Beta-Blocker Use during Pregnancy Correlates with Less Aortic Root Dilatation in Patients with Marfan Syndrome

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Aorta (Stamford) 2023;11:63–70.

Abstract

Background Pregnant patients with Marfan syndrome (MFS) are at an increased risk for adverse aortic outcomes. While beta-blockers are used to slow aortic root dilatation in nonpregnant MFS patients, the benefit of such therapy in pregnant MFS patients remains controversial. The purpose of this study was to investigate the effect of beta-blockers on aortic root dilatation during pregnancy in MFS patients.

Methods This was a longitudinal single-center retrospective cohort study of females with MFS who completed a pregnancy between 2004 and 2020. Clinical, fetal, and echocardiographic data were compared in patients on- versus off-beta-blockers during pregnancy.

Results A total of 20 pregnancies completed by 19 patients were evaluated. Beta-blocker therapy was initiated or continued in 13 (65%) of the 20 pregnancies. Pregnancies on beta-blocker therapy experienced less aortic growth compared with those off-beta-blockers (0.10 [interquartile range, IQR: 0.10–0.20] vs. 0.30 cm [IQR: 0.25–0.35]; $p = 0.03$). Using univariate linear regression, maximum systolic blood pressures (SBP), increase in SBP, and absence of beta-blocker use in pregnancy were found to be significantly associated with greater increase in aortic diameter during pregnancy. There were no differences in rates of fetal growth restriction between pregnancies on- versus off-beta-blockers.

Conclusion This is the first study that we are aware of to evaluate changes in aortic dimensions in MFS pregnancies stratified by beta-blocker use. Beta-blocker therapy was found to be associated with less aortic root growth during pregnancy in MFS patients.

Keywords
- Marfan syndrome
- pregnancy
- beta-blockers
- aorta
- aortic dilation

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received
June 2, 2022
accepted after revision
April 7, 2023
accepted manuscript online
April 13, 2023

DOI https://doi.org/10.1055/a-2072-0469.
ISSN 2325-4637.

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

Introduction

Marfan syndrome (MFS) is an inherited connective tissue disorder that affects the cardiovascular, skeletal, and ocular systems. MFS is most commonly caused by autosomal dominant inheritance of a mutation in the *fibrillin-1* (*FBN1*) gene on chromosome 15, although sporadic mutations in *FBN1* can also occur.[1] Cardiovascular complications of MFS include mitral valve prolapse with or without regurgitation, progressive aortic dilation occurring predominantly in the area of the root, and aortic dissection, which is the leading cause of morbidity and mortality.[2]

Pregnancy is associated with an increased risk for adverse aortic outcomes, and this risk is amplified among females with MFS.[3–5] Aortic root growth rate is accelerated during pregnancy in MFS patients as compared with the nonpregnant state, often without return to prepregnancy baseline.[6] This is in contrast to the general population, where aortic root diameter remains stable throughout pregnancy.[7] Risk factors for adverse aortic outcomes in pregnancy include preconception aortic root diameter of 40 mm or greater, progression of aortic root dilatation, decreased cardiac function, and hypertension.[5,8] Studies have suggested use of prophylactic beta-blockers in patients with MFS to slow aortic root dilation and prevent adverse aortic outcomes.[9] The proposed mechanisms for beta-blocker benefit in MFS include reduction in the amplitude of aortic wave reflections and reduction in the heart rate (HR), both contributing to decrease the forces impacting the aortic wall.[10] Despite the high risk of adverse aortic outcomes during pregnancy in patients with MFS, data supporting beta-blocker use in pregnancy are limited, and the recommendation for its use needs to be balanced with potential fetal side effects.[11] The purpose of this study was to explore the potential effects of beta-blocker therapy on blood pressure and adverse aortic outcomes in pregnant individuals with MFS.

Materials and Methods

Study Population

This was a longitudinal single-center retrospective cohort study of females with MFS who completed a pregnancy. University of Washington Institutional Review Board (IRB) approval was granted, and patients were identified using the electronic medical record between January 2004 and March 2020. Requirement for patient consent was waived by the IRB. For inclusion, patients had to meet the specific criteria, which consisted of confirmed diagnosis of MFS (Ghent nosology),[12] at least one blood pressure measurement prior to, during, and after pregnancy, and a transthoracic echocardiogram performed prior to, during, and after pregnancy.

Twenty-three pregnancies were identified in 22 females with MFS, and of those, three individuals were excluded due to prior prophylactic aortic root replacement. For the others, each pregnancy was considered as a separate event.

