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# Aortic Complications Associated with Pregnancy in Marfan Syndrome: The NHLBI GenTAC Registry

**Roman: Pregnancy Risk in Marfan Syndrome**

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## ABSTRACT

Background: The risk of aortic complications associated with pregnancy in women with Marfan syndrome (MFS) is not fully understood.

Methods and Results: MFS women participating in the large National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) were evaluated. Among 184 women with MFS in whom pregnancy information was available, 94 (51%) had a total of 227 pregnancies. Among the women with pregnancies, 10 (10.6%) experienced a pregnancy-related aortic complication (4 Type A and 3 Type B dissections, one coronary artery dissection, and 2 with significant [≥3 mm] aortic growth. Five of seven aortic dissections, including all 3 Type B, and the coronary dissection (75% of all dissections) occurred in the post-partum period. Only 5 of 8 women with pregnancy-associated dissection were aware of their MFS diagnosis. The rate of aortic dissection was higher during the pregnancy and post-partum period (5.4 per 100 person-years vs. 0.6 per 100 person-years of non-pregnancy, rate ratio 8.4 [95% C.I. = 3.9, 18.4], p<0.0001).

Conclusions: Pregnancy in MFS is associated with an increased risk of aortic dissection, both Types A and B, particularly in the immediate post-partum period. Lack of knowledge of underlying MFS diagnosis before aortic dissection is a major contributing factor. These findings underscore the need for early diagnosis, pre-pregnancy risk counselling, and multi-disciplinary peri-partum management.

Key Words: aneurysm; aortic disease; aortic dissection; Marfan syndrome; pregnancy and postpartum



## INTRODUCTION

Estimates of the risk of cardiovascular complications, primarily aortic dissection, associated with pregnancy in women with Marfan syndrome (MFS) have varied widely. Complication rates may be systematically overstated due to publication bias, ascertainment bias, case reports or small sample size, and inclusion of women whose aortic dissection precedes and results in the diagnosis of MFS. Women who are aware of their underlying diagnosis may receive pre-pregnancy counseling, choose to forego pregnancy, have careful monitoring and take beta blockers during pregnancy, or undergo prophylactic aortic surgery in anticipation of pregnancy, if indicated.

In addition, few serial imaging data to permit correlation of aortic diameters with risk of progressive dilatation and/or dissection associated with pregnancy are available. As a consequence, recommendations regarding aortic root dimensions above which pregnancy is discouraged vary (1-5) and are based on limited historical imaging data (1-2). Furthermore reported event rates may be confounded by pre-pregnancy counseling.

The NHLBI-sponsored National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) offers an opportunity to address some of these limitations by providing comprehensive information on a large population of well-characterized patients with MFS.

## METHODS

Study Population The rationale and design of the GenTAC have been previously described (6). In brief, GenTAC was established as a longitudinal observational cohort study of individuals with genetically-triggered thoracic aortic aneurysm. Between 2006 and 2014, 3700 participants were enrolled in the original 6 centers (Johns Hopkins University, Baylor College of Medicine, Oregon Health & Sciences University, University of Pennsylvania, University of Texas Health Science Center at Houston, Weill-Cornell Medical College) and the 2 additional centers (National Institute of Aging-Harbor Hospital, Queen's Medical Center) added in the second phase (7). Standardized data collection included clinical information, patient questionnaire, imaging studies, and details of surgical interventions. A Core Phenotyping Laboratory provided validation of eligibility diagnoses. Institutional Review Board approval was obtained for this study at each of the 8 participating GenTAC regional clinical centers. Individual informed consent was obtained from each GenTAC Registry patient.

At the conclusion of registry enrollment (December 31, 2013), 893 patients with Marfan syndrome had been enrolled in the GenTAC database, of whom 298 were women over the age of 17 years. Of these, 184 (62%) who completed and returned the Enrollment Patient Questionnaire and included information on presence or absence of pregnancy and form the basis for the current analyses. Requested information for each pregnancy included age at pregnancy, outcome of pregnancy, and complications during and following pregnancy, including aortic dissection and aortic growth.

