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Cardiac and obstetric outcomes in pregnant women with heart disease: appraisal of the 2018 mWHO classification

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ABSTRACT

Objective To appraise the application of the 2018 European Society of Cardiology-adapted modified WHO (mWHO) classification to pregnant women with heart disease managed at our maternal–fetal medicine referral centre and to assess whether the lack of a multidisciplinary Pregnancy Heart team has influenced their outcomes.

Methods A retrospective cohort study including all pregnancies with heart disease managed at our centre between June 2011 and December 2020. Cardiac conditions were categorised in five classes according to the mWHO classification. An additional class, named X, was created for conditions not included in this classification. Outcomes were compared among all classes and factors potentially associated to cardiac complications were assessed.

Results We identified 162 women with 197 pregnancies, for a prevalence of 0.7%. Thirty-eight (19.3%) gestations were included in class X. Caesarean section was performed in 64.9% pregnancies in class X, a rate similar to that of class II, II-III, and III/IV, and mostly for obstetric indications; in turn, it was more commonly performed for cardiology reasons in class II–III and III/IV. Cardiac complications occurred in 10.7%, with class X and II pregnancies showing the highest number of events (n=30.8% and 34.6%, respectively). Multiple gestation and urgent caesarean section associated with a 5-fold and 6.5-fold increase in complication rates.

Conclusions Even in a maternal–fetal medicine referral centre, the lack of a multidisciplinary team approach to women with heart disease may negatively impact their outcomes.

Key questions

What is already known about this subject?

- A team-based approach to care of pregnant women with heart disease that includes multidisciplinary collaboration among maternal–fetal medicine specialists and cardiologists has been recently proposed by the European Society of Cardiology as pivotal to improve maternal outcomes.

What does this study add?

- Our findings support the hypothesis that implementation of a multidisciplinary team may possibly ameliorate both cardiac and obstetric outcomes of women with heart disease, even when they are managed in a maternal–fetal medicine referral centre.

How might this impact on clinical practice?

- Our data can be useful for local counselling as well as for promoting the implementation of a specific management protocol including a multidisciplinary approach to care of women with heart disease.

INTRODUCTION

Maternal heart disease (HD) is the leading cause of indirect maternal death in several high-income countries, including Italy. It is also associated with substantial maternal and feto-neonatal morbidity.[1–4]

Maternal HD complicates 0.2%–4% of pregnancies.[5] Its prevalence has progressively risen during the last decade, and it is expected to grow further, due to an increasing number of women with congenital HD (CHD) reaching childbearing age as well as a higher prevalence of risk factors for cardiovascular disease (CVD) among pregnant women, such as advanced age, obesity, chronic hypertension and smoking.[6 7]

The European Society of Cardiology (ESC) Task Force on HD during pregnancy has recently highlighted the importance of a multidisciplinary team, the Pregnancy Heart team, in managing these women to potentially improve their outcomes.[5] One of the tasks of this team is to jointly assess all women with HD to define their risk of experiencing cardiac complications and, thus, to tailor their follow-up during pregnancy.[8] Such risk assessment should be carried out according to the modified WHO (mWHO) classification, which comprises five classes with progressively increasing risk of mortality

and morbidity.[5 9] However, not all cardiac conditions are included in this classification, thus making its use in clinical practice challenging, particularly for acquired HDs in which validation of the classification is still limited.[10 11]

Recently, at our Institution, a clinical protocol as well as a Pregnancy Heart team for managing women with HD have been implemented. A detailed assessment of all pregnancies complicated by HD managed at our centre over a decade was pivotal to provide data for drafting the protocol and identifying areas that could be targets of the Pregnancy Heart team's initial activity.

Here, we present the findings of this analysis, with a critical appraisal of the 2018 ESC-adapted mWHO classification, and assess whether the lack of a multidisciplinary Pregnancy Heart team in managing pregnant women with HD has possibly influenced their outcomes. Also, we provide data that may be useful for local counselling and management protocol drafting.

METHODS

This was a retrospective cohort study on all pregnancies with HD managed at our maternal–fetal medicine referral centre between 1 June 2011 and 31 December 2020. Patients with HD known before pregnancy as well as cases diagnosed during gestation were included. For those women with more than one pregnancy during the study period, all pregnancies were included in the analyses due to the potential for progression of HD's severity during the interpregnancy time interval.

Maternal HDs were retrospectively categorised according to the 2018 ESC-adapted mWHO classification.[5 9] For cases with more than one diagnosis, the HD with the highest potential for maternal complications was considered for classification. We created an additional class, named X, to allow for categorisation of HDs not included in the mWHO classification. Each class X-HD was thoroughly assessed (NB, AA, FC) and controversies were resolved by a consultant cardiologist and a maternal–fetal medicine specialist (ML, PV).