Demographic, anthropometric, imaging, pharmacological, and fetal data were collected. Baseline systolic blood pressure (SBP) was defined as the most recent blood pressure recorded in the 6-month period prior to pregnancy during an outpatient visit. Maximum SBP was defined as the highest value recorded during pregnancy. Blood pressure was not measured in every trimester; therefore, we elected to use maximum blood pressure and increase in blood pressure in pregnancy as a surrogate of hypertension in pregnancy.

All echocardiograms were performed at the University of Washington Montlake campus. They were accessed and measurements of the aortic root were performed at the level of the sinuses of Valsalva using standardized technique by one of the investigators (J.B.).[13] Measurements were reread by the investigator, who was blinded to the original read. The original reads were then compared with the investigator's read, and intraobserver variability was assessed by percent error of the mean (the difference between the two measurements was divided by the mean of those two measurements) and by intraclass correlation coefficient (ICC) using a random effects model measuring absolute agreement. An ICC of $\geq$0.75 was deemed acceptable intra- or interobserver variability.

Fetal growth data during pregnancy were extracted from the medical records to screen for fetal growth restriction (FGR), which was defined as an estimated fetal weight or fetal abdominal circumference of $<$10th percentile for current gestational age noted during ultrasound measurements during the second and third trimesters. Small for gestational age (SGA) outcomes were also assessed, and SGA was defined as birthweight less than 10th percentile for gestational age.

The hypothesis of the study was that beta-blocker usage would be associated with less aortic root growth, and the primary exposure was defined as beta-blocker use before or during pregnancy. Patients taking beta-blockers ("on-beta-blockers group") were compared with those who were not taking beta-blocker therapy prior to or during pregnancy ("off-beta-blockers group"). Prophylactic beta-blocker use was defined as preventative use in patients with MFS as a means to slow aortic growth rate independent of comorbid hypertension. The primary outcome was change in aortic root diameter as measured on transthoracic echocardiogram. Secondary outcomes included change in blood pressure during pregnancy, search for predictors of aortic root growth, as well as fetal outcomes including FGR and SGA.

Statistical Analysis

Statistical analysis was performed in R using the base package and gtsummary. ►**Fig. 2** was produced using the ggplot2 package. Descriptive statistics were summarized using median and interquartile range (IQR) for continuous variables and percentages for categorical variables. Comparisons between the two groups stratified by beta-blocker use was made using the Wilcoxon rank sum test for continuous variables and the Fisher's exact test for categorical variables. Univariate linear regression was used to assess predictors of change in aortic diameter. Beta coefficients were reported per unit change for continuous variables in regression analysis. A p-value of $<$0.05 was considered statistically significant. This study was approved by the University of Washington IRB prior to the initiation of the study.

Results

Twenty pregnancies in 19 patients, all aware of their diagnosis of MFS prior to the pregnancy event, were evaluated. Of the 20 pregnancies, beta-blocker therapy was initiated or continued during 13 pregnancies (65%) and was not used in 7 (35%; ►**Table 1**). In those pregnancies that used a beta-blocker, 9 initiated the therapy prior to pregnancy, 1 during the second trimester, and 3 during the third trimester. Beta-blocker therapy was initiated for all patients due to diagnosis of MFS. Three patients initiated beta-blocker treatment at weeks 28, 28, and 30, due to unwillingness to take the medication in the first and second trimesters. In those who were taking a beta-blocker prior to pregnancy, an equivalent dose[14] of 25 mg of metoprolol succinate was used in all cases, and the maximum beta-blocker dose during pregnancy was an equivalent dose of 75 mg metoprolol succinate (IQR: 50–75 mg). All 13 patients who were started on a beta-blocker received this drug prophylactically for diagnosis of MFS, whereas none carried a prior diagnosis of hypertension.

Demographics and Baseline Cardiovascular Characteristics of Patients with and without Beta-Blocker Use in Pregnancy

Cohort demographics during the pregnancies by beta-blocker therapy at any point during pregnancy are presented in ►**Table 1**. Age at the beginning of pregnancy, BMI, race or ethnicity, gravidity, and parity did not significantly differ between both groups. Baseline SBP was significantly higher among the 13 pregnancies on beta-blocker therapy (110 [IQR: 107–120] vs. 100 mm Hg [IQR: 98–106], on- and off-beta-blocker therapy, respectively; $p = 0.019$). The baseline aortic diameter was not significantly different between the two groups (3.80 [IQR: 3.60–4.00] in the on beta-blocker group vs. 3.20 cm [IQR: 3.15–3.80] in the off-beta-blocker group; $p = 0.139$). Maximum HR did not differ between those on- versus off-beta-blockers (80 [IQR: 72–84] vs. 72 bpm [IQR: 66–82]; $p = 0.341$). Other cardiovascular parameters, including baseline HR, peak HR, and diastolic blood pressure were similar between the groups.