Based on questionnaire responses, as well as data on pre-enrollment occurrence of aortic dissection or prophylactic aortic surgery provided by the clinical centers, more detailed information was requested regarding all women with aortic complications. Aortic complications were defined as aortic dissection, excessive aortic growth (≥ 3 mm) during pregnancy, need for prophylactic proximal aortic surgery due to large or rapidly-expanding aneurysm. Since virtually all pregnancies preceded enrollment in the GenTAC registry, imaging data regarding peri-partum aortic diameters were not systematically available. In those women who indicated significant aortic growth had occurred during pregnancy in the Patient Questionnaire, supporting data was retrospectively requested from the clinical center. Data

regarding medication use during pregnancy, the method of delivery and breast feeding were not available.

Statistical Analysis Demographic and phenotypic characteristics of never-pregnant and ever-pregnant women with Marfan syndrome were compared using independent samples t-test for continuous variables and Fisher's exact test for categorical variables. In order to determine age-adjusted rates of aortic surgery and dissection, the period of exposure to need for prophylactic aortic surgery and acute aortic dissection was calculated by subtracting 15 (presumed age at which pregnancy and associated dissection risk might begin) from the age of enrollment in GenTAC (to determine the number of years of risk before enrollment) and multiplying by the number of women in the given group. Pregnancy exposure was considered to occupy one year, including the 3-month post-partum period. 95% confidence intervals were generated using the log of the rate ratio and the standard error of its log, and then calculating the exponential. Rate ratios were compared using a generalized linear model with a Poisson probability distribution and a log link function.

## RESULTS

Pregnancies Among 184 women in whom pregnancy information was available, 94 (51%) reported a total of 227 pregnancies (mean 2.5, median 2.0, range 1-6). Average maternal age was 29 and ranged from 13 to 43 years (2 women who had pregnancies before the age of 18 are included in the analysis). Pregnancy outcomes included 147 live births (two sets of twins), 3 still births, 30 miscarriages, 38 abortions, 3 ectopic pregnancies, and 3 ongoing pregnancies; 3 did not respond to the outcome question on the survey. Pregnancy was complicated by hypertension in 19, diabetes in 1, and premature rupture of membranes in 6. Woman who completed the patient questionnaire were older at the time of enrolment (42 vs. 36 years, p=0.002) and more likely to have had Type B aortic dissection and prophylactic surgery than those who did not complete the questionnaire, however the latter differences were eliminated when adjusted for differences in age.

Comparison of Never-Pregnant and Ever-Pregnant Women Demographic and phenotypic features of ever-pregnant and never-pregnant Marfan women are compared in Table 1.

Women who never became pregnant were significantly younger at age of Marfan diagnosis and at enrollment into GenTAC. Although heights were similar, never-pregnant women weighed significantly less. Average systemic score was higher in the never pregnant women. Phenotypic features that differed between the two groups included a significantly higher proportion with arachnodactyly, both wrist and thumb signs, and pes planus in never-pregnant women. In addition, never-pregnant women tended to have a higher proportion with thoracic skeletal abnormalities such as pectus carinatum and kyphosis.

At the time of GenTAC enrollment, ever-pregnant women were more likely to have had a previous aortic dissection (25/94 [27%] vs. 13/90 [14%], p=0.047) and more likely to have undergone prophylactic proximal aortic surgery (13/94 [14%] vs. 4/90 [4%], p=0.04). Prophylactic proximal surgery in ever-pregnant woman followed rather than preceded pregnancy in all instances. Ever-pregnant women who had an aortic dissection were less likely than never-pregnant women to be aware of their Marfan diagnosis before their dissection (8/25 [32%] vs. 10/13 [77%], p=0.016). Among the women who had not undergone proximal aortic surgery at time of registry entry and in whom imaging data were available (n=53), there were no differences in aortic root dimensions (3.9±0.47 vs. 4.0±0.56 cm, p=0.44) or aortic root Z scores (3.4±1.75 vs. 3.4±2.27, p=0.92) in never-pregnant vs. ever-pregnant women, respectively, including following adjustment for differences in age between the two groups.

