Thesis

Peripartum Cardiomyopathy (PPCM): Prevalence and clinical characteristics in Styria

submitted by

Julian Nemeth

for obtaining the academic degree

Doktor der gesamten Heilkunde (Dr. med. univ.)

from the

Medical University of Graz

accomplished at the

Division of Cardiology, Department of Internal Medicine and the Division of Obstetrics, Department of Obstetrics and Gynaecology

under the guidance of

Assoz. Prof. Priv.-Doz. Dr.med. Dr.Med.Sci Peter Rainer

and

Ao.Univ.-Prof. Dr.med.univ. MSc Wolfgang Schöll

Graz, May 14th 2020

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 14.05.2020 *Julian Nemeth, eh.*

Acknowledgment

I feel very fortunate to have Dr. Peter Rainer and Dr. Wolfgang Schöll as my supervisors along my thesis. I would like to express my deep gratitude to them and to all the people who supported me along the way especially to my colleagues and my mother.
Special thanks go to all my insane but beloved mates from university, you guys rendered those past five years unique.
And last but not least, I wholeheartedly thank my family and especially my grandparents Josefine and Erich for enabling me to live and study here in Graz.

Table of Contents

Abbreviations

KAGes	*Krankenhausanstaltsgesellschaft*
LKH	*Landeskrankenhaus*
HF	*Heart failure*
PPCM	*Peripartum cardiomyopathy*
DCM	*Dilated cardiomyopathy*
CM	*Cardiomyopathy*
EF	*Ejection fraction*
LV	*Left ventricular*
LVEF	*Left ventricular ejection fraction*
LVEDD	*Left ventricular end diastolic diameter*
ePAP	*Estimated pulmonary artery pressure*
ECG	*Electrocardiogram*
WHO	*World Health Organization*
HDP	*Hypertensive disorder in pregnancy*
IFN-β	*Interferone-beta*
IL-1β	*Interleukin-1 beta*
IL-6	*Interleukin-6*
TNF-α	*Tumor necrosis factor alpha*
CRP	*C-reactive protein*
miR-146a	*microRNA-146a*
ACE	*Angiotensin-converting enzyme*
ACEI	*ACE-Inhibitors*
mg	*Milligram*
PET	*Preeclampsia*
HTN	*Hypertension*
CI	*Confidence interval*
Bpm	*Beats per minute*
SD	*Standard deviation*
RR	*Riva Rocci (Blood Pressure)*
eGFR	*Estimated glomerular filtration rate*
ID	*Identification*
CPAP	*Continuous positive airway pressure*
LMWH	*Low-molecular-weight heparin*
APGAR	*Activity Pulse Grimace Appearance Respiration*
ARNi	*Angiotensin receptor neprilysin inhibitor*
NOAC	*Novel oral anticoagulants*
SOB	*Shortness of breath*
PA	*Prolactin antagonist*
R^2	*Measure of certainty*
IPAC	*Investigations of pregnancy-associated cardiomyopathies*
sFLT1	*Soluble fms-like tyrosine kinase 1*
VEGF	*Vascular endothelial growth factor*
kDa	*Kilo-Dalton*
PTHLH	*Parathyroid hormone like hormone*
TTN	*Titin*
CKD-EPI	*Chronic kidney disease-epidemiology collaboration*
ICD-10	*International statistical classification of diseases*
PRL	*Prolactin*
CathD	*Cathepsine D*
ROS	*Reactive oxygen species*
MnSOD	*Manganese-dependent superoxide dismutase*
ERBB4	*Encoding receptor tyrosine-protein kinase erbB-4*
STAT3	*Transcription factor*
PGC-1	*Transcription coactivator VEGFA&B: vascular endothelial growth factors,*
16kD	*16-kDa-fragment*

List of Figures

List of Tables

Zusammenfassung

Die Peripartale Kardiomyopathie (PPCM) ist eine seltene, aber potentiell lebensbedrohliche Erkrankung, deren Ätiologie bis dato unbekannt ist. Da aktuell noch keine Prävalenz für die PPCM in der Steiermark existiert, lautet das Ziel dieser Diplomarbeit eine solche in Bezug auf die Lebendgeburten zu beschreiben und weiter den Phänotyp der raren Erkrankung zu charakterisieren. Eine KAGes-weite Suche vom 01.01.2001 bis 23.10.2018 ergab sechszehn (n = 16) Patientinnen, welche im peripartalen Zeitraum Symptome kardialer Natur aufwiesen und/oder mit PPCM, DCM oder anderen CM-Formen diagnostiziert wurden. Nach sorgfältiger Exklusion ungeeigneter Patienten und Inklusion zwei weiterer valider PPCM Fälle, welche außerhalb des Suchzeitraums lagen, waren elf (n = 12) für eine retrospektive Analyse geeignet. Im weiteren Verlauf wurde eine deskriptive Statistik mit Hilfe von Programmen wie SPSS und Microsoft Excel angewandt. Ein Großteil der Variablen waren Quantitative, welche später als Mittelwert inklusive Standardabweichung dargestellt wurden, kategorische Variablen wurden hingegen als Häufigkeiten und Prozentzahlen angeführt. Danach wurden die Resultate analysiert, interpretiert und mit aktuellen internationalen Daten verglichen. Mit einer periodischen Prävalenz von in etwa 0.006% (entspricht einem Fall pro 16 667 Lebendgeburten) ist die PPCM, verglichen mit internationalen Daten, sehr selten in der Steiermark. Limitationen von retrospektiven Analysen tragen zu einer wahrscheinlich hohen Dunkelziffer bei und unterschätzen vermutlich die tatsächliche Prävalenz. Die PPCM präsentiert sich zumeist mit Dyspnoe, Beinödemen, Husten, Abgeschlagenheit und/oder Orthopnoe und zeigt von milden bis schwerwiegend akute Verlaufsformen, ein breites Spektrum an klinischer Charakteristik. Weiter Untersuchungen zeigen hierbei häufig sowohl eine reduzierte Ejektionsfraktion und einen dilatierten linken Ventrikel als auch Pleura- und Perikardergüsse. Laborparameter sind wichtig, um eine PPCM auszuschließen und deren Prognose zu bestimmen, dürfen jedoch um die Erkrankung zu diagnostizieren, niemals alleine verwendet werden. Wegen des variablen Erscheinungsbilds verlangt auch das Management der PPCM interdisziplinäre Expertise. In Zukunft könnten bessere Screening Verfahren, genauso wie eine spezifische Therapie dazu beitragen, potentiell fatale Krankheitsverläufe abzuwenden.

Abstract

Peripartum Cardiomyopathy is a rare, but potentially life-threatening condition, however its etiology still remains unknown.(1,2) No prevalence for it has yet been described for Styria. The goal of this thesis is to present a prevalence referred to the number of live births and furthermore characterize its phenotype. A KAGes-wide research from the Jannuary 1st, 2001 to October 23rd, 2018 was performed and resulted with sixteen patients (n = 16) who were symptomatic at some point in the peripartal period and/or diagnosed with the disease. After careful exclusion and inclusion of two valid PPCM cases that occurred outside of the search period, twelve of them (n = 12) were eligible for closer retrospective analyzation. Descriptive statistics was applied with the help of programs as SPSS and Microsoft Excel. The majority of the collected variables were quantitative and expressed as mean values with standard deviations. Categorical variables were demonstrated as frequencies and percentages. Results have later been interpreted compared to current international data. With a periodic prevalence of about 0.006% (1:16 667) PPCM, compared to international data is noticeably rare in Styria. Several limitations of this study may suggest a high number of unreported cases and underestimate the actual prevalence. However, its clinical presentation, which mostly includes heart failure symptoms like shortness of breath, peripheral edema, cough, fatigue and/or orthopnea, ranges from moderate, mild forms up to severe acute HF and cardiac death. (3) In physical examination, patients frequently show reduced ejection fraction and dilated LVEDD, as well as pleural and pericardial effusion. Laboratory parameters are important to rule out PPCM and predict its prognosis but should always be used together with other diagnostic methods. Due to its varying appearance, the management of PPCM requires interdisciplinary expertise. In the future, better screening procedures and specific therapy could help clinicians prevent potentially fatal outcomes.

1 Introduction

1.1 Definitions and Theoretical Background

> "Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure–related disability."(4)

1.1.1 Classification

According to the American Heart Association, cardiomyopathy is classified into primary and secondary. Primary cardiomyopathies, which commonly are genetic, mixed (genetic and non-genetic) or acquired, are often or exclusively confined to the heart muscle and are rather few in number.

Secondary ones emerge with pathological myocardial conditions as a result of systemic diseases and vary in frequency and degree across their large spectrum.(4)

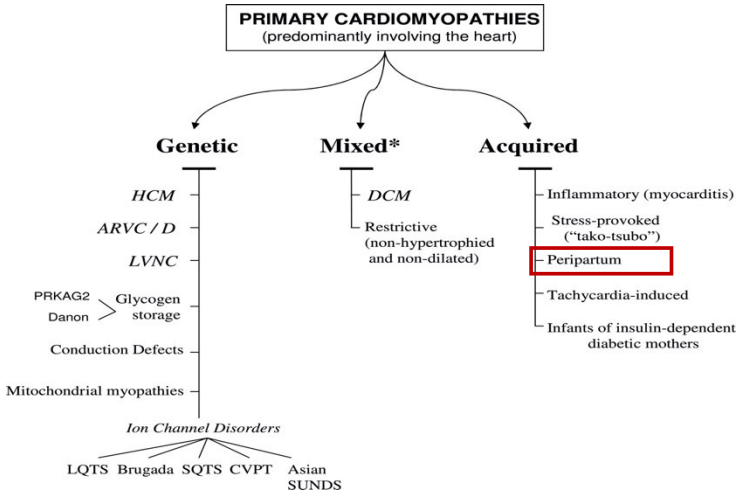

Figure 1: Primary Cardiomyopathies

1.1.2 Definition of Peripartum Cardiomyopathy

“The working group on PPCM of the European Society of Cardiology recently provided an updated operational definition of PPCM as cardiomyopathy with reduced EF, usually <45%, presenting toward the end of pregnancy or in the months after delivery, affecting woman without previously known structural heart disease.”(5) Furthermore, the National Heart, Lung and Blood Institute and the Office of Rare Diseases set the following criteria to diagnose PPCM:

- Development of HF during the last month of pregnancy or up to 5 months postpartum
- Absence of another cause for HF
- No demonstrable cardiac event before the last month of pregnancy
- Decreased left ventricular systolic function demonstrated by echocardiographic imaging (2)

From a historical point of view, PPCM was first described by Ritchie from the Glasgow Royal Infirmary in 1849, who denoted it as an idiopathic myocardial degeneration with onset in the late pregnancy or puerperium. Later, Gouley & Hull et. al., 1937 reported a clinical syndrome called postpartum heart failure. The term peripartum cardiomyopathy as it stands today was coined by Denmakis et al., 1971 and further used by the National Heart, Lung and Blood Institute and the Office of Rare Diseases mentioned above.(6) Peripartum Cardiomyopathy is a rare, but potentially life-threatening condition for pregnant women and for mothers in puerperium, however its etiology still remains unknown.(1,2)

1.1.3 Epidemiology

We are facing a major issue, when it comes to describe epidemiology for PPCM. Unfortunately, the condition is poorly distinguishable from other forms of CM, like familial or idiopathic DCM. From 2004 to 2006, 14 323 731 hospitalizations in the USA have been studied. The rate of 1000 hospitalizations for CM in the period after delivery was 0.46, less than half of it was because of peripartum cardiomyopathy (0.18 for PPCM, 0.28 for other cardiomyopathies per 1000 hospitalizations). What seems most interesting is that there is a significant variation in the incidences of PPCM between ethnic groups and regional differences. Most of the data is represented from South Africa, America or Haiti. The creation of a European epidemiological profile is almost impossible due to sparse data. In Nigeria, incidence is 1 per 100 women, in Haiti, there is 1 PPCM diagnosis in 299 live deliveries, in South Africa, there is 1 per 1000 births, whereas in South Korea, incidence is 1 in 1741 deliveries and for the USA, numbers exist from 1 per 1149 to 4000. The reason for this geographical difference is barely understood but might be associated to socioeconomic factors and racial predispositions. Studies compared incidences of PPCM between ethnic groups in the USA and identified a huge variance: 1 per 1421 in African American women, 1 per 2675 in Asian women, 1 in 4075 in white women and 1 per 9861 women in Hispanic women.(1,7–9) As a matter of fact, PPCM not only occurs more often in black women than it does in other ethnic groups, it also has a worse prognosis among them (lower recovery rate of LVEF), according to data from the US, Germany and South Africa.(5,10)

