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Reducing late maternal death due to cardiovascular disease - A pragmatic pilot study

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ABSTRACT

Background: Late maternal mortality (up-to 1-year postpartum) is poorly reported globally and is commonly due to cardiovascular disease (CVD). We investigated targeted interventions aiming at reducing peripartum heart failure admission and late maternal death.

Methods and results: Prospective single-centre study of 269 peripartum women presenting with CVD in pregnancy, or within 6-months postpartum. Both cardiac disease maternity (CDM) Group-I and Group-II were treated by a dedicated cardiac-obstetric team. CDM Group-II received additional interventions: 1. Early (2–6 weeks) postpartum follow-up at the CDM clinic and immediate referral to dedicated CVD specialist clinics. 2. Beta-blocker therapy was continued in women with LVEF<45% while pregnant, or immediately started postpartum. Of 269 consecutive women (mean age 28.6 ± 5.9), 213 presented prepartum, 22% in NYHA groups III–IV and 79% in modified WHO groups III–IV. Patients were diagnosed with congenital heart disease (30%), valvular heart disease (25%) and cardiomyopathy (31%).

The groups were similar in age, diagnosis, NYHA, modified WHO, BP and HIV, but Group-II had a higher rate of previously known CVD ($p < 0.001$) and a lower rate of being nulliparous ($p < 0.0005$). Of Group-I patients 9 died within the 12-month follow-up period versus one death in Group-II ($p = 0.047$). Heart failure leading to admission was 32% in Group-I versus 14% in Group-II ($p = 0.0008$), with Group-II having a higher beta-blocker use peripartum ($p = 0.009$). Perinatal mortality rate was 22/1000 live births with no differences between groups.

Conclusion: Early follow-up in a dedicated CDM clinic with targeted pharmacological interventions led to a significant reduction in peripartum heart failure admission and mortality.

1. Introduction

Maternal death can be due to direct causes such as postpartum hemorrhage, or indirect causes such as cardiovascular disease (CVD) or thromboembolism. Most countries record maternal death only up to 42 days postpartum because of the assumption that death in pregnant women occurs during pregnancy or shortly thereafter. Although limited, the available data suggest otherwise. Globally, there are more postpartum and late maternal deaths (up to 1 year postpartum) from indirect obstetric causes than maternal deaths during pregnancy [1]. Death occurring >42 days postpartum can, for example, be due to peripartum cardiomyopathy (PPCM). PPCM often presents with clinical symptoms only two to five months postpartum and mortality due to this condition therefore falls outside the period of 42 days. Similarly patients with familial cardiomyopathy, right heart failure in complex congenital heart disease or thromboembolic events commonly have a late morbidity and mortality triggered by fluid shifts postpartum.

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The WHO Group on Maternal Mortality (WHO International Classification of Disease 2013. http://www.who.int/classifications/icd/en/ - accessed 25 April 2016) has suggested International Classification of Diseases Code (ICD) coding principles that define maternal death up to a year after delivery from causes directly related to pregnancy, or indirectly precipitated by the effects of pregnancy on underlying diseases. However, this recommendation is largely ignored on a global scale [2]. This has led to a profound lack of research on any form of targeted intervention towards late maternal death, including death due to cardiovascular and thromboembolic causes. Research and especially blinded randomized trials are difficult to perform in peripartum women with CVD in pregnancy. Observational studies such as CARPREG [3], ZAHARA [4] and ROPAC [5] are the primary sources of information.

In 2010, a dedicated weekly 'Cardiac Disease and Maternity Clinic (CDM)' was established at the Division of Cardiology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, to provide multi-disciplinary systematic care for women with suspected, or previously known, CVD presenting in pregnancy or postpartum. Data from this single-centre on the maternal (6 months only) and foetal outcome of consecutive patients recruited over a 2-year period, were previously analyzed and reported for the period 2010–2012. We found that the disease patterns were markedly different to those seen in high-income countries [6]. Joint obstetric-cardiac care in this low-resource setting was associated with excellent survival rates, even for those with complex cardiac disease and/or who booked late. Surprisingly, eight of the nine patients who died within the 6-month follow-up died >42 days postpartum, which is currently the standard limit for recording maternal death.

Based on this finding we enhanced our service by adding two specific interventions: (i) establishing dedicated multi-specialist care until one year postpartum and (ii) continuing beta-blocker therapy in women with a left ventricular EF of <45%, either while pregnant or when started immediately postpartum (prior to discharge from hospital). The aim of this study was to investigate the effect of these targeted interventions on late maternal death in women with previously documented CVD.

2. Methods

2.1. Study design

Women presenting with symptoms and signs suggestive of CVD while pregnant, or within 6 months postpartum, were studied in a single-centre, prospective ongoing study over a period of 6 years. Patients were assessed at the joint cardiac-obstetric clinic, having been sent to this clinic via a referral algorithm (Supplementary Fig. 1), from primary and secondary care facilities, and from within the tertiary hospital.

