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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

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