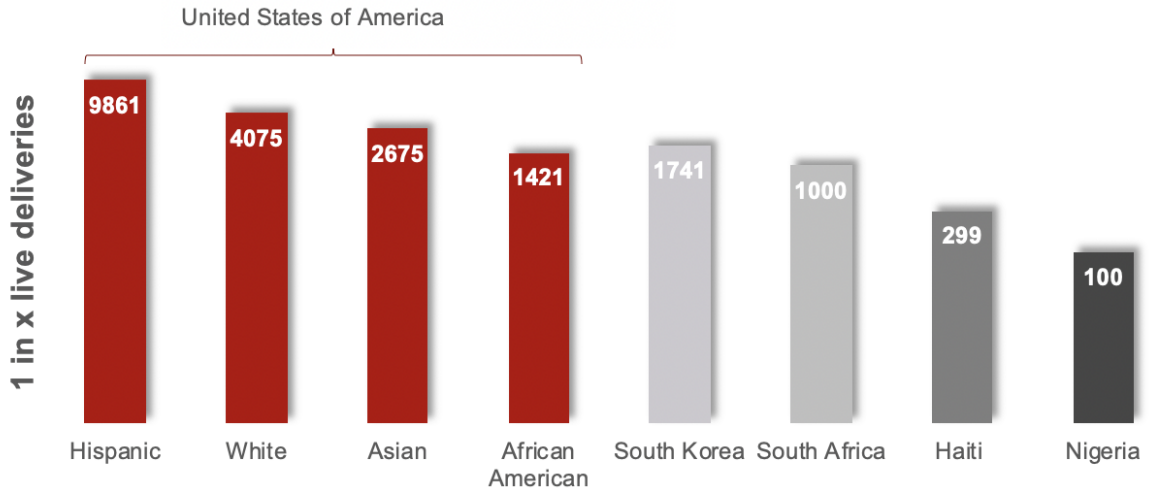

Figure 2: Incidence for PPCM across the world. Numbers for the US were divided into ethnic groups and marked in red.

1.1.4 Pathophysiology

There are a lot of theses and propositions of how pathophysiology in PPCM really works. One of them is that hemodynamic shifts in pregnancy, including the rise of preload by an increased red blood cell mass and volume and simultaneously increased cardiac output (elevated heart rate and stroke volume). This leads to high hemodynamic stress levels to the LV in form of high pre- and afterload in women during the first two trimesters. Women with pre-existing structural heart conditions then eventually present with clinical heart failure. However, PPCM commonly appears in the last weeks of pregnancy and particularly in the first month postpartum, which causes additional hemodynamic stress. Caesarian sections lower stress levels in pregnant women but do not seem to make an impact on the risk of developing PPCM. Other proposed causes are that women with PPCM are exposed to malnutrition like selenium deficiencies (mainly in sub-Saharan Africa) or harbored viral pathogens like coxsackie and echovirus. However, in the further course these hypotheses could not be confirmed.

A multi-hit model is currently used to understand the pathophysiological processes of the disease, in which vasculo-hormonal mechanisms are linked to underpinning genetic predispositions. Without doubt, the nursing hormone prolactin is one of the responsible factors for the onset of PPCM. Due to an unknown mechanism, oxidative stress exposed cardiomyocytes produce an abnormal large amount of Cathepsin D, which cleaves Prolactin to the vasoinhibin 16-kDa-fragment. Studies have found that 16-kDa-fragment does not only promote apoptosis in endothelium cells, but also leads to cardiomyocyte damage, by inducing endothelium cells to package and release microRNA-146a into exosomes, which are further internalized by cardiomyocytes. Once there, they inhibit the neuregulin/ErbB pathway and induce apoptosis. Furthermore, soluble Fms-like tyrosine kinase-1 (sFLT1) inhibits pro angiogenic vascular endothelial growth factors (VEGFA&B) and therefore contributes to the aforementioned cell damaging mechanisms. For better understanding pathways were illustrated in figure 3.(5)

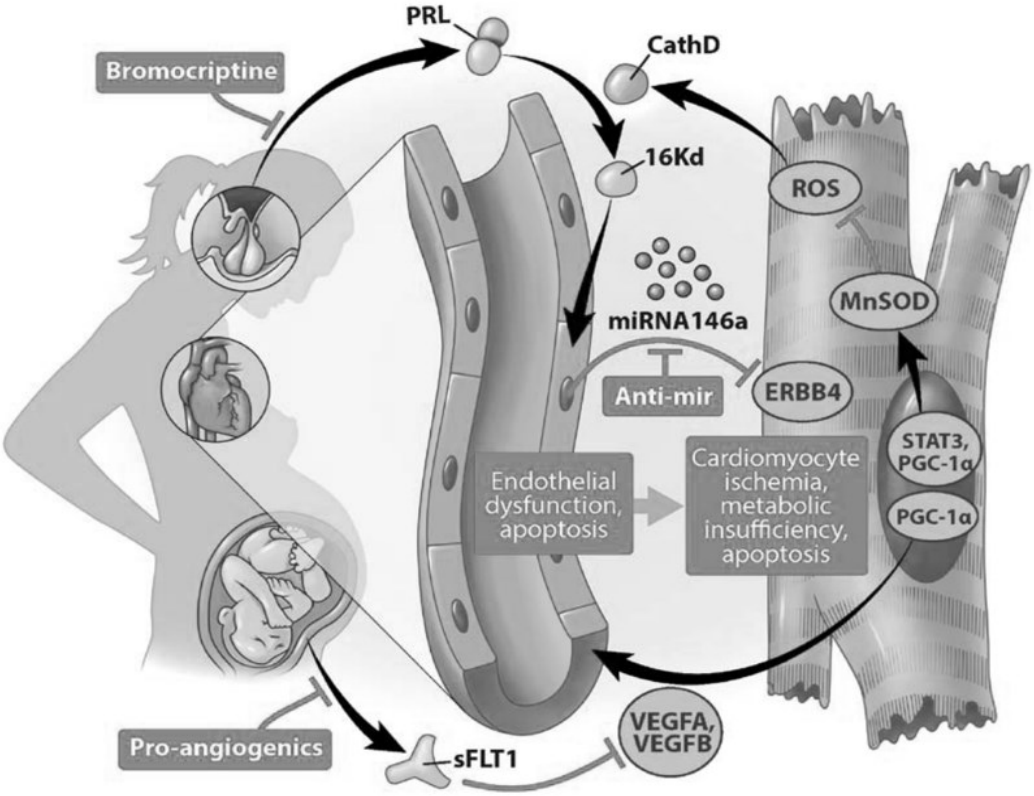

Figure 3: vasculo-hormonal hypothesis of the pathophysiology of PPCM. PRL: Prolactin, CathD: Cathepsine D (enzyme), ROS: reactive oxygen species, MnSOD: manganese-dependent Superoxide dismutase (enzyme), ERBB4 (gene): encoding receptor tyrosine-protein kinase erbB-4, STAT3: transcription factor, PGC-1α: transcription coactivator, VEGFA&B: vascular endothelial growth factors, sFLT1: Soluble fms-like tyrosine kinase-1 (free receptor), miRNA146a: microRNA 146a (inflammatory mediator), 16kD: 16-kDa-fragment

PPCM does not reappear in second pregnancies very frequently. Thus, one can assume that any genetic origin is not completely penetrant. Recently a single-nucleotide polymorphism near the PTHLH-Gene, which regulates vascular homeostasis was associated with PPCM in a genome-wide association study. Furthermore, PPCM and DCM both seem to share genetic predispositions. The analysis of pedigrees shows that truncating variants of the TTN-Gene are harbored in both PPCM and DCM as well as many hereditary cardiomyopathies, although they are not clinically identical.(5,8,11)

1.1.5 Risk Factors and Clinical Characteristics

Even though PPCM's etiology is not fully understood, there are some risk factors, which occur in most of the literature and are closely linked to the above described two-hit model. Hypertensive Disorder of Pregnancy and Preeclampsia for example favor antiangiogenic factors like 16kDa prolactin which contributes to the vascular stress level in pregnant women. Normotensive women had a significantly lower risk of PPCM than women with HDP-complicated pregnancies. Furthermore, the risks for PPCM also depend on the severity of HDP as it is described in table 1 from a nationwide study in Denmark. Smoking, age (>30 years), genetics, multiparity and obesity were also mentioned as risk factors in the article.(12,13) A South Korean study has shown that patients with PPCM were older, had multiple pregnancies and had a higher prevalence of gestational diabetes and preeclampsia. In addition to that, a high number of deaths in women between 5-12 months after delivery were found, even though numbers of reported PPCM cases decreased over time after delivery.(9) Mentioned previously, the disease's epidemiology varies across different socioeconomic groups, although its clinical presentation remains similar over multiple ethnic backgrounds.(3,12) PPCM most likely emerges with heart failure symptoms, orthopnea and paroxysmal nocturnal dyspnea. Physical examination shows tachycardia, increased jugular venous pressure, pulmonary rales and peripheral edema. ECG should be done in all patients, even though there is not a specific pattern for PPCM. Left bundle branch block could be a sign for structural heart damage, whereas long QTc interval and tachycardia are identified as predictors for a bad outcome. A third heart sound and displaced apical impulse are not common. However, the disease does have severe forms in which acute respiratory distress and low-output cardiac failure demand pharmacological and mechanical intervention. To differentiate PPCM from pneumonia, pulmonary embolism, acute pulmonary edema from prolonged tocolysis or preeclampsia, myocardial infarction or takotsubo cardiomyopathy, imaging, laboratory examinations and clinical exam help. Further, echocardiography shows LV dilatation, LVEF reduction, heart muscle enlargements, valvular regurgitation and pulmonary hypertension.(3,5) Biomarkers like brain natriuretic peptide and its N-terminal fragment (NT-proBNP) are secreted from cardiomyocytes when myocardial filling pressure rises and are commonly used to evaluate heart failure. Their high

sensitivity and cost-effectiveness made them an essential part in the management of HF. Even though they are non-specific markers, high levels of NT-proBNP (>100pg/ml for BNP and >300pg/ml for NT-proBNP) during pregnancy are associated with increased risk of cardiovascular conditions. Due to slightly elevated, but fairly stable levels of BNP and NT-proBNP throughout pregnancy and in the postpartum period, significant increased amount of those biomarkers could indicate PPCM, or rather give information about the improvement of LVEF afterwards.(14) A study has shown that women who had low levels of NT-proBNP at the onset of PPCM, experienced a significant improvement of LVEF within 6 months postpartum, compared to women with higher levels of the biomarker. Increased amounts of brain natriuretic peptide and its amino terminal fragment may suggest a worse prognosis with respect to LV recovery, even though their non-specificity impede clinicians to differentiate from other cardiac conditions and therefore should not be used solely in diagnostics.(3,14–16) Inflammatory markers have also been investigated and seem to play a role in PPCM. Markers like IFN-β , IL-1β, IL-6, TNF-α and CRP were all at higher levels in women with acute PPCM. Most of them saw a decrease of markers within 6 months of follow up, however IL-1β and IL-6 did not seem to decrease. In addition, IFN-β decreased in women who showed good LV function improvement but remain high in patients with prolonged LVEF reduction. Because of the inability of those marker to differentiate from other cardiac conditions, more specific markers for PPCM need to be discovered. A potential candidate is miR-146a, which not only plays a major role in the still unclear pathogenesis of PPCM, but also is able to distinguish DCM from its close relative PPCM, where miR-146a levels remained significantly higher, compared to 30 women with dilated cardiomyopathy according to a study.(16)

Table 1: Risk ratio of peripartum cardiomyopathy with hypertensive disease in pregnancy. PET preeclampsia, HTN hypertension, CI confidence interval

	Risk ratio	CI (lower)	CI (upper)
Severe PET	21.2	12	37.4
Moderate PET	10.2	6.18	16.9
Gestational HTN	5.16	2.11	12.6

