Prospective assessment of risk estimation models in pregnant women with congenital heart disease


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No conflicts of interest to disclose
Background

- Women with CHD reach adult age and wish to pursue pregnancy

- Risk of pregnancy varies
  - Underlying disease
  - Clinical condition

- Risk assessment should be performed pre-pregnancy

- Different methods of risk assessment
Objective

ZAHARA II study
Pregnant women with structural CHD followed prospectively

Objective of substudy
Assess and compare the value of different pregnancy risk estimation systems in the ZAHARA II cohort
Methods

Inclusion from March 2008 to February 2010

Baseline data

• Maternal age and parity
• Detailed cardiac and obstetric history
• Present cardiac status
• Medication, smoking
Methods:
Risk estimation models

Risk of maternal cardiovascular events

1. CARPREG predictors and risk score
   Siu 2001

2. ZAHARA I predictors and risk score
   Drenthen 2010

3. Sum of CARPREG and ZAHARA I predictors as well as predictors identified by Khairy
   Khairy 2006

4. WHO risk classification
   (modification according to Thorne)
   WHO 1998
   Thorne 2006

5. Classification according to disease complexity
   (simple, moderately complex and complex CHD)
   Warnes 2001
Definitions 1/3:
Predictors of cardiovascular events

CARPREG
• Prior arrhythmias or cardiac event
• NYHA functional class > II or cyanosis
• Left heart obstruction
• Systemic ventricular dysfunction (EF < 40%)
Siu 2001

ZAHARA I
• Prior arrhythmias
• NYHA functional class > II
• Left heart obstruction
• Cardiac medication before pregnancy
• Systemic AV valve regurgitation
• Pulmonary AV valve regurgitation
• Mechanical valve prosthesis
• Cyanotic heart disease
Drenthen 2010
### Definitions 1/3: Predictors of cardiovascular events

#### CARPREG

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
<th>Total Points</th>
<th>Risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior arrhythmias or cardiac event</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>NYHA functional class &gt; II or cyanosis</td>
<td>1</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>Left heart obstruction</td>
<td>1</td>
<td>&gt;1</td>
<td>75</td>
</tr>
<tr>
<td>Systemic ventricular dysfunction (EF &lt; 40%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Siou 2001*

#### ZAHARA I

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
<th>Total Points</th>
<th>Risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior arrhythmias</td>
<td>1.5</td>
<td>0</td>
<td>2.9</td>
</tr>
<tr>
<td>NYHA functional class &gt; II</td>
<td>0.75</td>
<td>0.5 - 1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Left heart obstruction</td>
<td>2.5</td>
<td>1.51 - 2.50</td>
<td>17.5</td>
</tr>
<tr>
<td>Cardiac medication before pregnancy</td>
<td>1.5</td>
<td>2.51 - 3.50</td>
<td>43.1</td>
</tr>
<tr>
<td>Systemic AV valve regurgitation</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary AV valve regurgitation</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical valve prosthesis</td>
<td>4.5</td>
<td>&gt; 3.51</td>
<td>70.0</td>
</tr>
<tr>
<td>Cyanotic heart disease</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Drenthen 2010*

#### Khairy et al.

- Severe pulmonary regurgitation or subpulmonary ventricular dysfunction
- Smoking history

*Khairy 2006*
Adapted WHO classification for estimating maternal risk of pregnancy.

Class I: No significant elevation of risk
Class II: Small increased risk
Class III: Significantly increased risk
Class IV: Pregnancy is contraindicated

Underlying disease
Presence of more than 1 cardiac disorder
Additional risk factors
Cardiovascular events were recorded during pregnancy and post partum

Defined as in CARPREG and ZAHARA I:
• Arrhythmia (needing treatment)
• Heart failure (needing treatment)
• Thromboembolic events
• Vascular events
Results:
Patient characteristics before pregnancy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All pregnancies n=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at conception (years)</td>
<td>29±4</td>
</tr>
<tr>
<td>Parity 0</td>
<td>61%</td>
</tr>
<tr>
<td>Parity ≥ 1</td>
<td>39%</td>
</tr>
</tbody>
</table>
Results:
Distribution of CHD in ZAHARA II

- Septal Defect: 26%
- Tetralogy of Fallot: 18%
- Aortic Stenosis: 14%
- Right-Sided Obstructive Lesion: 13%
- Coarctation: 12%
- Transposition of the Great Arteries: 8%
- Marfan: 4%
- Ebstein Anomaly: 2%
- Fontan Physiology: 1%
- Other: 3%
Results:
Prevalence of predictors in ZAHARA II

