How to diagnose and manage heart disease in pregnancy & implications for prevention

Karen Sliwa, MD, PhD, DTM&H, FESC, Hatter Institute for Cardiovascular Research in Africa

Department of Medicine & Cardiology, Faculty of Health Sciences, University of Cape Town, South Africa
• **Epidemiology** of heart disease & heart failure in pregnancy & postpartum

• **An approach** to a peripartum women presenting with heart failure

• **Diagnosis** of heart failure in pregnancy & post partum

• **Contributing factors** to heart failure in pregnancy & postpartum

• **Management**

• **Prevention**
### Maternal mortality ratio (per 100,000 live births)

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>2003</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worldwide</strong></td>
<td>283.2 (258.6 to 306.9)</td>
<td>273.4 (251.1 to 296.6)</td>
<td>209.1 (186.3 to 233.9)</td>
</tr>
<tr>
<td></td>
<td>376,034 (343,483 to 407,574)</td>
<td>361,706 (332,230 to 392,393)</td>
<td>292,982 (261,017 to 327,792)</td>
</tr>
<tr>
<td><strong>Annualised rate of change in maternal mortality ratio (%)</strong></td>
<td>−0.3% (−1.1 to 0.6)</td>
<td>−2.7% (−3.9 to −1.5)</td>
<td>−1.3% (−1.9 to −0.8)</td>
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</tbody>
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### Number of maternal deaths

<table>
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### Developed countries

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<tbody>
<tr>
<td><strong>Worldwide</strong></td>
<td>24.5 (23.0 to 26.1)</td>
<td>16.0 (14.9 to 17.0)</td>
<td>12.1 (10.4 to 13.7)</td>
</tr>
<tr>
<td><strong>Annualised rate of change in maternal mortality ratio (%)</strong></td>
<td>−3.3% (−3.8 to −2.8)</td>
<td>−2.9% (−4.2 to −1.5)</td>
<td>−3.1% (−3.7 to −2.5)</td>
</tr>
</tbody>
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### Southern sub-Saharan Africa

<table>
<thead>
<tr>
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<th>1990</th>
<th>2003</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worldwide</strong></td>
<td>150.8 (115.9 to 182.6)</td>
<td>490.4 (367.8 to 626.1)</td>
<td>279.8 (202.6 to 381.5)</td>
</tr>
<tr>
<td><strong>Annualised rate of change in maternal mortality ratio (%)</strong></td>
<td>9.1% (6.5 to 11.8)</td>
<td>−5.6% (−8.1 to −3.0)</td>
<td>2.7% (1.2 to 4.4)</td>
</tr>
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### South Africa

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<tr>
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<th>2013</th>
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</thead>
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<tr>
<td><strong>Worldwide</strong></td>
<td>134.0 (93.3 to 175.2)</td>
<td>341.8 (227.8 to 481.0)</td>
<td>174.1 (96.3 to 274.9)</td>
</tr>
<tr>
<td><strong>Annualised rate of change in maternal mortality ratio (%)</strong></td>
<td>7.2% (3.3 to 11.1)</td>
<td>−6.9% (−11.1 to −2.7)</td>
<td>1.0% (−1.6 to 3.8)</td>
</tr>
</tbody>
</table>

Indirect causes include: Rheumatic heart disease, cardiomyopathy, congenital heart disease


<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Timing of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abort</td>
<td>Haem</td>
</tr>
<tr>
<td>Western Europe</td>
<td>55 (45–62)</td>
</tr>
</tbody>
</table>

Abort = abortion; Haem = Haemorrhage; HPT = hypertension; Obs Lab = obstructed labour; Sep = Sepsis; Indir = Indirect; Anti-P = Antipartum; Intra-P = Intrapartum; Post-P = postpartum