1.1.6 Treatment

As a consequence of PPCM's similarity to other forms of heart failure, its treatment is also concentrating on volume status, thromboembolic prevention, neurohormonal therapies and arrhythmic complications. For volume control, diuretic agents as loop diuretics and nitrates are useful, although prenatal hypotension has to be avoided. ACE-inhibitors or Angiotensin receptor blockers are common for neutralizing maladaptive neurohormonal response but are contraindicated before delivery. At this time, organic nitrates, hydralazine or β-blockers as metoprolol can be used instead. Another option is Digoxin, which can be safely used on pregnant women but is currently being questioned in the treatment of systolic heart failure.(5) Although medical care in western society advanced, treatment concepts to improve the prognosis of PPCM failed. Due to rising incidence and few disease-specific therapeutics the call for a new strategy of treatment grows. In a 2015 published German study(17), bromocriptine, a dopamine receptor agonist is used to prevent cleaved prolactin fragments from damaging cardiomyocytes and endothelium cells. They used low-dose bromocriptine (2.5-5mg/day) and ensured sufficient prophylactic anticoagulation during the treatment, as women are exposed to a higher procoagulant activity postpartum. By blocking 16kDa prolactin, bromocriptine eliminates harmful effects like cell death or fibrosis and improves cardiac function in women with acute PPCM. In addition to standardized heart failure therapy, the drug is associated with high rate of left ventricular recovery and low rate of bad outcome. Bromocriptine has been available on the market for a long time and is commonly used for the suppression of lactation. Moreover, it also contributes to the healing process of an injured myocardium by modulating inflammatory pathways, regulating immunologic response, acting cytoprotective and increasing antioxidative capacity. Beside its side effects of nausea, headache, dizziness, fatigue etc., bromocriptine has already proven its effectiveness and has therefore the permission for application according to European Society of Cardiology. Diagnosis and management require a multidisciplinary team including cardiologists, obstetricians, neonatologists and intensivists, however the initial therapy of acute heart failure in women with suspected PPCM is no different from the therapy of other unspecific acute heart failures. The following figure could illustrate an algorithm to properly diagnose and treat PPCM.(8,18)

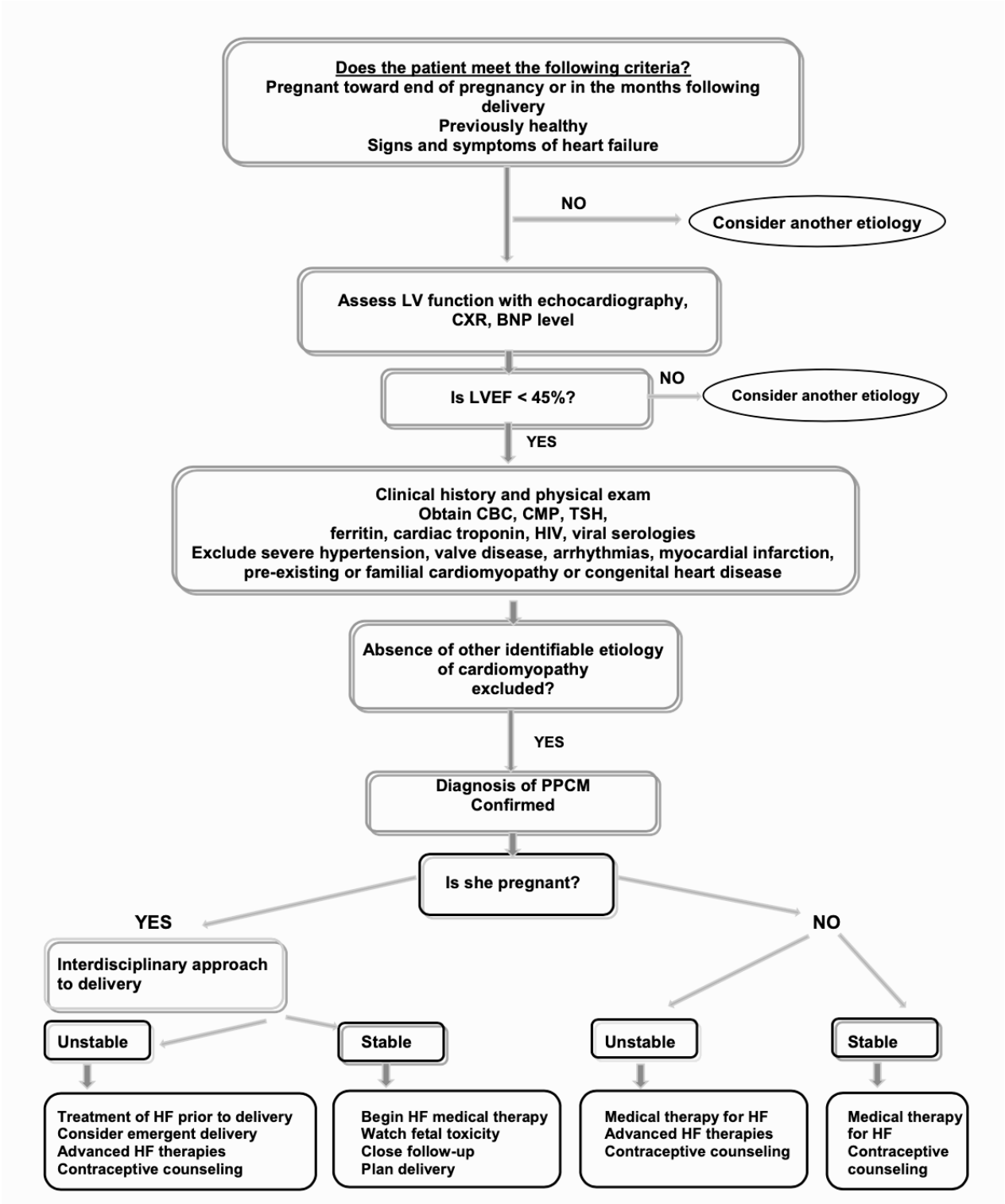

Figure 4: Proposed algorithm for diagnosis and initial management of peripartum cardiomyopathy (18) *CXR: Chest x-ray, CBC: complete blood count, CMP: comprehensive metabolic panel, TSH: Thyroid stimulating hormone.*

1.2 Hypothesis & Aims

Peripartum Cardiomyopathy is a relatively rare but potentially severe disease and it affects a vulnerable group of patients, which are pregnant women or women in puerperium. No prevalence has yet been described in Styria. The goal of this thesis is to characterize that prevalence and its phenotype based on data from the last 19 years related to the number of recorded childbirths. Furthermore, results should be compared with international data with respect to morbidity, progression, treatment and complications.

1.2.1 Research Question

- What is the prevalence for PPCM in Styria?
- How does PPCM present clinically in Styria?

1.3 Ethics Approval

Ethics approval (number: 31-141 ex 18/19) was given on January 25th, 2019.

2 Material & Methods

2.1 Organization of Research

Data was collected by a MEDOCS search for the terms (*Peri*, *par*, *myopa*, *peripar*, *post*, *part*, *postpart*, *PPCM*) and for the ICD10-Code: 090.3 over a period of 19 years. MEDOCS itself is a documentation system which was launched in January 1st, 2001 and contains patient records from the Krankenhausanstaltsgesellschaft (KAGes) in Styria. The search included records from the LKH Graz, Hartberg, Feldbach-Fürstenfeld, Graz II (Hörgas), Bruck, Murtal – Knittelfeld, Leoben, Deutschlandsberg and Bad Aussee.

2.2 Study Population

The search revealed sixteen patients (n = 16), who were symptomatic at some point in the peripartal period and/or have been diagnosed with PPCM, DCM during puerperium or other forms of cardiac conditions similar to peripartum cardiomyopathy. Each PPCM diagnosis was validated through a detailed manual review of patient records. After careful evaluation and inclusion of two confirmed PPCM cases that occurred outside of the search period, twelve (n = 12) were eligible for closer analysis. In one case the initial PPCM diagnosis dates back to May 1997. She was included due to the dramatic course of the disease, which was particularly evident during the period of our study. Three patients were initially diagnosed outside the LKH Graz, before they were transferred there later on. Two of them came from the LKH Feldbach-Fürstenfeld and one was transferred from the LKH Deutschlandsberg. The number of live births in Styria during the period from 2001 to 2019 (n = 200000) was taken from the Statistik Austria database. However, the number for births in 2019 (n = 10891) is a preliminary result (include all information submitted by February 4, 2020) and can still slightly change, according to Statistik Austria (19)

2.3 Statistical Analysis

After data has been collected, its quality has been reexamined in terms of accuracy and completeness record by record. If data-gaps could not be filled, they were indicated as “missing”. A retrospective data analysis was performed with statistical programs IBM SPSS Statistics Version 25 and Microsoft Excel Version 16.35. The majority of the collected variables were quantitative and expressed as mean values and standard deviation (SD). If nothing else is noted, the data refer to the time of onset (baseline). Categorical variables were described as frequencies (n) and percentages (%).

2.4 Inclusion & Exclusion Factors

Exclusion factors are gender (men were excluded), duplicates (same patient but different ID-number due to a transfer during hospitalization), age referred to fertility (females younger than 1 or older than 72 years were excluded) and preexisting forms of cardiomyopathies which were not associated with pregnancy. Unclear PPCM cases have also been excluded due to a lack of data and inconsistency of genesis. Included were all those who fulfilled the PPCM diagnostic criteria defined by the European Society of Cardiology, the National Heart, Lung and Blood Institute and the Office of Rare Diseases as mentioned above.

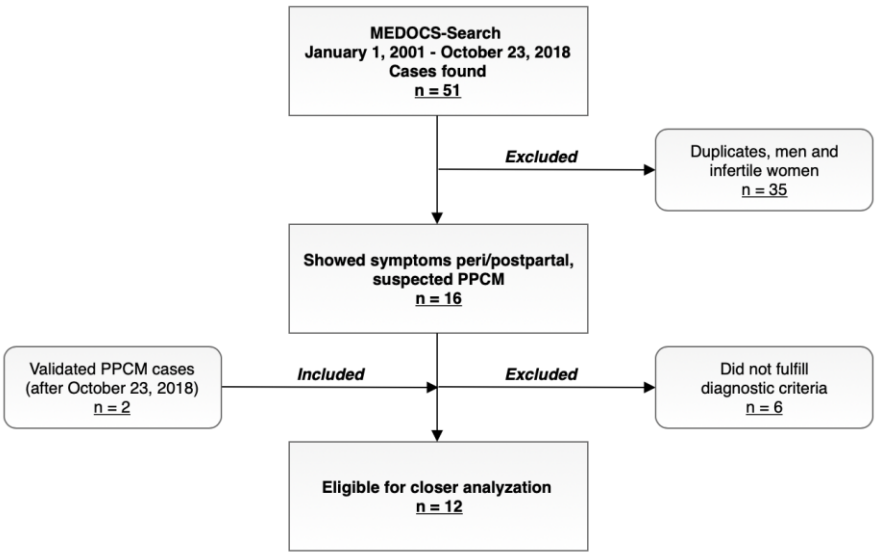

Figure 5: Flowchart of the study population with stated inclusion and exclusion factors.

2.4.1 Excluded Cases

Table 2: Excluded Cases with reason for exclusion on individual level; DOB: date of birth, AVR: aortic valve replacement, MVR: mitral valve reconstruction.

Patient	Year of Onset	Current Age	Reason for exclusion	Ejection Fraction
1	2018	19	Sinustachycardia (140bpm), minimal pericardial effusion, NT-proBNP normal	50%
2	2007	25	No evidence of any cardiomyopathy, wrong coded	-
3	2010	33	Staph aureus induced spesis, bilateral pneumonia, NT-proBNP over 1000pg/mL	marginal
4	2011	32	Heart surgery 1996 (AVR & MVR), atrial fibrillation (IIa) 8 monthts postpartum (sectio 6/2010)	normal
5	2006	38	High-grade DCM and sarcoidosis, unclear date of partus	35%
6	2003	28	DCM diagnose 12/2002, Partus I in 4/2003	35%
7	2004	64	Gender	-
8	2007	88	No Data and Age	-
9	2015	0	Age, transient tachypnea of the newborn	-
10	2006	0	Age, postpartum cardiogenic shock of the newborn	-
11	2007	77	Age	-
12	2008	88	Age	-
13	2007	84	Age	-
14	2008	85	Age	-
15	2016	90	Age	-
16	2017	72	Age	-
-	-	-	Duplicates (n = 25)	-

3 Results

3.1 Prevalence & Population

The percentage of PPCM cases related to the number of live births in Styria from 2001 to 2019 was 0.006% or 1 in 16 667 live births, which was calculated from dividing the number of patients (n = 12) by the number of live deliveries (n = 200 000) during this period. All of the examined patients were Caucasian, between 25 - 36 years of age at birth (mean = 29.4 years ± 3.2) and were diagnosed shortly after delivery (mean = 17th postpartal day ± 26.2). The following figure shows, that the majority of the affected women were diagnosed within seven days after childbirth (n = 10, 83.3%). Half of the patients were primiparous (n = 6, 50.0%; multiparous n = 3, 25.0%; missing n = 3, 25.0%) moreover, a majority had caesarean section delivery (n = 8, 66.7%) and only two of them had a vaginal birth (n = 2, 16.7%; missing n = 2, 16.7%). Later deliveries after women were diagnosed with PPCM were less common (n = 2, 16.7%; missing n = 1, 8.3%). In addition, a third (n = 4, 33.3%) suffered from preeclampsia at some point during pregnancy according to their patient records.