Maternal and Fetal Outcomes

No adverse aortic events occurred during any of the pregnancies or were recorded during the follow-up clinic visits, which took place at a median of 12 weeks' postpartum (range: 2–35 wk). All pregnancies resulted in live births. There was no difference in the diagnosis of FGR between those on- versus off-beta-blockers (31 [$n = 4$] vs. 14% [$n = 1$], respectively; $p = 0.613$). Similarly, there was no difference in SGA between those on- versus off-beta-blockers (23 [$n = 3$] vs. 22% [$n = 2$], respectively; $p = 0.90$).

The maximal value and the overall increase in the SBP were measured for each pregnancy and are presented in ►**Table 2**. While the maximum SBP was not significantly different between the on- versus off-beta-blockers groups (123 [IQR: 112–128] vs. 124 mm Hg [IQR: 118–130], respectively; $p = 0.633$), there was a significantly greater increase in

Table 1 Demographics and baseline cardiovascular characteristics

Variable	Beta-blocker use		*p*-Value
	No, $N = 7$	Yes, $N = 13$	
Prepregnancy beta-blocker dose[a,b]		25 (25, 25)	
Number of patients off-beta-blockers at start of pregnancy		4	
Maximum beta-blocker dose[a,b]		75 (50, 75)	
Baseline aortic diameter[b]	3.20 (3.15, 3.80)	3.80 (3.60, 4.00)	0.139
Baseline SBP (mm Hg)[b]	100 (98, 106)	110 (107, 120)	**0.019**
Baseline DBP (mm Hg)[b]	67 (64, 70)	64 (59, 74)	0.812
Baseline HR (bpm)[b]	65 (56, 66)	67 (60, 73)	0.204
Maximum HR (bpm)[b]	72 (66, 82)	80 (72, 84)	0.341
Age at start of pregnancy[b]	34.0 (29.5, 38.0)	30.0 (29.0, 33.0)	0.524
BMI (kg/m^2)[b]	22.2 (19.8, 23.3)	24.5 (22.3, 28.0)	0.241
Race or ethnicity:			0.214
White	5 (71%)	11 (85%)	
Hispanic	2 (29%)	0 (0%)	
Black	0 (0%)	1 (7.7%)	
Unknown	0 (0%)	1 (7.7%)	
Gravidity[b]	2.00 (1.50, 3.00)	3.00 (1.00, 3.00)	0.934
Parity[b]	0.00 (0.00, 0.50)	0.00 (0.00, 2.00)	0.262

Abbreviations: BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
[a]In equivalent mg of metoprolol succinate.
[b]Value reported as mean, interquartile range.

Table 2 Aortic root and systolic blood pressure changes during pregnancy

Characteristic	Overall $N = 20$	Beta-blocker use		*p*-Value
		No $N = 7$ (35%)	Yes $N = 13$ (65%)	
Maximum aortic diameter (cm)	3.90 (3.68, 4.20)	3.60 (3.45, 4.05)	3.90 (3.90, 4.20)	0.223
Change in aortic diameter (cm)	0.20 (0.10, 0.30)	0.30 (0.25, 0.35)	0.10 (0.10, 0.20)	**0.028**
Maximum SBP (mm Hg)	124 (115, 128)	124 (118, 130)	123 (112, 128)	0.633
Increase in SBP (mm Hg)	12 (4, 19)	24 (16, 25)	8 (3, 13)	**0.012**

Abbreviation: SBP, systolic blood pressure.
Note: Values reported as mean, interquartile range.

SBP compared with baseline in the off-beta-blocker group (8 [IQR: 3–13] vs. 24 mm Hg [IQR: 16–25]; $p = 0.012$; ►**Fig. 1**).

Aortic root dimensions prior to pregnancy, during pregnancy, and postpartum for each patient are displayed in ►**Fig. 2**. The maximum aortic root diameter at any point during pregnancy did not significantly differ between the on- versus off-beta-blocker groups (3.90 [IQR: 3.90–4.20] vs. 3.60 cm [IQR: 3.4–4.05], respectively; $p = 0.223$). However, there was a significantly greater change in aortic root diameter in the off-beta-blocker group (0.10 [IQR: 0.10–0.20] vs. 0.30 cm [IQR: 0.25–0.35]; $p = 0.028$; ►**Table 2**). The percent error of the mean interobserver variability was 3.1% (−8 to 15%), and the ICC was 0.98, both indicating a nonstatistically significant difference between the aortic root measurements.