*Indirect causes include: Rheumatic heart disease, cardiomyopathy, congenital heart disease
<table>
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<tr>
<th>CAUSE OF HEART FAILURE</th>
<th>ALL AGES YDL (THOUSANDS)</th>
<th></th>
<th></th>
<th>YLDS ( PER 100 000)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1990</td>
<td>2010</td>
<td>% Δ</td>
<td>1990</td>
<td>2010</td>
<td>% Δ</td>
</tr>
<tr>
<td>Cardiovascular and circulatory diseases</td>
<td>14 373 (11 094–18 134)</td>
<td>21 985 (16 947–27 516)</td>
<td>53 · 0%</td>
<td>53 · 0% 271 (209–342)</td>
<td>319 (246–399)</td>
<td>17 · 7%</td>
</tr>
<tr>
<td>Rheumatic HD</td>
<td>290 (191–412)</td>
<td>420 (278–592)</td>
<td>45 · 1%</td>
<td>5 (4–8)</td>
<td>6 (4–9)</td>
<td>11 · 6%</td>
</tr>
<tr>
<td>Ischaemic HD</td>
<td>894 (609–1236)</td>
<td>1518 (1038–2128)</td>
<td>69 · 9%</td>
<td>17 (11–23)</td>
<td>22 (15–31)</td>
<td>30 · 8%</td>
</tr>
<tr>
<td>Hypertensive HD</td>
<td>292 (202–412)</td>
<td>460 (315–639)</td>
<td>57 · 4%</td>
<td>6 (4–8)</td>
<td>7 (5–9)</td>
<td>21 · 1%</td>
</tr>
<tr>
<td>HF due to Cardiomyopathy including PPCM</td>
<td>272 (183–378)</td>
<td>394 (269–551)</td>
<td>44 · 8%</td>
<td>5 (3–7)</td>
<td>6 (4–8)</td>
<td>11 · 4%</td>
</tr>
<tr>
<td>HF due to endocarditis</td>
<td>42 (28–59)</td>
<td>61 (42–87)</td>
<td>45 · 8%</td>
<td>1 (1–1)</td>
<td>1 (1–1)</td>
<td>12 · 2%</td>
</tr>
<tr>
<td>HF due to other circulatory diseases</td>
<td>183 (123–259)</td>
<td>268 (180–372)</td>
<td>46 · 3%</td>
<td>3 (2–5)</td>
<td>4 (3–5)</td>
<td>12 · 6%</td>
</tr>
</tbody>
</table>

Table: Global years lived with disability (YLDs) for heart failure from a comprehensive list of 289 causes and select sequelae in 1990 and 2010 for all ages, both sexes combined and per 100 000; HD= heart disease, PPCM= Peripartum Cardiomyopathy

An approach to a **peripartum** women presenting with heart failure

**Important Questions**

- **Is the patient known to have an underlying heart disease?**
  - **No** Follow diagnostic algorithm
  - **Yes** Manage according to underlying disease

- **Comorbidities?** Aggravating factors?

- **Weeks of gestation?**
  - **>16 weeks:** Can the patient be stabilized? Intervention needed? Early delivery?
  - **< 16 weeks:** Pregnancy desired? ? Termination

- **Severity of HF?**
Diagnostic Algorithm

Breathless woman in pregnancy/early post partum

- History, clinical examination
- ECG or Natriuretic peptides AND echocardiography

Any abnormalities

- Urgent cardiology review

All normal

Consider non-cardiovascular causes of breathlessness
Manage according to **underlying disease** presenting in HF

- **Rheumatic heart disease**
  - (native valves/operated)
  - Medical therapy
  - Surgery/balloon valvotomy

- **Others**:
  - Marfan’s disease
  - Cardiac sarcoidosis
  - Constritive pericarditis

- **Congenital heart disease**
  - Successfully operated: More imaging needed (e.g., MRI for coartation)?
  - Residual defects?
  - Not operated: Single defects? Complex defects?

- **Cardiomyopathy**
Differential diagnosis

• Patient can have a **known pre-existing heart disease**, such as congenital heart disease, Marfan’s, known cardiomyopathy, known rheumatic heart disease and valve prosthesis.

• Patient can present with a **newly diagnosed heart disease unmasked by pregnancy**, such as rheumatic heart disease, familial cardiomyopathy, undiagnosed rheumatic heart disease.

