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

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## 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.

## 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, but also women with Turner syndrome (TS) and congenital heart malformations like bicuspid aortic valve (BAV) may be more prone.<sup>12</sup>

Data obtained from the GenTAC registry on MFS show a significantly higher aortic dissection rate of 5.4 per 100 person-years during pregnancy and the postpartum period compared with a non-pregnancy

dissection rate of 0.6 per 100 patient-years.<sup>3</sup> However, data on the immediate and long-term effects of pregnancy on aortic outcome are not uniform due to publication and ascertainment biases, reports on small sample sizes and inclusion of women in whom dissection was the first presentation of the underlying disease.<sup>13</sup>

Multiple factors impact the aorta during pregnancy. Increased haemodynamic stress and structural changes of the vascular wall may weaken the aortic wall in pregnant women with aortopathies.<sup>4–8</sup> The increased risk for aortic complications persists in the postpartum period, but clear management guidelines for this period are lacking.

Current guidelines advocate the use of beta-blockers in women known with underlying aortic disease throughout pregnancy to prevent complications, but the evidence supporting this is weak and the effect on fetal growth needs further research.<sup>9</sup> Atenolol has been associated with higher rates of fetal growth retardation. In contrast, metoprolol, labetalol, bisoprolol, propranolol and celiprolol in case of vEDS may be used safely during pregnancy, although caution with regard to fetal growth remains warranted.<sup>9</sup>

Use of large prospective datasets can help in addressing these specific issues and in determining the impact of pregnancy in women with aortic disease. In 2007, the Registry Of Pregnancy And Cardiac disease (ROPAC) was established by the EURObservational Research Programme (EORP) of the European Society of Cardiology (ESC) in order to provide contemporary information on the impact of pregnancy on a wide range of cardiovascular diseases. With this ancillary analysis, we aim to study the pregnancy outcome of women with thoracic aortic disease.

## METHODS

The rationale and design of the ROPAC have been described previously.<sup>10</sup> In brief, the registry started in January 2007. Women with structural heart disease from 60 hospitals in 28 countries (both developed and developing countries) were enrolled. It collected the following data relating directly to the pregnancy: age at conception, cardiovascular complications, obstetric complications, fetal complications, medication use, pregnancy duration and mode of delivery.



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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 cut-off 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.<sup>10</sup>

### 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. Differences in variables between diagnostic groups were evaluated by Student's t-test, Mann-Whitney U test, analysis of variance, Kruskal-Wallis test and  $\chi^2$  test where appropriate. Data analyses were performed with SPSS V.27.0. A p value of <0.05 (two-sided test) was considered significant. Complete-case analysis was performed.

### Patient and public involvement

Patients were not involved in the design, conduct, reporting or dissemination plans of our research.

## 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 81 patients, in 49 cases no data were available (tables 1 and 2). Eleven patients had a history of aortic dissection—10 type A dissections (5 patients with MFS and 5 patients with TAD of which 2 had a traumatic dissection) and 1 type B dissection in a patient with vEDS. Data on the extent of the dissection and type of surgery was not available. One patient with vEDS underwent stenting for a ruptured superior femoral artery 1 year before pregnancy. Seventeen women underwent a valvular intervention prior to pregnancy of which seven had a mechanical valve (one mitral and six aortic valves (one Bentall)). In five patients, prior valve sparing ascending aortic replacement was indicated in the questionnaire.

Data on left ventricular function were reported in 119 cases of which 3 (2.5%) had a decreased ejection fraction prior to pregnancy. Two of these had a mildly impaired ejection fraction of 49% and 50%, respectively (one patient with MFS and one patient with TAD) and one patient with MFS had a moderate reduced ejection fraction of 35% treated with furosemide and a beta-blocking agent preconception.

Forty-nine per cent (20/41) and 51% (21/41) of the women with MFS known to have aortic dilatation were treated with a beta-blocking agent preconception and during pregnancy, respectively. Two out of the four included patients with vEDS were on beta-blockers (but none on celiprolol). Five women

