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REVIEW ARTICLE

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Cardiovascular outcomes of pregnancy in Marfan's syndrome patients: A literature review

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Abstract

Aims: Pregnancy in patients with Marfan's syndrome (MFS) carries an increased risk of cardiovascular complications, resulting in increased maternal and fetal mortality and morbidity. Literature on MFS pregnant patients is relatively sparse, and there has yet to be a concrete consensus on the management of this unique patient population. The purpose of our paper is to provide a literature review of case reports and studies on MFS during pregnancy (published between 2005 and 2015) and to explore cardiovascular outcomes of patients with MFS.

Methods and Results: Of the 852 women in our review, there were 1112 pregnancies, with an aortic dissection rate of 7.9% and mortality of 1.2%. Data demonstrated a trend that patients whose aortic diameter $\geq$40 mm had a greater rate of dissection than MFS patients whose aortic diameter $<$40 mm (Fisher's exact test, $P = .0504$). Fetal outcome included a 5.6% mortality rate and 41% of births were cesarean deliveries and of those reported, 75% secondary to cardiac emergencies.

Conclusions: Patients with MFS, especially those whose initial aortic diameters $\geq$40 mm, planning a pregnancy or currently pregnant should be carefully counseled about the maternal and fetal risks throughout pregnancy. MFS patients whose aortic diameters $\geq$40 mm should be advised to ideally await pregnancy until prophylactic aortic surgery. As MFS varies in its phenotypic expression, each patient's risk of adverse cardiac events should be assessed individually through a joint Maternal Fetal Medicine and Cardiology Center.

KEYWORDS

aortic diameter, cardiovascular, dissection, Marfan's syndrome, pregnancy, review

1 | INTRODUCTION

Marfan's syndrome (MFS) is an autosomal dominant connective tissue disease, which affects several organ systems including skeletal (Figure 1; CXR), ocular, cardiac, and dural systems.[1] Affecting about 1 of 5000 people, the disease carries no gender or ethnic specificity. While most of the syndrome is due to mutations in the fibrillin-1 gene on chromosome 15q21, which is responsible for elastin organization, and dysregulation of transforming growth factor-β (TGF-β), about 15%–25% of the syndrome is due to spontaneous mutations.[2,3] Given its phenotypic variability, MFS can often go undiagnosed. It is currently diagnosed by the revised 2010 nosology, which compared to the old nosology, places a greater emphasis on cardiac complications.[4]

Cardiovascular disease is a major cause of morbidity and mortality in MFS patients with an estimated 80% suffering from cardiac complications sometime in their lifetime.[5,6] Cardiac complications include aortic dilation (Figure 2) with or without aortic insufficiency, and aortic dissection, mitral valve prolapse (Figure 3; echo MVP) and regurgitation, and atrial arrhythmias.[1] According to the European Society of Cardiology (ESC) guidelines, MFS patients are recommended to undergo aortic repair if their aortic root is greater than 50 mm, a cut point which has been shown to have a fourfold increase in death or dissection outside of pregnancy.[7]

Pregnant patients with MFS offer a challenge to physicians because of the required cardiovascular adaptation to the pregnant state. Pregnancy by itself has been shown to have cardiac implications,

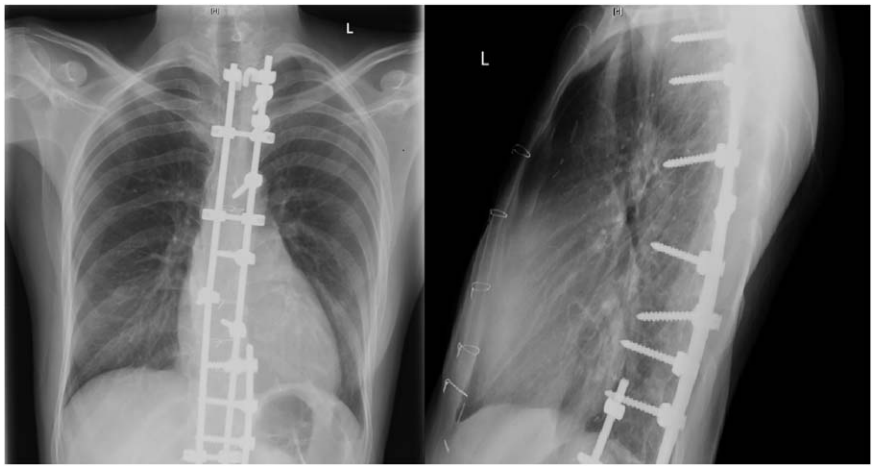

FIGURE 1 Chest x-ray of a MFS patient with skeletal involvement after corrective surgery

