Original research

Pregnancy outcome in thoracic aortic disease data from the Registry Of Pregnancy And Cardiac disease

Laurence Campens, Lucia Baris, Nandita S. Scott, Craig S Broberg, Antione Bondue, Guillaume Jondeau, Jasmine Grewal, Mark R Johnson, Roger Hall, Julie De Backer, Jolien W Roos-Hesselink

On behalf of the ROPAC investigators group

INTRODUCTION

Aortic complications during pregnancy are particularly a concern in women with underlying connective tissue diseases such as Marfan syndrome (MFS), vascular Ehlers-Danlos syndrome (vEDS), Loeys-Dietz syndrome (LDS) and SMAD3 aortopathy. Women with congenital heart malformations such as bicuspid aortic valve (BAV) have a higher incidence of aortic dissection (AD) and aortic wall in pregnant women with aortopathies.

METHODS

The ESC EORP Registry Of Pregnancy And Cardiac disease (ROPAC) is a prospective global registry that enrolled 5739 women with pre-existing cardiac disease. This analysis reports on 58% of patients and 6% had a history of aortic dissection. Four patients, of whom three were patients with MFS, had an acute aortic dissection (three type A and one type B aortic dissection) without maternal or fetal mortality.

RESULTS

Thoracic aortic disease was reported in 189 women (3.3%). Half of them were patients with Marfan syndrome (MFS), 26% had a BAV, 8% Turner syndrome, 2% vascular Ehlers-Danlos syndrome and 11% had no underlying genetic defect or associated congenital heart defect. Aortic dilatation was reported in 58% of patients and 6% had a history of aortic dissection. Four patients, of whom three were patients with MFS, had an acute aortic dissection (three type A and one type B aortic dissection) without maternal or fetal mortality.

CONCLUSION

This ancillary analysis provides the largest prospective data review on pregnancy risk for patients with thoracic aortic disease. Overall pregnancy outcomes in women with thoracic aortic disease followed according to current guidelines are good.

ABSTRACT

Background Cardiovascular disease is the leading cause of death during pregnancy with thoracic aortic dissection being one of the main causes. Thoracic aortic disease is commonly related to hereditary disorders and congenital heart malformations such as bicuspid aortic valve (BAV). Pregnancy is considered a high risk period in women with underlying aortopathy.

Methods The ESC EORP Registry Of Pregnancy And Cardiac disease (ROPAC) is a prospective global registry that enrolled 5739 women with pre-existing cardiac disease. With this analysis, we aim to study the maternal and fetal outcome of pregnancy in women with thoracic aortic disease.

Results Thoracic aortic disease was reported in 189 women (3.3%). Half of them were patients with Marfan syndrome (MFS), 26% had a BAV, 8% Turner syndrome, 2% vascular Ehlers-Danlos syndrome and 11% had no underlying genetic defect or associated congenital heart defect. Aortic dilatation was reported in 58% of patients and 6% had a history of aortic dissection. Four patients, of whom three were patients with MFS, had an acute aortic dissection (three type A and one type B aortic dissection) without maternal or fetal mortality.

No complications occurred in women with a history of aortic dissection. There was no significant difference in median fetal birth weight if treated with a beta-blocker or not (2960 g (2358–3390 g) vs 3270 g (2750–3570 g), p value 0.25).

Conclusion This ancillary analysis provides the largest prospective data review on pregnancy risk for patients with thoracic aortic disease. Overall pregnancy outcomes in women with thoracic aortic disease followed according to current guidelines are good.

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Aortic and vascular disease

In this substudy, we focus on patients with aortic disease including (1) women with known heritable thoracic aortic disease (HTAD) in particular MFS, vEDS or TS or with BAV (not associated with one of the former conditions) with and without aortic dilatation/dissection and (2) women without one of the prespecified HTAD or BAV, but with aortic dilatation or previous aortic dissection, grouped under the term ‘Thoracic Aortic Dilatation/Dissection—TAD’. Because no specification of the exact location of aortic dilatation was requested in the questionnaires, we used the term ascending aorta throughout the paper referring to the ascending part of the thoracic aorta comprising both the root and tubular ascending aorta. No cutoff values for aortic dilatation were given in the questionnaires where the indication of aortic dilatation was left to the discretion of the including physician.

