SUPPLEMENTAL MATERIAL

PROSPECTIVE RANDOMIZED STUDY ON IMPLANTED CARDIAC RHYTHM RECORDERS IN PREGNANT WOMEN WITH SYMPTOMATIC ARRHYTHMIA AND/OR STRUCTURAL HEART DISEASE

Authors: Karen Sliwa MD, PhD, FESC, FACC\textsuperscript{1,2}.  
Feriel Azibani PhD\textsuperscript{1}  
Mark R. Johnson MBBS, MRCOG \textsuperscript{3}  
Charle Viljoen MBChB, MMed, FCP\textsuperscript{1,2}  
Johann Baard MBChB\textsuperscript{1}  
Ayesha Osman MBChB\textsuperscript{4}  
Olivia Briton\textsuperscript{1,2}  
Mpiko Ntsekhe MD, PhD\textsuperscript{2}  
Ashley Chin MBChB, MPhil, \textsuperscript{2}

Affiliations:

\textsuperscript{1} Hatter Institute for Cardiovascular Research in Africa, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa  
\textsuperscript{2} Division of Cardiology, Department of Medicine Groote Schuur Hospital, University of Cape Town, South Africa  
\textsuperscript{3} Imperial College London, Chelsea and Westminster Hospital, London, United Kingdom  
\textsuperscript{4} Division of Obstetrics and Gynecology Groote Schuur Hospital, University of Cape Town, South Africa
The Cardiac Disease in Maternity Project Phase II

Sub-project: Use of small implantable ECG recorder in pregnant women with arrhythmia

Background

Worldwide, the numbers of women who have a pre-existing cardiovascular disease or develop cardiac problems during pregnancy are increasing and, due to the lack of evidenced-based data, this provides challenges for the treating physician. Cardiovascular disease in pregnancy is a complex topic as women can present either pre- or postpartum, due to a pre-existing heart disease such as e.g. operated or unoperated congenital heart disease, valvular heart disease, and chronic hypertension or familial dilated cardiomyopathy. On the other hand, there are diseases which are directly associated with pregnancy such as hypertensive disorders of pregnancy and peripartum cardiomyopathy (PPCM). Women often present with symptoms and signs of cardiovascular disease such as palpitations and shortness of breath, or even directly in acute heart failure. There is, in particular, a paucity of data from developing countries of this unique disease pattern and presentations. Pregnancy poses a physiological stress test as cardiac output increases by 30-50% close to term. Further haemodynamic stress occurs during labour and many of the effects of pregnancy on cardiovascular disease (CVD) persist for several months after delivery.

Awareness of the different cardiovascular diseases that can occur in pregnancy or postpartum has received limited attention and the main focus has been on hypertension and preeclampsia. The global impact of elevated blood pressure (BP)/hypertension, in general, is profound, as it is responsible for more deaths worldwide than any other cardiovascular risk factor, including tobacco use, obesity and lipid disorders (Vos, Sliwa et al. Lancet 2012; Gersh & Sliwa, Eur Heart J 2010).

Beyond the higher income countries, 80% of worldwide CVD-related deaths now occur in low- and middle-income countries (LMICs) (Sliwa, Stewart Circulation 2011; Abergunde, Mathers et al, Lancet, 2007). In LMICs, morbid and fatal CVD-related events typically occur at a younger age and affect more women (commonly in pregnancy), thereby exerting a more profound impact on the family unit and the workforce. The recently published Global Burden of Disease Study which reports on Years Lived with Disabilities (YLDs) for 1160 sequelae of 289 diseases and injuries does not report on the prevalence of CVD pre- and postpartum as an entity. However, globally, it is estimated that CVD and, in particular, hypertensive disorders of pregnancy, complicate 2-8% of pregnancies contributing, to a major extent, to maternal mortality worldwide (Sliwa, Cardiovascular Research, in press 2014). Chronic hypertension is now prevalent in 3% of women falling pregnant in the US (Seely and Ecker, N Engl J Med, 2011) and will also influence the prevalence of acute coronary syndromes (ACS) in pregnancy.
The recent confidential inquiry into maternal death in South Africa reported that of the 4867 deaths reported over 2 years, 14% were due to hypertensive disorders, with another 8.8% due to medical and surgical conditions (www.hst.org.za/saving-mothers-2008-2010). This makes cardiac disease in pregnancy a key focus area, with the aim of reducing morbidity and mortality, not only by the South African Department of Health but also by the World Health Organization and World Heart Federation.