Patients were stratified into 4 risk groups using a modified WHO risk classification for pregnant women with cardiac disease. Depending on the diagnosis and severity of the disease, the risk classification ranged from Class I (low risk), to Class IV (contraindication for pregnancy), as also recently used in the European Society of Cardiology Guidelines on the Management of Cardiovascular Disease during Pregnancy [7]. Diseases not accounted for by this classification were scored by 2 authors, a cardiologist (KS) and an obstetrician (JA) [8]. Agreement was achieved for all cases. Comorbidities such as HIV status were also documented. The modified WHO classification has a prediction value in the management of pregnant women but is also based on the underlying severity of heart disease. Uniformity in the classification has been secured by applying this classification to both antenatal and postpartum patients. Only patients in Modified WHO risk Groups II–IV were followed up at the CDM clinic and participated in this study. Risk stratification deemed appropriate for a health system with limited human and facility resources was applied. The study was approved by the Ethics Committee of the University of Cape Town (HEC ref.: 173/2010). All patients provided written informed consent prior to being included into the study.

CDM Group I consisted of women assessed in 2010–2012 and CDM Group II consisted of women assessed in 2013–2015. While pregnant, both groups of patients were offered close follow-up via a dedicated cardiac-obstetric team including senior cardiology and/or pediatric cardiology and obstetric consultants, with input from other specialists (radiology, endocrinology and anesthetics). Patients were managed jointly throughout their pregnancy and those presenting postpartum were seen once at this clinic and managed further at the general cardiac clinic or a dedicated cardiomyopathy clinic at Groote Schuur Hospital (KS).

Postpartum patients from Group I were booked according to standard management which could include a waiting period of up to 4 months for review. Patients were commonly not discharged on appropriate cardiac medication by the obstetric junior doctor or pharmacological therapy was not up-titrated during this period.

CDM Group II patients received additional targeted interventions. [1] They received 2–6 weeks postpartum CDM clinic appointments from where they were referred to dedicated cardiovascular sub-specialist clinics (e.g. heart failure clinic), remaining under close supervision and care of the CDM team for a period of 1 year (Supplementary Fig. 1). [2] Beta-blocker therapy was continued in women with left ventricular EF <45%, while pregnant or when started immediately postpartum (prior to discharge) with appropriate up-titration. Other heart failure medication, such as angiotensin receptor antagonists and aldosterone antagonists, were started as soon as possible postpartum. Anticoagulation for patients with e.g. prosthetic valves or in atrial fibrillation was closely monitored. Patients needing cardiac surgery for e.g. mitral stenosis were referred for further management. Follow-up data on maternal mortality and re-admission was collected over a period of 1 year post diagnosis.

2.2. Data

Baseline data recorded at the first visit included socio-demographic factors, family history of CVD, any history of pre-eclampsia or chronic hypertension, HIV-status, onset of symptoms and signs, parity, prior cardiac events, prior surgery or cardiac interventions and use of medication. In addition, New York Heart Association Functional Class (NYHA FC), ECG and transthoracic echocardiography (KS) were recorded, including assessments of left and right ventricular function, Doppler quantification of inflow and outflow obstruction, quantification of valvular regurgitation and systolic pulmonary artery pressure were measured according to standard practice guidelines [9].

Follow-up data were obtained at clinical visits for most patients during the second trimester (<28 weeks), third trimester (28–37 weeks), the peripartum period (onset of labor until hospital discharge) and at 6 weeks and 12 months postpartum. The frequency of visits was adapted to the severity of the disease and transport logistics of the patient. Mode of delivery and perinatal outcome were obtained for all patients from the referring physician and by examining the obstetric records of the patients. Newborns of mothers with congenital heart disease were examined for cardiac defects via foetal ultrasound and post-delivery pediatric echocardiography.

Prepartum, peripartum and postpartum complications were grouped into cardiac, neonatal and obstetric events.

Cardiac events were defined by (re)admission for heart failure/pulmonary edema (documented by chest radiograph or by crackles heard over more than one-third of posterior lung fields), symptomatic tachycardia requiring therapy, arrhythmia, stroke and cardiac death. Date of death was obtained using the Home Affairs on Alive Status Verification self-help service SMS link (http://www.gov.za/home-affairs-alive-status-verification-self-help-service). Six months and 1 year post-delivery alive status was obtained using the South African identification number (ID) of patients. For some patients whose ID was not in the hospital folder, we phoned the patient or her family directly to obtain the Alive Status. Information on admission was obtained from the Groote Schuur Hospital Clinicom system for the Western Cape Region.