Medical records of all identified cases were reviewed and information regarding demographics, comorbid conditions, pregnancy course and perinatal outcomes were collected and recorded in a dedicated log-book. Need for urgent endovascular or surgical procedures during gestation was also assessed. Gestational age (GA) at birth was calculated based on the first trimester ultrasound scan report or, when not available, on the last menstrual period.

Risk factors for CVD included maternal age ≥40 years, pregestational body mass index (BMI) >35 kg/m^2, black, Asian or minor ethnicities (BAME), pregestational diabetes, chronic hypertension, substance abuse (smoking, drugs, alcohol) and history of cardiotoxic chemotherapy.[12 13]

Cardiac adverse events were defined as the occurrence of maternal death, heart failure (HF) requiring treatment, symptomatic documented tachyarrhythmias and thromboembolic events.

Statistical analyses

The prevalence rate was calculated as the number of HDs per 100 maternities with a 95% CI, assuming the Poisson approximation to the binomial distribution.

Descriptive statistics were calculated and expressed as median values and IQRs for continuous variables and as absolute numbers and percentages for dichotomous data.

Maternal characteristics and outcomes were assessed among pregnancies in class X and compared with those in the other mWHO classes. Due to small group size, mWHO class III and IV were lumped together for analysis purposes. Fisher's exact test or Pearson χ^2 test of homogeneity were used when appropriate to compare outcomes. Pairwise comparisons among classes were performed for dichotomous variables identified as significantly different at the χ^2 tests by means of z-test of two proportions followed by Bonferroni's correction to adjust for multiple comparison.

Logistic regression models were employed to estimate dose-response associations with cardiac adverse events. A p<0.05% and 95% CIs not containing the unit were used to designate statistical significance (SPSS software, V.26; SPSS).

Patient and public involvement

Since the retrospective nature of our study, it was not possible to involve patients or the public in its design, or conduct, or reporting.

RESULTS

During the study period, 162 women with 197 pregnancies were identified, for an overall prevalence of maternal HD of 0.7% (95% CI 0.6% to 0.8%). Precisely, 28 women had 2 pregnancies, 2 had 3 pregnancies and 1 had 4 pregnancies.

Table 1 displays general characteristics, obstetric history and pregnancy course of the study population.

The most common HDs were valvular (28.9%) and congenital (27.4%), followed by arrhythmia (22.3%). In 18 (33.3%) CHD pregnancies, surgical correction had been performed before gestation. Five (2.5%) cases had a permanent pacemaker and 7 (3.6%) an implantable cardioverter defibrillator. There were four (2%) cases requiring endovascular or surgical treatment during gestation: two cases of severe mitral stenosis managed with percutaneous balloon valvuloplasty, and two cases of severe aortic insufficiency surgically treated.

Assisted reproductive technology (ART) was identified in 7% of pregnancies, 6 (46.2%) of which were multiple. Three (23.1%) women with an ART-conceived pregnancy were obese (BMI ≥30 Kg/m^2), whereas 4 (30.8%) had ≥40 years.

Application of the mWHO risk classification led to categorisation of 159 (80.7%) pregnancies (figure 1). In 38 (19.3%) gestations, maternal HD could not be categorised

Table 1 General and obstetric characteristics of the study population

	Study population
General characteristics	N=197 pregnancies
Maternal age (years)	34 (30–37)
>40	31 (15.7)
BAME ethnicity	32 (16.2)
Pregestational BMI (kg/m^2)	22.6 (20.4–25.6)
>30	16 (9.3)
Diabetes mellitus	2 (1.0)
Chronic hypertension	15 (7.6)
Substance abuse	21 (10.7)
Risk factors for CVD	78 (39.6)
Type of HD	
Arrhythmia	44 (22.3)
Coronary artery disease	7 (3.6)
Cardiomiopathy	26 (13.2)
Congenital	54 (27.4)
Valvular	57 (28.9)
Other	9 (4.6)
Obstetric history and pregnancy course	N=197 pregnancies
First pregnancy	64 (32.5)
Nulliparity	130 (66.0)
Previous caesarean delivery	46 (23.4)
>1	11 (23.9)
For cardiology reasons (n=9 missing)	10 (21.7)
ART conception	13 (6.6)
Multiple gestation	12 (6.1)
GA at first antenatal obstetric assessment (weeks)	9 (8–11)
Low dose aspirin	45 (22.8)
Low molecular weight heparin	34 (17.3)
therapeutic dosage	10 (29.4)
Miscarriage	4 (2.0)
Stillbirth (>22 weeks)	3 (1.5)
Pregnancy induced hypertension	33 (16.8)
GDM	22 (11.2)

Data presented as median (IQR) or number (percentage).
Substance abuse includes cigarette smoking, drugs, alcohol.
Risk factors for CVD include maternal age ≥40 years, pregestational BMI ≥35 kg/m^2, BAME ethnicity, pregestational diabetes, chronic hypertension, substance abuse, history of cardiotoxic chemotherapy.
Type of HD: bicuspid valve disease was classified within the valvular category; isolated pulmonic stenosis was categorised as valvular, but if pulmonic stenosis existed concurrently with any other cardiac malformations, it was categorised as CHD.
Low-molecular-weight Heparin, therapeutic dosage: 6000 IU two times a day in 9 pregnancies and 8000 IU two times a day in one pregnancy.
Pregnancy-induced hypertension includes gestational hypertension and pre-eclampsia.
ART, assisted reproductive technology; BAME, black, Asian and minor ethnicities; BMI, body mass index; CHD, congenital HD; CVD, cardiovascular disease; GA, gestational age; GDM, gestational diabetes mellitus.; HD, heart disease.