We have recently carried out a single-centre prospective study on women presenting with CVD in pregnancy at Groote Schuur Hospital, University of Cape Town, South Africa (manuscript submitted). This study investigates an appropriate referral algorithm and reports on disease presentation (n=226) and outcome of those patients, with significant disease warranting followup at a tertiary care (n=152). Of the 152 women that were asked to come back for follow-up, the CDMC 122 (80.2%) presented prepartum. The most common diagnoses where congenital heart disease, valvular heart disease, cardiomyopathy and other diagnoses such as e.g. WolfParkinson-White, atrial fibrillation, arrhythmogenic right ventricular cardiomyopathy.

Management of these patients is complex as palpitations in pregnancy are common due to increased sympathetic tone. It is important to distinguish palpitations secondary to benign tachycardias, such as sinus tachycardia, from more important arrhythmias, such as supraventricular or ventricular tachyarrhythmias. Supraventricular arrhythmias are known to increase in pregnancy, presumably because of an increase in sympathetic tone. Ventricular arrhythmias secondary to some long QT syndrome subtypes are known to increase in the peripartum period. On the other hand, undiagnosed complex arrhythmia can have serious consequences for the mother and fetus, including stroke and death. Most CV drugs are contraindicated in pregnancy or have a FDA class C and D classification – e.g. beta-blockers (C & D), sotalol (C) and amiodarone (D). The treating physician therefore needs to document the exact nature of the arrhythmia-causing symptoms, such as palpitations, dizziness and syncope, prior to making a decision on pharmacological or device management. As 24-hour Holters have a low diagnostic yield, the use of an ECG loop recorder (REVEAL) could potentially influence management.

Interestingly, we have used the REVEAL XT in 2 pregnant women with newly diagnosed arrhythmogenic right ventricular cardiomyopathy and a strong family history of sudden cardiac death. Sinus tachycardia was present and correlated with the symptoms of palpitations. As only supraventricular tachycardia was detected, patients could be managed conservatively and had good maternal and foetal outcome. On the other hand, 2 other women presenting with palpitations and dizziness in pregnancy were subsequently diagnosed with cardiac sarcoidosis, a serious condition associated with sudden cardiac death.

1. Objectives:
1.1. To investigate the use of a small ECG loop recorder (REVEAL devices) in pregnant women, with or without structural heart disease, in whom supra/ventricular tachyarrhythmias and bradyarrhythmias are suspected.

2.1. To investigate if the REVEAL device will change management compared to a single 24-hour Holter done at presentation.

Our research question is based on preliminary information, having used the REVEAL XT in 2 pregnant women with newly diagnosed arrhythmogenic right ventricular cardiomyopathy and a strong family history of sudden cardiac death. As only supraventricular sinus tachycardia was detected, patients could be managed conservatively and had good maternal and fetal outcome. On the other hand, 2 other women presenting with palpitations and dizziness in pregnancy were subsequently diagnosed with cardiac sarcoidosis, a serious condition associated with sudden cardiac death. A REVEAL device should have been used to guide the physician in management.

2. Patient population

The patients will be recruited via a single-centre, prospective study of women with cardiovascular disease presenting pre- or postpartum, attending Groote Schuur Hospital. Since 1 July 2010, these patients have been seen at a weekly clinic, jointly run by cardiologists and obstetricians, under the leadership of Prof. Karen Sliwa and Prof John Anthony. We see about 100 new patients presenting with cardiovascular disease in pregnancy per annum. About 200 newly diagnosed pregnant women with documented or suspected cardiovascular disease will be screened for the indication to insert a REVEAL device. Those patients will be part of an ongoing registry entitled: Registry of newly diagnosed cases with cardiac disease in maternity-Phase II (CDM-2).