Neonatal events were defined as any of the following: premature birth (<37 weeks gestation), low birth weight (<2500 g) and still birth (>20 weeks gestation, birth weight > 500 g). Perinatal mortality rates were calculated based on the number of foetal deaths and early neonatal deaths per 1000 live births. Obstetric events that were documented included non-cardiac death, pregnancy-induced hypertension (PIH) and (pre)-eclampsia.

2.3. Blood tests

Routine laboratory workup on all patients included a hemoglobin and HIV test. In addition, TSH and other blood tests, as determined by the physician, were performed in certain cases.

2.4. Statistical analysis

Cardiac, neonatal and obstetric events were analyzed separately.

Database management and statistical analyses were performed with GraphPad Prism version 7.03 for Windows (GraphPad Software, La Jolla California, USA). Continuous data were expressed as mean ± SD or median (range). Comparison of means and proportions between sub-groups at baseline were performed by independent *t*-test and Chi-square statistics (or Fisher exact test where necessary) respectively and, where data were not normally distributed, a Mann-Whitney test was used.

Kaplan-Meier survival curves were plotted including the number of censored patients at each point and survival rate was calculated. The Log-rank test was used to comparing median survival rates between CDM group I and CDM group II. Significance was assumed at a two-sided value of $p < 0.05$.

3. Results

The study enrolled 269 consecutive women presenting with symptoms and signs of modified WHO Groups II–IV (Table 1). CDM Group I consisted of 152 women assessed between 1 July 2010 and 30 June

Table 1
Baseline maternal characteristics of 269 cohort presenting in mod. WHO II–IV.

	All Patients (n = 269)	CDM I (n = 152)	CDM II (n = 117)	P value
Age at enrolment (years)	28.6 ± 5.9	28.5 ± 6.1	28.7 ± 5.6	0.73
Ethnicity, n (%)				
African or Black (n, %)	127 (47)	79 (52)	48 (41)	0.10
Mixed race	116 (43)	56 (37)	60 (51)	
White	22 (8)	15 (10)	7 (6)	
Other (Arab, Indian, other)	3 (1)	2 (1)	1 (1)	
General medical history, n (%)				
Chronic hypertension	24 (9)	10 (7)	14 (12)	0.14
Hypercholesterolemia	5 (2)	3 (2)	2 (2)	1.00
HIV	57 (21)	36 (24)	21 (18)	0.29
Syphilis	5 (2)	1 (1)	4 (3)	0.17
Tuberculosis	13 (5)	4 (3)	9 (8)	0.08
Clinical history and presentation, n (%)				
Previously known CVD	144 (53)	89 (58)	109 (93)	<0.001
Previously operated CVD	47 (17)	30 (20)	18 (15)	0.33
NYHA FC I–II	210 (78)	120 (79)	90 (77)	0.76
NYHA FC III–IV	59 (22)	32 (21)	27 (23)	
SBP in mm Hg	119 ± 16	119 ± 16	118 ± 16	0.96
DBP in mm Hg	73 ± 11	74 ± 11	72 ± 11	0.09
Heart rate in beats per minute	88 ± 15	90 ± 19	86 ± 16	0.04
Weight in kg	70.9 ± 17.7	72.1 ± 18.6	69.4 ± 16.4	0.36
Obstetric history, n (%)				
Gestational age at presentation[a]	n = 213	n = 122	n = 91	
<12 weeks	10 (5)	4 (3)	6 (7)	0.39
12–24 weeks	94 (44)	52 (43)	42 (46)	
>24 weeks	109 (51)	66 (54)	43 (47)	
Gravida (median, range)	2 (1–7)	2 (1–7)	2 (1–7)	0.14
Para (median, range)	1 (0–6)	1 (0–5)	1 (0–6)	0.03
Nulliparous, n (%)	45 (17)	36 (24)	9 (8)	0.0005
Twin pregnancies	7 (3)	3 (2)	5 (4)	0.27

CVD = Cardiovascular disease; NYHA FC = New York Heart Association Functional Class; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure.

[a] A number of women were either not pregnant or presented postpartum. Gestational age at presentation percentages calculated towards 213, 122 and 91 respectively.

2012, with 1-year follow up and CDM Group II consisted of 117 patients assessed between 1 July 2013 and 30 June 2015, with 1-year follow-up.

3.1. Baseline maternal characteristics of 269 patient cohorts

Of the 269 women presenting for the first time at the joint cardiac maternity clinic, mean age was (28.6 ± 5.9 years) and 213 (79%) presented prepartum (Table 1). Fifty-six were classified as modified WHO class II (moderate risk), 91 in WHO Class III (high risk) and 122 in WHO Class IV (pregnancy not recommended). The ethnic background of this cohort was 47% Black African, 43% Mixed race, 8% White and 1% were of Indian or other descent. Twenty-one percent were HIV positive. More than half of the patients presenting for the first time at the CDM clinic were > 24 weeks pregnant.