Three of the 20 patients experienced an aortic root growth of 0.1 cm in the postpartum period compared with their maximum antepartum diameter, two of whom did not use a beta-blocker during pregnancy (►**Fig. 2**). Seven of the 20 patients had no change in aortic diameter postpartum, and the remaining 10 pregnancies experienced decrease in aortic diameter postpartum compared with the maximum antepartum diameter, yet these were minimal and may have been related to margin error measurement. Overall, the mean change in aortic diameter postpartum compared with maximum antepartum diameter was a decrease of 0.05 ± 0.09 cm (data not shown).

Predictors of Change in Aortic Diameter

Results of the univariate linear regression performed to identify parameters associated with increase in aortic diameter is presented in ►**Table 3**. Absence of beta-blocker use during pregnancy, maximum SBP, and increase in SBP were

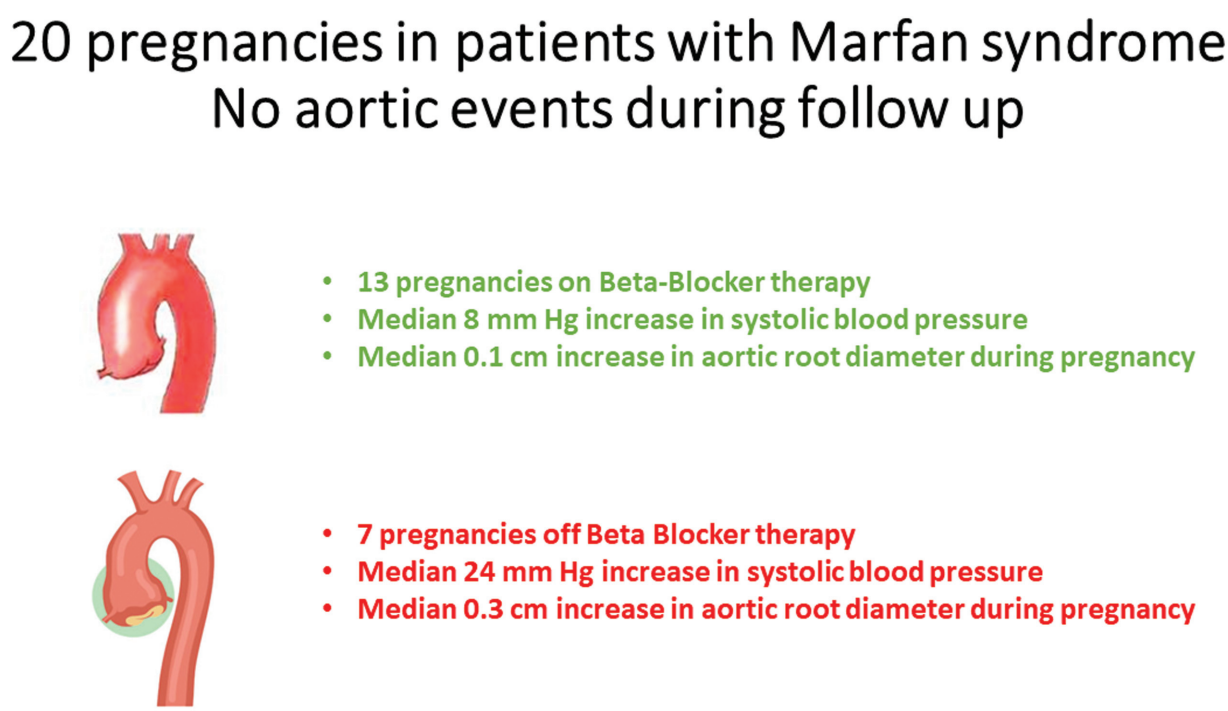

Fig. 1 Beta-blocker use in pregnant patients with Marfan syndrome is associated with less aortic root dilatation. Twenty pregnancies were observed in 19 patients with Marfan syndrome, 13 of which were on beta-blockers during pregnancy, and 7 of which were not. Patients taking beta-blockers experienced significantly less aortic root growth and less increase in systolic blood pressure (SBP) compared with those who did not take beta-blockers (0.1 vs. 0.3 cm and 8 vs. 24 mm Hg, respectively). Lack of beta-blocker use and increase in SBP were found to be predictors of aortic root growth.

