

MANAGEMENT OF
CARDIAC DISEASE
IN PREGNANCYPatient profile of a tertiary
obstetric-cardiac clinicJ.L. van der Merwe^{*}, D.R. Hall^{*}, P. Herbst[#] and A. Doubell[#]

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INTRODUCTION

Normal pregnancy is characterised by significant maternal cardiovascular adaptation that aims to ensure adequate utero-placental blood flow for sustainable fetal development. This physiological cardiovascular adaptation also allows the pregnant mother to cope with the increased metabolic demands instituted by the pregnancy state. However, underlying cardiac conditions affect 0.2-3% of all pregnancies.⁽¹⁻³⁾ Limited cardiovascular reserve coupled with these, often substantial, haemodynamic changes place a subset of these women at risk of decompensation during pregnancy. This is associated with significant cardiovascular and obstetric complications and drives poor outcomes in high risk groups.^(3,4) Maternal cardiac disease in pregnancy is not infrequently complicated by heart failure, arrhythmias and stroke while these babies are at increased risk of low birth weight, prematurity and death.⁽⁵⁻⁷⁾ It is therefore not surprising to find that maternal cardiac disease is the leading cause of maternal mortality in many first world countries.⁽⁸⁾ In South Africa "medical conditions" as a group is ranked fifth in terms of causes of maternal mortality and cardiovascular disease is foremost amongst the medical conditions in this group by some margin. Cardiac failure and ventricular dysfunction are important presenting problems amongst recorded mortalities from cardiac disease.⁽⁹⁾

The individuality and uniqueness of each pregnancy complicates decision making and guideline setting significantly. The complexity that arises from what superficially appears to be a

ABSTRACT

Background: Cardiac disease is the most important medical cause of maternal mortality in South Africa. Management of women with cardiac disease in pregnancy is highly specialised and they should ideally be evaluated early in pregnancy and in a multidisciplinary fashion with the aim of formulating a perinatal management plan. In order to facilitate the efficient management of these patients in the context of a large tertiary hospital in South Africa a combined obstetric-cardiac (O-C) clinic was established at Tygerberg Academic Hospital (TBH) in 2010.

Objective: The purpose of this review is to describe the patient profile of an obstetric-cardiac clinic in South Africa, specifically the TBH O-C clinic and to share the lessons learnt from establishing this clinic.

Methods: Retrospective review performed at TBH, a referral centre in the Western Cape Province of South Africa. All women evaluated and/or managed at the Obstetric-Cardiac clinic between 10 August 2010 and 4 December 2012 were included.

Results: There were 231 women, rheumatic heart disease (n=79; 34.2%) was the predominant cardiac disease followed by congenital heart disease (n=78; 33.8%), medical conditions (n=38; 16.4%) and previous peripartum cardiomyopathy (n=9; 3.9%). Eighty-two women (35.5%) were perceived to be extremely high risk and their entire pregnancies were managed in the Obstetric-Cardiac clinic. The most common RHD lesion was mitral regurgitation (34.2%) and mixed mitral valve disease (24.1%). The most frequent CHD was ventricular septal defects (n=27; 35%).

Conclusions: The cardiac disease profile of patients seen at this obstetric-cardiac clinic in a South African tertiary hospital reflects a transition from the disease profile of a typical developing country (high burden of rheumatic heart disease) to the disease profile seen in a more developed country (high burden of congenital heart disease). This could indicate improved quality of socio-economic development and the health care system. The increasing complexity of cardiac pathology that has to be dealt with in pregnant patients presenting to a tertiary hospital requires close collaboration between the obstetrician, cardiologist, cardiac surgeon and anaesthetist caring for these patients. A dedicated obstetric-cardiac clinic is a good model to utilise in a tertiary hospital when aiming to optimise the care of patients with cardiac disease in pregnancy. SAHeart 2014;11:80-85

relatively fixed combination of factors, can often surprise one. Gestational age at presentation, the unique combination of maternal functional status at a given gestation coupled with the severity of cardiac disease and the known natural course

of the disease in pregnancy, maternal comorbidities, fetal health and perceived viability in the era of modern neonatal care and a mother's wishes to carry to term a precious baby or her consideration for a young family at home are just a few factors that conspire to make each case unique. In addition, decision-making requires a sound knowledge of the available therapeutic strategies, the risks inherent in each for mother and child and the timing of such a strategy that will limit risk as far as possible. The age-old mantra of mother first must therefore in each case be weighed against what is the perceived true risk for mother and fetus and a management strategy decided on that will lead to the best fetal outcome without compromising maternal outcome. In order to achieve this, a multi disciplinary approach needs to be followed.