There were no differences between CDM Groups I and II in age, ethnic background, number of patients with chronic hypertension, hypercholesterolemia, HIV, syphilis, tuberculosis or symptoms defined by NYHA FC, blood pressure and gestational age at presentation. Patients in CDM Group II had a higher percentage of previously known CVD ($p < 0.001$), fewer were nulliparous ($p < 0.0005$) and they had a lower heart rate ($p = 0.04$).

3.2. Socioeconomic factors, medical and obstetric history of CDM Group I and CDM Group II patients presenting pre- and postpartum

Table 2 shows race, ethnicity (defined by language), educational level, disposable income, general medical history (including smoking), cardiac and obstetric history of patients presenting pre- or postpartum for CDM Group I and CDM Group II.

Black patients were represented in a higher percentage in postpartum cohorts for CDM Groups I ($p < 0.05$). Women presenting in the postpartum period in CDM Group II (n = 26 had a lower level of education ($p < 0.05$), had more hypertension ($p < 0.05$), a higher proportion smoked ($p < 0.5$) and had a higher average alcohol use ($p < 0.05$), compared to prepartum CDM Group II patients. However, there were no differences in these parameters either in CDM Group I patients presenting pre- versus postpartum or between CDM Group I and Group II patients.

CDM Groups I and II patients developing symptoms postpartum had significantly larger left ventricular dimensions and a markedly lower EF on echocardiography, compared to patients presenting prepartum in both groups ($p < 0.05$). Indeed, patients with poor EF (<30%) mainly presented postpartum with comparable proportions in both groups.

3.3. Diagnosis

The diagnosis of women presenting in modified WHO Classes II–IV are shown in Fig. 1. The most common diagnoses of the 269-patient cohort needing close follow-up were congenital heart disease (30%, 26 operated previously), valvular heart disease (25%, 17 operated previously), cardiomyopathy (31%) and other (14%), including 4 cases of Takayasu's disease. There were no statistical differences between CDM Groups I and II in the categories of congenial heart disease, valvular heart disease, cardiomyopathy and other.

3.4. Medication

Supplementary Table 1 shows that beta-blocker use was markedly higher in CDM Group II, with 26/91 patients (29%) presenting prepartum, and 22/26 (85%) presenting postpartum receiving a beta-blocker, compared to 17/122 patients (14%) and 19/30 patients (63%) respectively in the prepartum and postpartum patients in CDM Group I, ($p = 0.009$). There was a significant difference in the use of beta-blockers in patients presenting during their second trimester between the two groups (Supplementary Table 2). In patients presenting postpartum in CDM Group II, significantly more patients received aldosterone antagonists (Supplementary Table 2). Four patients in CDM Group II presented to the clinic while pregnant and had ACE-inhibitors. These were stopped immediately due to the potentially detrimental foetal effects. There were no other differences in the use of medications.

3.5. Overall and cardiac outcome

By one year of follow-up 94.1% of patients from CDM I survived, compared to 99.1% of CDM II. There was a significant difference between survival times in the 2 groups ($p = 0.031$). Ten/269 patients (4%) died within the 1-year postpartum follow-up period (9 from CDM1 and 1 from CDM II). Diagnoses of women that died were familial and PPCM (n = 8), and 2 cases of prosthetic valve complications (thrombosis and sepsis). The majority of these deaths were due to PPCM(Table 3). Of the prosthetic valve patients, 1 patient developed hospital-acquired endocarditis from an intravenous line used to administer unfractionated heparin, which had been given to avoid warfarin-induced embryopathy, and one presented 50 days postpartum with valve thrombosis. Nine of the 10 patients who died did so >42 days postpartum, which is the limit of South African defined pregnancy-related mortality. One year mortality data were available for all patients.

Of the women from CDM Group I who were diagnosed prepartum, 34% developed signs and symptoms of heart failure while pregnant, leading to admission in 20% of cases, whereas of the women from CDM Group II 9 developed signs and symptoms of heart failure while pregnant, leading to admission in 10% of cases ($p = 0.057$). There was a marked difference in total admission rate for heart failure in patients from CDM Group I versus CDM Group II within 1 year postpartum, 48 (32%) versus 16 (14%) ($p = 0.0008$). Within the late maternal death period (>42 days up to 1 year postpartum) there were no deaths

Table 2
Socioeconomic factors, medical and obstetric history of CDM Group I and CDM group II patients presenting pre- and postpartum.