The following endpoints were studied: death; cardiovascular events: aortic dissection (type A and B), need for aortic surgery or intervention; obstetric complications: pregnancy-induced hypertension, (emergent) caesarean section (CS), premature birth and small for gestational age.

Details on ethical approval have been described previously.10

Statistical analysis

Data are presented as mean values and SD if normally distributed and as median with IQR if skewed. Categorical data are presented as count divided by the total number of valid/available data and percentages between brackets.

RESULTS

Baseline characteristics

Thoracic aortic disease was reported in 189 out of 5739 women (3.3%) included in the registry from 2007 until 2018. More than half of these were patients with MFS followed by patients with BAV. Prior to pregnancy, ascending aortic dilatation was documented in all 81 patients, in 49 cases no data were available (tables 1 and 2).

Table 1  Baseline characteristics (prior to pregnancy) for each diagnostic group

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number included</th>
<th>MFS N=100</th>
<th>BAV N=49</th>
<th>TS N=16</th>
<th>vEDS N=14</th>
<th>TAD N=20</th>
<th>Total N=189</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median (IQR))</td>
<td>29.1 (25.4–32.8)</td>
<td>31.2 (25.4–34.3)</td>
<td>30.2 (27.6–34.3)</td>
<td>28</td>
<td>31.5 (28.5–36.5)</td>
<td>31.5 (29.6–36.9)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Nulliparity</td>
<td>5/100 (5.7%)</td>
<td>18/48 (38%)</td>
<td>10/16 (63%)</td>
<td>2/4 (50%)</td>
<td>12/20 (60%)</td>
<td>99/188 (53%)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>12/97 (12%)</td>
<td>3/49 (6%)</td>
<td>4/16 (25%)</td>
<td>1/4 (25%)</td>
<td>4/15 (27%)</td>
<td>5/78 (6%)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Smoking (former smoker)</td>
<td>4/40 (10%)</td>
<td>1/6-36</td>
<td>0/315</td>
<td>1/4 (25%)</td>
<td>1/6-315</td>
<td>6-191/4</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>BMI (median (IQR))</td>
<td>22 (20.4–24.7)</td>
<td>25.3 (21.9–30.7)</td>
<td>27.3 (24.3–30.8)</td>
<td>24.4 (20.4–28.4)</td>
<td>24.5 (22.2–26.5)</td>
<td>24.5 (22.2–26.5)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Emerging country</td>
<td>19/100 (19%)</td>
<td>18/49 (37%)</td>
<td>0/16</td>
<td>0/4</td>
<td>3/20 (15%)</td>
<td>40/189 (21%)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Aortic dilatation</td>
<td>1/59 (6.9%)</td>
<td>24/42 (57%)</td>
<td>1/16</td>
<td>0/3</td>
<td>15/20 (75%)</td>
<td>81/189 (43%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Dimension AA in mm (median (IQR))</td>
<td>40 (35–45)</td>
<td>42 (40-44.3)</td>
<td>42 (42-42)</td>
<td>/</td>
<td>41.5 (39.3–46.8)</td>
<td>42 (38–45)</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Prior aortic dissection</td>
<td>5/100 (5%)</td>
<td>0/42</td>
<td>0/16</td>
<td>1/4 (25%)</td>
<td>5/20 (25%)</td>
<td>11/182 (6%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Categorical variables are presented as count divided by the total number of valid/available data and percentages between brackets.
were on atenolol during pregnancy, the other women (of whom we have data) were treated with propranolol, labetalol, bisoprolol, celiprolol or metoprolol (56/91).

We have data) were treated with propranolol, labetalol, bisoprolol, celiprolol or metoprolol (56/91).

Cardiovascular complications
Four patients (2%) had an acute aortic dissection during pregnancy or in the postpartum period. Three were type A dissections requiring urgent surgical intervention and one type B aortic dissection that was treated conservatively. There was no maternal mortality. The patient with the type B dissection had known MFS and was treated with beta-blockers before and throughout pregnancy. Her ascending aorta was moderately dilated up to 43 mm prior to pregnancy with a small insignificant increase of the diameter of 2 mm measured by echocardiography, descending thoracic aortic dimensions were not available. She presented with a type B aortic dissection in the third trimester. The three patients with type A dissections were not known with MFS or aortic dilatation prior to pregnancy and were thus not presented with a type B aortic dissection in the third trimester.