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

Diagnosis	MFS N=100	BAV N=49	TS N=16	vEDS N=4	TAD N=20	Total N=189	P value
Age (median (IQR))	29.1 (25.4–32.8)	31.1 (25.4–34.3)	30.2 (27.6–34.3)	28	31.1 (28.5–36.5)	31.5 (29–36.9)	0.17
Nulliparity	57/100 (57%)	18/48 (38%)	10/16 (63%)	2/4 (50%)	12/20 (60%)	99/188 (53%)	0.18
Arterial hypertension	12/97 (12%)	3/48 (6%)	4/16 (25%)	1/4 (25%)	4/19 (21%)	24/184 (13%)	0.33
Smoking (current-former)	4-10/76	1-6/36	0-3/15	1-0/4	0-0/13	6-19/144	0.32
BMI (median (IQR))	22 (20.4–24.7)	25.3 (21.9–30.7)	27.3 (24.3–30.8)	22.4 (20–29.4)	24.5 (22.2–26.5)	24.5 (22.2–26.5)	0.01
Emerging country	19/100 (19%)	18/49 (37%)	0/16	0/4	3/20 (15%)	40/189 (21%)	0.01
Aortic dilatation	41/59 (69%)	24/42 (57%)	1/16 (6%)	0/3	15/20 (75%)	81/140 (58%)	<0.001
Dimension AA in mm (median (IQR))	40 (35–45)	42 (40–44.3)	42 (42–42)	/	41.5 (39.3–46.8)	42 (38–45)	0.68
Prior aortic dissection	5/100 (5%)	0/42	0/16	1/4 (25%)	5/20 (25%)	11/182 (6%)	<0.001
A	5				5	10/11	
B				1		1/11	
BB	4/5			1/1	2/2		
BAV	4/96 (4%)	49	1/16 (6%)	0/4	0	54/185 (29%)	<0.001
Valvular intervention	9/34 (26%)	6/17 (35%)	0/3	0/1	2/9 (22%)	17/64 (27%)	0.92
Aortic	4 (1M, 1B, 2?)	6 (3M, 1B, 2R)	/	/	2 (2M)	12 (6M, 2B, 2R, 2?)	
Mitral	5 (1M, 1B, 3?)	/	/	/	/	5 (1M, 1B, 3?)	
Treatment							
BB	27/54 (50%)	5/18 (28%)	4/7 (57%)	2/2 (100%)	6/10 (60%)	44/91 (48%)	0.037
ACE-I	1/49 (0.02%)	1/18 (0.06%)	0/7	0/3	1/13 (0.08%)	3/90 (0.03%)	0.34
ARB	1/47 (0.02%)	0/18	0/7	0/2	0/13	1/87 (0.01%)	0.56
Diuretics	1/49 (0.02%)	0/18	0/7	0/3	0/13	0/90	0.93
VKA	4/17 (24%)	4/8 (50%)	0/1	0/0	1/7 (14%)	9/33 (15%)	0.59

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

?, unknown; AA, ascending aorta; ACE-I, ACE inhibitor; ARB, angiotensin receptor blocking agent; B, bioprosthesis; BAV, bicuspid aortic valve; BB, beta-blocking agent; IQR, interquartile range; M, mechanical valve; MFS, Marfan syndrome; OAC, oral anticoagulation; R, valve repair; TAD, thoracic aortic aneurysms and dissections; vEDS, vascular Ehlers-Danlos syndrome; VKA, vitamin K antagonist.

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

	Ascending aortic dilatation* N=81	No aortic dilatation† N=59	P value
Age (median (IQR))	31.1 (28.1–34.3)	28.3 (25.7–32.3)	0.01
Nulliparity	42/81 (52%)	31/59 (53%)	0.59
Hypertension	9/81 (10%)	11/59 (19%)	0.18
Smoking (current-former)	1-10/62	3-7/54	0.51
BMI (median (IQR))	23.7 (21.3–27.8)	24.4 (20.5–27.9)	0.98
Aortic diameter	42 (38–46.5)	/	/
Prior aortic dissection	3/81 (4%)	5/59 (8%)	0.36
A	3	5	
B	/	/	
BAV	27/81 (33%)	18/59 (31%)	0.72
Valvular intervention			
Aortic	8 (6M, 2R)	3 (1B, 2?)	
Mitral	5 (1M, 1B, 3?)	/	
Treatment			
BB	27/49 (55%)	14/27 (52%)	0.81
ACE-I	3/55 (5.5%)	0/30	0.55
ARB	0/47	1/25 (4%)	0.35
Diuretics	1/55	0/30	1.0
VKA	9/23 (39%)	0/9	0.035

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.

were on atenolol during pregnancy, the other women (of whom we have data) were treated with propranolol, labetalol, bisoprolol, celiprolol or metoprolol (56/91).

In total, nine women were treated with oral vitamin K antagonists, seven of which had a mechanical valve, the indication in two women was unknown. Demographic characteristics for each diagnostic group and for patients with or without aortic dilatation are described in tables 1 and 2, respectively.