	CDM I (n = 152)		CDM II (n = 117)	
	Presenting Prepartum (n = 122)	Presenting Postpartum (n = 30)	Presenting Prepartum (n = 91)	Presenting Postpartum (n = 26)
Age at enrolment (years)	28.2 ± 6.2	29.6 ± 5.8	28.8 ± 5.3	28.6 ± 6.5
Ethnicity, n (%)				
African or Black	55 (45)	24 (80)*	35 (39)	13 (50)$
Mixed race	50 (41)	6 (20)*	49 (55)	11 (42)
White	15 (12)	0 (0)	5 (5)	2 (8)
Other (Arab, Indian, other)	2 (2)	0 (0)	1 (1)	0 (0)
NYHA FC				
III	13 (11)	11 (37)*	12 (13)	8 (31)
IV	2 (2)	6 (20)*	2 (2)	5 (19)#
Vital signs				
Heart rate in bpm	88 ± 18	102 ± 19*	83 ± 13&	98 ± 17#
SBP in mm Hg	121 ± 16	111 ± 16*	120 ± 13	113 ± 22
DBP in mm Hg	74 ± 12	74 ± 10	72 ± 10	73 ± 15
Language, n (%)				
Afrikaans	40 (33)	3 (10)	21 (23)	1 (4)#
English	29 (24)	4 (13)	36 (40)&	11 (42)$
isiXhosa	41 (34)	17 (57)	29 (32)	11 (42)
isiZulu	9 (7)	3 (10)	3 (4)	1 (4)
Other	3 (2)	3 (10)	1 (1)	2 (8)
Education level, n (%)				
No school	0 (0)	1 (3)	1 (1)	0 (0)
Year 1–7	36 (30)	10 (33)	9 (10)&	8 (31)#
Year 8–11	73 (60)	19 (63)	75 (85)	17 (65)#$
Year 12/>Year 12	13 (10)	0	3 (4)	1 (4)
Income per month, n (%) (ZAR)				
<300	39 (33)	17 (57)	28 (32)	9 (34)
300–999	31 (26)	7 (23)	32 (36)	13 (50)
1000-9999	48 (40)	6 (20)	26 (30)	4 (16)
≥10,000	2 (2)	0 (0)	2 (2)	0 (0)
General medical history (%)				
Chronic hypertension	10 (8)	0 (0)	8 (9)	6 (23)#$
Hypercholesterolemia	3 (2)	0 (0)	2 (2)	0 (0)
HIV	26 (21)	10 (33)	17 (19)	4 (15)
Syphilis	1 (1)	0 (0)	4 (4)	0 (0)
Tuberculosis	3 (2)	1 (3)	8 (9)&	1 (4)
Family history of CVD	21 (17)	2 (7)	13 (14)&	4 (15)
Family history of PCM/CMO	10 (8)	1 (3)	0 (0)&	0 (0)
Heart valve replacement/repair	16 (13)	0 (0)	17 (19)	0 (0)#
Obstetric history, n (%)				
Gestational age at presentation, women presenting prepartum				
12–24 weeks	52 (43)	0	42 (46)	0 (0)
>24 weeks	66 (54)	0	43 (47)	0 (0)
Nulliparous n (%)	32 (26)	4 (13)	10 (11)&	1 (4)
Parous n (%)	90 (74)	26 (87)	81 (89)&	25 (96)
Social history, n (%)				
Smoking	10 (8)	2 (7)	10 (11)	8 (31)#$
Alcohol use	3 (2)	2 (7)	1 (1)	5 (19)#
Laboratory tests				
Hemoglobin (g/dl)	11.5 ± 1.7	11.4 ± 2.4	11.9 ± 1.4	11.5 ± 1.5
HIV pos	26 (21)	10 (36)	17 (19)	4 (15)
ECG, n (%)				
Sinus rhythm	103 (84)	24 (86)	64 (70)&	24 (92)#
Sinus tachycardia	8 (7)	5 (17)	5 (5)	0 (0)
Atrial fibrillation	1 (3)	0 (0)	2 (2)	0 (0)
Echocardiogram				
LVEDD (mm)	48.6 ± 7.7	58.7 ± 6.5*	47.9 ± 6.8	60.6 ± 7.4#
LVESD (mm)	33.4 ± 7.6	50.4 ± 6.9*	33.8 ± 6.9	49.9 ± 7.1#
EF (%)	59.1 ± 11.2	27.9 ± 9.3*	57.2 ± 11.3	29.7 ± 8.1#
EF <30%, n (%)	3 (2)	14 (47)*	2 (2)	13 (50)#

due to other causes such as thromboembolism, cancer or mental disorders such as postpartum depression leading to suicide.

3.6. Obstetric and foetal outcome

The mean gestational stage was 25 ± 8 weeks for CDM group I and 24 ± 8 for CDM group II, when women presented prepartum (p = 0.1831). There was a high overall rate of operative delivery, with 117 of 269 women (43%) having had a Caesarian section. Thirteen patients developed gestational hypertension and 5 patients had pre-eclampsia while pregnant. Preeclampsia was found in 0:43 nullipara and 1:104 multiparous women. There were no cases with eclampsia.

Obstetric records for patients presenting postpartum were incomplete as some patients delivered at local clinics, with insufficient documentation of the amount of postpartum hemorrhage.