Obstetric and fetal outcome
Overall, we observed a high CS rate of 63% (86/137), but it was not performed more in women with aortic dilatation versus women with normal aortic dimensions (p=0.37). Half (29/58) of the patients with MFS underwent an elective CS and 16% (9/58) urgent CS, (one patient with type A and one with type B aortic dissection, one due to aortic dilatation, five for obstetric reasons). All patients with vEDS (4/4) underwent an elective CS and 69% (11/16) of the women with TS had a CS (7 elective and 4 urgent for non-cardiac reasons). All but one patient with previous aortic dissection had a CS of whom two urgent (one because of fetal distress and one for unknown reason).

No significant difference of pregnancy-induced hypertension or pre-eclampsia was noticed between the different disease groups (total of four women with pregnancy-induced hypertension and four with pre-eclampsia, p=0.68 and p=0.85, respectively).

There were no fetal deaths. The median gestational age was 38 weeks (37–39 weeks). Median birth weight was 2980 g (2660–3450 g) and median birth weight centile11 50th (22–77.5th).

There was no significant difference in birth weight and birth weight centile in women treated with a beta-blocking agent compared with untreated women (2960 g (2358–3390 g) vs 3270 g (2750–3570 g), p value=0.25 and 46.5th (12.5–76th) vs 44th centile (19.5–69th), p value=0.96). No significant differences were found in rates for intrauterine growth retardation or preterm birth.

DISCUSSION
The purpose of the ROPAC registry was to study maternal and fetal outcomes in pregnant women with structural and ischaemic heart disease, pulmonary arterial hypertension and aortic disease. It is the largest prospective dataset to date. Pregnancy outcomes collected over a 10-year period in 5739 pregnancies were recently published. Patients with aortic disease constituted a relatively small subgroup within this registry.

The spectrum of thoracic aortic disease included in ROPAC was broad. Half of the women included were patients with MFS who had the highest rate of cardiovascular complications during pregnancy and peripartum period. Despite this, the rate of aortic dissection was low (3/100) in those with MFS and no admissions for congestive heart failure were reported. All three aortic dissections in the patients with MFS occurred during the last trimester or shortly postpartum underscoring the risk for aortic dissection during the peripartum period. Only one of these three patients was known to have MFS prior to pregnancy. This

Table 2 Baseline characteristics (prior to pregnancy) for patients with and without aortic dilatation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No aortic dilatation</th>
<th>Aortic dilatation* N=81</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median (IQR))</td>
<td>28.3 (25.7–32.3)</td>
<td>31.1 (28.1–34.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>31/59 (53%)</td>
<td>42/81 (52%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11/59 (19%)</td>
<td>9/81 (10%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Smoking (current-former)</td>
<td>3/59 (5%)</td>
<td>1-10/62</td>
<td>0.51</td>
</tr>
<tr>
<td>BMI (median (IQR))</td>
<td>24.2 (20.5–27.9)</td>
<td>23.7 (21.3–27.8)</td>
<td>0.98</td>
</tr>
<tr>
<td>Aortic diameter</td>
<td>41 (39–46.5)</td>
<td>42 (38–46.5)</td>
<td></td>
</tr>
<tr>
<td>Prior aortic dissection</td>
<td>5/59 (8%)</td>
<td>3/81 (4%)</td>
<td>0.36</td>
</tr>
<tr>
<td>A</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>BAV</td>
<td>14/27</td>
<td>27/81 (33%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Valvular intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>8 (6M, 2F)</td>
<td>3 (1B, 2T)</td>
<td></td>
</tr>
<tr>
<td>Mitral</td>
<td>5 (1M, 1B, 3T)</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td>27/49 (55%)</td>
<td>14/27 (52%)</td>
<td>0.81</td>
</tr>
<tr>
<td>ACE-I</td>
<td>3/55 (5.5%)</td>
<td>0/30</td>
<td>0.55</td>
</tr>
<tr>
<td>ARB</td>
<td>0/47</td>
<td>1/25 (4%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1/55</td>
<td>0/30</td>
<td>1.0</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0/23</td>
<td>0/9</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Categorical variables are presented as count divided by the total number of valid/available data and percentages between brackets.