• Patient can have a **newly developed heart disease**, such as peripartum cardiomyopathy, acute coronary syndrome, gestational hypertension/preeclampsia/severe hypertension, leading to heart failure.
152 consecutive pregnant women assessed at cardiac maternity clinic over a period of 24 months (Sliwa et al. Heart 2014)

Cardiomyopathy (27%)
- PPCM
- DCMO
- HTCMO
- HIVCMO
- ARVC

Rheumatic HD (26%)
- MR
- MS
- mixed MV disease
- MV repair
- MV replacement

Congenital HD (32%)
- ASD
- VSD
- Pul VD
- TOF
- Coarctation
- PDA
- Transposition
- PV return abn
- UV Heart
- Cong. AS
- abn. RCA

Other (15%)
- Marfan
- sev. Arrythmia
- Takayasu
- myxom. Valve/MR
- sev. HT/CVA
- Sarcoid
- Const. Peri.
Mode of Presentation: **Symptoms and signs**

**Most common**
- Dyspnoea (NYHA class III-IV)
- Cough
- Fatigue

**Common**
- Lower extremity edema
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Palpitations
- Dizziness

**Less common**
- Nocturia
- Right upper quadrant pain (hepatic congestion)
- Chest pain
- Postural hypotension
- Syncope

Symptoms can be subtle to dramatic

Highly variable presentation

Often ignored by patients, nurses and doctors
Mode of Presentation: **Acute, dramatic presentation needing circulatory support**

- Left ventricular assisted device (LVAD) may be considered before listing the patient for cardiac transplantation.
- Optimum strategy is not known and discussion between experts on a case-by-case basis may be helpful.
- Thrombotic complications possibly more often because pregnancy is a pro-thrombotic condition.
- Size of device also remains a limiting factor as not all fully implantable devices will fit into a small woman.
Contributing factors to heart failure in pregnancy & postpartum
Contributing factor 1: Maternal Age

Figure: Global maternal mortality ratio in 1990 and 2013, by age. Shaded areas show 95% uncertainty intervals.

Contributing factor 2: **Anemia? Fever? On medication? Underlying infection (e.g. HIV, malaria)? Sepsis?**

- **Plasma volume by 40%**
- **Systemic Vascular resistance**
- **Physiologic anaemia**
- **Transient LV dilatation**
- **Cardiac output by 30 - 50%**
- **Hypercoagulable state**
- **Cardiac output during delivery/postpart**
- **Weeks to months for CO and SVR to normalise**

Maternal adaptation to pregnancy and delivery
**Contributing factor 3: Access to health care**


<table>
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<th>Medium Gini (0.38–0.55)</th>
<th>High Gini (&gt;0.55)</th>
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<tbody>
<tr>
<td>Australia</td>
<td>Argentina</td>
<td>Bolivia</td>
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<tr>
<td>Austria</td>
<td>Bangladesh</td>
<td>Brazil</td>
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<tr>
<td>Belgium</td>
<td>Botswana</td>
<td>Burkina Faso</td>
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<tr>
<td>Canada</td>
<td>Bulgaria</td>
<td>Cameroon</td>
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<tr>
<td>China</td>
<td>Chile</td>
<td>Central African Republic</td>
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<td>Denmark</td>
<td>Costa Rica</td>
<td>Colombia</td>
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<td>Finland</td>
<td>Dominica</td>
<td>Ecuador</td>
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<td>France</td>
<td>Egypt</td>
<td>Gambia</td>
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<td>Great Britain</td>
<td>El Salvador</td>
<td>Guinea</td>
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<td>Greece</td>
<td>Ethiopia</td>
<td>Honduras</td>
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<tr>
<td>Ireland</td>
<td>Ghana</td>
<td>Jamaica</td>
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<tr>
<td>Italy</td>
<td>Guatemala</td>
<td>Lesotho</td>
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<td>Madagascar</td>
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<td>Luxembourg</td>
<td>Indonesia</td>
<td>Mali</td>
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<td>Mongolia</td>
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<td>Trinidad and Tobago</td>
<td>Swaziland</td>
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<td>Turkey</td>
<td>Thailand</td>
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<tr>
<td>Switzerland</td>
<td>Uganda</td>
<td>United Republic of Tanzania</td>
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Contributing factor 3: **Echocardiography**: Left Ventricular Dysfunction often with Mitral Regurgitation and Pulmonary Hypertension
TAPSE: An index of RV function but also a predictor of mortality in cardiomyopathy!