Aortic Complications Associated with Pregnancy Among the 94 women with at least one pregnancy, 10 (10.6%) developed an aortic complication in the peri-partum period (defined as pregnancy and 3 months post-partum), including 4 Type A dissections, 3 Type B dissections, 2 with significant (≥3 mm) aortic growth, and one coronary artery dissection. Details of these complications are presented in Table 2. Of note, all 3 Type B dissections, two of the Type A dissections, and the coronary artery dissection (overall 75% of dissections) occurred in the post-partum period.

Knowledge of Marfan Diagnosis before Pregnancy and Before Aortic Dissection Among the 94 ever-pregnant women, only 42% were aware of their diagnosis before their first pregnancy. 5 of the 8 women who experienced pregnancy-related aortic or coronary dissections were aware of

their diagnosis before the event. Aortic dissections occurred in 17 the 84 ever-pregnant women but were not pregnancy-related, 8 of whom were aware of their diagnosis before the occurrence of the aortic dissection. Among the 90 never-pregnant women in whom 13 aortic dissections occurred, 10 were aware of their diagnosis before the dissection occurred. Thus 12 of 30 (40%) non-pregnancy-related dissections occurred in women who were unaware of their diagnosis whereas 60% occurred following the diagnosis.

Comparison of Ever-Pregnant Women with and without Aortic Complications Demographic and phenotypic features of pregnant women who did not have aortic complications are compared to those who did have complications in Table 3. There were no significant differences between the 2 groups. In addition, the mean number of pregnancies did not differ between those without and with aortic complications (2.5 vs. 2.4, p=0.82). Use of beta-blocking agents was more common at the time of enrollment in those with complications (50% vs. 13%, p=0.012).

Impact of Pregnancy on Rates of Aortic Dissection and Prophylactic Surgery The rate of prophylactic proximal aortic surgery among ever-pregnant women was 0.43 per 100 patient years (95% C.I. = 0.198, 0.668) and 0.20 per 100 patient-years (95% C.I. = 0.004, 0.405) among never-pregnant women, rate ratio = 2.12 (95% C.I. = 0.690-6.494), p=NS. Aortic dissection rates associated with pregnancy and the post-partum period were significantly higher than non-pregnancy dissection rates: 5.4 per 100 person-years (95% C.I. 1.7, 9.2) vs. 0.6 per 100 patient-years (95% C.I. = 0.42-0.87), rate ratio = 8.4 (95% C.I. = 3.9-18.4), p<0.0001.

## DISCUSSION

The GenTAC Registry represents the largest analysis to date of pregnancy risk in women with Marfan syndrome. Our results underscore the risk of the peri-partum period for aortic dissection. The rates of aortic dissections unrelated and related to pregnancy (0.6 and 5.4 per 100 patient-years) noted in the GenTAC Registry far exceed recently-published population-based rates of aortic dissection among women (0.0024 per 100 patient-years in Oxfordshire, UK [8] and 0.0029 per 100 patient-years in Emilia-Romagna, Italy [9]). The lack of knowledge of underlying Marfan syndrome diagnosis in almost 50% of registry women with aortic dissection related to pregnancy is a common finding in the existing literature and underscores the need

for early diagnosis, pre-pregnancy risk counselling, and multi-disciplinary peri-partum management (5,10).

The early literature on pregnancy risk in women with Marfan syndrome is limited to publication of single case reports (11-14) or very small series (15-17). In addition, the diagnosis of Marfan syndrome was not always firmly established, but presumptive based on non-specific skeletal features (12, 16-17) or in the setting of underlying bicuspid aortic valve (15), a known risk factor for aortic aneurysm and dissection. Furthermore, some women with a firm diagnosis of Marfan syndrome at the time might have actually had Loeys-Dietz syndrome which had not yet been described and may carry a higher risk of dissection than Marfan syndrome. In contrast, Marfan diagnosis in the present study was based on systematic application of revised Ghent criteria (18) with central review by the GenTAC Phenotyping Core.