Healthy pregnant women without underlying cardiac disease who present with symptoms mimicking cardiac disease represent another challenging group to evaluate. Fatigue, dyspnoea and even syncope are found in healthy pregnant women and if associated with physical, ECG or echocardiographic findings that simulate cardiovascular pathology in their own right, may complicate the evaluation of the pregnant mother. Differentiating normal from abnormal within a screening context as well as the management of patients with established cardiac disease in pregnancy are challenges that warrant a specialised solution. The risk stratification strategy chosen to address these complexities should also be comprehensive and evidence based as far as possible.

The need for a specialised combined Obstetric-Cardiac Clinic (O-C clinic) at our own institution (Tygerberg Hospital) had become more and more evident in the last decade. The requirement for cardiovascular evaluation of the pregnant patient with known or suspected cardiac disease (as well as those planning pregnancy) had become a large service component in an already overburdened general cardiology clinic. Waiting times for the referral of pregnant patients where decision-making often requires an expedited evaluation necessarily makes elective clinic planning difficult. Furthermore, the combined service burden to both obstetrics and cardiology was clearly greater because of the typical evaluate – refer – reassess cycle that was initiated between the services. Patient counselling pre-pregnancy and during pregnancy often necessitated a visit to both the cardiac and obstetric clinics which decreased service efficiency. A combined O-C clinic was established in Tygerberg Hospital in August 2010 for the screening, evaluation, risk stratification and management of pregnant patients with suspected or established cardiac disease. The combined O-C clinic consists of a cardiologist performing detailed echocardiography and a team of obstetricians lead by a sub-specialist in maternal-fetal medicine. Patients screened at either primary, secondary or tertiary level are referred to the clinic if they are known to have a cardiac lesion or are suspected of having undiagnosed cardiac disease and are either pregnant or are planning pregnancy.

The purpose of this review is to describe the patient profile of this clinic and to share the lessons learnt from establishing the clinic.

MATERIALS AND METHODS

This retrospective review of records was performed at Tygerberg Academic Hospital, a secondary and tertiary level referral centre in the Western Cape Province of South Africa. The study population consisted of all women with known or suspected cardiac conditions in pregnancy that were evaluated and/or managed at the O-C clinic. Patients not known to the O-C clinic who were admitted to the labour ward on an emergency basis were not included in this study.

Data was collected from the clinic records and patient files by the principal investigator. Women evaluated at the O-C clinic underwent a thorough antenatal and obstetric review by a consultant and resident obstetrician. Thereafter they underwent meticulous cardiovascular and echocardiographic evaluation by a dedicated cardiologist. Following these steps, comprehensive antenatal care, including the anticipated delivery plan, was formulated. During this process all women were assigned a risk estimation according to the modified World Health Organisation (WHO) classification of maternal cardiovascular risk⁽¹⁰⁾ as well as the CARPREG score⁽¹¹⁾ as documented by Sui, et al. Women who were deemed at an exceptionally high risk of adverse cardiac events during pregnancy i.e. those with WHO class III-IV or a CARPREG score of >1 were managed throughout their pregnancy by this specialist clinic/team including peripartum planning. Patients not meeting these criteria were referred back to their appropriate obstetric clinics with specific instructions for antenatal care and delivery.

The study was approved and registered by the Human Research and Ethics Committee of the University of Stellenbosch.

RESULTS

A total of 231 patients were evaluated at the O-C clinic from 10 August 2010 - 4 December 2012. The documented underlying cardiac diseases and maternal characteristics are depicted in Table I. The most common reason for "screening" at the primary assessment was for previously managed or suspected RHD in 15 of the 27 visits.

The numbers of first and subsequent follow-up visits performed at the O-C clinic are depicted in Figure 1. Furthermore, women classified as WHO Class III-IV or with a CARPREG score of >1, whose pregnancies were managed entirely by the O-C clinic, are indicated in this figure. The breakdown of the pathology profile of these specific women is shown in Figure 2.