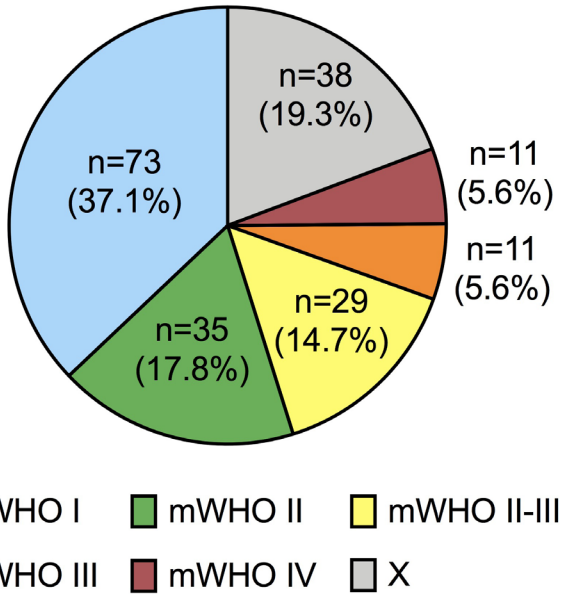

Figure 1 Distribution of maternal HDs among the 2018 ESC-adapted mWHO classes. Pie chart shows the distribution of the 197 pregnancies (n=31 patients with >1 pregnancy during the study period) among the five classes of the 2018 ESC-adapted mWHO classification. Thirty-eight (19.3%) pregnancies could not be categorised according to this classification and were therefore included in a newly created class named X. ESC, European Society of Cardiology; HD, heart disease; mWHO, modified WHO.

because it was not included in the mWHO classification. These HDs constituted the class X, as specified in the Methods section, and are listed in table 2. Yearly contribution of class X-HDs to the overall rate of maternal HDs during the study period is shown in figure 2.

Class X-HDs were highly heterogeneous. Moderate left ventricle (LV) hypertrophy without LV impairment was the most common HD (36.8%), followed by pericardial effusion/pericarditis and prior myocardial infarction without LV impairment (13.2% each). Among pregnancies classified in class X there were three women who experienced an acute cardiovascular event in the absence of history of HD or cardiac anomalies.

Maternal characteristics and outcomes were assessed among pregnancies in class X and compared with those in the other mWHO classes (table 3).

Cases in class III/IV were more frequently of BAME ethnicity and with risk factors for CVD compared with the other classes. In turn, pregnancies in class X showed the highest rates of ART conception and multiple gestation (18.4% each). Stillbirth occurred in 3 (1.5%) cases, two of whom had severe pre-eclampsia with fetal growth restriction (n=1 in class X at 23 weeks, n=1 in class II–III at 30 weeks); the remaining case was diagnosed at 22 weeks in a class I pregnancy complicated by premature rupture of the membranes at 16 weeks. In almost 16% of pregnancies, HD was diagnosed during gestation, and this occurred more commonly in class III/IV.

Table 2 List of maternal HDs included in class X

Maternal HDs included in class X*	N=38 pregnancies
Mild LV hypertrophy (no LV impairment)	1 (2.6)
Moderate LV hypertrophy (no LV impairment)	14 (36.8)
Pericardial effusion/pericarditis	5 (13.2)
Previous myocarditis (no sequelae)	1 (2.6)
Previous myocardial infarction (no LV impairment)†	5 (13.2)
Previous trivasal coronaropathy requiring coronary artery bypass graft	1 (2.6)
Previous massive pulmonary embolism with cardiac arrest and hypoxic encephalopathy	1 (2.6)
Left-sided superior vena cava with coronary sinus dilation	1 (2.6)
Previous PSVT with acute pulmonary oedema and mildly elevated PAP‡	2 (5.3)
Atrioventricular block with PPM	3 (7.9)
Brugada syndrome with ICD	2 (5.3)
Sino-atrial node disease with PPM	1 (2.6)
Cardiovascular event without history of HD§	3 (7.9)