*Presence of aortic dilatation at moment of inclusion.

Data on aortic dilatation were missing in 49 cases.

ACE-I, ACE inhibitor; ARB, angiotensin receptor blocking agent; BAV, bicuspid aortic valve; B, bioprosthesis; BB, beta-blocking agent; M, mechanical valve; R, valve repair; VKA, vitamin K antagonist.

Table 3 Characteristics of patients presenting with aortic dissection during pregnancy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pregnancy duration</th>
<th>Type of dissection</th>
<th>Diagnosis</th>
<th>AA diameter</th>
<th>Therapy during pregnancy (prior to dissection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>26 weeks</td>
<td>A</td>
<td>?</td>
<td>60 mm</td>
<td>None</td>
</tr>
<tr>
<td>Patient 2</td>
<td>37 weeks</td>
<td>B</td>
<td>MFS (known)</td>
<td>45 mm</td>
<td>BB</td>
</tr>
<tr>
<td>Patient 3</td>
<td>37 weeks</td>
<td>A</td>
<td>MFS (not known)</td>
<td>55 mm</td>
<td>None</td>
</tr>
<tr>
<td>Patient 4</td>
<td>1 week pp</td>
<td>A</td>
<td>MFS (not known)</td>
<td>?</td>
<td>None</td>
</tr>
</tbody>
</table>

7, unknown; AA, ascending aortic; BB, beta-blocking agent; MFS, Marfan syndrome; pp, postpartum.
It is widely accepted to treat pregnant patients with MFS with beta-blockers. The 2018 pregnancy guidelines advise that beta-blocking agents should be considered throughout pregnancy in women with MFS and other HTAD and indicate that it is the preferred therapy in the case of coexistent arterial hypertension. In ROPAC, only 51% of pregnant women with MFS with aortic dilatation were treated with a beta-blocker. Birth weight tended to be lower when the mother had been treated with a beta-blocking agent, although this was not significant. Retrospective data from the UK demonstrate beta-blocker use in 64.2% of pregnant women with MFS with significant lower birth weight in patients on beta-blocking agents. Again, more prospective data are needed in order to draw definite conclusions.

There was a strikingly high rate of delivery by CS in this cohort (63%). All patients with vEDS had an elective CS as recommended by the guidelines. Most Turner women also had a CS for unclear indications, most presumably related to small body size of the mother. There are limited data on the effect of labour, specifically the active phase of labour on the risk of aortic dissection. Although CS is considered an attractive option as it is scheduled and changes of maternal haemodynamics are less compared with labour, vaginal delivery is the preferred mode of delivery in the majority of patients with cardiovascular disease due to lower risk of infection, bleeding and morbidity postpartum. Data recently published by Minsart et al suggested that vaginal delivery with rigorous pain control and avoidance of the Valsalva manoeuvre might be safe in women with MFS and an aortic root diameter ≤45 mm. However, further research addressing the mode and timing of delivery in TAD is necessary.

A dedicated ROPAC registry (ROPAC 3) for patients with aortic pathology has been initiated recently within the EORP with the aim of more accurately assessing the risks and outcomes during pregnancy. Some important issues, not yet included in ROPAC 1–2, are addressed such as data on aortic growth during pregnancy, dimensions of the distal aorta, details on genetic data and family history of aortic dissection.

CONCLUSION

The aortic dissection rate in women with thoracic aortic disease included in the ROPAC registry was low with good maternal and fetal outcomes. In three out of four women (75%) with aortic dissection, this occurrence was the first presentation of the underlying disease. This highlights the importance of early recognition of the diagnosis and preconception counselling in order to achieve better pregnancy outcome. Type A dissections in patients with MFS occurred at diameters above the 45 mm guideline recommendation, suggesting a relatively safe margin. However, this does not exclude the risk for type B dissections. Complete aortic imaging prior to pregnancy in patients with MFS by CT scanning or MRI is therefore advised. In this registry, the use of beta-blockers was surprisingly low with no significant effect on birth weight, whereas CS rates were high despite lack of supporting data. If a woman after preconception counselling decides to pursue pregnancy despite the risks, close proximity to a tertiary care centre with experienced obstetricians, anaesthesiologists, cardiac surgeons and cardiologists with serial follow-up throughout pregnancy and the postpartum period with an individualised plan for delivery is advised.