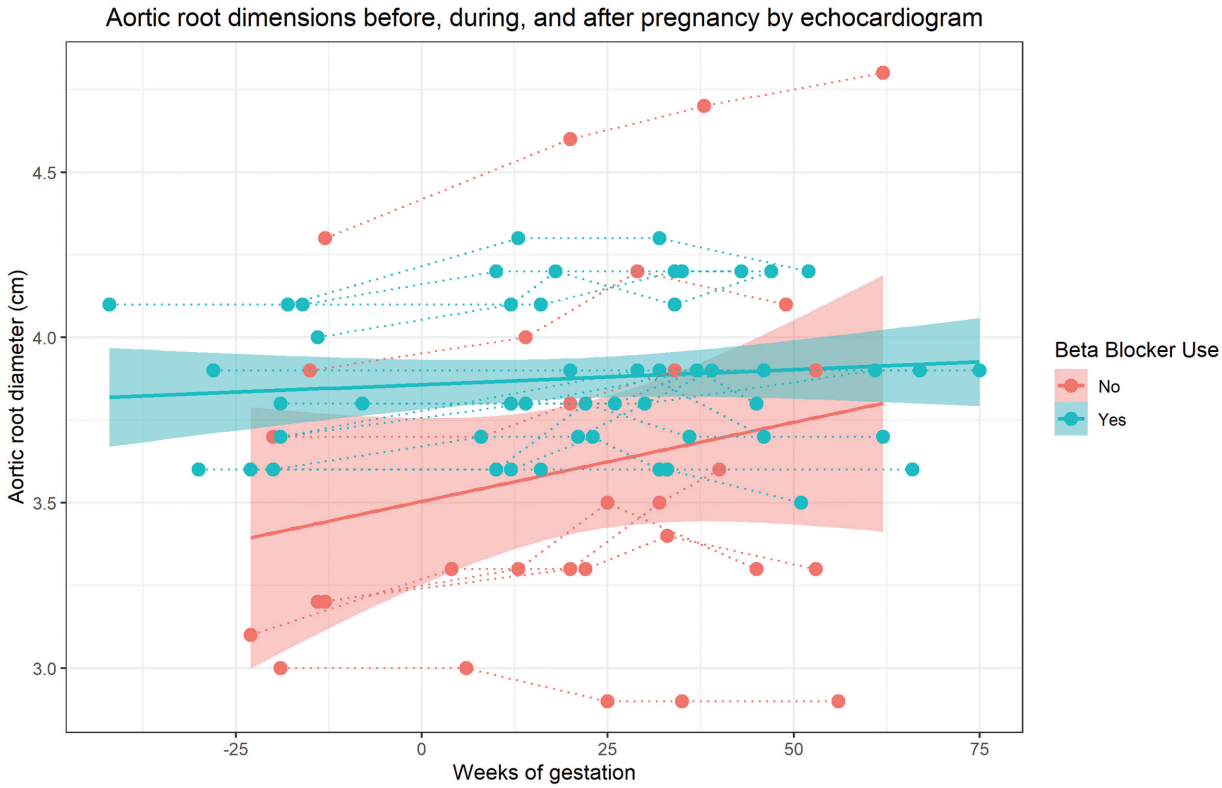

Fig. 2 Aortic root dimensions before, during, and after pregnancy by echocardiogram. Echocardiography was used to measure aortic root dimensions before, during, and after pregnancy in all 20 observed pregnancies. Individual pregnancies are represented by circles, and aortic root change is displayed using connecting dotted lines. Pregnancies on beta-blockers are displayed in blue, and pregnancies not on beta-blockers are displayed in red. Solid blue and red lines delineate average trend in aortic root dimension change during pregnancy. Pregnancies not on beta-blockers have a significantly greater increase in aortic diameter than pregnancies not on beta-blockers.

found to be associated with increase in aortic diameter ($p = 0.014$, 0.044, and 0.003, respectively). Beta-blocker use prior to pregnancy on an equivalent dose of 25 mg metoprolol succinate was associated with significantly less aortic growth ($p = 0.041$). Baseline aortic diameter, baseline SBP, maximum HR, and maximum beta-blocker dose did not have a significant impact on increase in aortic diameter during pregnancy.