<table>
<thead>
<tr>
<th>Predictor</th>
<th>N</th>
<th>(%)</th>
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<tr>
<td>CARPREG</td>
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</tbody>
</table>
| • Prior cardiac event or arrhythmia                                       | 13  | (8.2)
| • NYHA functional class > II or cyanosis                                 | 2   | (1.3)
| • Left heart obstruction                                                 | 10  | (6.3)
| • Systemic ventricular dysfunction (EF < 40%)                            | 2   | (1.3)
| ZAHARA I                                                                 |     |      |
| • History of arrhythmias                                                 | 11  | (6.9)
| • Cardiac medication before pregnancy                                   | 20  | (12.6)
| • NYHA functional class > II                                             | 2   | (1.3)
| • Left heart obstruction (PG > 50 mmHg or AVA < 1.0 cm²)                 | 1   | (0.6)
| • Systemic AV valve regurgitation (moderate/severe)                      | 4   | (2.5)
| • Pulmonary AV valve regurgitation (moderate/severe)                     | 7   | (4.4)
| • Mechanical valve prosthesis                                            | 8   | (5.0)
| • In origin cyanotic heart disease (corrected and uncorrected)           | 44  | (27.7)
| Khairy                                                                    |     |      |
| • Severe pulmonary regurgitation or depressed subpulmonary ventricular ejection fraction | 18  | (11.3)
| • Smoking history                                                         | 29  | (18.2)
## Results:
### Prevalence of predictors in ZAHARA II

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</table>

Siu 2001

Drenthen et al. 2010

Khairy et al. 2006

Khairy et al. 2006
Results: Disease complexity and WHO class

Complexity of CHD

- Simple CHD: 29%
- Moderate Complex CHD: 56%
- Complex CHD: 17%

WHO Class

- WHO 1: 22%
- WHO 2: 55%
- WHO 3: 22%
- WHO 4: 0.6%
Results:
Expected and Observed cardiovascular events

Total cardiovascular events: 13/159 (8.2%)

ZAHARA I
\[ y = 0.67x + 4.36 \]
\[ R^2 = 0.92 \]

CARPREG
\[ y = 0.38x + 4.46 \]
\[ R^2 = 0.99 \]
Results:

\[ y = 3,6397e^{0,5884x} \]

\[ R^2 = 0,9852 \]

Observed cardiovascular events (%) vs. Total number of predictors
(CARPREG, ZAHARA I and Khairy)
## Results:

<table>
<thead>
<tr>
<th>Disease complexity</th>
<th>ZAHARA II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed cardiovascular events</td>
</tr>
<tr>
<td>Simple</td>
<td>2/46 (4.3%)</td>
</tr>
<tr>
<td>Moderate complex</td>
<td>6/89 (6.7%)</td>
</tr>
<tr>
<td>Complex</td>
<td>4/17 (23.5%)</td>
</tr>
<tr>
<td>Not possible to score</td>
<td>1/7 (14.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>ZAHARA II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed cardiovascular events</td>
</tr>
<tr>
<td>WHO 1</td>
<td>0/35 (0.0%)</td>
</tr>
<tr>
<td>WHO 2</td>
<td>4/88 (4.5%)</td>
</tr>
<tr>
<td>WHO 3</td>
<td>8/35 (22.9%)</td>
</tr>
<tr>
<td>WHO 4</td>
<td>1/1 (100.0%)</td>
</tr>
</tbody>
</table>
Results:
ROC of risk estimation systems

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZAHARA I</td>
<td>0.72</td>
<td>0.01</td>
</tr>
<tr>
<td>WHO Classification</td>
<td>0.80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total no of Cardiovascular Predictors</td>
<td>0.70</td>
<td>0.02</td>
</tr>
<tr>
<td>Disease Complexity</td>
<td>0.65</td>
<td>0.07</td>
</tr>
<tr>
<td>CARPREG</td>
<td>0.59</td>
<td>0.29</td>
</tr>
</tbody>
</table>
Conclusions

• All risk estimations show increase in risk with increasing class, risk score or number of predictors

• Adapted WHO classification performs overall best in our cohort

• ZAHARA I risk score and the total number of predictors are equally valuable in predicting pregnancy risk

• CARPREG risk score and disease complexity perform poorly in estimating the risk of cardiovascular events in our cohort
The ZAHARA II investigators

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M.A. Oudijk
A.C.C. Van Oppen

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### Number of events

<table>
<thead>
<tr>
<th>CARPREG Expected cardiovascular event rate</th>
<th>ZAHARA II Observed primary cardiovascular event rate</th>
<th>ZAHARA I Expected cardiovascular event rate</th>
<th>ZAHARA II Observed cardiovascular event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>9/135 (6.7%)</td>
<td>2.9%</td>
<td>4/83 (4.8%)</td>
</tr>
<tr>
<td>27%</td>
<td>3/21 (14.3%)</td>
<td>7.5%</td>
<td>2/56 (3.6%)</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>1/3 (33.3%)</td>
<td>17.5%</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43.1%</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70%</td>
<td>5/10 (50%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of cardiovascular predictors found by Khairy et al.</th>
<th>ZAHARA II Observed cardiovascular event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9/117 (7.7%)</td>
</tr>
<tr>
<td>1</td>
<td>4/36 (11.1%)</td>
</tr>
<tr>
<td>2</td>
<td>0/6 (0%)</td>
</tr>
<tr>
<td>3</td>
<td>0/0 (0%)</td>
</tr>
</tbody>
</table>