### 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 under medical attention. In two of them, the diagnosis of MFS was made following the acute event. One of them presented

with dissection 1 week postpartum (aortic diameter not known) and the second one presented at 37 weeks of gestation, with an ascending aortic diameter of 55 mm. The last patient experienced a type A aortic dissection at an ascending aortic diameter of 60 mm at 26 weeks of gestation. Data are summarised in table 3.

### 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 centile<sup>11</sup> 50th (22–77.5th). There was no significant difference in birth weight and in 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.<sup>12</sup> 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.<sup>3 13 14</sup> Only one of these three patients was known to have MFS prior to pregnancy. This

**Table 3** Characteristics of patients presenting with aortic dissection during pregnancy

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

?, unknown; AA, ascending aorta; BB, beta-blocking agent; MFS, Marfan syndrome; pp, postpartum.

supports previous data that the awareness for preconception diagnosis of MFS is not common in women with pregnancy-associated aortic dissection.<sup>1</sup> Data from the GenTAC registry showed a high prevalence of pregnancy-related aortic dissections in MFS of up to 7.4%, of which only 42% was aware of the diagnosis prior to pregnancy.<sup>3</sup> Due to its retrospective design, it is assumable that there might have been an inclusion bias in the GenTAC registry. The same limitation may have played a role in ROPAC, although patients were prospectively included in the ROPAC registry three women were enrolled due to the occurrence of aortic dissection during index pregnancy.

Currently, there is no consensus at which dimension to recommend prophylactic aortic surgery preconception. European guidelines advise against pregnancy in patients with MFS with an aortic root diameter of >45 mm. Dissection rates below the threshold of 45 mm are low with prospective studies including patients with MFS with an aortic diameter ≤45 mm not reporting any cases of aortic dissections.<sup>14</sup> A positive family history of dissection and rapid root growth >3 mm/y are however important risk factors to consider in the pre-pregnancy counselling.<sup>9</sup>

Unfortunately, even if preconception prophylactic aortic surgery is performed, this does not reduce the risk of vascular complications in other territories with a reported type B dissection rate in patients with MFS between 5.4% and 10% outside of pregnancy.<sup>15 16</sup> This underscores the importance of imaging of the entire aorta prior to pregnancy in patients with MFS.<sup>9</sup> Type B dissections might occur irrespective of aortic root dimensions.<sup>17 18</sup> Data from a retrospective multicentre observational study reporting on pregnancy outcome in 151 patients with MFS with 258 pregnancies documented type B dissection in four patients (1.6%)—one of these patients had previously undergone aortic root replacement.<sup>19</sup>

The next largest patient population in this registry were women with BAV. Fifty-seven per cent had aortic dilatation (24/42), but no aortic complications occurred. The reported dissection rate during pregnancy in BAV patients ranges from 0% to 4%.<sup>20</sup> In total, 16 women with TS were included. Unlike in MFS, much less is known about the risk of pregnancy-related aortic complications in TS. Underlying congenital and acquired cardiovascular anomalies including BAV, coarctation of the aorta or aortic dilation were present in the majority of published cases of aortic dissection.<sup>21</sup> In the current analysis, none of the 16 women with TS experienced any cardiovascular event. Four had known preconception arterial hypertension and one had a BAV. Aortic dilatation was documented in one patient (with an ascending aorta diameter of 42 mm—aortic size index 21.6 mm/m<sup>2</sup>).

Although last ESC guidelines contraindicated pregnancy in women with vEDS, four patients were enrolled, but no adverse events occurred.<sup>9 22</sup> A retrospective analysis by Murray *et al*<sup>23</sup> reported a pregnancy-related maternal mortality rate of 4.9% per delivery. The prevalence of arterial dissection/rupture and uterine rupture was 9.2% and 2.6%, respectively.

Eleven per cent (20/189) of women were classified as ‘TAD’ because the underlying (genetic) diagnosis was not known. Post hoc, two of these TAD women were found to carry a pathogenic variant in a HTAD gene (one in *SMAD3* and one in *TGFBR2*). It is possible that more of the women in the TAD group had an underlying genetic disorder explaining the presence of aortic dilatation/dissection in women of such a young age. Indeed, the presence of a pathogenic variant might predict a worse outcome, which is an important issue in the care for these patients with TAD.<sup>24</sup>

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.<sup>9</sup> 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.<sup>19</sup> 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,<sup>4</sup> 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*<sup>18</sup> 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



## 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.

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 Osteoarthritis Syndrome may have inadvertently been included in the MFS group.

A threshold diameter to define aortic dilatation was not specifically defined in the questionnaires, it was only filled in as ‘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 completion 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 often not provided.

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## Appendix 1.

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