCM developed	Total duration of breastfeeding during the pregnancy during which PPCM developed
					Age of pregnancy during which mortality occurred	Date of delivery	Date of delivery
						Gestational HTN	Gestational HTN
						Gestational DM	Gestational DM
						Gestational HPL	Gestational HPL
						Confirmation of PPCM diagnosis	Confirmation of PPCM diagnosis
						The modality used for confirmation of PPCM	The modality used for confirmation of PPCM
						Important differential diagnosis if PPCM diagnosis was not confirmed	Important differential diagnosis if PPCM diagnosis was not confirmed

AIDS: Acquired immunodeficiency syndrome; ASCVD: Atherosclerotic cardiovascular disease; CMP: Cardiomyopathy; CRT: Cardiac resynchronization therapy; CVD: Cardiovascular disease; D/C: Dilation and curettage; DM: Diabetes mellitus; DOD: Date of diagnosis; HF: Heart failure; HIV: Human immunodeficiency virus; HPL: Hyperlipidemia; HTN: Hypertension; ICD: Implantable cardioverter-defibrillator; LVEF: Left ventricle ejection fraction; MI: Myocardial infarction; PPCM: Peripartum cardiomyopathy.

Table 2. Data to be collected in the ARTEMIS registry (cont'd)

Physical examination	Clinical status during presentation	Mechanical support during hospitalization	Intravenous therapy during hospitalization	Per oral therapy during hospitalization	Other treatment during hospitalization	Health status of the newborn	Assessments	Follow-up Variables	Transplantation
Height	Acute HF syndrome	CPR	Furosemide	Beta blocker	Insulin	Single or multiple birth	ECG	Date of last follow-up visit and outcome	Date of transplantation, if present
Weight	Inpatient or outpatient management	MV duration	Nitrate	ACEI	OAD	Vitality	CXR	Date of complete recovery, if detected	Last LVEF
Waist Circumference	Preliminary diagnosis	NIMV duration	Magnesium	ARB	Allopurinol	Weight	Imaging	Other diagnoses during follow-up and DOD	Date of withdrawal of heart failure medication, if withdrawn
BP	Referring department	LVAD duration	Digoxin	ARNI	NSAID	Head circumference	ECHO		
Pulse rate	DOD	ECMO duration		AA	Antidepressant	APGAR (1 minute)	CMR		
Respiratory rate		Rhythm device and type of device		Alpha blocker	Blood and blood products	APGAR (5 minute)	LAB (total cholesterol, triglycerides, HDL, LDL, TSH, FBG, HbA1c, liver enzymes, uric acid, HsCRP, erythrocyte sedimentation rate, cardiac enzymes, BNP)		
Body temperature		IV inotrope use		Alpha methyl dopa		Anomalies of the baby, if present			
SaO2				Hydralazine					
NYHA class				Nitrate					
Consciousness symptoms				CCB					
Hyperfusion signs and symptoms				Antiarrhythmic					
Pulmonary edema				Antiaggregant					
s3				Anticoagulant					
Rales				Bromocriptine					
Pleural effusion				Other drug not mentioned in this list					
PTE									
JVD									

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor neprilysin inhibitor; AA: Aldosterone antagonist; BP: Arterial blood pressure; BNP: Brain natriuretic peptide; FBG: Fasting blood glucose; HbA1c: Glycated hemoglobin; HF: Heart failure; HsCRP: High sensitivity C-reactive protein; CCB: Calcium channel blocker; CMR: Cardiac magnetic resonance imaging; CPR: Cardiopulmonary resuscitation; CXR: Chest X ray; DOD: Date of diagnosis; ECHO: Echocardiography; ECMO: Extracorporeal membrane oxygenation; HDL: High density lipoprotein; IV: Intravenous; JVD: Jugular venous distention; LAB: Laboratory values; LDL: Low density lipoprotein; LVAD: Left ventricular assistance device; LVEF: Left ventricular ejection fraction; MV: Mechanical ventilation; NSAID: Non-steroid antiinflammatory drug; NIMV: Noninvasive mechanical ventilation; NYHA: New York Heart Association; OAD: Oral antidiabetic; PTE: Prethibial edema; SaO2: Arterial oxygen saturation; S3: Third heart sound; TSH: Thyroid stimulating hormone.

lected by the investigators from the patients' medical records. The data to be collected in ARTEMIS-I are summarized in Table 2.

ARTEMIS-II will prospectively enroll at least 500 PPCM patients from 50 cardiology centers representing the 24 statistical regions in Turkey based on the European Union nomenclature of territorial units for statistics classification and proportional to the latest population distribution of Turkey.^[9] Primary objectives will be also an evaluation of the management and clinical outcomes in PPCM patients. As secondary goals, the utilization of diagnostic modalities and medical treatment and outcome variables will be examined in comparison with the ARTEMIS-I registry. Another aim of this study is the foundation of an ongoing electronic database for the enrollment of virtually all future patients presenting at participating institutions, enabling big-data analysis in the coming years. In addition, quality of life (QOL) and follow-up data will be collected (Table 2). Two documents will be completed for the ARTEMIS-II registry. The first form will be completed by the investigator, and will consist of clinical, demographic, and outcome data to be completed as the follow-up progresses. The second form will be completed by the patient and will consist of quality of life (QOL)-14 questionnaire and the Hospital Anxiety Depression Score, and a third, custom questionnaire to assess the knowledge and attitude of the patient regarding the disease. Primary goals will be freedom from persistent HF, evaluation of cardiovascular outcomes occurring during follow-up, and the utilization of advanced HF treatments, such as cardiac resynchronization therapy, extracorporeal membrane oxygenation, an LV assist device, or heart transplantation. Secondary goals consist of increasing awareness about the disease and promoting early diagnosis.