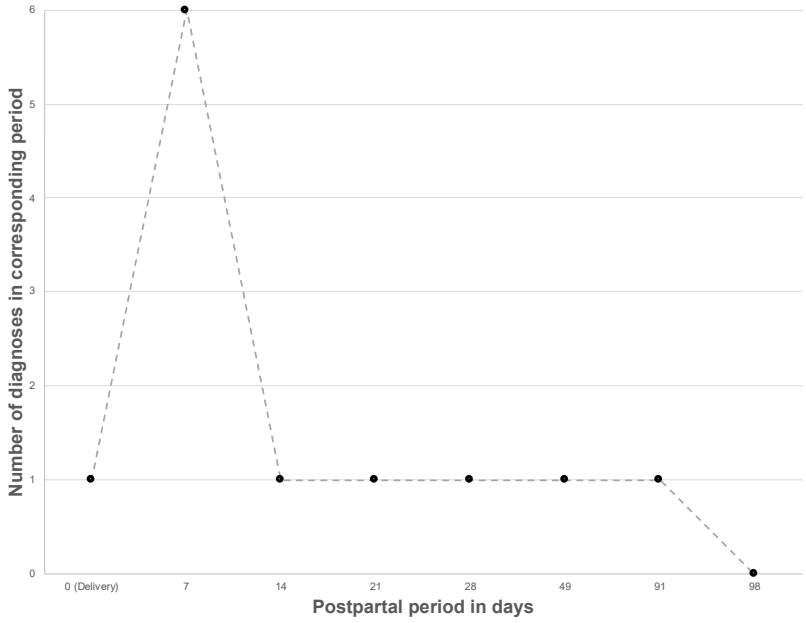

Figure 6: Number of diagnoses in corresponding period of time postpartum.

3.2 Clinical Presentation

Ten out of tewelve patients (n = 10, 83.3%; eupnea n = 1, 8.3%; missing n = 1, 8.3%) presented with dyspnea, while almost half of them suffered from peripheral edema (n = 5, 41.7%; missing n = 1, 8.3%). Dyspnea was categorized in grades according to the New York Heart Association-Classification, as it is shown underneath in figure 7. First grade dyspnea did not occur in patient records, whereas in two cases the symptom was just mentioned but not categorized by NYHA-classification.

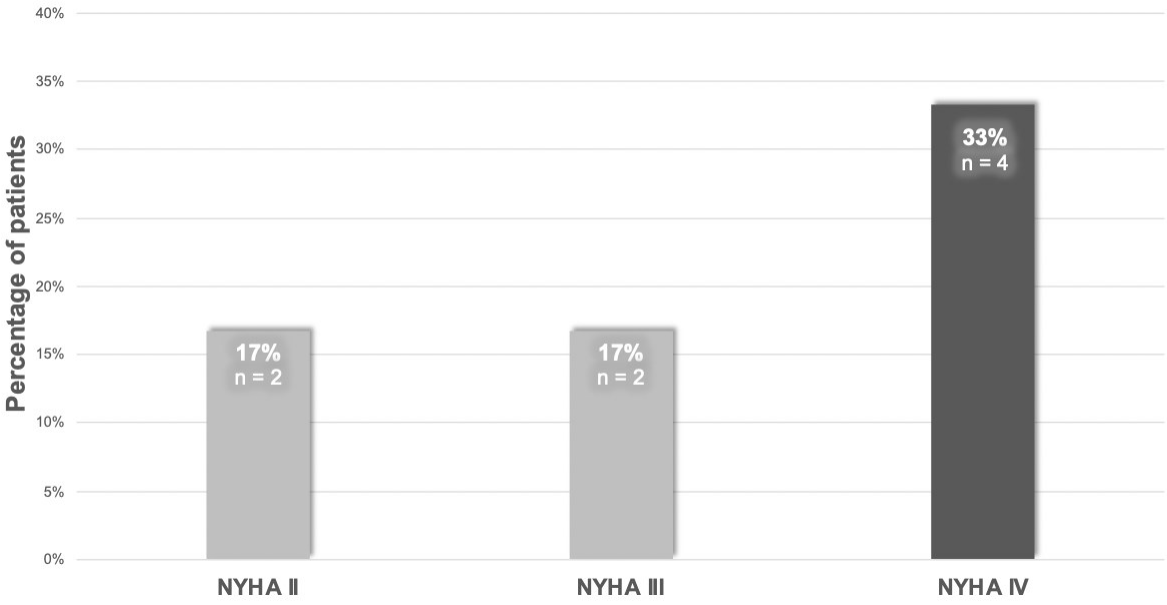

Figure 7: NYHA-Stages

Results from hemodynamic parameters such as heart rate and blood pressure varied across the mothers. Records contained frequencies from a minimum 40 bpm up to 150 bpm (mean = 91.3bpm ± 32.2bpm), RR-values ranged from severe hypotension (min. RR-Systole = 55mmHg) up to rather hypertensive values (max. RR-Systole = 150mmHg; mean RR-Systole = 122mmHg ± 32mmHg, RR-Diastole mean = 78mmHg ± 24mmHg). Deviations in heart rhythms were not found across patients (n = 10, 83.3%, missing n = 2, 16.7%). Half of them showed pleural effusion (n = 6, 50%; missing n = 1, 8.3%) in their findings. Echocardiographic data was sparse and inconsistent among its completeness, so that only left ventricular end diastolic diameter, ejection fraction, left atrium and estimated pulmonary artery pressure (ePAP) were closer analyzed. Dimensional parameters including LVEDD

(mean = 6.0cm ± 0.85cm) and LA (mean = 4.8cm ± 0.54cm) showed LV and LA dilation, in addition LV systolic function assessed by EF (mean = 39.3 ± 13.36) and ePAP (mean = 36.0mmHg ± 11.7mmHg) indicated heart failure with reduced ejection fraction and pulmonary hypertension. Laboratory data at onset is presented in Table 2. Mean values were calculated by nine of the twelve patients (n = 9, 75%; missing n = 3, 25%). Levels of white blood count and CRP were elevated, as well as uric acid, CK, CK-Mb and LDH. Red blood count, hemoglobin, Ca^{+}, total protein and albumin were all decreased. There were no big changes in platelet count, creatinine, urea, eGFR (calculated by CKD-EPI equation), Na^{+} and K^{+} levels referred to the reference ranges. NT-proBNP (mean = 3659pg/ml ± 3210pg/ml) and Troponin-T (mean = 0.11µg/ml ± 0.16µg/ml) are both presented at baseline and in relation to time, as figures 8 and 9 show.

Table 3: Laboratory data at onset. SD = Standard Deviation, eGFR = estimated Glomerular Filtration Rate, G = Giga, T = Tera, U = Enzyme-Activity, g = gram, mg = milligram, L = Liter, dL = deciliter, min = minute, mmol = millimole

Laboratory Data	***Mean***	***± SD***	***Unit***	***Reference Range***
White Blood Count	13.3	9.4	G/L	4.4 – 11.3
Red Blood Count	3.8	0.67	T/L	4.1 – 5.1
Hemoglobin	11.1	1.8	g/dL	12 – 15.3
Platelet	297	92	G/L	140 - 440
Creatinin	0.78	0.10	mg/dL	< 1
Urea	25.2	7.5	mg/dL	10 - 45
Uric Acid	6.3	0.89	mg/dL	2.4 – 5.7
eGFR (CKD-EPI)	95.8	16.9	ml/min	90 - 120

Laboratory Data	*Mean*	*± SD*	*Unit*	*Reference Range*
Na^+	140.9	1.2	mmol/L	135 - 145
K^+	4.1	0.73	mmol/L	3,5 - 5,0
Ca^{2+}	2.1	0.13	mmol/L	2.20 – 2.65
CK	167.3	96.5	U/L	< 145
CK-Mb	34	23.3	U/L	< 21
LDH	273.3	71.8	U/L	120 - 240
Total Protein	6.3	0.72	g/dL	6.6 – 8.3
Albumin	3.0	0.78	g/dL	3.5 – 5.3
CRP	33.1	34.3	mg/L	< 5
Troponin - T	0.11	0.16	ng/mL	< 0.04
NT-proBNP	3659	3210	pg/mL	< 300

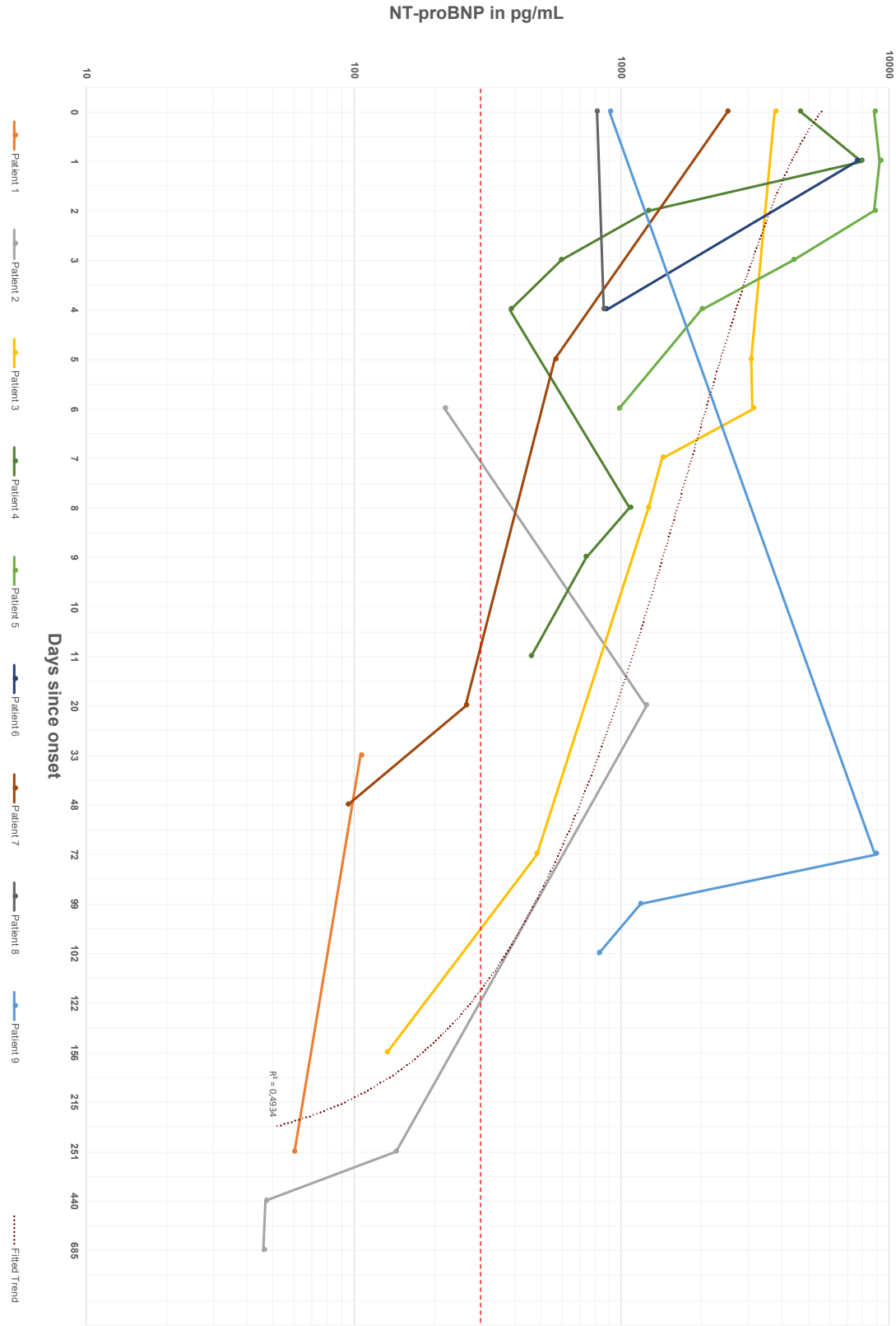

Figure 8: NT-proBNP at baseline and follow-up. Red line marks cut-off value of 300pg/ml. Fitted trendline demonstrates mean values of measurements over time. Y-Axis is scaled logarithmically.