Data shown as number (%).
*Sum of pregnancies in each category exceeds total (n=40) due to presence of patients with more than one diagnosis. For these patients, the HD with the highest potential for complications was considered for classification.
†This group includes: myocardial infarction with non-obstructive coronary arteries (n=1), ventricular fibrillation with cardiac arrest and myocardial infarction with non-obstructive coronary arteries (n=3), myocardial infarction with recurrent pericarditis (n=1).
‡This is a patient with two pregnancies during the study period, in 2013 and 2015. In 2009, during her first pregnancy, she underwent a caesarean section for failure to progress at complete dilation; surgery was complicated by an episode of paroxysmal supraventricular tachycardia responsive to pharmacological treatment. Three hours after delivery, acute pulmonary oedema was diagnosed, which required admission to the intensive care unit for 36 hours. Mildly elevated pulmonary arterial pressure was identified, which resolved a few days after the acute event.
§This group includes: myocardial infarction with congestive heart failure (n=1), myocardial infarction with non-obstructive coronary arteries (n=1), hypokinetic cardiomiopathy with congestive heart failure (n=1). All these women displayed risk factors for CVD, including maternal age ≥40 years (n=2), pregestational BMI ≥35 kg/m^2 (n=1), chronic hypertension (n=2) and cigarette smoking (n=3).
BMI, body mass index ; CVD, cardiovascular disease; HD, heart disease; ICD, implantable cardioverter defibrillator; LV, left ventricle; PAP, pulmonary arterial pressure; PPM, permanent pacemaker; PSVT, paroxysmal supraventricular tachycardia.

There were 18 (9.1%) cases who did not receive a cardiology assessment during gestation. In all of them, a recent assessment report was available at the time of the first obstetric visit. Cardiology evaluation was more frequently performed during pregnancy (137/179, 76.5%), at a median GA of 26 weeks (IQR, 20–32). There was one (0.6%) consultation requested during labour for palpitations, and it was in a class X pregnancy with moderate LV hypertrophy without LV impairment and an incomplete right bundle branch block.

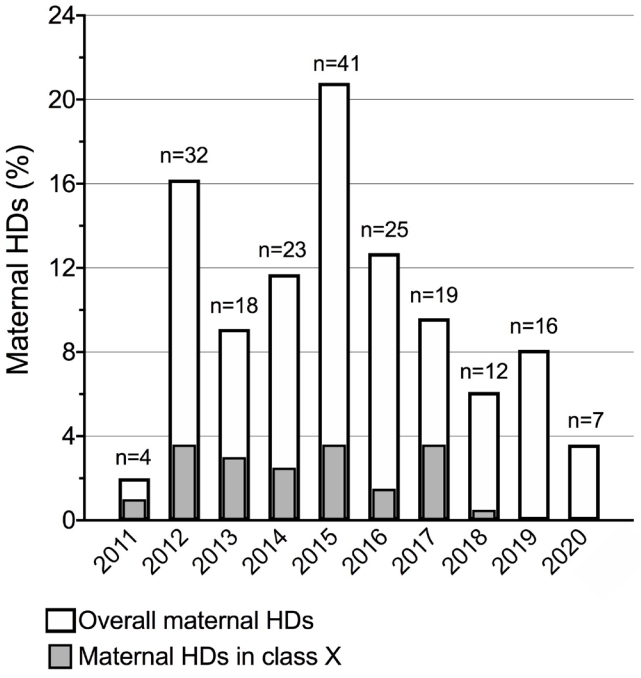

Figure 2 Yearly distribution of maternal HDs during the study period with class X contribution. HD, heart disease.

Overall, 45 (23.3%) pregnancies underwent induction of labour, with similar rates among all classes. Almost 51% of labouring women (n=108) received epidural analgesia, with rates ranging from 36.4% in class II to 82%–90% in the highest risk classes (II–III and III/IV).

Median GA at delivery was 38 weeks (IQR, 36–39), with 51 (26.8%) pregnancies delivering preterm and 15 (7.9%) giving birth at ≥41 weeks' gestation.

Caesarean section (CS) was performed in 50.8% of pregnancies, and it was a scheduled pre-labour surgery in 46.9% of them. Pregnancies in class I showed the lowest rate of CS (35.7%), whereas similar rates were identified among the remaining classes. Overall, operative delivery for cardiology indications was performed in 41 (42.3%) cases, most commonly in the highest risk classes. There was only one vacuum delivery for cardiology reasons and it was in a class II pregnancy.

Postpartum intensive care monitoring was needed for 21 (10.7%) pregnancies, more frequently for those in class II–III and III/IV compared with the others.

We observed 26 maternal cardiac adverse events in 21 pregnancies, for an overall rate of 10.7%. Occurrence of two different adverse events in the same pregnancy was identified in 5 cases, and in three the events were concomitant. A detailed description is provided in table 4.

The most common complication was HF requiring treatment (n=14), followed by symptomatic documented tachyarrhythmia (n=6), thromboembolic events (n=3), myocardial infarction (n=2) and cardiac arrest (n=1). Pre-eclampsia was diagnosed in 4 out of the 14 pregnancies complicated by HF compared with 1/7 pregnancies with other complications.