Reduced TAPSE, signifying RV systolic dysfunction, is defined as value of ≤ 14 mm
Medical Treatment of **Heart Failure in peripartum women**

- **Non Pregnant (cardiomyopathy)**: According to standard heart failure guidelines
  - Diuretics
  - Hydralazine
  - Beta Blocker

- **Early Pregnancy**
  - Diuretics
  - Hydralazine
  - Beta Blocker

- **Late Pregnancy**
  - Diuretics
  - Hydralazine
  - Beta Blocker

- **Postpartum**
  - Diuretics
  - Ace-inhibitor
  - Beta blocker

**Effect on fetus**
Overall Management

Cardiac Drugs in Pregnancy
## Medical management of acute and chronic heart failure in pregnancy

<table>
<thead>
<tr>
<th>Drug/Class</th>
<th>Purpose</th>
<th>Comment</th>
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<tbody>
<tr>
<td><strong>DIURETICS</strong></td>
<td></td>
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</tr>
<tr>
<td>Furosemide</td>
<td>Generally reserved for treatment of pulmonary oedema</td>
<td>Can result in uteroplacental hypoperfusion, oligohydramnion, milk production can be reduced. FDA class C*</td>
</tr>
<tr>
<td></td>
<td>Use of lowest possible dose</td>
<td></td>
</tr>
<tr>
<td>Hydrochloro-thiazide</td>
<td>Diuretic</td>
<td>Oligohydramnion, FDA class B</td>
</tr>
<tr>
<td><strong>VASODILATORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Commonly used oral antihypertensive agent in pregnancy</td>
<td>Demonstrated efficacy in hypertension Risk of hypotension; FDA class C</td>
</tr>
<tr>
<td></td>
<td>Can be substituted for ACE inhibitor during pregnancy</td>
<td></td>
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*U.S. Food and Drug Administration (FDA) class: A (controlled studies show no risk), B (no evidence of human risk in controlled studies), C (risk cannot be ruled out), D (positive evidence of risk), X (contraindicated in pregnancy). ACE angiotensin converting enzyme; ARB angiotensin receptor blocker; IUGR intrauterine growth retardation; SVR systemic vascular resistance
Medical management of **acute and chronic heart failure in pregnancy**

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<tr>
<td>Amlodipine</td>
<td>Alternative to ACE inhibitor in pregnancy</td>
<td>Can be used with hydralazine if needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA class C</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Might be used to treat decompensated heart failure</td>
<td>Bradycardia, FDA class B</td>
</tr>
<tr>
<td><strong>BETA BLOCKERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol,</td>
<td>Essential component to chronic heart failure therapy</td>
<td>Controlled studies in pregnant women not available. Risk stratification.</td>
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Medical management of **acute and chronic heart failure in pregnancy**

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<tr>
<td><strong>ACE-INHIBITORS &amp; ALDOSTERONE ANTAGONISTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone, Epleronone</td>
<td>Prolong survival in selected heart failure patients</td>
<td>Antiandrogenic effects, oral clefts; No data to support safety in pregnancy FDA class D</td>
</tr>
<tr>
<td>All ACE-inhibitors &amp; Angiotensin II receptor blocker</td>
<td>Prolongs survival in heart failure patients</td>
<td>Renal dysplasia, growth retardation, ossification disorder of skull, intrauterine fetal death; FDA class D</td>
</tr>
</tbody>
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*U.S. Food and Drug Administration (FDA) class: A (controlled studies show no risk), B (no evidence of human risk in controlled studies), C (risk cannot be ruled out), D (positive evidence of risk), X (contraindicated in pregnancy). ACE angiotensin converting enzyme; ARB angiotensin receptor blocker; IUGR intrauterine growth retardation; SVR systemic vascular resistance*
Cardiac medication during pregnancy, data from the ROPAC

Titia P.E. Ruys, Aldo Maggioni, Mark R. Johnson, Karen Sliwa, Luigi Tavazzi, Markus Schwerzmann, Petros Nihoyannopoulos, Mirta Kozelj, Ariane Marelli, Uri Elkayam, Roger Hall, Jolien W. Roos-Hesselink

Birth weight in patient with and without beta-blockers per WHO class adjusted for gestational age, smoking, fetal sex, maternal age, diabetes and pre-eclampsia.
Contradictory evidence concerning the consequences of b-blocker treatment during pregnancy.
Survey explores effects of b-blocker exposure during pregnancy in a Danish birth cohort comprising all births in Denmark between 1995 and 2008.