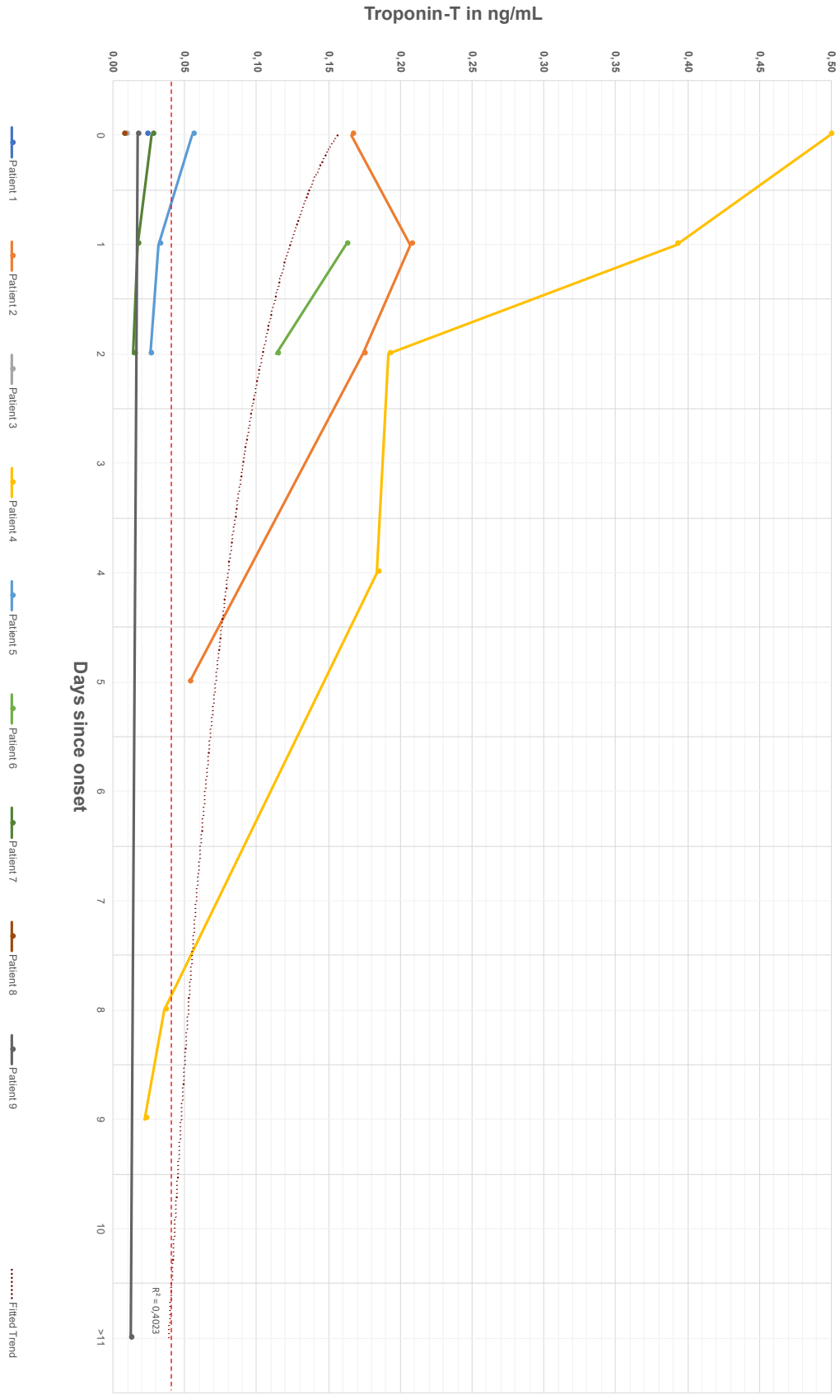

Figure 9: Troponin-T at baseline and follow-up. Red line marks threshold of 0,04ng/ml. Fitted trendline demonstrates mean values of measurements over time.

3.3 Obstetric Parameters

In this chapter, some of the most important obstetric parameters for both mother (gestational age, parity, birth mode) and newborn (sex, weight, umbilical artery pH, APGAR-Score) are presented. Half of the mothers were primiparous (n = 6, 50.0%; multiparous n = 3, 25.0%; missing n = 3, 25.0%) and at the time of delivery mean gestational age was 36.9 ± 3.7 weeks of gestation. As previously mentioned in the prevalence and population section, the majority (n = 8, 66.7%) had a cesarean section delivery whilst only two mothers (n = 2, 16.7%) had a vaginal birth (missing birth mode n = 2, 16.7%). There were no multiple gestations among this population. A majority (n = 7, 58.3%) of the mothers were diagnosed within the first seven days postpartum as shown in figure 6. Three patients (n = 3, 25%) were diagnosed between the second and fourth week postpartum and the two remaining patients (n = 2, 16.7%) were diagnosed forty-eight and eighty-eight days after childbirth. Half of the newborns were female (n = 6, 50%; missing sex n = 4, 33.3%) and the mean birth weight was = 2945g ± 1059g. Fetal outcome parameters remained within normal ranges. In particular, mean umbilical artery pH was mean = 7.30 ± 0.05, APGAR-Scores are illustrated in figure 10. APGAR-Score is a point scale to assess the clinical condition of newborns in a standardized manner. APGAR not only is the last name of its inventor (Dr. Virginia Apgar), but also a mnemonic for appearance, pulse, grimace, activity and respiration of the newborn. Each element of the score is assessed with zero to two points, one (A1), five (A5) and ten (A10) minutes postpartum. Scores below seven points after five minutes are considered moderately abnormal, while less than 3 points deemed as life threatening.(20) Given minimal A1 Scores of 8 within the newborns of our population, there were no distressed neonates registered in this study.

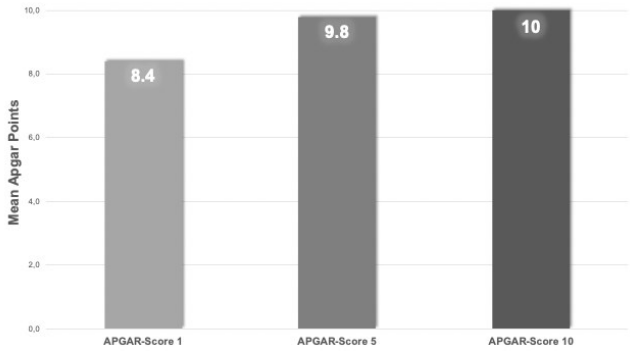

Figure 10: Mean APGAR-Score, X-Axis shows APGAR measurement time points, Y-Axis signalizes the assessed mean APGAR points.

3.4 Therapeutic Procedure

A majority of the patients (n = 8, 66.7%) were admitted to the intensive care unit. Nearly half (n = 5, 41.7%) of them needed some form of ventilation. Endotracheal intubation was the most common form (n = 4, 33.3%), whereas only one patient (n = 1, 8.3%) received non-invasive ventilation by continuous positive airway pressure (CPAP). Catecholamines were only used in three women (n = 3, 25%). A third of the patients (n = 4, 33.3%) had some kind of thromboembolic event in their records including peripheral or central pulmonary embolism as well as deep vein thrombosis. Nine out of twelve mothers (n = 9, 75%; missing n = 3, 25%) were medicated with anticoagulating drugs or antiplatelet agents. The potential risk of prolactin antagonists for cerebral and cardiovascular complications and the importance of sufficient prophylactic therapy is currently being discussed.(8) One third (n = 4, 33.3%) received low-molecular-weight heparin (LMWH) in prophylactic dose (e.g. enoxaparin 40mg, one later switched to edoxaban), two (n = 2, 16.7%) received LMWH in therapeutic dose (e.g. enoxaparin 60 - 80mg, both later switched to phenprocoumon) and one of the mothers (n = 1, 8.3%) was medicated with oral anticoagulation (phenprocoumon, dose according to prescription). Additionally, two patients (n = 2, 16.7%) received antiplatelet agents (acetylsalicylic acid 100mg). Heart failure symptoms were treated with neurohumoral therapy, which consisted of diuretics, ACE-Inhibitors, mineralocorticoid receptor antagonists, β-blockers, inotrope medication, or sometimes angiotensin receptor blockers in different constellations. Every patient (n = 12, 100%) received such therapy and for better understanding, frequencies of the variating medical intakes are illustrated in figure 11. Furthermore, half of the patients (n = 6, 50%) were treated with rather specific therapeutics like prolactin antagonists. Five of the mothers (n = 5, 41.7%) received bromocriptine whereas only one took cabergoline (n = 1, 8.3%), as figure 12 shows.

In addition, there were differences in dose and duration of the therapy. Three of the mothers (n = 3, 25%) received those antagonists (bromocriptine 2.5 or 5mg and cabergoline 0.5mg) for four weeks or even longer, while one (n = 1, 8.3%) took bromocriptine 2.5mg for one week. Due to sparse data the duration for the two remaining patients (n = 2, 16.7%) is missing, one of them received bromocriptine in high dose 5mg, and one of them in low dose 2.5mg. There was no usage of prolactin antagonists prior to 2010.

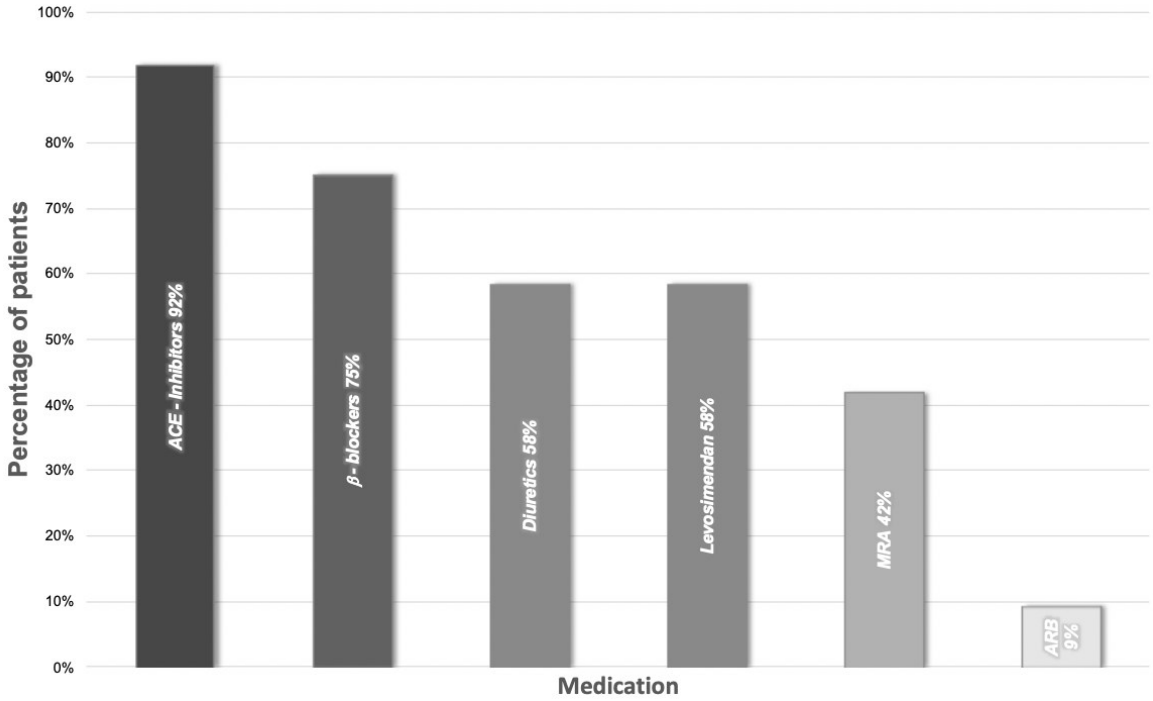

Figure 11: Neurohumoral therapy, frequencies of medical intakes. ACE: Angiotensin Converting Enzyme, MRA: Mineralocorticoid receptor antagonists, ARB: Angiotensin receptor antagonists.