Table 3 Maternal characteristics and obstetric and cardiac outcomes among 2018 ESC-adapted mWHO classes and class X

General characteristics (n=197 pregnancies)	Class X (n=38)	Class I (n=73)	Class II (n=35)	Class II-III (n=29)	Class III/IV (n=22)	P value
BAME ethnicity	5 (13.2) $_a$	12 (16.4) $_a$	3 (8.6) $_a$	2 (6.9) $_a$	10 (45.5) $_b$	0.002
Risk factors for CVD	13 (34.2) $_a$	26 (35.6) $_a$	10 (28.6) $_a$	12 (41.4) $_a$	17 (77.3) $_b$	0.003
First pregnancy	15 (39.5)	27 (37.0)	9 (25.7)	8 (27.6)	5 (22.7)	0.474
Previous caesarean delivery	10 (26.3)	12 (16.4)	7 (20.0)	8 (27.6)	9 (40.9)	0.054
ART conception	7 (18.4) $_a$	2 (2.7) $_b$	1 (2.9) $_b$	3 (10.3) $_a$	0 $_b$	0.010
Multiple gestation	7 (18.4) $_a$	3 (4.1) $_b$	0 $_b$	2 (6.9) $_b$	0 $_b$	0.006
Stillbirth (≥22 weeks)	0	2 (2.7)	0	1 (3.4)	0	0.574
Low dose aspirin	9 (23.7)	17 (23.3)	6 (17.1)	7 (24.1)	6 (27.3)	0.912
LMWH	8 (21.1)	13 (17.8)	3 (8.6)	8 (27.6)	2 (9.1)	0.218
PIH	11 (28.9)	9 (12.3)	4 (11.4)	3 (10.3)	6 (27.3)	0.078
HD unknown before pregnancy	3 (7.9) $_a$	5 (6.8) $_a$	7 (20.0) $_b$	8 (27.6) $_b$	9 (40.9) $_c$	0.002
Cardiology assessment	38 (100.0) $_a$	57 (78.1) $_b$	33 (94.3) $_a$	29 (100.0) $_a$	22 (100.0) $_a$	<0.001
In pregnancy	26 (68.4)	48 (84.2)	20 (60.6)	24 (82.8)	19 (86.4)	
Childbirth outcomes (n=193 pregnancies)	**Class X (n=37)**	**Class I (n=70)**	**Class II (n=35)**	**Class II-III (n=29)**	**Class III/IV (n=22)**	**P value**
Induction of labour	8 (21.6)	17 (24.3)	8 (22.9)	8 (27.6)	4 (18.2)	0.949
Epidural analgesia (in labouring women)	9/18 (50.0) $_a$	20/47 (42.6) $_a$	8/22 (36.4) $_a$	9/11 (81.8) $_b$	9/10 (90.0) $_b$	0.009
Preterm delivery <37$^{0/7}$ wks	12 (32.4)	20/68 (29.4)	6 (17.1)	6/28 (21.4)	7 (31.8)	0.527
Vacuum delivery	0	1 (1.4)	1 (2.9)	0	2 (9.1)	0.067
CD	24 (64.9) $_a$	25 (35.7) $_b$	17 (48.6) $_a$	19 (65.5) $_a$	13 (59.1) $_a$	0.014
Operative delivery for cardiology reasons	4/24 (16.7) $_a$	8/26 (30.8) $_b$	5/18 (27.8) $_b$	14/19 (73.7) $_c$	10/15 (66.7) $_c$	<0.001
PPH ≥1000 mL	7 (18.9) $_a$	4 (5.7) $_b$	0 $_b$	2 (6.9) $_b$	0 $_b$	0.011
Postdelivery ICU admission	2 (5.4) $_a$	3 (4.3) $_a$	2 (5.7) $_a$	5 (17.2) $_{a,b}$	9 (40.9) $_c$	<0.001

Data presented as number (percentage).
Cardiology assessment refers to a clinical evaluation by a consultant cardiologist with echocardiography performed when deemed necessary.
Cases with miscarriage excluded from analysis of childbirth outcomes.
Cases with stillbirth excluded from analysis of preterm delivery <37 weeks' gestation.
Operative delivery includes both vacuum vaginal delivery and caesarean delivery.
There was only one patient, in class X, who underwent elective, pre-labour caesarean delivery neither for cardiology nor for obstetric reasons but for neurology indication (previous massive pulmonary embolism complicated by cardiac arrest and hypoxic encephalopathy).
Pearson χ^2 with Bonferroni's post hoc analysis to adjust for multiple comparison (shown as a, b, c).
ART, assisted reproductive technology; BAME, black, Asian and minor ethnicities; CD, caesarean delivery; CVD, cardiovascular disease; ESC, European Society of Cardiology; HD, heart disease; ICU, intensive care unit; LMWH, low molecular weight heparin; mWHO, modified WHO; PIH, pregnancy induced hypertension; PPH, postpartum haemorrhage.