The first large series, published in 1981 with the goal of providing a more representative assessment of pregnancy risk, included 105 pregnancies in 26 women with Marfan syndrome seen at the Johns Hopkins Medical Genetics Clinic (1). 12 of these 26 women had evidence of cardiovascular disease (heart murmurs in 6, mitral prolapse in 2, "some degree of aortic dilatation" in 3, and palpitations in 1). Three of the 12 women had cardiovascular complications (transient murmur, progressive heart failure due to severe mitral regurgitation, atrial tachycardia); there were no aortic complications. The number of women having echocardiograms was not provided but none were reported to have aortic root diameters over 42 mm. Based on these data, Pyeritz recommended against pregnancy in women with aortic diameters over 40 mm (1).

A subsequent prospective study of 45 pregnancies in 21 women with MFS evaluated at Johns Hopkins between 1983 and 1992 noted aortic dissections in 3 women (19), one Type B dissection at 20 weeks gestation (previously published as a case report by Mor-Yosef at al. [16]), a Type A dissection misconstrued as rapid aortic expansion until elective surgery post-partum, and distal extension of a previous Type A dissection operated upon before pregnancy and occurring post-partum in the setting of intravenous drug use. Importantly, echocardiographic

surveillance was performed in 22 of 28 pregnancies carried through the third trimester with "little or no change in aortic root diameter during pregnancy."

More recent studies have provided somewhat more comprehensive peri-partum imaging data to permit better assessment of risk of aortic complications. In a Dutch study of 127 women with MFS evaluated between 1993 and 2004, 61 had been pregnant, of whom 23 women with 33 pregnancies had aortic dimensions determined by echocardiography (only 10 before and after pregnancy) (4). Only one woman, with a previous Type A dissection, developed a Type B dissection during her second pregnancy. Nine of the other 22 women had aortic root diameters ≥40 mm (range 40-45 mm) with insignificant pregnancy-associated diameter change. Based on these data, the authors suggested that pregnancy in the absence of pre-existing aortic dissection is safe up to 45 mm.

The most comprehensive study to date including imaging data involved 69 women with a total of 199 pregnancies evaluated in Salt Lake City (5); 32 of these women were aware of their Marfan diagnosis, had not had previous aortic surgery, and were followed prospectively for a total of 52 pregnancies. In 14 pregnancies (27%), aortic root diameter was ≥40 mm. Although there were no aortic peri-partum complications, women who had been pregnant were more likely to receive prophylactic aortic surgery than the 29 never-pregnant women (13.0 vs. 6.5%, p=0.03), similar to findings in the current study. However, because women in our study who had had pregnancies were older than those who had never been pregnant, there was no significant difference between the two groups in annual rate of proximal aortic surgery. None of the 69 women with pregnancies in the Salt Lake City study experienced a peri-partum dissection, and none of the nulliparous women experienced aortic dissection. Lower rates of aortic dissection in these women compared to GenTAC women may be due to older age in the latter cohort and hence longer duration of exposure.

Lack of knowledge of the underlying diagnosis of Marfan syndrome was common in pregnancy-associated aortic dissection in the GenTAC Registry as well as in earlier reports. In an English registry including 36 women with Marfan syndrome, 6 women had pregnancy-related complications (20). Three of four women with acute dissections and both women with

rapid aortic expansion necessitating post-partum surgery were unaware of their Marfan diagnosis before their pregnancies. In a letter survey sent to members of the Dutch Marfan Association, five aortic dissections occurred in 44 women, only three of whom were aware of their diagnosis (21). In a retrospective analysis of a French outpatient Marfan clinic, 7 of 85 women suffered a peri-partum aortic complication, only three of whom were aware of their diagnosis (22). The same group followed 18 women prospectively using standardized guidelines, including serial echocardiography, beta-blockade therapy, and tailored delivery approaches (10). The sole aortic dissection occurred in a woman referred at 35 weeks of pregnancy with an aortic diameter of 47 mm who had an acute Type A dissection at 37 weeks just before a planned cesarean delivery. In the current study, the significantly earlier age at diagnosis of Marfan syndrome in the never-pregnant group (13±11 vs. 27±17 years) may have influenced recommendations and decisions regarding reproduction.