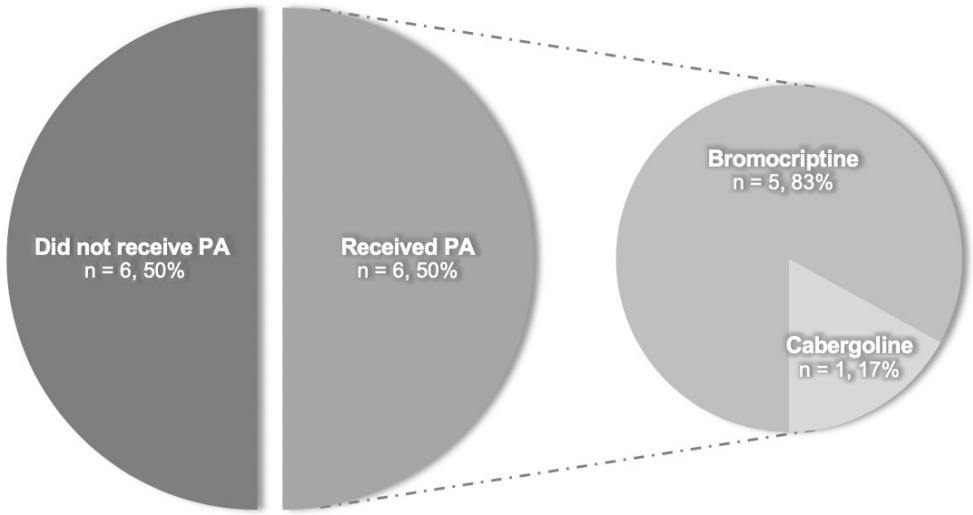

Figure 12: Prolactin antagonist intake. Primary pie: Amount of patients who received prolactin antagonists (PA). Secondary pie: Type of prolactin antagonists were used.

3.5 Maternal Outcome

Patient records were then searched for further cardiological follow ups and echocardiographic findings. If there were no clinical symptoms or signs of decreased ejection fraction, wall motion abnormalities or dimensional deviations in follow ups, their condition was defined as restitution. Half of the women (n = 6, 50%) attained restitution, whereas four out of twelve (n = 4, 33.3%; missing n = 2, 16.7%) patients' left ventricular function remained decreased. Two cases were indicated as missing because no or too few follow ups were available due to their recent date. Figure 13 and 14 illustrate progression of LVEF and LVEDD in relation to time and provide information about recovery. Further treatment consisted mainly of neurohumoral antagonists as described above, in addition to that, the patients were counseled on the risk of recurrence for later pregnancies. Despite intensive medical care, one woman (n = 1, 8.3%) died 34 days after initial diagnosis due to an untreatable ventricular fibrillation. Two of the mothers, who had no remaining LV dysfunction (n = 2, 16.7%) had later deliveries, neither of them faced PPCM again.

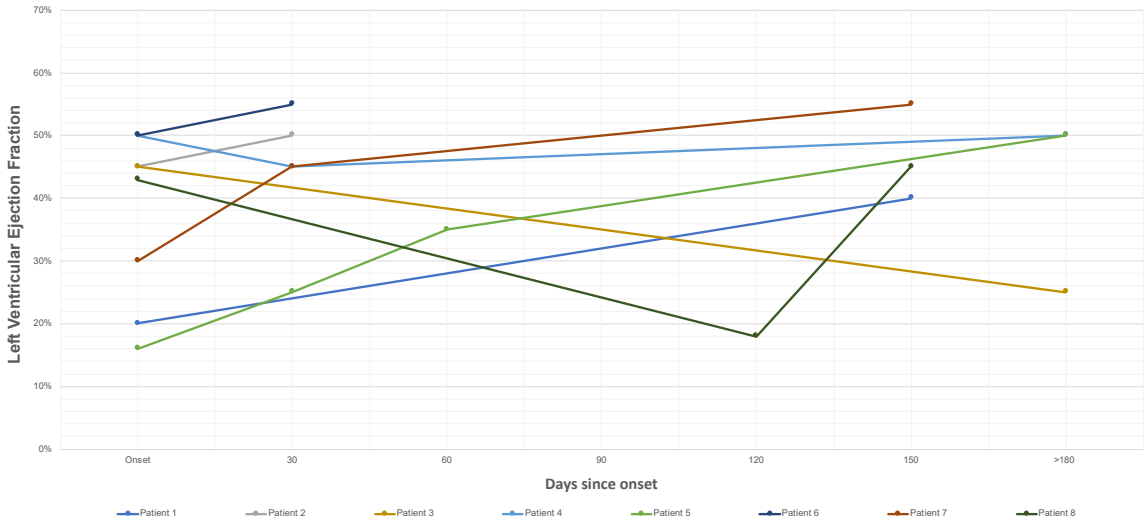

Figure 13: Course of left ventricular ejection fraction. Seven patients (n = 8, 66.7%) had more than one measured value (LVEF) in their records and were therefore eligible for this figure.

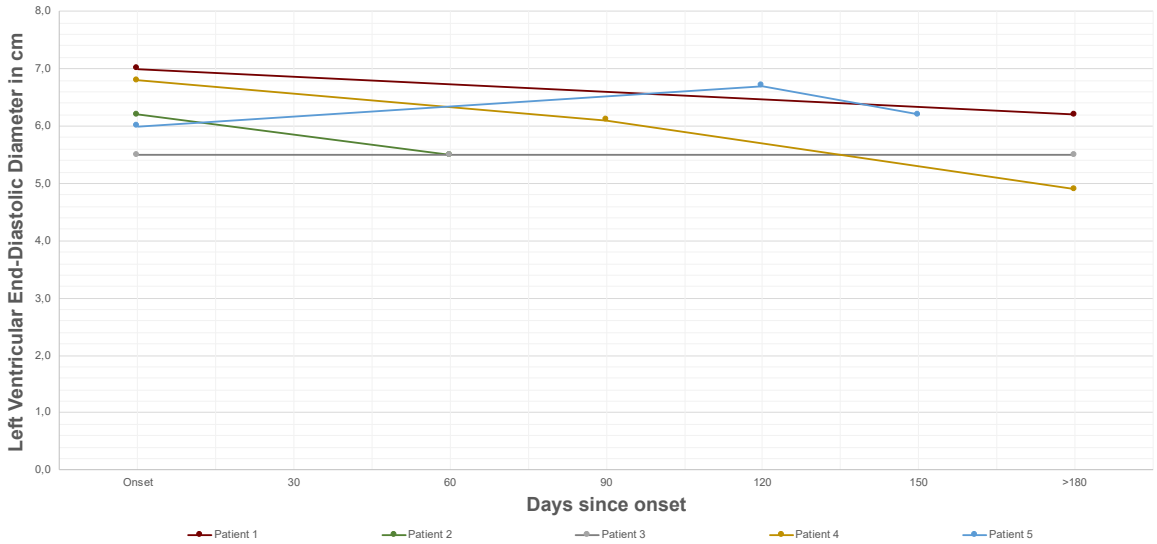

Figure 14.: Course of left ventricular end-diastolic parameter. Four patients (n = 5, 41.7%) had more than one measured value (LVEDD) in their records and were therefore eligible for this figure.

3.6 Limitations

There are several limitations to this study. Although MEDOCS documentation system is partially connected to the old KIS (Krankenhausinformationssystem) system, data before 2001 is very difficult to access and incomplete, which makes it very hard to follow up old patient records or search for earlier findings. Furthermore, the increase in quality of data documentation over time is immense, which helps when collecting recent data but can be limiting if searching for old ones. Screening for PPCM patients by using only certain terms and ICD-10 codes, may result in a lack of cases because there is a chance that pregnant women or women in puerperium were assigned with an incorrect or delayed diagnosis. Summarized, retrospective studies often rely on accurate recording of data and are therefore susceptible to this bias (Observer and Selection Bias). Confusable clinical characteristics and mild forms of the disease not only impede clinicians to diagnose correctly, but also discourage pregnant women and mothers in puerperium to express their concerns (Reporting Bias). Factors and biases like these might contribute to a high number of unreported PPCM cases around the world and simultaneously affect severity and fatality of the study.(21)

3.7 Case Reports

3.7.1 PPCM-Case 1

The patient presented herself in November 2001 with shortness of breath (NYHA II) and peripheral edema three days after delivery. Physical examination showed tachycardia and normal blood pressure, EF of 25% and advanced remodeling processes (LVEDD: 7.0cm, LA: 4.2cm, RVEDD: 3.7cm, RA: 4.1cm) as well as pericardial effusion and pulmonary hypertension (ePAP: 50mmHg). Medical therapy consisted of β-blockers, ACE-Inhibitors, Loop Diuretics and MRA (Mineralocorticoid Antagonists). Unfortunately, the five months follow up showed remained oversized LA and LVEDD, in addition, left ventricular function remained decreased (LVEF: 40%).

3.7.2 PPCM-Case 2

In this case, symptoms emerged almost three months after childbirth in September 2004. With severe dyspnea (NYHA IV) and EF of 20%, the patient was transferred to LKH Graz for intervention with VAD. At the point of admission, circulation was stable with the use of regular heart failure therapy and catecholamines, but in the further course, she developed untreatable ventricular fibrillation. Due to exhaustion of intensive medical care, the mother died four months after her delivery.

3.7.3 PPCM-Case 3

Due to shortness of breath (SOB), peripheral edema and pericardial effusion, the patient was admitted to the ICU two days after giving birth to a healthy newborn in March 2006. CRP was elevated, EF reduced and furthermore ventilation was required. As per her records, she experienced some form of thromboembolic event thus she received oral anticoagulation. In addition to regular heart failure therapy (ACEI, diuretics and β-blockers) she was medicated with Levosimendan. Fortunately, the therapy was successful and the mother made a full LV recovery.

Despite known preeclampsia in her first pregnancy, the mother gave birth to her second child three years later without facing PPCM again.

3.7.4 PPCM-Case 4

Data was very sparse in this case, but what was striking was that this patient was not compliant at all (did not take her prescribed medication), which resulted in a significant worsening of PPCM (remaining LV dysfunction) in her tracked patient records. She was diagnosed in May 1997, her first cardiological findings date back to November 1998 (LVEDD: 7.0cm, EF: 45%) and last control ECG was made in April 2002, which showed massive dilation (LVEDD: 8.0cm, LA: 7.1cm), hypokinesia and decreased LVEF to 25%. Obstetric parameters showed premature birth (30^{th} pregnancy week) and an APGAR Score of 4/8/10. The newborn weighed approximately 1500g.

3.7.5 PPCM-Case 5

PPCM emerged in February 2007 at the time of childbirth in this patient. Clinical characteristics showed NYHA II dyspnea, marginal dilation of LVEDD (5.5cm) and reduction of EF (50%) with myocardial concentric hypertrophy of the left heart. Thromboembolic events and preeclampsia were documented in her records. She was later admitted to the ICU, where ventilation and catecholamines were required. CK-MB, CRP, NT-proBNP and Troponin-T were all elevated in laboratory findings at onset. She received enoxaparin in therapeutic dose and a heart failure therapy with ACEI. In addition to that, she was medicated with Levosimendan. The mother gave birth to a healthy newborn and obtained restitution.

3.7.6 PPCM-Case 6

This patient faced signs and symptoms as NYHA IV dyspnea, pericardial and pleural effusion two months after the birth of her second healthy child in December 2009. ECG showed harsh EF reduction and noticeable dilation (LA: 5.5cm, LVEDD: 6.8cm, LVEF: 16%, ePAP: 45mmHg). NT-proBNP was significantly elevated

(3763pg/mL), whereas CRP and Troponin-T remained in reference range. During her stay at the ICU, she received heart failure therapy, was medicated with Levosimendan and enoxaparin in prophylactic dose. Moreover, she received specific therapy with prolactin antagonist bromocriptine (2,5mg). Nevertheless, cardiac function remained decreased (LVEF: 50%, with asynchronous contraction and hypokinesia) and heart failure therapy was still required (ARB, β-blockers and MRA).

3.7.7 PPCM-Case 7

Patient 7 presented herself with NYHA IV dyspnea and tachycardia immediately after childbirth in August 2010. The mother was in her 34th pregnancy week, suffered from preeclampsia, had a caesarean section delivery and gave birth to a healthy girl with 1560g. She was admitted to the ICU, where endotracheal intubation and ventilation, as well as catecholamines were necessary. Physical examination showed moderate reduction of left ventricular function (LVEF: 50%) concentric hypertrophy, pleural and pericardial effusion. White blood cells (37.9G/L), CRP (10.3mg/L), Troponin-T (0.25ng/mL) and NT-proBNP (2294pg/ml), were significantly increased. She received heart failure therapy (β-blockers, ACEI), Levosimendan, acetylsalicylic acid 100mg 0-1-0 and bromocriptine (5mg for more than 4 weeks). The patient made a full recovery and gave birth to a second child two years later, PPCM did not reappear.