Pregnancies in class X had a substantially higher rate of cardiac events (18.4%) compared with class I (1.4%), and II–III (6.9%) (p=0.007); this rate was similar to that identified in class II (20.0%) and III/IV (18.2%). Women in class X, alongside those in class II, experienced the highest number of adverse events (n=8 and n=9, respectively, p=0.007) (figure 3).

Also, cardiac complications more commonly occurred during the postpartum period (n=17, 65.4%); there was one (3.8%) intrapartum event, and the remaining eight events happened during pregnancy at a median GA of 26 weeks (IQR, 22–37; min 10 weeks, max 40 weeks) (p=0.044).

Pregnancies with cardiac complications showed several characteristics, including prevalence of CVD risk factors, pre-eclampsia and therapy with anticoagulant or antiplatelet agents, similar to those of uncomplicated gestations. In turn, higher rates of multiple pregnancy (19.0% *vs* 4.5%, p=0.027), urgent caesarean delivery (85.7% vs 47.6%, p=0.009) and PPH ≥1000 mL (19.0% vs 5.2%, p=0.039) were identified. Logistic regression models confirmed increased odds of cardiac complications for multiple gestation (OR 4.941, 95% CI 1.136 to 17.313, p=0.016) and urgent caesarean delivery (OR adjusted for multiple gestation: 6.567, 95% CI 1.358 to 31.759, p=0.019).

There were no maternal deaths during the study period.

Neonatal outcomes were assessed among 205 neonates (four miscarriages, 3 stillbirths, 9 twins and 3 triplets). We did not observe any difference among mWHO classes and class X. Median birth weight was 2925 grams (IQR,

Table 4 Description of cardiac adverse events

Case #	Class	Adverse event	Timing	Mode of delivery (indication)	Maternal HD	Risk factors for CVD	Other risk factors
n.1	X	Myocardial infarction HF	Post partum (day 4)	CS (breech)	No history of HD	44 yo BMI 44 Smoker	ART Twins
n.2	II–III	Atrial fibrillation	Pregnancy (26 weeks)	CS (HD)	Aortic stenosis with congenital bicuspid aortic valve	None	
n.3	X	Hypokinetic cardiomiopathy HF	Post partum (day 4)	CS (2 previous CSs)	No history of HD	41 yo CH Smoker	
n.4	II	HF	Post partum (day 9)	VD	WPW syndrome (not treated)	None	
n.5	II	Deep vein thrombosis PSVT	Pregnancy (10 weeks) Post partum (day 9)	CS (severe preterm PE)	PSVT	None	
n.6	II	HF	Post partum (day 2)	CS (severe preterm PE)	Prolonged QT interval	None	
n.7	I	HF	Post partum (day 9)	VD	Mild valvular insufficiency Previous surgery for ALCAPA syndrome	BAME	
n.8	X	Myocardial infarction with non-obstructive coronary arteries	Post partum (day 1)	CS (failure to progress)	No history of HD	BAME Smoker	
n.9	III	HF	Post partum (day 0)	CS (severe preterm PE)	Moderate LV impairment	42 yo	
n.10	X	HF	Post partum (day 0)	CS (severe preterm PE)	Pericardial effusion	None	Twins
n.11	III	Myocardial infarction HF	Post partum (day 5)	CS (failure to progress)	Previous PPCM w/out any residual LV impairment	BMI 37	
n.12	IV	HF	Post partum (day 3)	VD (vacuum)	Severe mitral and aortic stenosis	CH	
n.13	X	HF	Pregnancy (29 weeks)	VD	Dilated coronary sinus due to persistent left superior vena cava	None	ART Twins
n.14	II	Atrial fibrillation	Pregnancy ($37^{6/7}$ weeks)	CS (breech)	Moderate LV hypertrophy w/out LV impairment	None	
n.15	X	Deep vein thrombosis	Pregnancy (24 weeks)	VD	Moderate LV hypertrophy w/out LV impairment Patent foramen ovale	None	
n.16	III	HF	Pregnancy ($23^{5/7}$ weeks)	VD ($25^{2/7}$ weeks after pPROM and placenta abruptio)	Moderate LV impairment	BAME	
n.17	II/III	HF Bilateral ovarian vein thrombosis	Post partum (day 1)	CS (chorioamnionitis after pPROM at $24^{6/7}$ weeks)	Moderate valvular insufficiency	BAME	
n.18	X	HF	Post partum (day 3)	CS (severe preterm PE)	Moderate LV hypertrophy w/out LV impairment	None	ART Triplets
n.19	II	PSVT HF	Pregnancy (40 weeks) Post partum (day 0)	CS (abnormal FHR in labour)	PSVT	None	
n.20	II	Wide complex tachycardia	Intrapartum	VD	Mild valvular insufficiency Right bundle branch block	None	
n.21	II	PSVT	Pregnancy (28 weeks)	CS (3 previous CSs)	PSVT	BAME Diabetes	

ALCAPA, anomalous left coronary artery from the pulmonary artery; ART, assisted reproductive technology; BAME, Black, Asian, and minor ethnicities; BMI, body mass index; CH, chronic hypertension; CS, caesarean section; CVD, cardiovascular disease; FHR, fetal heart rate; HF, heart failure; LV, left ventricle; PE, pre-eclampsia; PPCM, peripartum cardiomiopathy; pPROM, preterm premature rupture of membranes; PSVT, paroxysmal supraventricular tachycardia; VD, vaginal delivery; WPW, Wolf-Parkinson-White; yo, years old.