especially during the third trimester. Net cardiac output increases during pregnancy, due to increase in heart rate by 10–20 beats/minute and increase in stroke volume, by 30%–40%.[8] At least 50% of this physiologic adaptation occurs by 8 weeks gestation and peak hemodynamic stress occurs at 20–24 weeks, and continues until the end of pregnancy.[8] In addition to hemodynamic stress, the increase in estrogen has been shown to disrupt elastic lamellae, and increase MMP-2 which makes patients more prone to aortic pathology.[9] High levels of estrogen and progesterone during pregnancy also lead to decreased elastin deposition resulting in weakening of aortic wall. One study showed that pregnancy by itself increases the risk for aortic dissection by 23-fold.[10] The overall rate of aortic dissection during pregnancy is still very low and represents 0.1% of all cases of aortic dissection.[11] It has been shown in one study that in MFS patients, pregnancy increases the dissection risk from 0.9% per year while not pregnant to 4.4% per year while pregnant, in the absence of medical care.[12]

ACCF/AHA guidelines for pregnancy in MFS patients advise against pregnancy for patients with aortic diameter >40 mm.[13] If patients with aortic diameter >40 mm still desire pregnancy, aortic root replacement is recommended.[13] Canadian and European guidelines advise against pregnancy at a higher threshold of diameter >45 mm.[14–17] Patients with aortic diameter 40–45 mm are not completely risk free from aortic dissection since dissection cases have been reported in Marfan's patients with prior root replacement.[18] Risk factors for increased risk of dissection include family history of premature dissection, an increased rate of aortic growth during pregnancy, dilated aortic root, aortic regurgitation, increased number of pregnancies, aortic diameter ≥40 mm at conception, and lack of beta-blocker use.[6]

Though MFS is not an extremely rare condition, affecting 1 in 5000 people, the literature only reports a handful of data, most of which are case reports or case series and very few which are prospective studies. The purpose of this article was to review and analyze published outcomes of MFS pregnant patients to better evaluate cardiovascular risks in the context of current ACCF/AHA, and European and Canadian guidelines and also obstetric risks to better guide and individualize patient management.

2 | METHODS

Search engines included OVID/Medline, Pubmed, Web of Science, and Embase and articles within the last 21 years from 2005 to 2015. An

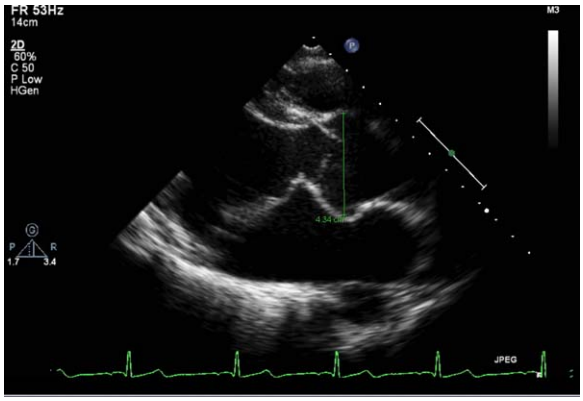

FIGURE 2 A MFS patient with aortic root dilation. Aortic root diameter measures 4.34 cm

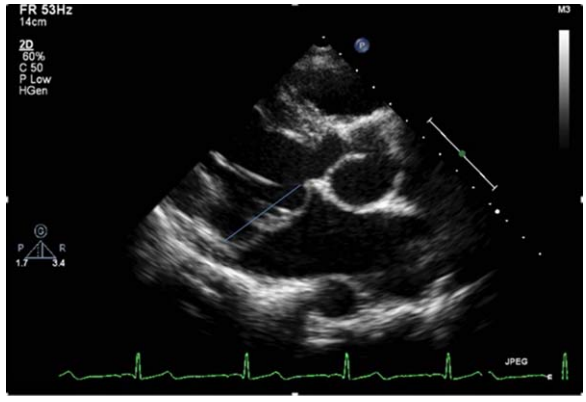

FIGURE 3 A MFS patient with mitral valve prolapse

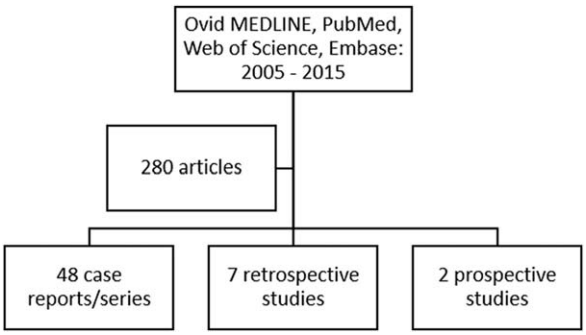

FIGURE 4 A literature search of Marfan's syndrome and pregnancy included the search engines Medline, Pubmed, Web of Science, and Embase between 2005 and 2015. There were 280 articles with 48 case reports, 7 retrospective studies, and 2 prospective studies