Table 3 Predictors of change in aortic diameter

Variable[a]	*N*	Beta	95% confidence interval	*p*-Value[a]
Baseline aortic diameter	20	0.00	−0.17, 0.18	0.963
Baseline SBP	20	0.00	−0.01, 0.00	0.312
Baseline DBP	20	0.00	−0.01, 0.00	0.440
Maximum SBP	20	0.01	0.00, 0.01	**0.044**
Increase in SBP	20	0.01	0.00, 0.01	**0.003**
Any beta-blocker use in pregnancy	20	−0.15	−0.25, −0.04	**0.014**
Prepregnancy beta-blocker dose	9	0.00	−0.01, 0.00	**0.041**
Maximum beta-blocker dose	13	0.00	0.00, 0.00	0.947
Baseline HR	20	−0.01	−0.01, 0.00	0.067
Maximum HR	20	0.00	−0.01, 0.00	0.470
Age at start of pregnancy	20	−0.01	−0.02, 0.01	0.379
BMI	20	0.00	−0.01, 0.01	0.864
Gravidity	20	−0.03	−0.06, 0.00	0.059
Parity	20	−0.04	−0.08, 0.00	0.051

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
[a]Univariate linear regression.

Discussion

This study demonstrates that beta-blocker use prior to and during pregnancy for patients with MFS is associated with less aortic root growth. Additionally, absence of beta-blocker use during pregnancy, maximum SBP, and absolute increase in SBP were found to be associated with an increase in aortic diameters. A small number of studies have previously described the effects of beta-blocker therapy on short- and long-term aortic outcomes in pregnant patients with MFS. To our knowledge, however, this is the first study that we are aware of to evaluate changes in aortic dimensions in MFS pregnancies stratified by beta-blocker use.

The association between hypertension and aortic complications in MFS is well established and is related to increased hemodynamic forces impacting the aortic wall.[15] Lazarevic et al[15] used serial echocardiograms to identify risk factors for rapid versus slow growth of the aortic root in patients with MFS and demonstrated that higher blood pressure was associated with higher risk of progression of aortic dilatation, most significantly at the sinuses of Valsalva. Our finding that beta-blocker use during pregnancy resulted in a significantly smaller increase in SBP, especially when considering that baseline blood pressure values were higher in patient who were treated with beta-blockers during their pregnancies (►**Table 1**), should not come as a surprise, given the antihypertensive effects of beta-blocker therapy. The finding that higher SBP was associated with greater aortic root dilatation in pregnancy is also in line with previous reports, and larger studies are needed to establish the causative effect between beta-blocker use, lower SBP, and a lesser degree of aortic root dilatation, although our results are suggestive of such relationship. The blood pressure increase identified in this study was rather robust, with a mean increase of 24 mm Hg in the non beta-blocker treatment group. Blood pressure changes in patients with MFS have rarely been evaluated in the past, and various assumptions can be made as to the reasons for this observation including abnormal placentation related to the underlying connective tissue disorder and more pronounced stiffening of the aorta during pregnancy, yet these need to be confirmed in larger studies.

The use of beta-blockade in pregnant and nonpregnant individuals with MFS has been studied, and prophylactic beta-blocker use is recommended in nonpregnant individuals with MFS.[9,16,17] In pregnant patients, beta-blocker use should be considered according to the European Society of Cardiology guidelines.[11] The hypothesis for beta-blockade benefit in MFS is reduction in rate of pressure change in the aortic root and the reduction in HR, decreasing stress on the aorta.[10] A randomized trial of propranolol use comparing aortic root dimensions and cardiovascular complications in nonpregnant adults with MFS found prophylactic beta-blockade effectively slowed the rate of aortic dilatation and reduced aortic complications in some patients with MFS over a 10-year follow-up.[9] Our data demonstrate a significant increase in SBP of 24 mm Hg in those without beta-blockade and 8 mm Hg in those with beta-blockade. Given this difference in increase in SBP may not be clinically significant, it may be hypothesized that the effect on aortic root dilatation was secondary to decrease in aortic wall stress rather than antihypertensive effects.

No randomized studies of beta-blocker use in pregnant females with MFS were conducted to date. Retrospective and prospective studies are limited and primarily evaluate acute aortic complications during pregnancy, rather than changes in the aortic root dimensions. A prospective study of 89 pregnant females with MFS from Martín et al[18] reported an aortic dissection rate of 2.2% (two Type A and one Type B with aortic root dimensions at dissection 43, 37, and 45 mm, respectively), lower than most rates previously reported, which they speculated may be due to high rate of beta-blocker use (82% of their patients). Additionally, a study by Lind and Wallenburg[19] reported 78 pregnancies in 44 females who experienced five aortic dissections (four Type A and one Type B), none of whom were on a beta-blocker. While some of these studies suggest beta-blockade may be effective in preventing aortic dissection, the data are conflicting and speculative.