Medical conditions that warranted continuous care at the O-C clinic consisted of a single case of hypertrophic cardiomyopathy, aortic aneurysm, aortic coarctation, 4 cases of ischaemic

TABLE 1: Epidemiological transition

	2010	2011	2012	All
Total new visits	34	86	111	231
Age in years[#]	25 (18-39)	26 (16-44)	27 (16-47)	
<18 years (n)	0	4	5	9
>35 years (n)	3	13	23	39
Gravidity[#]	1 (1-5)	2 (1-6)	3 (1-6)	-
Parity[#]	0 (0-4)	1 (0-5)	1 (0-4)	-
Gestational age[#] (at clinic evaluation)	25 (11-38)	24 (7-39)	24 (6-38)	-
<24w (n)	15	29	49	93
Indication for assessment				
Screening (n %)	2	7	18	27 (11.7)
Medical (n %)	1	20	17	38 (16.4)
Prev PCMO	2	4	3	9 (3.9)
CHD (n %)	11	33	34	78 (33.8)
RHD (n %)	18	22	39	79 (34.2)

[#]Median (Range), CHD: congenital heart disease, RHD: rheumatic heart disease. Prev PCMO: previous peripartum cardiomyopathy.

heart disease, 2 cases of primary pulmonary hypertension and 2 cases of severe restrictive lung disease with pulmonary hypertension. A single case of cardiac arrhythmia was documented. This patient had persistent atrial fibrillation with no discernible cause. Nine patients with previous peripartum cardiomyopathy were evaluated. Four of these women booked late (>24weeks gestation). During their initial evaluation 3 were asymptomatic and had a normal echocardiography evaluation

(with left ventricular ejection fraction of >60%) while 2 women had not fully recovered, retaining severe left ventricular (LV) dysfunction on echocardiography (left ventricular ejection fraction of <35%).

The most common structural heart disease encountered in the clinic was rheumatic heart disease (RHD), accounting for 79 (34.2%) of the women. The specific breakdown of the valvular heart disease encountered in these women is depicted in Figure 3. Mitral regurgitation (34.2%), mixed mitral valve disease (24.1%) and mitral stenosis (11.4%) were the most common RHD abnormalities. Furthermore 12.7% of the RHD women had already had a mitral valve – and 6.3% an aortic valve replacement.

Congenital heart disease accounted for 78 of the women seen at the clinic (33.8% of all first evaluations). The specific numbers of the underlying congenital heart disease are depicted in Figure 4. The most common pathology was ventricular septal defect (VSD) of which 10 (53%) had previous surgical repair; 6 (31.6%) had no previous surgery and only a residual restrictive defect whereas 3 (15.8%) had no surgery without any evidence of a residual VSD on echocardiography.

DISCUSSION

The emphasis of this moderately sized retrospective study, that included all women seen from the inception of a dedicated O-C clinic, was to describe the patient profile of such an O-C clinic in a South African tertiary hospital. The most significant finding of this study is the apparent transition from the disease

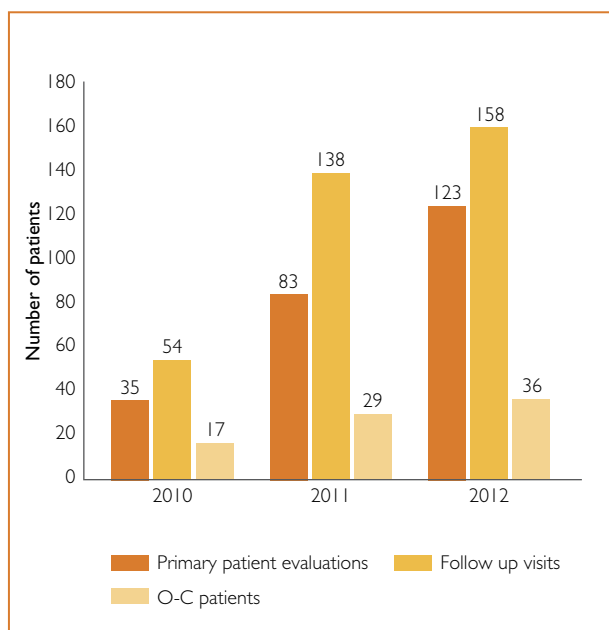


FIGURE 1: Obstetric-Cardiac Clinic visits.

O-C patients: WHO Stage 3-4 or CARPREG >1 patients that received all their care at the O-C clinic.