Perinatal death occurred in 6/269 with 6 still births, translating to a perinatal mortality of 22/1000 live births. One and five foetal births respectively occurred in CDM group I and II (p = 0.088). In addition, there were 2 medically indicated terminations in CDM group I and 4 miscarriages (1 in CDM group I and 3 in CDM group II).

Mean birth weight for the entire cohort was 2841 ± 688 g, with 54/236 born weighing <2500 g and 72/252 born preterm (<37 weeks duration). The use of beta-blockers in pregnant women did not affect the birthweight, p = 0.2717.

Of the 228 babies, 12 had an Apgar score of <7 at 5 min. Women presenting with cardiac disease prepartum had a non-significant greater proportion of neonates who had a lower Apgar score (5% versus 2%; p = 0.4684).

4. Discussion

This is the first prospective study targeting late maternal death in peripartum women with CVD. It shows that (i) a multi-disciplinary team with limited resources, looking after a group of women with modified WHO Classes II–IV cardiac disease, which co-exists with substantial co-morbid conditions, can achieve an excellent short term (<42 days) maternal and foetal outcome; (ii) of a total of 269 patients, all but 1/10 deaths occurred outside the standard limit for reporting maternal mortality of <42 days, but within the period of late maternal death of up to 1 year postpartum; (iii) all deaths were due to cardiovascular complications such as heart failure and thromboembolism; (iv) targeted inventions, with follow-up in a dedicated CDM clinic, timely referral to other specialists, the continuation of beta-blockers, when indicated, and appropriate pharmacological management postpartum led to a significant reduction in peripartum heart failure admission and mortality. The direct impact of each intervention cannot be separated as they were interlinked reflecting a "real-life scenario".

CVD is a leading cause of maternal mortality and morbidity and is a major concern for cardiologists, specialist physicians, obstetricians, anesthesiologists and other healthcare providers caring for pregnant women. Furthermore, CVD is becoming more prevalent in the pregnant population of higher income countries, predominantly because maternal age is rising and older women have more pre-existing CVD, including chronic hypertension and coronary artery disease. Further, due to the successes of cardiothoracic surgery and Grown Up Congenital Heart Disease clinics, more women with operated and sometimes

Notes to Table 2:
CVD = Cardiovascular Disease; PPCM = Peripartum Cardiomyopathy; CMO = Cardiomyopathy; LVEDD = Left Ventricule in End Diastrolic Diameter; LVEDD = Left Ventricle in Endsystolic diameter.
* p < 0.009, CDM I patients presenting Prepartum vs. Postpartum.
# p < 0.05, CDM II patients presenting Prepartum vs. Postpartum.
& p < 0.05, CDM I patients presenting Prepartum vs. CDM II patients presenting Prepartum.
$ p < 0.05, CDM I patients presenting Postpartum vs. CDM II patients presenting Postpartum.