A small number of studies have discussed aortic root diameter change in pregnant patients with MFS on beta-blockers. In a prospective study of 18 females with MFS, Omnes et al[20] reported 15 patients received beta-blockers, with no significant change in aortic diameter globally among the cohort. A prospective study of 23 females from Meijboom et al[21] found that 52% were on beta-blocker therapy, and there was no significant aortic diameter change in 31 pregnancies. While these studies discuss beta-blocker use and aorta diameter change, they do not stratify aortic change by beta-blockade use, and no conclusions can be drawn regarding the association between these variables. One study from Narula et al[3] compared aortic diameter between the cohorts of those on beta-blockers versus those off-beta-blockers in 74 pregnancies with 112 live births, finding that mean pregnancy aortic diameters were significantly smaller in those on beta-blockers; however this study did not evaluate change in aortic diameter throughout pregnancy. Unlike Narula et al, our study did not find significant differences in maximum aorta diameter in those taking versus those not taking beta-blockers, although these findings could be limited by small sample size.

While prophylactic use of beta-blockade is recommended in nonpregnant individuals with MFS, its use in pregnancy may be associated with maternal and fetal adverse events, the primary being FGR. Beta-blocker use in pregnancy has been shown to be associated with FGR and SGA infants, however this is not seen in all studies.[22] Our study did not find significant differences in the prevalence of FGR or SGA infants in pregnancies with beta-blockers versus those without. Given the lack of convincing evidence that beta-blockade causes adverse fetal events, beta-blockade should be strongly considered when indicated in pregnancy.

The need for further studies on the topic of aortic dilatation rates during pregnancy has been recognized by the Aortic Dissection Collaborative, a network of researchers and stakeholders studying aortic dissection, who have recently identified aortic dissection in pregnancy as a high-

priority research topic of interest.[23] One multicenter study of Pregnancy and other Reproductive Outcomes in Women with Genetic-Predisposition for Aortic Dissection is currently ongoing to study cardiac outcomes in females with connective tissue disease such as MFS. Our study suggests that beta-blockers may play a protective role in aortic dilatation in pregnancy, raising the possibility that their use may mitigate adverse long-term cardiac complications in patients with MFS who experience a pregnancy. This benefit may be particularly prominent in those with larger baseline aortic diameters, given that aortic growth rate increases with increasing baseline aortic diameter[24] and would align with hypothesis that prophylactic beta-blocker use in non-pregnant individuals reduces the development of adverse aortic outcomes.[9] Larger, randomized controlled studies examining a potential protective role of beta-blockers on short- and long-term cardiac outcomes would be insightful and better guide clinical management of pregnant patients with MFS.

Finally, all patients in this study were aware of MFS diagnosis prior to conception and did not experience adverse cardiac outcomes. Lack of knowledge about MFS diagnosis is a risk factor for adverse aortic events, and our study supports the importance of early diagnosis of MFS and preconception counseling.[4] Preconception counseling guidelines for MFS patients include imaging of the entire aorta, strict blood pressure control, and discussion regarding prophylactic beta-blockade and prophylactic aortic root repair. Our study specifically supports the importance of early diagnosis as it relates to decision-making regarding beta-blockade in pregnancy.

Limitations and Strengths

Our study is limited by small sample size, limiting the ability to perform multivariate analyses to demonstrate the interaction between beta-blockade and univariate outcomes. Additionally, given that the overall the rate of dissection in MFS pregnancies is low ($\sim$3%)[11] our small sample size limited the ability to observe acute aortic complications and observe trends in event rates on beta-blockade. We also identified a very mild decrease of the aortic diameters in several of our patients. This effect may be related to a reversible increase in the total body volume during pregnancy and the vasodilatory effects of estrogen and progesterone and has been described before in pregnant Marfan patients.[3] It is possible, however, that some of the measurement differences are related to margin of error, as echocardiographic aortic diameter measurement is known to be notoriously susceptible to this effect. Finally, we found no statistically significant differences in the peak HRs between the treated and the nontreated groups in our cohort. This lack of effect may be related to the small sample size and possibly also to chronotropic incompetence that is not uncommon among MFS patients, as previously shown in exercise studies.[25]

This study has several strengths. We were able to longitudinally and systematically assess aortic root dimensions over a multiyear period. And as stated previously, this is the first study that we are aware of that has evaluated changes in aortic dimensions in MFS pregnancies stratified by beta-blocker use. This study adds to the current literature that lack of beta-blockade in pregnant females with MFS is associated with significantly greater increase in aortic root dilatation and supports the current literature that higher SBP during pregnancy is associated with significantly greater aortic root dilatation.

Conclusion

Our study finds that beta-blocker use prior to and during pregnancy is associated with less aortic root dilatation in pregnant patients with MFS and suggests that beta-blockade may play a protective role in aortic dilatation in MFS pregnancies. It additionally supports the need for further studies examining a potential long-term protective role and supports the importance of early diagnosis and preconception counseling.