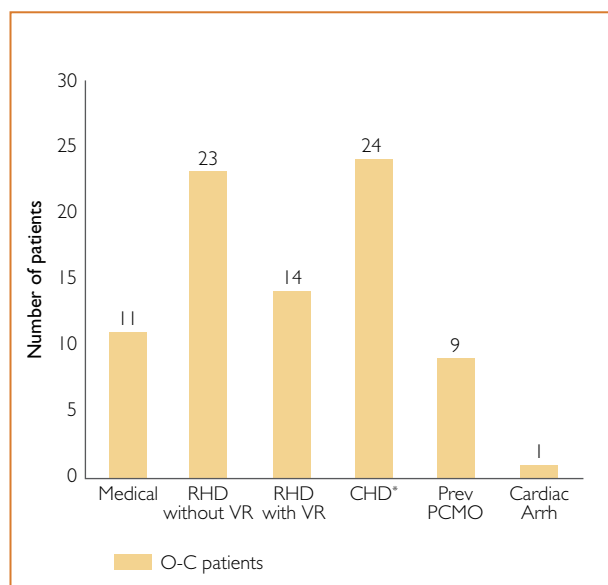


FIGURE 2: Distribution of obstetric-cardiac clinic patients

Medical: medical conditions, RHD: rheumatic heart disease, VR: valve replacement, CHD: congenital heart disease, Prev PCMO: previous peripartum cardiomyopathy, Cardiac Arrh: cardiac arrhythmias.

*No valve replacements in this group.

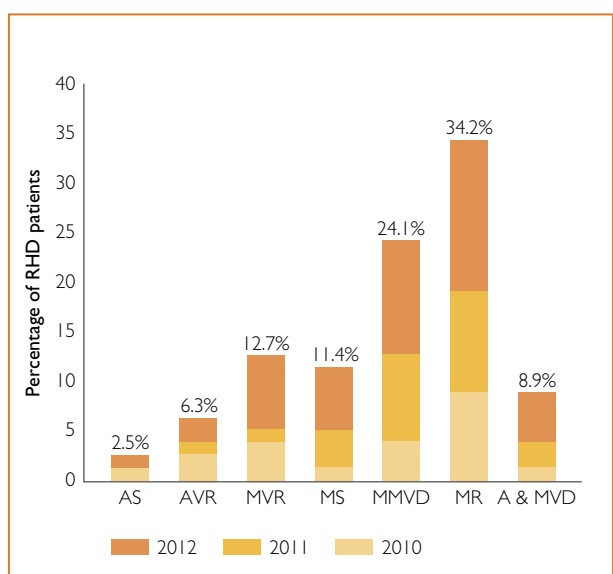


FIGURE 3: Rheumatic heart disease.

AS: aortic stenosis, AVR: aortic valve replacement, MVR: mitral valve replacement, MS: mitral stenosis, MMVD: mixed mitral valve disease, MR: mitral valve regurgitation, A & MVD: mixed aortic and mitral valve disease.

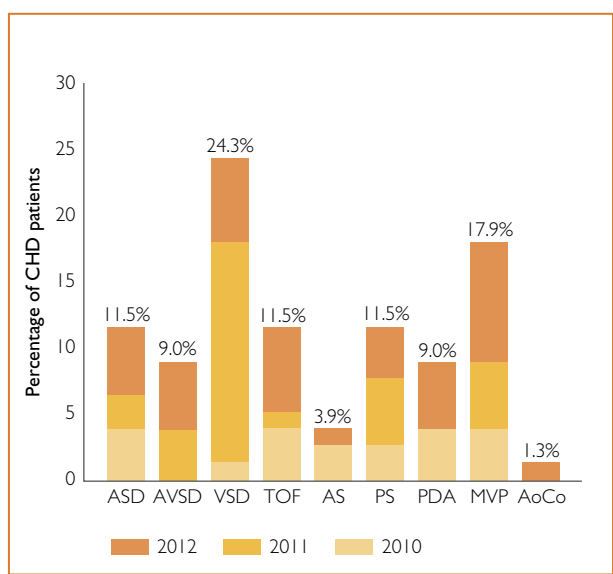


FIGURE 4: Congenital heart disease.

ASD: atrial septal defect, AVSD: atrioventricular septal defect, VSD: ventricular septal defect, TOF: Tetralogy of Fallot, AS: Aorta stenosis, PS: pulmonary stenosis, PDA: persistent ductus arteriosus, MVP: mitral valve prolapse, AoCo: aorta coarctation.

profile of a typical developing country (high burden of rheumatic heart disease) towards the disease profile associated with a more developed country (high burden of congenital heart disease) seen in a dedicated O-C clinic in this South African tertiary hospital. Furthermore, the lessons learnt from establishing this clinic yielded some important principles for clinicians caring for pregnant patients with severe and complex cardiac disease.