3.7.8 PPCM-Case 8

Just a few days after childbirth in September 2010, this mother suffered from NYHA IV dyspnea and peripheral edema. During pregnancy, she suffered from preeclampsia but gave birth to a healthy girl in her 36th week (birth mode: section). However, she had normal heart rate and blood pressure. The transthoracic echocardiography showed pleural and pericardial effusion. Patient records contained thromboembolic events therefore she received enoxaparin in therapeutic dose and later phenprocoumon. LVEF was reduced (35%), whereas PAP was increased (35mmHg). LDH (382U/L), CRP (28.7mg/L) and NT-proBNP (8843pg/mL) as well as Troponin-T (0.06) were all extremely elevated. Once

admitted to the ICU, she was treated with Levosimendan, heart failure therapy (ACEI, β-blockers, Loop-diuretics and diuretics) and bromocriptine (5mg). The patient made significant improvement, however showed mild EF reduction (55%) in following controls and therefore still received β-blockers and ACEI. Apart from that, the final examinations can be considered as restitution, according to her records.

3.7.9 PPCM-Case 9

Within one month postpartum, patient 9 was diagnosed with PPCM in August 2017. She had a vaginal birth for her second child and was in the 41st week of pregnancy. Her newborn girl was healthy with an APGAR score of 9/10/10. At onset, she suffered from shortness of breath (NYHA III) and was quite bradycardic in electrocardiogram (50bpm). Further findings showed pleural effusion and moderately reduced EF (40%), whereas dimensional parameter remained normal. Laboratory markers (LDH: 290U/L, CRP: 75mg/L, NT-proBNP: 7579pg/mL, Troponin-T: 0.16ng/mL) indicated acute heart failure, wherefore she was admitted to the ICU. The patient received heart failure therapy (ACEI, MRA, Loop-Diuretics), acetylsalicylic acid 100mg 0-1-0 and prolactin antagonist cabergoline (1mg) for more than four weeks. Therapy succeeded and the mother made a full recovery.

3.7.10 PPCM-Case 10

The mother was in her 38th week of pregnancy when she gave birth to her 3222g healthy newborn girl in May 2017. She was primiparous and had a caesarean section delivery. A week in puerperium, she faced NYHA III dyspnea and showed reduced EF (40%), pleural and pericardial effusion, as well as dilation of left heart (LVEDD: 6.0cm, LA: 4.7cm). High levels of CRP (19.5mg/L), NT-proBNP (2496pg/mL) and Troponin-T (0.03ng/mL) confirmed the diagnosis. At the ICU was treated with heart failure therapy (ACEI, β-blockers, MRA), Levosimendan, enoxaparin in prophylactic dose and bromocriptine but only for two days with 2.5mg. Continuous positive airway pressure ventilation was required initially, but in the further course she obtained restitution.

3.7.11 PPCM-Case 11

This patient was a recent case of PPCM in June 2019. She was primiparous, had prolonged pregnancy (42nd week) and a vaginal birth. The newborn boy was healthy (APGAR = 9/10/10) and weighed 4050g. The mother presented herself one week after childbirth with significant bradycardia (40bpm), hypertension (160/90mmHg) and peripheral edema. Her NT-proBNP (810pg/mL) was slightly elevated. Therapy with ACEI and enoxaparin in prophylactic dose was started.

3.7.12 PPCM-Case 12

In this case, PPCM was first diagnosed four days after birth in October 2019. After an uneventful pregnancy, the mother (BMI: 47.9, preexistent hypertension) had a caesarean section delivery in her 31st week of gestation, moreover an appendectomy was performed at the same time, due to an inflamed and perforated appendix. Both went well and postoperative course was without complication. Due to left bundle branch block, cardiological follow up had been done and showed widened QRS-complex and moderately reduced LVEF (43%), whereupon PPCM was suspected. Heart failure therapy and prolactin antagonists were recommended as well as control ECG until normalization of LV function. Her former general practitioner refused to adhere to recommended therapy because it was “not evidence-based”, which led to drastic worsening of PPCM and cardiac decompensation. The mother was readmitted to emergency room in February 2020, where she suffered from peripheral edema, pleural effusion and severe SOB (NYHA IV). Initial recompensation with Levosimendan was started, ECG showed harsh reduction of LVEF (18%) and significant dilation of LVEDD (6.7cm). Diagnosis was confirmed by biopsy and therapy with bromocriptine 5mg for two weeks (later 2.5mg for six weeks), edoxaban, ACEI, β-blockers, MRA and loop diuretics was initiated. At the last cardiological follow up examination, the patient stated that she was taking the prescribed medication and that she felt subjectively better, even though LVEF was still reduced (45%).

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Age	28	26	31	31	26	35	26	30	29	29	35	27
Year of Onset	2001	2004	2006	1997	2007	2009	2010	2010	2017	2017	2019	2020
Postpartal Day of Onset	3	88	2	19	1	48	0	4	22	4	9	4
Parity	-	-	-	Primipara	Multipara	Multipara	Primipara	Primipara	Multipara	Primipara	Primipara	Primipara
Birthmode	-	-	Sectio	Sectio	Sectio	Sectio	Sectio	Sectio	Vaginally	Sectio	Vaginally	Sectio
NYHA-Stage	II	unclassified	unflassified	-	II	IV	IV	IV	III	III	*	IV
LVEF (Onset)	25%	20%	45%	45%	50%	16%	50%	35%	40%	40%	60%	43%
LVEDD (Onset)	7.0cm	-	6.2cm	7.0cm	5.5cm	6.8cm	-	-	4.8cm	6.0cm	4.8cm	6.0cm
LA (Onset)	4.2cm	-	-	4.7cm	-	5.5cm	-	-	-	4.7cm	-	-
NT-proBNP (Onset)	-	-	106pg/mL	-	219pg/mL	3763pg/mL	4662pg/mL	9249pg/mL	7579pg/mL	2496pg/mL	810pg/mL	907pg/mL
Troponin-T (Onset)	-	-	0.023ng/mL	-	0.17ng/mL	0.009ng/mL	0.50ng/mL	0.060ng/mL	0.16ng/mL	0.027ng/mL	0.007ng/mL	0.017ng/mL
CRP (Onset)	-	-	10.7mg/L	-	46.4mg/L	2.0mg/L	10.3mg/L	28.7mg/L	75.1mg/L	19.5mg/L	5.5mg/L	100.1mg/L
ICU-Admission	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Ventilation	-	Yes (ETI)	Yes (ETI)	No	Yes (ETI)	No	Yes (ETI)	No	No	Yes (CPAP)	No	No
Catecholamines	No	Yes	No	No	Yes	No	Yes	No	No	No	No	No
Heart Failure Therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Prolactin Antagonist	No	No	No	No	No	Bromocriptine	Bromocriptine	Bromocriptine	Cabergoline	Bromocriptine	No	Yes
Restitution	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	-	-

*Table 4: Demonstration of patient data on individual level. ETI: endotracheal intubation, CPAP: continuous positive airway pressure, dashes (-) indicate missing data, unclassified: in two of eleven patients (n = 2, 18.2%) SOB was just mentioned but not classified, * indicates patient showed no signs of dyspnea, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LA: left atrium.*

4 Discussion

4.1 Epidemiological Comparison

We are the first to describe prevalence (ratio of cases to live births) and clinical characteristics for PPCM in Styria. With twelve cases and 200 000 live deliveries over the last eighteen years (which corresponds to one case per 16 667 live births in this time frame), the disease is truly rare, but as the results demonstrate possibly fatal. In fact, we are nowhere near to comparable prevalences from Denmark, United States or South Korea. Besides potentially true higher prevalences, those countries might have better awareness for PPCM, other screening methods and/or higher quality in data collection all of which help to achieve more precise results. According to data from the United States white women have a prevalence of one case per 4075 deliveries there. A Denmark study recently provided new data with a periodic prevalence of 1:6500 deliveries. Assuming that socio-economic conditions and racial predispositions are similar to those in Styria, a plausible prevalence could range from 1:4000 to 1:8000 live deliveries. However epidemiological results as age at diagnosis (~30 years) and the fact that most women were diagnosed within the first month postpartum, both match with current temporal trends of PPCM. What was striking was that there were no PPCM diagnoses before delivery. Furthermore, even though there is no data that elective caesarean section improves fetal outcome and/or ameliorate PPCM, it was by far the most common birth mode (n = 8, 66.7%; vaginal birth n = 2, 16.7%) among our population, as well as in comparable studies. Mean gestational age of just 36.9 weeks ± 3.7, suggesting that increased maternal risk required immediate delivery could explain the high rate of caesarean section.(5) Risk factors like age or preeclampsia, both were quite common among the patients, frequently occur in current literature mentioned above. Vasculotoxicity is not solely caused by cleaved prolactin fragments, but also by soluble Fms-like tyrosine kinase 1 (sFlt1), which neutralizes pro-vascular growth factors like VEGF (vascular endothelial growth factor). 16kDa-fragment and increased levels of sFlt1 create an anti-angiogenic setting in late pregnancy, which might trigger PPCM seen in both mice and women (figure 3).(22) Elevated levels of sFlt1 can also be found in women

with preeclampsia, but usually return to normal within the first week postpartum. Among our collective, a third (n = 4, 33.3%) suffered from preeclampsia, compared with pregnant women without PPCM in which incidence was only 2.31% according to a Swiss study or a worldwide average rate of 5% for preeclampsia in pregnancy.(23,24) There is evidence that preeclampsia can lead to cardiac dysfunction independently of PPCM. However, the strong epidemiologic relationship suggests that the two diseases may share pathophysiological mechanisms. The phenotype of PPCM is similar to that of a normal physical exam in pregnant women. Moreover, incorrect and delayed diagnosis as a result of missing awareness for PPCM in Styria along with the consequences of common biases of retrospective study design all may contribute to a high number of unreported cases and at the same time disguise the true prevalence. Aforementioned missing diagnoses antepartum could also be linked to the same reason. The fact is that epidemiological data and risk factors match with studies all around the world and it is therefore very unlikely that the prevalence in this country will so drastically stand out from the others.(9,13,25)

4.2 Clinical Characteristics

4.2.1 Physical Examination

Shortness of breath is stated as the leading symptom for PPCM in most of the literature. Unfortunately, as widespread as it is across peripartum cardiomyopathy patients, it is also unspecific, can indicate a lot of events and is often present (60 – 70%) during pregnancy.(18,26) What is interesting is that the results show a rather high number of mothers (n = 4, 33.3%) suffering from NYHA IV (dyspnea at rest) dyspnea. A multicentric study in Germany provides the same severity of the symptom, demanding quick intervention. (8) Along with dyspnea, peripheral edema and pleural effusion were notably common symptoms. Blood pressure also varies in comparable studies, but often shows normotensive mean values. However, mean heart rate (91.3bpm ± 32.2) was lower among our cohort, compared to the latest studies. According to current literature, these are typical findings in physical examination.(11,21) In Nigeria, where PPCM has high incidence, a study showed LVEDD of mean = 6.3cm ± 0.07cm, LA of mean = 4.4cm ± 0.006cm and LVEF of

mean = 30.7% ± 7.8% at onset.(21) Those pathognomonic changes correspond to our echocardiographic results at onset, even though ejection fraction was almost 10% higher in mean (39.3% ± 13.4%), but still reduced among our population. LV remodeling processes (Dilation of LA and LVEDD) and LVEF reduction by 30%, all have prognostic impact on left ventricular recovery and are therefore important parameters for clinicians at the onset of PPCM. If time of diagnosis and therapeutic management should be accurate, physical examination must be carried out carefully and adapted to the situation, since the diagnostic procedure is discerning and there are no specific signs and symptoms for PPCM.(18)

4.2.2 Laboratory Data

During pregnancy, a lot of physiological changes occur to accommodate the demands of the growing fetus, which can modify blood values.(27) It is therefore demonstrated which values are commonly increased and which ones cannot be considered physiological even during pregnancy and further indicate PPCM. In addition to that, the informative value of the different laboratory parameters is being discussed. Third trimester reference ranges were taken to represent the peripartal period as accurately as possible. Red blood count and hemoglobin, as well as total protein and albumin are all physiologically decreased during late pregnancy. At the same time, white blood count and lactate-dehydrogenase are elevated for this period. Compared to non-pregnant women, our population displayed these kinds of pregnancy related modifications. However, it is striking that women with PPCM had higher values of C-reactive Protein (mean = 33.1mg/L ± 34.3mg/L, reference range for third trimester = 0.4 – 8.1mg/L), uric Acid (6.3mg/dL ± 0.89mg/dL, 3.1 – 6.3mg/dL) and creatine kinase-myoglobin (34U/L ± 23.3U/L, 1.8 – 4.2U/L) compared to healthy pregnant women in peripartum. Apart from that, estimated glomerular filtration rate (eGFR is calculated by CKD-EPI equation) should be increased in late pregnancy. However, our PPCM patients had lower values for it (mean = 95.8ml/min ± 16.9ml/min, 117 – 182ml/min). Also, ionized calcium was reduced in relation to adapted reference ranges (2.1mmol/L ± 0.13mmol/L, 4.4 – 5.3mmol/L). (27) Such results should help clinicians to be able to differentiate physiological deviations from proven pathological changes in laboratory analysis.