LIMITATIONS

ROPAC only includes a small fraction of all the women with MFS or other aortopathy. On the one hand, it may be biased by the overrepresentation of an acute event allowing recognition of type B dissections irrespective of aortic root dimensions. Two of these women were found to carry a pathogenic variant because the underlying (genetic) diagnosis was not known. Postterm uterine rupture was 9.2% and 2.6%, respectively.
Aortic and vascular disease

Acknowledgements EROP oversight Committee, ROPAC Executive Committee (see online supplemental appendix 1). Data collection was conducted by the EROP department from the ESC by Elin Folkesson Lefrancq as Project Officer; Viviane Missiaen, Gérard Gracia and Sébastien Authier as Data Managers. Overall activities were coordinated and supervised by Dr Aldo P Maggioni (Scientific Coordinator). Data have been presented at the congress of the European Society of Cardiology in 2019. Julie De Backer was a senior clinical researcher by the Research Foundation Flanders and by a Grant for Medical Research from the Baillie Foundation.


of the aortopathy and on the other hand the sample is inherently biased towards aortopathy patients who may inherently be considered more safe for pregnancy.

No genetic or HTAD-specific phenotypic data or details on family history were available in the database. It is likely that the diagnosis of MFS was based on clinical manifestations in some cases. Patients with genetic TAD entities, overlapping with MFS such as LDS or Aneurysm Osteoarthropathy Syndrome may have inadvertently been included in the MFS group.

A threshold hour to define aortic dilatation was not specifically defined in the questionnaires, it was only defined in the form of ‘dilatation yes/no’ and dimensions were often not provided. The number of patients with aortic dilatation may therefore be underestimated. Nor was the exact location of aortic dilatation (root or tubular ascending aorta) prespecified in the questionnaires—we used the term ‘ascending aorta’ to keep uniformity throughout the paper.

Another limitation is that a registry relies on correct and complete collection of questionnaires by the enrolling centres, data on baseline characteristics are unfortunately missing in some cases. Also data on previous aortic interventions and complications that may have occurred were not often provided.

Author affiliations
1 Department of Cardiology, Ghent University Hospital, Gent, Belgium
2 Cardiology Department, Erasmus Medical Center, Rotterdam, Netherlands
3 Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA
4 Department of Cardiology, Ghent University Hospital, Gent, Belgium
5 Department of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada
6 Department of Cardiology, CUB Hôpital Erasme, Université Libre de Bruxelles, Bruxelles, Brussels, Belgium
7 Department of Cardiology, CRMR Syndrome of Marfan and Apparenters, Bichat-Claude Bernard Hospital, Université de Paris, INSERM U1148, Paris, France
8 Department of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada
9 Department of Metabolism, Digestion and Reproduction, Imperial College London, Chelsea and Westminster Hospital, London, UK
10 Department of Cardiology, University of East Anglia, Faculty of Medicine, Norwich Research Park, Norwich, UK
11 Center for Medical Genetics, Ghent University Hospital, Gent, Belgium

Twitter Julie De Backer @judbacke


Key messages

What is already known on this subject?
► Several retrospective data indicate a pregnancy-related risk for aortic dissection in women with aortopathy. However, these data are biased by the overrepresentation of an acute event allowing recognition of the aortopathy.

What might this study add?
► This ancillary analysis of the Registry Of Pregnancy And Cardiac disease registry provides the largest prospective data review on pregnancy risk for patients with a wide range of thoracic aortic disease who elect to pursue pregnancy. The overall complication rate was low with favourable maternal and fetal outcomes.

How might this impact on clinical practice?
► A multidisciplinary approach with serial follow-up in expert centres throughout pregnancy and the postpartum period with an individualised plan for delivery is advised in women with thoracic aortic disease.
Aortic and vascular disease


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ORCID iDs

Laurence Campens http://orcid.org/0000-0002-5045-2449
Jasmine Grewal http://orcid.org/0000-0001-7312-6278
Julie De Backer http://orcid.org/0000-0001-8878-1507
Jolien W Roos-Hesselink http://orcid.org/0000-0002-6770-3830

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