Women with known cardiac conditions who desire children, should ideally be evaluated prior to pregnancy or before clinical changes precipitate acute events. This is not always achievable in a developing country, nonetheless, in this study 40.3% presented before 24 weeks gestation. Pregnant women with cardiac lesions need early and thorough evaluation in order to formulate a plan to optimise the outcomes for both the mother and her baby. Prior to August 2010, no formal O-C clinic existed at Tygerberg Academic Hospital and complex cases were evaluated by a cardiologist on an ad-hoc basis.

After the O-C clinic had been formally established, the criteria for evaluation and admission to this clinic needed to be clarified. While the criteria for evaluation were necessarily broad, only a select group of women with complex cardiac pathology could be continuously accommodated within the clinic due to capacity constraints. The criteria chosen were in line with the modified WHO risk classification⁽¹⁰⁾ and the CARPREG⁽¹¹⁾ as well as the subsequent ZAHARA studies⁽¹²⁾ for describing risk scores and predictive factors.

This moderately sized retrospective evaluation over a 28 month period revealed that RHD (34.2%), CHD (33.8%) and medical conditions including previous PCMO (20.3%) constituted the vast majority of cases evaluated in the clinic. Of these patients 82 (35.5%) were retained for continued follow up in the O-C clinic. The disease profile of patients kept in the clinic was similar to those referred for evaluation. Several small retrospective reports and descriptive series from developing countries exist.⁽¹³⁻¹⁶⁾ As would be expected in developing countries, all of these studies show a predominant RHD profile, constituting 65% - 90% of their pregnant cardiac cases. A more recent retrospective review, similar in size to this study, in an urbanised community still noted that RHD accounted for 63.5% while CHD accounted for less than 10% of cases.⁽¹⁷⁾ The RHD:CHD ratio in the patients assessed at our clinic study still reflected the dominance of RHD, although to a lesser extent.

Pregnancies in asymptomatic patients with regurgitant valve lesions and preserved ventricular function are typically uncomplicated. This is in contrast to stenotic lesions, which are associated with a limited ability to adapt to the haemodynamic changes related to pregnancy. Mitral stenosis (MS) represents the most common and problematic valve lesion in developing countries. In this study MS of any severity comprised 35 of the 79 RHD patients (44.3%). This lesion is associated with a high fetal and maternal mortality as documented in a series from South Africa.⁽¹⁸⁾ Furthermore, Silversides, et al., documented that in pregnant patients with moderate or severe mitral stenosis (mitral valve areas <1.5cm²), 67% developed a maternal cardiac event and 44% of infants were born prematurely or died (25%).⁽¹⁹⁾ In contrast, mild mitral stenosis

rarely results in cardiac events. This further emphasises the need for early and meticulous assessment of these women in pregnancy.

In women of childbearing-age, aortic stenosis is a rare condition.^(16,20) The data reported here supports this with only 2 cases of aortic stenosis and 4 patients seen with aortic valve replacement due to RHD. The presence of a prosthetic heart valve places patients in a high risk category (WHO III) and constitute an important group requiring follow up at a specialist clinic. The anticoagulant management of these women has been a topic of substantial debate over recent times and requires meticulous care.^(21,22)

In developed countries degenerative and congenital disorders predominate over rheumatic heart disease. Until the latter half of the twentieth century, women with congenital heart disease often died during pregnancy or before reaching reproductive age. Improved techniques of surgical repair have resulted in larger proportions of women with congenital heart disease achieving reproductive potential.^(23,24) Recently the first results of the multicentre European study "Registry on Pregnancy and Cardiac disease" were published. This prospective study included 1 321 pregnancies from 28 countries. The study found CHD to be the most prevalent form of structural heart disease (66%).⁽²⁵⁾ This finding differs markedly from the previously mentioned studies from developing countries where the incidence ranged from 9% - 14%.⁽¹³⁻¹⁵⁾ The incidence of CHD (33.8%) reported in this study is relatively high compared to other publications from developing countries but it is still similar to a study from India (36%).⁽¹⁶⁾ The prominence of congenital heart disease in the pregnant population may be presumed to be a marker of the quality of socio-economic development and the health care system. However, this interpretation must be made with caution as the referral bias created by establishing a tertiary O-C clinic may have skewed the patient profile.