Natriuretic peptides' key roles are to rule out heart failure (with a threshold < 300pg/ml for NT-proBNP, low probability of heart failure) and simultaneously predict bad left ventricular recovery if BNP values exceed a certain threshold (1860 pg/ml) at onset. (3) Considering that we may have missed mild cases due to selection bias, our results show that a majority of the women were way beyond the threshold at onset and remained above 300pg/ml within one month. Furthermore, the measurement of Troponin T is a simple and helpful method to detect myocyte damage and has a moderate predictive value for persistent left ventricular dysfunction with a cut-off value over 0,04ng/ml.(28) Half of the examined mothers exceeded this cut-off value at the time of diagnose or shortly thereafter. The two parameters do not normally rise as significantly or remain as constantly high. As a matter of fact, half of patients (n = 6, 50%) were left with remaining LV function dysfunction. Laboratory parameters as mentioned above are useful to suspect and rule out diseases and sometimes roughly predict prognosis but should always be used in relation to current circumstances and with the help of other diagnostic material and methods.

4.2.3 Therapy and Maternal Outcome

Subsequent therapeutic procedure should be compared to current international methods with respect to maternal outcome. Further, it is discussed whether and how the management for PPCM stands out from therapies of other diseases that result in heart failure. A German study on contemporary management described improvement of LVEF by ten absolute percentage units within 6 ± 3 months if patients were medicated with β-blockers and/or ACE-Inhibitors/angiotensin-receptor-blockers (ARB). Bromocriptine was used (in a dose from 2.5-5mg for 4 weeks or longer) in more than half of their cases with a significant number of patients who improved their left ventricular function, compared to patients who did not receive bromocriptine.(29) Similar to our results, a vast majority (66.7%) of patients, who received both ACE-Inhibitors and/or β-blockers and prolactin antagonists like bromocriptine (2.5-5mg) or cabergoline (0.5mg), had high rates of recovery for left ventricular function or even obtained restitution. The therapy for PPCM may vary dependent on stage and severity. Acute and chronic heart failure should be treated according to current guidelines; however, one should always consider that

medication for heart failure may be teratogenic or fetotoxic. In addition, drugs such as ARB, ARNi or NOAC are contraindicated if mothers are breastfeeding. Heart failure should be treated with neurohumoral antagonists until full recovery and 12-24 months beyond.(3) All of our patients were diagnosed in postpartum and this explains the frequent use of ACE Inhibitors and Aldosterone Antagonists, which can have a teratogenic effect during pregnancy. Levosimendan was widely used among the patients in this study (n = 7, 58.3%), five of them obtained restitution, thus the drug seems promising. However, in a randomized controlled study, PPCM patients who received the calcium sensitizer showed no difference in clinical outcome.(30) Specific medication for PPCM with prolactin antagonists is still relatively young (not in use before 2010 in Styria), whereas common heart failure therapy has been used for a long time. Combined, they achieve promising results, thus further use is appropriate. Previously mentioned, the patients among this study had relatively high LVEF (mean = 39.3% ± 13.4%) and LVEDD (mean = 6.3cm ± 0.61cm) at onset, compared to a black collective from the North American IPAC (Investigations of Pregnancy-Associated Cardiomyopathies) study where the patients had lower LVEF (mean = 31% ± 0.09%) and LVEDD (mean = 5.8cm ± 0.07cm) at study entry and 59% of the patients achieved full recovery (LVEF >50%).(31) According to the study, combined baseline LVEDD and LVEF allow accurate prediction of recovery with a recovery rate of >91% (LVEF >50%) if baseline LVEF is >30% and LVEDD is <6.0cm. In addition, it is shown that black women, compared to whites presented with a lower LVEF at onset that persisted up to 12 months postpartum. Always considered that we might have missed mild cases due to retrospective study design and its susceptibility to selection biases, the recovery rate among our patients was just 50% with mean LVEF at 5 months follow-up of 46% ± 0.19%. It can thus be suggested that racial predisposition but also time of diagnosis, severity at onset, therapeutic procedure and patient compliance are decisive for the prognosis of PPCM. Patients in our study were counseled on the risk of recurrence for later pregnancies. Nevertheless, two (n = 2 16.7%) had further deliveries and fortunately PPCM did not reappear. A recent comprehensive review of this topic showed that patients with persistent LVEF dysfunction had significant higher risk of relapse and worse fetal outcome in further pregnancies. The best predictor for recurrence of PPCM and deterioration of cardiac function is baseline LVEF. However, physiological LV function does not assure uneventful subsequent pregnancy.

Women should be cogently counseled that they have high risk even if left ventricular function recovered. If the decision to proceed with pregnancy is made, a multidisciplinary team of well-informed clinicians is necessary. Close monitoring of symptoms, LVEF, LVEDD and brain natriuretic peptides is highly recommended.(32)

5 Conclusion

Notwithstanding its limitations, the research well demonstrates first numbers for PPCM in Styria (1:16 667) and simultaneously accurately characterizes the phenotype of the disease. As risk factors and epidemiological profile seem to coincide with current international data, it is very unlikely that our calculated periodic prevalence so drastically stands out from the others (Incidence Denmark 1:6500). Assuming similar socioeconomic circumstances and racial predispositions, we expect the incidence to range from 1:4000-8000. Taken into account that mild cases might have been missed due to common biases of the retrospective study design, PPCM struck hard among our collective with a recovery rate of just 50% and one fatal outcome. To unveil the true prevalence in Styria and avoid potentially fatal outcomes, awareness must increase. As current medical care for PPCM exhausts, the call for novel specific therapy grows and should be explored in further studies.

6 References

1. Hilfiker-Kleiner D, Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. Nature Reviews Cardiology. 2014.
2. Wu VC-C, Chen T-H, Yeh J-K, Wu M, Lu C-H, Chen S-W, et al. Clinical outcomes of peripartum cardiomyopathy. Medicine (Baltimore) [Internet]. 2017;96(43):e8374. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29069030%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5671863%0Ahttp://Insights.ovid.com/crossref?an=00005792-201710270-00057
3. Bauersachs J, Konig T, van der Meer P, Petrie MC, Hilfiker-Kleiner D, Mbakwem A, et al. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. Eur J Heart Fail. 2019 Jul;21(7):827–43.
4. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functi. Circulation. 2006 Apr;113(14):1807–16.
5. Cunningham FG, Byrne JJ, Nelson DB. Peripartum Cardiomyopathy. Obstet Gynecol. 2019;133(1):167–79.
6. Cunningham FG, Byrne JJ, Nelson DB. Peripartum Cardiomyopathy. Obstet Gynecol. 2019;
7. Sliwa K, Hilfiker-Kleiner D, Mebazaa A, Petrie MC, Maggioni AP, Regitz-Zagrosek V, et al. EURObservational research programme: A worldwide registry on peripartum cardiomyopathy (PPCM) in conjunction with the Heart Failure Association of the European Society of Cardiology Working Group on PPCM. Eur J Heart Fail. 2014;
8. Hilfiker-Kleiner D, Haghikia A, Berliner D, Vogel-Claussen J, Schwab J, Franke A, et al. Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. Eur Heart J. 2017 Sep;38(35):2671–9.
9. Lee S, Cho GJ, Park GU, Kim LY, Lee TS, Kim DY, et al. Incidence, Risk

Factors, and Clinical Characteristics of Peripartum Cardiomyopathy in South Korea. Circ Hear Fail. 2018;

10. Azibani F, Pfeffer TJ, Ricke-Hoch M, Dowling W, Pietzsch S, Briton O, et al. Outcome in German and South African peripartum cardiomyopathy cohorts associates with medical therapy and fibrosis markers. ESC Hear Fail. 2020 Feb;
11. Honigberg MC, Givertz MM. Peripartum cardiomyopathy. BMJ. 2019 Jan;364:k5287.
12. Ballard LC, Cois A, Kea B. Peripartum Cardiomyopathy: A Review. Curr Emerg Hosp Med Rep. 2019 Sep;7(3):127–34.
13. Behrens I, Basit S, Lykke JA, Ranthe MF, Wohlfahrt J, Bundgaard H, et al. Hypertensive disorders of pregnancy and peripartum cardiomyopathy: A nationwide cohort study. PLoS One. 2019;14(2):e0211857.
14. Balaceanu A. B-type natriuretic peptides in pregnant women with normal heart or cardiac disorders. Med Hypotheses. 2018 Dec;121:149–51.
15. Azibani F, Sliwa K. Peripartum Cardiomyopathy: an Update. Curr Heart Fail Rep. 2018 Oct;15(5):297–306.
16. Lau ES, Sarma A. The Role of Cardiac Biomarkers in Pregnancy. Curr Treat Options Cardiovasc Med. 2017 Jul;19(7):49.
17. Haghikia A, Podewski E, Berliner D, Sonnenschein K, Fischer D, Angermann CE, et al. Rationale and design of a randomized, controlled multicentre clinical trial to evaluate the effect of bromocriptine on left ventricular function in women with peripartum cardiomyopathy. Clin Res Cardiol. 2015;104(11):911–7.
18. Stergiopoulos K, Lima F V. Peripartum cardiomyopathy-diagnosis, management, and long term implications. Trends Cardiovasc Med [Internet]. 2019;29(3):164–73. Available from: https://doi.org/10.1016/j.tcm.2018.07.012
19. STATISTIK AUSTRIA. Lebendgeborene (mit inländischem Geburtsort) seit 2000 nach Entbindungsort und Wohnbundesland der Mutter Lebendgeborene (mit inländischem Geburtsort) seit 2000 nach Entbindungsort und Wohnbundesland der Mutter [Internet]. 2019. Available from: http://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/bevoelkerung/geborene/medizinische_und_sozialmedizinische_merkmale/110627.html

20. Simon L V, Hashmi MF, Bragg BN. APGAR Score. In Treasure Island (FL); 2020.
21. Wang WW, Wang Y. Peripartum women with dyspnea in the emergency department Is it peripartum cardiomyopathy? Med (United States). 2018;97(31).
22. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature. 2012;485(7398):333–8.
23. Purde M-T, Baumann M, Wiedemann U, Nydegger UE, Risch L, Surbek D, et al. Incidence of preeclampsia in pregnant Swiss women. Swiss Med Wkly. 2015;145:w14175.
24. Bello N, Rendon ISH, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. J Am Coll Cardiol. 2013 Oct;62(18):1715–23.
25. Dhaval K, Sahil K, S. AW, Chandrasekar P, Marjan M, Chul A, et al. Temporal Trends in Incidence and Outcomes of Peripartum Cardiomyopathy in the United States: A Nationwide Population-Based Study. J Am Heart Assoc [Internet]. 2020 Feb 13;3(3):e001056. Available from: https://doi.org/10.1161/JAHA.114.001056
26. Gilbert R, Auchincloss JHJ. Dyspnea of pregnancy. Clinical and physiological observations. Am J Med Sci. 1966 Sep;252(3):270–6.
27. James D. Studies : A Reference Table for Clinicians To the Editor : In Reply : :868.
28. Hu CL, Li YB, Zou YG, Zhang JM, Chen JB, Liu J, et al. Troponin T measurement can predict persistent left ventricular dysfunction in peripartum cardiomyopathy. Heart. 2007;93(4):488–90.
29. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol [Internet]. 2013;108(4):366. Available from: https://doi.org/10.1007/s00395-013-0366-9
30. Biteker M, Duran NE, Kaya H, Gündüz S, Tanboğa HI, Gökdeniz T, et al. Effect of levosimendan and predictors of recovery in patients with peripartum cardiomyopathy, a randomized clinical trial. Clin Res Cardiol. 2011;
31. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, et al.

Clinical Outcomes for Peripartum Cardiomyopathy in North America: Results of the IPAC Study (Investigations of Pregnancy-Associated Cardiomyopathy). J Am Coll Cardiol. 2015;66(8):905–14.

32. Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States: Diagnosis, prognosis, and management. J Am Coll Cardiol [Internet]. 2011;58(7):659–70. Available from: http://dx.doi.org/10.1016/j.jacc.2011.03.047