Key messages
- Redeeming prescriptions of b-blockers were found to be significantly associated with increased risk of being born SGA, preterm birth and perinatal mortality.
- Confounding factors: Women using beta-blockers had cardiovascular disease.
- Management in South Africa: Continuation of Beta-blockers in pregnancy if EF < 45% but reduction of dose in early pregnancy.
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| **Digoxin** | • Not considered first-line therapy for heart failure in pregnant patients  
• No improvement in mortality | • Generally considered safe, serum levels unreliable in pregnancy;  
• FDA class C |
| **Warfarin** | Risk/benefit ratio needs to be discussed with the patient for treatment and prophylactic anticoagulation in severe left ventricular dysfunction | • First trimester teratogenesis  
• Dosing is complicated in pregnancy  
• FDA class X (contraindicated) |
• 72 reports were included;

• 37 articles (118 well-documented cases) described the prenatal exposure to ACE-Is; and 35 articles (68 cases) described the prenatal exposure to Angiotensin Receptor Antagonists (ARBs).
Results: 48% of the newborns exposed to ACE-Is and 87% of the newborns exposed to ARBs did exhibit any complications (P< 0.0001).

Bullo M et al. Hypertension 2012;60:444-450
Prevalence of fetal renin-angiotensin system blockade syndrome related to a period of exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Bullo M et al. Hypertension 2012;60:444-450
Prevention and Focused Interventions
To be considered:

- the risk of pregnancy and the consequences of an unplanned pregnancy
- the risks of the contraceptive method
- failure rates
- non-contraceptive benefits
- the availability
- individual's preferences
- protection against infection
- costs

In some women with heart disease, the issues may be complex and require the input of both a cardiologist and an obstetrician (or other feto-maternal expert) to identify the optimal approach.
Figure 1
Sketch illustrating different types of contraceptives.

1. Safe period
2. Oral contraception (COC or POP)
3. Injectable (DMPA)
4. Implant
5. Patch
6. Hysteroscopic tubal occlusion
7. Intrauterine contraceptive device
8. Tubal Ligation
9. Diaphragm
10. Vaginal Ring
11. Male condom
12. Vasectomy
Breast feeding

Based on the postulated negative effects of prolactin sub-fragments (*Hilfiker-Kleiner, Cell 2007, Sliwa Eur J Heart Failure 2014*), breastfeeding is not advised in patients with suspected PPCM, even if this practice is not fully evidence-based.

Breast feeding increases cardiac output and is not advisable in very ill women.
Preventing and tackling heart failure in pregnancy and peripartum through awareness creation

Targeting pregnant women

www.hedu-africa.org / www.hatter.uct.ac.za
More information needed!

Original Article

EURObservational Research Programme: a worldwide registry on peripartum cardiomyopathy (PPCM) in conjunction with the Heart Failure Association of the European Society of Cardiology Working Group on PPCM

Karen Sliwa, Denise Hilfiker-Kleiner, Alexandre Mebazaa, Mark C. Petrie,
Aldo P. Maggioni, Vera Regitz-Zagrosek, Maria Schaufelberger, Luigi Tavazzi,
Dirk J. van Veldhuisen, Jolien W. Roos-Hesselink, Ajay J. Shah, Petar M. Seferovic,
Uri Elkayam, Karin van Spaendonck-Zwarts, Katrin Bachelier-Walenta,
Frederic Mouquet, Elisabeth Kraigher-Krainer, Roger Hall, Piotr Ponikowski,
John J. V. McMurray, Burkert Pieske

First published: February 2014  Full publication history
DOI: 10.1002/ejhf.68
Conclusions

• The is a lack of epidemiological data on the factors contributing to cardiovascular disease and specifically heart failure in pregnancy

• Understanding the precursors and preventing heart failure in pregnancy will have the highest impact

• A multi-disciplinary approach including cardiologist, obstetricians, anaesthetists, cardiothoracic surgeons and others should be facilitated

• Large registries will provide new knowledge and improve patient care
Thank you

Hatter Institute for Cardiovascular Research in Africa