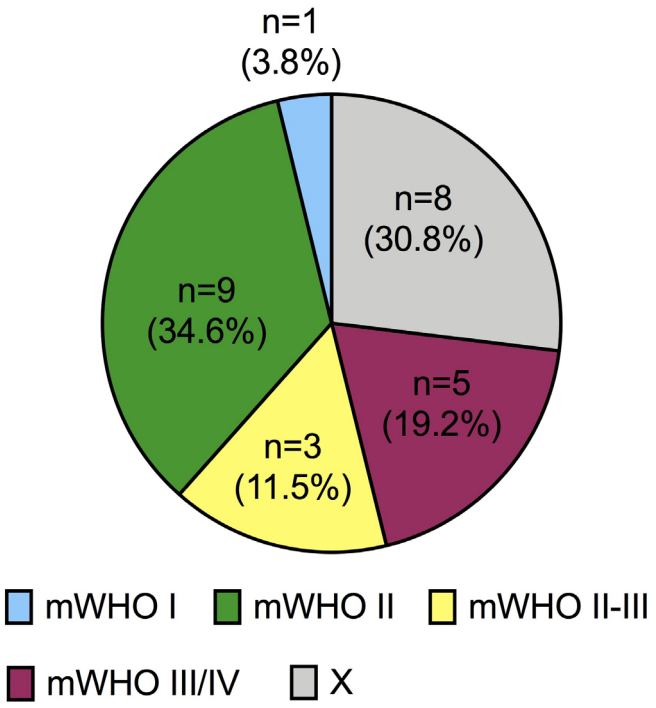

Figure 3 Distribution of cardiac adverse events among 2018 ESC-adapted mWHO classes and class X. Pie chart shows the distribution of the 26 cardiac adverse events which occurred in 21 pregnancies (n=5 pregnancies with two events) during the study period among the five classes of the 2018 ESC-adapted mWHO classification and class X. ESC, European Society of Cardiology; mWHO, modified WHO.

2300–3362.5 g), with 10.7% prevalence of birthweight <10th centile for GA according to INeS charts.[14] Neonatal Intensive Care Unit (NICU) admission occurred in 20.5% of cases. There were four (2.0%) neonatal deaths, all in extremely preterm newborns (≤26 weeks' gestation).

DISCUSSION

Our findings show that pregnant patients with HDs not included in the 2018 ESC-adapted mWHO classification are at increased odds of cardiac adverse outcomes. In addition, we identified a substantially high rate of caesarean delivery among these women, although more frequently performed for obstetric and not cardiac indications.

The 2018 ESC guidelines introduced for the first time the concept of the Pregnancy Heart team for improving assessment of pregnant women with HD, thus possibly decreasing the odds of cardiac complications.[5 15 16] A multidisciplinary team is pivotal for adequate risk assessment, as this requires to combine the mWHO classification with predictors, a detailed lesion-specific evaluation, and expert clinical judgement of the potential effects of pregnancy on patient's HD.[12 17 18]

We observed an overall rate of cardiac complications of 10.7%, in line with published literature reporting rates ranging from 9% to 16%.[9 11 19 20]

Among the 26 cardiac adverse events identified in our population, pregnancies with unclassifiable HDs, alongside those in class II, showed the highest number (n=8 and n=9, respectively) compared with the other classes. Of note, class X women displayed an overall rate of complications similar to that of class II and III/IV. The recently published CARPREG II study has observed a rate of cardiac complications among unclassifiable HD pregnancies as high as that identified in class II–III.[11] Similar data have been also reported by Fernández-Campos *et al*.[10] Our findings are in line with these reports and support the hypothesis that the absence of a multidisciplinary approach may lead to inadequate management of women with unclassifiable HDs, and, possibly, to increased odds of complications.

The most common adverse event found in our cohort was HF, with an overall rate of 7.1%, similarly to published data.[11 19–21] Importantly, 7/14 cases of HF occurred in the first 3 days after delivery, which are characterised by the largest haemodynamic changes,[22 23] with the remaining cases all within 10 days post partum. These data highlight the importance of intensive monitoring post partum and of a close cardiology follow-up within 7–14 days of discharge.[12 19]

We observed 7.9% women giving birth at ≥41 weeks' gestation. This is likely explained by our institutional policy of labour induction at or after 41 weeks' gestation if no or only mild gestational complications are identified (eg, polyhydramnios, gestational diabetes with adequate diet-related glycaemic control), in the absence of a multidisciplinary team approach to women with HD. Of note, both the 2018 ESC and 2019 American College of Obstetrics and Gynecology (ACOG) guidelines suggest to consider induction of labour at 39–40 weeks' gestation in all these women.[5 12] This finding is in line with the relatively low rate of labour induction identified in our cohort (23.3%).[15]