In a large prospective study from Roos-Hesselink, et al., the 2 most frequent CHD lesions were septal defects and Tetralogy of Fallot (TOF).⁽²⁵⁾ The most frequent CHD lesions reported here were septal defects followed by mitral valve prolapse, pulmonary stenosis and TOF. Patients with TOF will almost always have undergone corrective surgery in infancy or childhood. These patients may still be afflicted by residual haemodynamic lesions of the right ventricular outflow tract in the shape of obstruction, regurgitation or both. Over time these haemodynamic effects cause pathophysiological changes including right ventricular hypertrophy, dilatation or dysfunction. However, Greutman, et al., found that most outcomes of pregnancies in patients with CHD and residual right ventricular outflow tract lesions were good.⁽²⁶⁾

Although the incidence of cardiac disease in pregnancy is reported to be stable, the clinical problems caused by these

lesions are increasing.⁽²⁷⁾ The increasing numbers seen at the clinic in this study probably reflect better recruitment of appropriate cases (Figure 1).

The prevention of maternal deaths is an absolute priority as reflected by the Millennium Development Goal number 5.⁽²⁸⁾ The establishment of sub-specialist pregnancy clinics, such as the O-C clinic, are an important tool in preventing maternal and perinatal morbidity and mortality. For the patient with cardiac disease, planning of pregnancy and assessment early in pregnancy are important determinants of maternal health. Unfortunately, the local experience is that patients with cardiac disease presenting in pregnancy have often not been counselled before the pregnancy and/or present late in the pregnancy. Women of reproductive age attending cardiology clinics must be continually informed of the risks of unplanned pregnancies. Cardiologists conducting such clinics should employ the assistance of family planning clinics, in this regard. The establishment of the dedicated O-C clinic in Tygerberg Hospital has heightened awareness of the low rate of pre-pregnancy counselling in the referring clinics. This deficiency is not addressed adequately by establishing a dedicated O-C clinic and greater awareness of the pre-pregnancy counselling of women with cardiac disease needs to be established at all levels of care. An equally important requirement at all levels of care is the ability to distinguish cardiac pathology from innocent murmurs during pregnancy. In the past the cardiac clinic in Tygerberg Hospital assessed a significant number of patients referred from obstetric clinics with innocent murmurs. The knowledge transfer that has occurred as a result of the dedicated O-C clinic has almost eliminated these referrals. Furthermore, the establishment of the O-C clinic has created an efficient system to ensure that pregnant patients with highly complex cardiac conditions have access to the required expertise on a continual basis. It is our assumption that the planning and outcome of pregnancies in these patients will be improved. However, this remains to be determined and the next critical step will be to evaluate the clinical outcomes of these women in order to determine the magnitude of "return" on the clinical "investment" required to establish and run such a clinic. This point will inform the objective of a planned follow-up study.

Potential shortcomings of this trial relate to the inherent shortcomings of a retrospective study based on registry/database type information. In the context of describing disease distribution in a clinic, referral bias is an important confounder that must be considered. Both referral patterns and disease characteristics may play a role here. Referrals to the O-C clinic were taken from all medical service tiers be it primary, secondary or tertiary level. This addresses one aspect of referral bias based on referral pattern but others remain and of course complete control over referral to any clinic is limited. In terms of disease characteristics one could postulate that easily detectable lesions such as those leading to loud systolic murmurs, e.g. small VSDs

would preferentially be referred to the clinic and may therefore contribute to the relatively high disease burden of these lesions found. This potential confounder is mitigated in the index study by the fact that all patients followed up long term in the clinic and therefore included in the study, come from referrals of patients with known previous cardiac disease rather than from screening referrals. The screening referrals of cases with a suspicious murmur to the O-C clinic all screened negative for structural cardiac disease after a thorough work-up. The high clinic disease burden of, for example VSDs, therefore rather reflects the known high prevalence of these lesions in the paediatric service and this should be similar (using similar reasoning) for any lesion reported on in the index trial.

Conflict of interest: none declared.