Device:

The REVEAL device has the size of a larger USB stick and can be inserted under local anaesthetic under sterile conditions as e.g. a minor procedure room. It is inserted under the skin and there are no wires connecting it e.g. to the cardiac chambers or any vessels. The device can record the cardiac rhythm for the period to up to one year. The REVEAL is routinely ised in South Africa for more than 10 years.
3. **Study design and treatment groups**

A single-centre, observational outcome study investigating peripartum women presenting with symptoms and signs of arrhythmia.

We aim to recruit 20 consecutive women with an indication for the REVEAL, from a population of about 200 pregnant women with documented or suspected cardiovascular disease as part of the ongoing cardiovascular disease in pregnancy registry.

Human Ethics Committee approval has been obtained for the overall prospective outcome study on cardiovascular disease in pregnancy (HEC REF: 173/2010)

Estimate study duration: 2 years
Estimate study start date: June 2014
Estimate study end date: May 2016

4. **Endpoints**

Our prospective study will answer the questions whether REVEAL devices:

4.1. Are acceptable as a diagnostic tool in pregnant women. This will be assessed by documentation of a number of women presenting with an indication to have the REVEAL inserted (based on standard criteria) and a number of women accepting to have the device. We see about 100 new patients presenting with cardiovascular disease in pregnancy per annum.

4.2. Detect arrhythmias in pregnancy and can guide the cardiologist and obstetrician in appropriate management, ranging from assurance, to medical therapy, to device therapy or termination of pregnancy.

4.3. Change the management of the condition compared to a single ECG performed at the day of offering insertion of the REVEAL device.

5. **Measurable outputs and Publication Plan**
Statistical analysis

Statistical analyses will be performed with GraphPad Prism version 7.03 for Windows (GraphPad Software, La Jolla California, USA). Continuous data will be expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR) depending on the data distribution. Comparison of means and proportions between sub-groups at baseline will be performed by independent t-test and Chi-square statistics (or Fisher exact test where necessary) respectively and, where data are not normally distributed, a Mann-Whitney test will be used. A P value of <0.05 will be interpreted as statistically significant.

Presentation of data

In the past decade I have been invited annually to present my research in the form of invited lectures at the following meetings: Congress of the Heart Failure Association of the ESC; European Cardiac Society of Cardiology, World Congress of Cardiology, South African Heart Failure Society, Pan African Cardiac Society. The data obtained from the study will be presented at those meetings.

Publication of Original Data

The data will be published as part of the overall cardiac disease in pregnancy registry and as a separate paper.

Budget:

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<thead>
<tr>
<th>Items</th>
<th>Unit price</th>
<th>Comments</th>
<th>Total per 20 patients</th>
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</thead>
<tbody>
<tr>
<td>20 patients with a REVEAL</td>
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<tr>
<td>Costs of ECG</td>
<td>R150.00</td>
<td>R150 x 20 patients (x 10 visits each)</td>
<td>30,000.00</td>
</tr>
<tr>
<td>Reimbursement of travel costs per visit</td>
<td>R150.00*</td>
<td>20 patients x 10 visits each. (Patients seen monthly, sometimes every 2 weeks = +/- 10 visits during pregnancy)</td>
<td>30,000.00</td>
</tr>
<tr>
<td>20 patients without a REVEAL (Control)</td>
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<tr>
<td>Costs of ECG</td>
<td>R150.00</td>
<td>R150 x 20 patients (x 10 visits each)</td>
<td>30,000.00</td>
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<td>30,000.00</td>
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<td><strong>Sub-total</strong></td>
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<td><strong>UCT Levy</strong></td>
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<td><strong>Total</strong></td>
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<td><strong>132,000.00</strong></td>
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We will receive additional funding for the technical aspect of the study as ECG data analysis.

*(Recommendation by Medical Research Council of South Africa)*