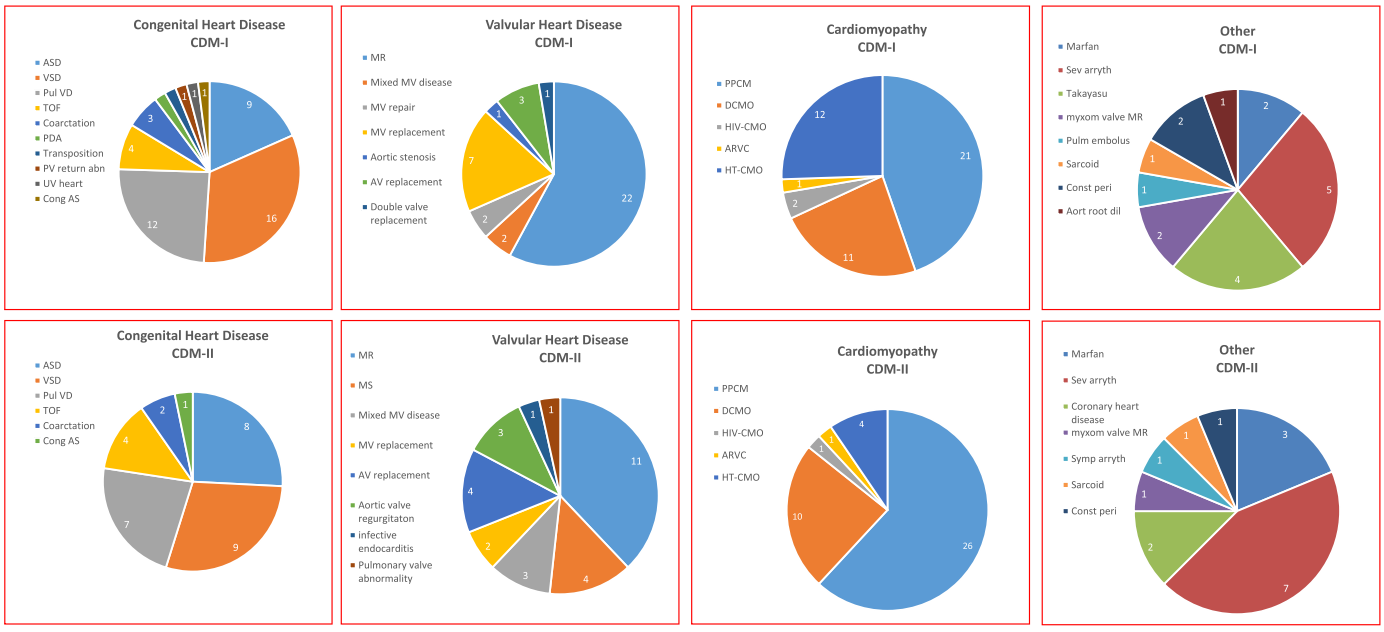

Fig. 1. Diagnosis of women classified as WHO II-IV in CDM group I and II. ARVC, arrhythmogenic right ventricular cardiomyopathy; AS, aortic stenosis; ASD, atrial septal defect; AV, aortic valve; CHD, congenital heart disease; CMO, cardiomyopathy; DCMO, dilated cardiomyopathy; HT, hypertension; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; PDA, patent ductus arteriosus; PPCM, peripartum cardiomyopathy; Pul VD, Pulmonary Valve disease; PV, pulmonary venous; TOF, tetralogy of Fallot; UV, Univentricular Heart; VHD, valvular heart disease; VSD, ventricular septal defect.

complex congenital heart diseases are now living to a reproductive age and choosing to become pregnant. In lower income countries, pregnant women often have rheumatic heart disease or unoperated congenital heart disease [10]. On a global scale PPCM, a condition that often only presents after the second month postpartum, is increasingly being recognized as a significant contributor to maternal morbidity and mortality [11]. Globally, the impact of CVD on maternal morbidity and mortality and, indirectly, on foetal outcome is not appreciated [10].

4.1. Global Maternal mortality and late maternal death due to indirect causes such as CVD

A recently published report entitled: Global, regional, and national levels of maternal mortality, 1990–2015: a systematic analysis for the Global Burden of Disease (GBD) 2015 [12], recommended that heath and data collection systems should be adapted to monitor late maternal death, especially in high Socio-Demographic Index (SDI) locations and that this information should be used to formulate strategies to ensure the optimum reproductive health of their populations. The report was only able to use late maternal death reporting from 39 countries, as per pre-specified criteria. Maternal mortality surveillance studies such as confidential inquiries have shown that late maternal death can account for up to 40% of deaths in high income settings [13]. As highlighted in the GBD study 2015 [12], many of the same countries, who have completed multiple confidential inquiries, have also not recorded a single late maternal death in their official statistics. These include the United Kingdom, Finland, France, Ireland, Denmark and South Africa. We have therefore recently highlighted that the recording of late maternal death is a neglected global responsibility [2]. The importance of CVD being the main indirect obstetric cause of death has been reported in a number of recent studies, including a maternity mortality surveillance system in Morocco (39% of indirect cases) [14] and in South Africa [12]. In South Africa, there has been a steady increase in the institutional maternal mortality rate (IMMR) for cardiac disease over the last decade. The maternal mortality rate for cardiac disease in 2005–2007 was 3.73, increasing to 5.64 during 2008–2010, and to 6.00 per 100,000 during 2011–2013. After non-pregnancy related infections such as HIV/AIDS, cardiac disease is the second most common cause of indirect maternal death.

Table 3
Maternal Mortality in women with structural heart disease within 1 year postpartum.

Diagnosis	Timing of Presentation	Mod WHO Class	NYHA class	Age (yrs)	EF (%)	When	Reason	Foetal outcome
CDM I								
PPCM with subsequent pregnancy	Prepartum	IV	II	24	45	61 days postpartum	Sudden death	Foetal survival
PPCM	Postpartum	IV	II	32	32	130 days postpartum	CCF	Foetal survival
Rheumatic HD with DVR	Prepartum	IV	I	19	30	50 days postpartum	Valve thrombosis	Foetal survival
PPCM	Postpartum	IV	III	24	24	122 days postpartum	CCF	Foetal survival
Familial CMO	Prepartum	IV	II	43	30	44 days postpartum	CCF	Foetal survival
PPCM	Prepartum	IV	II	32	25	95 days postpartum	Sudden death	Foetal survival
Familial CMO	Prepartum	IV	III	25	26	92 days postpartum	CCF	Foetal survival
PPCM post miscarriage	Postpartum	IV	IV	24	31	150 postpartum	CCF	miscarriage 20 weeks
Rheumatic HD with MVR	Prepartum	IV	I	25	60	16 weeks prepartum	SBE	Foetal death
CDM II								
PPCM	Postpartum	IV	IV	28	24	132 days postpartum	CCF	Foetal survival

PPCM = Peripartum Cardiomyopathy; HD = Heart Disease; DVR = Double valve replacement, MVR = mitral valve replacement; CCF = Congestive Cardiac Failure.