REFERENCES

- Weiss BM, von Segesser LK, Alon E, et al. Outcome of cardiovascular surgery and pregnancy: A systematic review 1984-1996. *Am J Obstet Gynecol.* 1998;179:1643-1653.
- Bhatla N, Lal S, Behera G, et al. Cardiac disease in pregnancy. *Int J Gynaecol Obstet.* 2003;82:153-159.
- Madazli R, Sal V, Cift T, et al. Pregnancy outcomes in women with heart disease. *Arch Gynecol Obstet.* 2010;281:29-34.
- Melchiorre K, Sharma R, Thilaganathan B. Cardiac structure and function in normal pregnancy. *Curr Opin Obstet Gynecol.* 2012;24:413-421.
- Whittemore R, Hobbins JC, Engle MA. Pregnancy and its outcome in women with and without surgical treatment of congenital heart disease. *Am J Cardiol.* 1982;50:641-651.
- Shime J, Mocarski EJ, Hastings D, et al. Congenital heart disease in pregnancy: Short and long-term implications (erratum in *Am J Obstet Gynecol* 1987; 156:1361) *Am J Obstet Gynecol.* 1987;156:313-322.
- Siu SC, Colman JM, Sorensen S, et al. Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. *Circulation.* 2002;105:2179-2184.
- Lewis G, Ed. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer – 2003-2005. The seventh report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH, 2007.
- Executive Summary. Fifth report on Confidential Enquiries into Maternal Deaths in South Africa 2008-2010. Pretoria: National Department of Health, 2012.
- Jastrow N, Meyer P, Khairy P, et al. Prediction of complications in pregnant women with cardiac diseases referred to a tertiary centre. *Int J Cardiol.* 2010;151:209-213.
- Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation.* 2001; 104:515-521.
- Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J.* 2010;31: 2124-2132.
- Rush RW, Verjans M, Spracklen FH. Incidence of heart disease in pregnancy. A study done at Peninsula Maternity Services hospitals. *S Afr Med J.* 1979;55:808-810.
- Nqayana T, Moodley J, Naidoo DP. Cardiac disease in pregnancy. *Cardiovasc J Afr.* 2008;19:145-151.
- Abdel-Hady ES, El-Shamy M, El-Rifai AA, et al. Maternal and perinatal outcome of pregnancies complicated by cardiac disease. *Int J Gynaecol Obstet.* 2005;90:21-25.
- Subbaiah M, Sharma V, Kumar S, et al. Heart disease in pregnancy: cardiac and obstetric outcomes. *Arch Gynecol Obstet.* 2013;288:23-27.
- Soma-Pillay P, MacDonald AP, Mathivha TM, et al. Cardiac disease in pregnancy: a 4-year audit at Pretoria Academic Hospital. *S Afr Med J.* 2008;98:553-556.
- Naidoo DP, Desai DK, Moodley J. Maternal deaths due to pre-existing cardiac disease. *Cardiovasc J S Afr.* 2002;13:17-20.
- Silversides CK, Colman JM, Sermer M, et al. Cardiac risk in pregnant women with rheumatic mitral stenosis. *Am J Cardiol.* 2003;91:1382-1385.
- Huisman CM, Zwart JJ, Roos-Hesselink JW, et al. Incidence and predictors of maternal cardiovascular mortality and severe morbidity in the Netherlands: A prospective cohort study. *PLoSOne.* 2013;8:e56494.
- Hall DR, Olivier J, Rossouw GJ, et al. Pregnancy outcome in women with prosthetic heart valves. *J Obstet Gynaecol.* 2001;21:149-153.
- McLintock C. Anticoagulation choices in pregnant women with mechanical heart valves: balancing maternal and fetal risks: The differences the dose makes. *Thromb Res.* 2013;131:S8-S10.
- Child, JS. Management of Pregnancy and contraception in Congenital Heart Disease. In: Congenital Heart Disease in Adults, 3rd ed, Perloff JK, Child JS, Aboulhosn J (Eds). Saunders/Elsevier, 2009.
- Khairy P, Ionescu-Ittu R, Mackie AS, et al. Changing mortality in congenital heart disease. *J Am Coll Cardiol.* 2010;56:1149-1157.
- Roos-Hesselink JW, Ruys TP, Stein JJ, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: Results of a registry of the European Society of Cardiology. *Eur Heart J.* 2013;34:657-65.
- Greutmann M, Von Klemperer K, Brooks R, et al. Pregnancy outcome in women with congenital heart disease and residual haemodynamic lesions of the right ventricular outflow tract. *Eur Heart J.* 2010;31:1764-70.
- Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: The task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;32:3147-3197.
- United Nations Secretary-General. Road map towards the implementation of the United Nations Millennium Declaration: Report of the Secretary-General 2001. United Nations, New York, NY (2001).