Marfan syndrome is classically associated with proximal aortic dilatation; accordingly, Type A dissections are much more common than dissections exclusively involving the distal aorta. Among 100 Marfan patients with aortic dissection, 80% involved the ascending aorta whereas 20% were isolated to the descending aorta (23). Strikingly similar results were reported in a Swiss population, wherein initial aortic dissection was Type A in 77% and Type B in 23% (24). Thus, it is noteworthy that 3 of the 7 aortic dissections in our series were Type B dissections, all of which occurred in the post-partum period and none of which were associated with previous proximal aortic surgery. Although cardiac output is increased during pregnancy due to increases in stroke volume and heart rate, substantial further increases occur in association with labor and delivery, potentially further increasing pulsatile stress on the aorta. Type B dissections have been described in previous reports (4, 13-16, 21, 22); of these, 5 of 8 were post-partum. Reports of post-partum Type A dissection are less common (21, 25), including one of 3 in our series.

Study Limitations There are several potential limitations to the current study. Although aortic dissection is unlikely to go unrecognized and miscategorized, the prevalence of significant aortic growth may be underestimated due to reliance on the patient questionnaire. However, all such instances reported on patient questionnaire were further explored through clarification by site

investigators. In addition, we did not collect systematic peri-partum imaging data since the pregnancies predated participation in the registry (average age of pregnancy 29 years vs. average age at enrollment of 47 years). The lack of systematic peri-partum imaging data in the GenTAC cohort precludes assessment of pregnancy risk based on aortic dimensions. Another limitation includes the lack of systematic information about peripartum medication use and lactation given the retrospective ascertainment of pregnancy data. Although the sites involved in GenTAC were, of necessity, referral centers for patients with genetically-mediated thoracic aortic aneurysms, each site made every effort to recruit all eligible patients as evidenced by the large number of total enrollees. Unfortunately GenTAC did not include funding for genotyping; however, any participants whose clinical genetic testing identified mutations in genes other than fibrillin 1 would have had their diagnosis changed from Marfan syndrome to the appropriate alternative diagnosis. Furthermore the GenTAC Phenotyping Core Laboratory at Johns Hopkins University provided standardization and validation of diagnoses. FBN-1 mutations were documented in 16 ever-pregnant and 11 never-pregnant women in the present study.

Conclusions Pregnancy in women with Marfan syndrome is associated with an 8-fold increase in risk of aortic dissection, both types A and B, particularly in the post-partum period. The current data support a recommendation for general cardiac check-up with echocardiographic assessments of the aortic root and ascending aorta prior to planned pregnancy or during unplanned pregnancy. Our findings also suggest that peri-partum ultrasound imaging should additionally include the descending thoracic aorta, although evidence that aneurysmal dilatation precedes Type B dissection is lacking. Lack of knowledge of underlying Marfan syndrome contributes to the risk of aortic complications during pregnancy. These findings underscore the need for early diagnosis, pre-pregnancy risk counselling, and multi-disciplinary peri-partum management.



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**Table 1: Comparison of Demographic and Phenotypic Features in Never-Pregnant vs. Ever-Pregnant Women**

| | Never-Pregnant (n=90) | Ever-Pregnant (n=94) | P value |
|---|---|---|---|
| Age at Diagnosis (years) | 13±11 | 27±17 | <0.0001 |
| Age at Enrollment (years) | 37±13 | 47±13 | <0.0001 |
| Height at Enrollment (cm) | 176±9 | 177±8 | 0.45 |
| Weight at Enrollment (kg) | 70.7±14 | 76.8±15 | 0.007 |
| SBP at Enrollment (mmHg) | 118±13 | 117±15 | 0.72 |
| DBP at Enrollment (mmHg) | 69±10 | 69±14 | 0.95 |
| Arm Span (cm) | 176±24 | 175±28 | 0.97 |
| Lower Segment (cm) | 91±16 | 91±14 | 0.81 |
| Pectus Carinatum (%) | 34 | 24 | 0.08 |