4.2. Beta-blocker use in pregnancy and pharmacological management postpartum

Based on our observation of a high morbidity and mortality due to heart failure obtained from the CDM I cohort study [6], we decided to continue medication with beta-blockers in women that presented to the CDM Clinic with pre-existing heart disease and a echocardiographic EF <45%, or commenced with this medication if the patient was not on a beta-blocker. The dose was titrated to moderate levels on a case-per-case basis, taking blood pressure (not <100 mm Hg) and heart rate (not >100 bpm) into consideration. The increased use of beta-blockers was based on the recently published observational data from the Registry on Pregnancy and Cardiac disease (ROPAC), a program included in the EurObservational Research Program (EORP) of the European Society of Cardiology [15]. This study showed that in a cohort of 1321 patients with structural heart disease, beta-blockers were used by 291 patients (22%) and, other than an average reduction in birth weight of 100 g, beta-blockers did not have any adverse effects. However, the importance of the 100 g fall in birth weight, and whether or not it has any longer term significance for outcome, should be established. In our cohort, the use of beta-blocker alone did not prevent hospital admission or death. However, intensified management, in association with increased use of beta-blockers pre- and postpartum, early start of angiotensin inhibitor and aldosterone antagonists postpartum contributed substantially to the reduction in heart failure admission and death. In addition, no differences in foetal birth weight nor in lower birth weight were observed between the two cohorts ($p = 0.2028$ and $p = 0.8752$, respectively).

4.3. Risk stratification and improving peripartum care for women with structural heart disease

This study has demonstrated that risk stratification based on a practical algorithm established by our team, which has been reported in South Africa as part of the Confidential Enquiry into Maternal Death (NCCEMD) 2011–2013 [16] and which has now been extended into intensified postpartum care, leads to a substantial reduction in mortality and morbidity. Our data suggest that increased postpartum medical surveillance of women with cardiac disease results in reduced adverse outcomes. The challenge now is to identify those women who would benefit from this approach earlier at primary and secondary care facilities. Currently, most tertiary care hospitals in South Africa provide weekly cardiac-obstetric clinics and regular obstetric medicine lectures in their registrar training programs. These should emphasize not only the importance of identifying women with CVD, but also the significant benefit that these women would gain if managed appropriately. Detection could be increased with more widespread use of the hand-held echocardiography [17] and point-of-care testing for early onset heart failure. The ability of these initiatives to identify at risk women at an early stage should be explored via research projects. This is of particular importance for low-to-middle income countries where long distances to tertiary care are common.

In general, as recently reported by Van Hagen et al. [18], all women with structural heart disease, particularly rheumatic heart disease, cardiomyopathy and other modified WHO Classes III–IV risk classification conditions [8,18], need careful risk assessment, including assessment of pre-pregnancy signs of heart failure and atrial fibrillation. All women need careful advice on contraception [19] to avoid pregnancies which pose a risk to the mother's life and pre-conceptual counselling for all young women with cardiac concerns.

5. Limitations

This study 1. confirms previous work highlighting the importance of cardiac disease as a cause of maternal mortality but, as this is a single-centre study drawing patients from a single province in South Africa, the data cannot be extrapolated to other regions in South Africa, Africa or even beyond. 2. Although this is a large prospective study with long-term outcomes, the cohort remains heterogeneous and the subgroups are small. The CDM group-1 and CDM Group-2 were similar but not matched in all parameters. 3. Beta-blocker dose was adjusted throughout the pregnancy and peripartum period based on clinical criteria and, therefore, dose correlations could not be performed. 4. Early visit to a dedicated heart failure clinic led to appropriate start of other heart failure medications. The interventions were partially interlinked and the impact can therefore not be evaluated separately. We have adhered to the published STROBE guidelines in reporting of this study [20].

6. Conclusion

Our data show a disease pattern in South Africa which is markedly different to that seen in the developed world. Joint obstetric–cardiac care is not only associated with an excellent survival rate of mothers (even those with complex diseases, presenting while pregnant), but also with that of their offspring. The greatest risk of adverse outcome is attributable to late presentation and left ventricular failure, with death commonly occurring outside the 42-day limit for maternal mortality reporting. Targeted intervention adding specified postpartum care via follow-up at the dedicated CDM clinic, other specialist care and continuation of beta-blockers while pregnant and early start of heart failure medication postpartum when indicated, is associated with a significant reduction in peripartum heart failure admissions and mortality.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.07.140.

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Conflicts of interest

There are no conflicts of interest related to this work.

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