Both registry protocols have been reviewed by the Ege University Institutional Review Board (IRB). The ARTEMIS-I protocol was approved with reference number 17-5.1/15 on June 20, 2017, and approval of ARTEMIS-II is currently pending. ARTEMIS-I is registered with www.clinicaltrials.gov (NCT03364140). Written informed consent will be obtained from all participants of ARTEMIS-II. The main IRB approval document was provided to centers upon acceptance of the invitation to the study. Investigators from each center obtained written permission from their local

institutional authorities and/or their local IRB for ARTEMIS-I, when requested. Informed consent will be obtained from all patients in the prospective arm (ARTEMIS-II). No interventional diagnostic or therapeutic approaches will be carried out in these programs.

The accuracy of the collected data will be verified by source document control by a data safety monitoring board using a random sample corresponding to 5% of the data collected in the respective center. Standard, commonly used statistical methods will be applied. A P value of less than 0.05 will be set for statistical significance. Descriptive measures will constitute the basis of the statistical analysis in the study cohort. The Student's t-test will be used for continuous variables, analysis of variance will be used for categorical variables, and Pearson's chi-square test will be used for binominal variables. Univariate analysis and logistic regression analysis will be used in the assessment of factors associated with outcomes. Survival analysis with selected statistical methods will be carried out to interpret the outcome data. A log-rank test will be used as needed when assessing the effect of factors associated with hazard and survival rates.

DISCUSSION

PPCM is a rare disease of young women, and has a poor prognosis. A wide range of prevalence values has been reported in different populations, such as 1 in 1149–4350 in the USA, 1 in 1000 in South Africa, and 1 in 300 in Haiti.^[3,10–18] The prognosis of PPCM also demonstrates geographic variations. Therefore, a genetic basis is one of the most suggested mechanisms in the etiopathogenesis of PPCM.^[19] Other etiologies, including inflammation, viral myocarditis, abnormal immune or hemodynamic response to pregnancy, increased oxidative stress, and malnutrition, have also been proposed.^[20]

For Turkey, there are only a few studies investigating PPCM, and its incidence is not known. Duran et al.^[21] reported a mortality rate of 30% over a 4-year follow-up period of 32 patients from a single tertiary center. Biteker et al.,^[22] found a mortality rate of 25% in 24 patients during a mean follow-up period of 20.9±9 months. Akil et al.^[23] reported a 15% mortality rate in 58 patients with PPCM during a mean follow-up of 32±22 months from 3 tertiary centers located

in eastern Turkey. None of these studies investigated the incidence of PPCM. However, a well-known high rate of consanguinity of 23.2% in the general Turkish population, might contribute to a high prevalence of PPCM in the country.^[24] Moreover, due to the different clinical profile of PPCM reported in different populations, defining the characterization of the geographical and the racial presentation of PPCM is extremely important to illuminate the etiopathogenesis and to improve the approach to these patients.^[16] Therefore, a national registry of PPCM patients is urgently needed in Turkey.

Diagnosis might be shadowed by the fact that dyspnea, palpitations, and lower extremity edema, which are the classic findings in PPCM, are relatively common in pregnant or lactating women.^[25] Making the diagnosis of PPCM is simply an area of debate, because it is suggested that many cases with a diagnosis of PPCM are simply exacerbation of previously sub-clinical LV systolic dysfunction due to other causes of dilated cardiomyopathy or myocarditis, since pregnancy is associated with increased intravascular volume, salt and water retention, and altered hemodynamic demand. Administration of conventional HF treatments is challenging, most of the time due to concerns about the fetal health in the prenatal period and transmission of medications to breastmilk in the post-natal period.^[26] Use of other drugs, such as ivabradine, levosimendan and cabergoline, is suggested in the literature, though the benefit of these agents needs to be proven by randomized controlled trials.^[27,28] Delayed recovery is observed frequently, but proper recognition and management of the disease is vital.^[29] The ARTEMIS registries are expected not just to oversee the current prevalence and incidence of PPCM, but also to improve outcomes of the disease by increasing awareness and knowledge.

An important proposed treatment modality for PPCM is inhibition of prolactin release, either by bromocriptine or cessation of lactation.^[30] The benefit of bromocriptine treatment, which was previously only supported by a few observational studies,^[31-33] was proven in a recent randomized controlled trial.^[34] Provisional experience suggests an underutilization of bromocriptine and other conventional, potentially protective heart failure regimens in this patient group, which might be associated with potentially life-threatening outcomes.^[35] The Turkish PPCM registries will clarify the rate of use of bromocriptine, its efficacy,

and possible side effects in a real clinical approach to PPCM patients. There is conflicting evidence whether discontinuation of breastfeeding is beneficial or not in patients with PPCM.^[36,37] The ARTEMIS registries will also look into this question.

While ARTEMIS-I will consist of a cross-sectional sample from participating institutions, ARTEMIS-II will use a more comprehensive sampling, and the study cohort will be a more representative sample of Turkish PPCM patients. As a result, it is expected to be more reflective of where we stand in the clinical management of this disease. Both studies are prone to errors related to the validity and completeness of the information recorded in the medical files, especially in the retrospective arm. The International Classification of Diseases (ICD) codes will be used to locate cases, and unfortunately ICD codes may not cover all PPCM patients. As PPCM is a diagnosis of exclusion, a mal-workup may also mask the real number of PPCM patients. Preliminary data point out that there are many parameters missing in the medical records of these patients; however, retrospective data collection will reflect the real-life clinical approach to this rare, but mortal disease of young women.

Conclusion

In conclusion, the ARTEMIS studies, as the first national registries of PPCM patients in Turkey, will provide many benefits to understanding the multiple dimensions in the clinical management of the disease, and will guide the establishment of a national strategy for the diagnosis and treatment of PPCM.

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