Analysis of childbirth data also showed a CS rate of 51%, in line with available literature.[15 19 20 24 25] Interestingly, CS rate among pregnancies with unclassifiable HDs was substantially high (64.9%), and similar to that of class II, II–III and III/IV. However, CS indication among these pregnancies, as well as those in class II, was mostly obstetric, as compared with cases in class II–III and III/IV who underwent CS mostly for cardiology reasons. Of note, there were no differences among classes regarding obstetric risk factors for CS, including nulliparity or history of previous caesarean birth, but women in class X showed a higher prevalence of multiple gestation.

CS in women with HD has been demonstrated to lack maternal benefit,[25] and it is recommended by the ESC only in few very high-risk cases, including aggressive aortic pathology, acute intractable HF and severe pulmonary hypertension.[5] Potential determinants of CS rate among HD women have been suggested to include the background population's rate and the experience of the attending cardiologist and maternal–fetal medicine specialist.[25] The yearly CS rate at our Institution

has ranged between 19.3% and 21.6% during the study period. Thus, our results further support the relevance of an experienced multidisciplinary team in managing women with HD to improve not only their cardiac but also obstetric outcomes. Also, our findings suggest that targeted interventions to ameliorate knowledge regarding the appropriate indications for CS in women with HD should be implemented for all obstetricians.

Maternal HDs have been associated with increased risk of pregnancy induced hypertension (PIH), including gestational hypertension and pre-eclampsia.[19 26] In our population, PIH was documented in 16.8% of pregnancies, as in other similar published cohorts.[15 21]

Of note, PIH, and particularly pre-eclampsia, has been reported as risk factor for HF in HD women.[27] Among the 21 pregnancies complicated by cardiac adverse events in our cohort, five had a diagnosis of severe preterm pre-eclampsia, and four of them experienced HF post partum.

The impact of fertility treatment on outcomes of women with HD is still insufficiently known.

According to ESC guidelines, ART is contraindicated in class IV patients and it should be carefully evaluated in those in class III.[5] ART associates with increased odds of multiple gestation,[28] which in turn is characterised by greater haemodynamic changes and odds of PIH than singleton pregnancies.[29] These may lead to an excessive burden for the heart and, thus, to complications. In our cohort there were 13 ART-derived pregnancies (none in class III or IV), six (46.2%) of which were multiple. Of note, multiple gestation associated with a fivefold risk increase in cardiac complications. Interestingly, an ART-derived multiple pregnancy was the only risk factor identified in 2 out of the 21 complicated cases. Also, we had a postpartum myocardial infarction and HF in an ART-derived twin pregnancy in a 44-year-old woman, smoker, and with a BMI of 44. A recent report by the Italian Obstetric Surveillance System has highlighted the contributing role of ART, frequently associated to advanced age, obesity and multiple gestation, to maternal deaths in our country, suggesting the application of stricter rules regulating access to ART.[1 6]

Maternal HDs can associate to adverse fetal and neonatal outcomes.[26]

We did not observe any difference among classes regarding these outcomes, although all of them occurred more frequently than the general population and with rates in line with previous reports.[15 20 21 24 30] The only exception was the prevalence of preterm birth, substantially higher in our cohort compared with others (27% vs 15%–18%).[19–21 30] A potential explanation may be our rate of multiple gestations, which are at increased risk of preterm delivery: 6.1% vs 0%–2.7%. The four (2.0%) cases of neonatal deaths were all extremely preterm, without cardiac malformations. Precisely, two cases were iatrogenic preterm deliveries, one for severe pre-eclampsia at 26 weeks and one for placental abruptio at 23 weeks, whereas the other two were spontaneous preterm births at 25 weeks.

Although being retrospective and conducted only at a single university, maternal–fetal medicine referral centre, our work included a substantially high number of pregnancies in women with HD managed over a 10-year period, as compared with previously published reports in similar settings.[20 21 30] Also, our findings highlight areas with the greatest need of improvement, such as risk estimation and labour and birth management, to ameliorate outcomes of pregnant women with HD.

Our data can be useful to other healthcare professionals taking care of these women both for counselling and for promoting the implementation of a specific management protocol including a multidisciplinary approach.

Future research perspectives include the creation of a prospective registry for collecting data of all pregnancies complicated by HD managed by our pregnancy heart team. Comparisons with data reported herein will allow to evaluate the impact of the multidisciplinary approach on outcomes and to identify areas where further improvements can be achieved.

CONCLUSION

Pregnancy in women with HD poses a substantial medical challenge. In the clinical setting, accurate individual risk assessment is of fundamental importance. Implementation of a multidisciplinary approach may be pivotal for providing adequate counselling and management of these women, thus possibly improving their outcomes.

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