Funding
None.

Conflict of Interest
The authors declare no conflict of interest related to this article.

Acknowledgments
None.

References

1 Dietz HC, Cutting GR, Pyeritz RE, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. Nature 1991;352(6333):337–339
2 Adams JN, Trent RJ. Aortic complications of Marfan's syndrome. Lancet 1998;352(9142):1722–1723
3 Narula N, Devereux RB, Malonga GP, Hriljac I, Roman MJ. Pregnancy-related aortic complications in women with Marfan syndrome. J Am Coll Cardiol 2021;78(09):870–879
4 Roman MJ, Pugh NL, Hendershot TP, et al; Aortic complications associated with pregnancy in Marfan syndrome: the NHLBI National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). J Am Heart Assoc 2016;5(08):e004052
5 Kamel H, Roman MJ, Pitcher A, Devereux RB. Pregnancy and the risk of aortic dissection or rupture: a cohort-crossover analysis. Circulation 2016;134(07):527–533
6 Donnelly RT, Pinto NM, Kocolas I, Yetman AT. The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. J Am Coll Cardiol 2012;60 (03):224–229
7 Ducas RA, Elliott JE, Melnyk SF, et al. Cardiovascular magnetic resonance in pregnancy: insights from the cardiac hemodynamic imaging and remodeling in pregnancy (CHIRP) study. J Cardiovasc Magn Reson 2014;16(01):1–1
8 Kuperstein R, Cahan T, Yoeli-Ullman R, Ben Zekry S, Shinfeld A, Simchen MJ. Risk of aortic dissection in pregnant patients with the Marfan syndrome. Am J Cardiol 2017;119(01): 132–137
9 Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. N Engl J Med 1994;330(19):1335–1341

10 Prokop EK, Palmer RF, Wheat MWJ Jr. Hydrodynamic forces in dissecting aneurysms. In-vitro studies in a Tygon model and in dog aortas. Circ Res 1970;27(01):121–127
11 Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al; ESC Scientific Document Group. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J 2018;39(34):3165–3241
12 Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010;47(07):476–485
13 Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28(01):1–39.e14
14 McGill JB. Optimal use of beta-blockers in high-risk hypertension: a guide to dosing equivalence. Vasc Health Risk Manag 2010; 6:363–372
15 Lazarevic AM, Nakatani S, Okita Y, et al. Determinants of rapid progression of aortic root dilatation and complications in Marfan syndrome. Int J Cardiol 2006;106(02):177–182
16 Ladouceur M, Fermanian C, Lupoglazoff JM, et al. Effect of beta-blockade on ascending aortic dilatation in children with the Marfan syndrome. Am J Cardiol 2007;99(03):406–409
17 Lacro RV, Dietz HC, Sleeper LA, et al; Pediatric Heart Network Investigators. Atenolol versus losartan in children and young adults with Marfan's syndrome. N Engl J Med 2014;371(22):2061–2071
18 Martín CE, Evangelista A, Teixidó G, et al. Aortic events in pregnant patients with Marfan syndrome. Lessons from a multicenter study. Rev Esp Cardiol (Engl Ed) 2022;75(07):552–558
19 Lind J, Wallenburg HC. The Marfan syndrome and pregnancy: a retrospective study in a Dutch population. Eur J Obstet Gynecol Reprod Biol 2001;98(01):28–35
20 Omnes S, Jondeau G, Detaint D, et al. Pregnancy outcomes among women with Marfan syndrome. Int J Gynaecol Obstet 2013;122 (03):219–223
21 Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJM. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. Eur Heart J 2005;26(09):914–920
22 Xie RH, Guo Y, Krewski D, et al. Beta-blockers increase the risk of being born small for gestational age or of being institutionalised during infancy. BJOG 2014;121(09):1090–1096
23 Lee JR, Lawrence SO, Soto M, et al; Aortic Dissection Collaborative. The Aortic Dissection Collaborative: methods for building capacity for patient-centered outcomes research in the aortic dissection community. Semin Vasc Surg 2022;35(01):9–15
24 Saeyeldin A, Zafar MA, Velasquez CA, et al. Natural history of aortic root aneurysms in Marfan syndrome. Ann Cardiothorac Surg 2017;6(06):625–632
25 Peres P, Carvalho AC, Perez ABA, Medeiros WM. Abnormal heart rate recovery and deficient chronotropic response after submaximal exercise in young Marfan syndrome patients. Cardiol Young 2016;26(07):1274–1281