| | | | |
|---|---|---|---|
| Pectus Excavatum (%) | 26 | 24 | 0.62 |
| Scoliosis (%) | 62 | 59 | 0.44 |
| Kyphosis (%) | 24 | 15 | 0.10 |
| Pes planus (%) | 53 | 38 | 0.04 |
| Lumbosacral dural ectasia (%) | 22 | 21 | 0.88 |
| Spontaneous pneumothorax (%) | 11 | 12 | 0.90 |
| Striae atrophicae (%) | 57 | 48 | 0.23 |
| Wrist Sign (%) | 61 | 44 | 0.0047 |
| Thumb Sign (%) | 65 | 46 | 0.0015 |
| Ectopia Lentis (%) | 47 | 43 | 0.46 |
| Myopia >4 diopters (%) | 31 | 22 | 0.18 |
| Mitral Prolapse (%)* | 65 | 63 | 0.52 |
| Systemic Score | 6.5±2.8 | 5.2±3.2 | 0.0025 |

Abbreviations: SBP=systolic blood pressure; DBP=diastolic blood pressure; *Ascertained from standardized Clinical Evaluation Form.

**Table 2: Aortic Complications Associated with Pregnancy**

| Patient | Pregnancy Age | Complication | Timing of Complication | Medication Use | Knowledge of Diagnosis | Outcome |
|---|---|---|---|---|---|---|
| 1 | 36 | Type A dissection | Peri-partum | Beta blocker | Yes | Dissection discovered after delivery with subsequent surgery |
| 2 | 35 | Type A dissection | Third trimester | No | No | Emergency Caesarian section followed by aortic surgery |
| 3 | 34 | Type A dissection | 6 days post-partum | No | No | Emergency aortic surgery |
| 4 | 25 | Type A dissection | 3 days post-partum | Other BP lowering drug | Yes | Emergency aortic surgery |
| 5 | 36 | Type B dissection | 6 weeks post-partum | Beta blocker | Yes | Elective surgery for expanding aneurysm |
| 6 | 29 | Type B dissection | 3 days post-partum | Unknown | Yes | Emergency aortic surgery |
| 7 | 27 | Type B dissection | 1 day post-partum | No | No | Elective surgery 5 years later |
| 8 | 33 | Left main coronary artery dissection | 2 weeks post-partum | No | Yes | Emergency coronary bypass surgery |

| | | | | | | |
|---|---|---|---|---|---|---|
| 9 | 28 | Aortic growth (3.6 to 4.0 cm) | Pregnancy | None | Yes | Subsequent surgery for Type A dissection |
| 10 | 34 | Aortic growth (4.7 to 5.3 cm) | Pregnancy | Beta blocker | Yes | Caesarian section; aortic surgery 6 months post-partum |

**Table 3: Comparison of Demographic and Phenotypic Features in Pregnant Women without vs. with Aortic Complications***

| | No Aortic Complication (n=84) | Aortic Complications (n=10) | P value |
|---|---|---|---|
| Age at Diagnosis (years) | 27±16 | 22±11 | 0.31 |
| Age at Enrollment (years) | 47±14 | 42±13 | 0.26 |
| Age at First Pregnancy (years) | 26±6 | 25±8 | 0.55 |
| Number of Pregnancies | 2.5±1.4 | 2.4±1.1 | 0.89 |
| Height at Enrollment (cm) | 177±8 | 177±9 | 0.91 |
| Weight at Enrollment (kg) | 77.0±15 | 74.2±14 | 0.60 |
| SBP at Enrollment (mmHg) | 117±14 | 118±13 | 0.73 |
| DBP at Enrollment (mmHg) | 70±13 | 66±10 | 0.06 |
| Arm Span (cm) | 175±25 | 179±24 | 0.76 |
| Lower Segment (cm) | 91±15 | 92±16 | 0.98 |
| Pectus carinatum (%) | 34 | 24 | 1.0 |
| Pectus excavatum (%) | 23 | 50 | 0.12 |
| Scoliosis (%) | 62 | 70 | 0.74 |
| Wrist Sign (%) | 48 | 40 | 0.75 |
| Thumb Sign (%) | 49 | 50 | 1.0 |
| Ectopia Lentis (%) | 46 | 40 | 0.75 |
| Mitral Prolapse (%)† | 75 | 70 | 0.29 |

Abbreviations: SBP=systolic blood pressure; DBP=diastolic blood pressure. *Coronary artery dissection patient is included in this group. †Ascertained from standardized Clinical Evaluation Form.