advanced search with subject headings, "Marfan's syndrome" and "pregnancy complications, cardiovascular" and multifield search "Marfan syndrome AND cardiovascular AND pregnancy" was completed for OVID/Medline. A MESH database with the keywords "Marfan syndrome" and "cardiovascular pregnancy complication," was completed for Pubmed. An advanced search with the keywords, "Marfan syndrome," "cardiovascular," and "pregnancy" was completed for Web of Science. A combined search, which included the keywords "marfan syndrome" and its suggested synonyms, and "pregnancy" and its synonyms, and "aortic dissection," and "cardiovascular disease" and its synonyms, was completed for Embase. There were a total of 280 articles. Inclusion criteria included case reports, case series, abstracts, retrospective studies, and prospective studies. Exclusion criteria included reviews, nonspecific articles such as articles focusing on anesthesia and pregnancy, articles written in foreign language. One retrospective study was excluded from analysis since there was overlap in the patients reported in a prospective study previously published. After accounting for inclusion and exclusion criteria, data from the 57 articles were compiled together for a series analysis. Comparison among subgroups was analyzed with Fisher's exact tests. Statistical analysis was completed using the GraphPad Prism 7 software.

3 | RESULTS

A total of 280 articles were obtained through the search protocol in the engines OVID/Medline, Pubmed, Web of Science, and Embase between the years 2005 and 2015. Of those, 48 were case reports or case series, 7 retrospective studies, and 2 prospective studies pertinent to focusing on the outcomes of pregnant MFS patients (Figure 4).

3.1 | Baseline characteristics

There were a total of 852 pregnant patients, a total of 1112 pregnancies, with MFS reported or studied between 2005 and 2015. Baseline characteristics are outlined in Table 1. For the specific ages of the 220 women available, the mean age was 28.6 ± 3.4. A total of 26 (3.1%) were reported to have prior repair of the aorta, and 53 (33%) of the 163 aortic root measurements reported had an initial aortic root ≥40 mm.

3.2 | Cardiac outcome and maternal mortality

Of the 1112 pregnancies, there were 88 (7.9%) dissections reported, with 50 (4.5%) Type A, 16 (1.4%) Type B, and 22 (2.0%) unspecified dissections. Other cardiac events reported included aortic rupture or tamponade in 5 (0.5%), moderate-to-severe aortic regurgitation reported in 27 (2.4%), mitral valve prolapse in 11 (1.0%), and dilated aortic root in 60 (5.4%) (Table 2). There were 1269 maternal deaths per 100,000 live births. Maternal deaths included cerebral hemorrhage eventually leading to cerebral herniation (1), seizures followed by respiratory arrest soon after a Type A dissection (1), rupture of dissection (3), left ventricular failure from aortic valve thrombosis (1), multi-organ failure (1), low cardiac output syndrome (1), and unreported (1). The rate of maternal deaths per 100 000 live births was much higher in MFS patients than that reported in 2010 in developed countries, including United States, 21 per 100 000 live births and Japan, 5 per 100 000 live births.[19]

Most number of cardiac events occurred in the third trimester (39%) with the second most number of events occurring postdelivery (26%) (Figure 5). Type A dissections were most frequent in the third trimester, 56%, after the exclusion of dissections occurring long after delivery. Type B dissection was also most frequent in the third trimester (38%), and second most frequent in the postdelivery period (31%) (Figure 6). Of the Type B dissections, 4 of 16 (25%) had prior repair of the aorta before pregnancy while 1 of 43 (2.3%) patients with Type A dissections and with data on whether or not patients had prior repair were reported to have prior repair of the aorta (Fisher's exact test, $P < .05$). At least 15% of patients with a dissection were reported to have a family history of dissections, sudden cardiac deaths, or aneurysms.

3.3 | Aortic dilation

Of the 163 aortic root measurements available, 53 (33%) were ≥40 mm. Of those whose aortic size was ≥40 mm and whose dissection status was individually known, 7 of 44 (16%) had a dissection and of those whose aortic size was <40 mm, 4 of 81 (4.9%) had a

TABLE 1 Baseline characteristics

N	Age	Prior repair (%)	Initial aortic root ≥40 mm (%, *n*)
852 women, 1112 pregnancies	28.6 ± 3.4 (*n* = 220)	26 (3.1)	53 (33%, *n* = 163)

There were a total of 852 pregnant patients with total 1112 pregnancies. The mean age was 28.6 ± 3.4 and 53 (33%) of the 163 aortic root measurements reported had an initial aortic root ≥40 mm.

TABLE 2 Cardiac complications

	N (%, *n* = 1112 pregnancies)	Initial aortic diameter ≥40 mm and known dissection result (*n* = 44) (%)	Initial aortic diameter <40 mm and known dissection result (*n* = 81) (%)	*P* value
Dissection	88 (7.9)	7 (16)	4 (4.9)	.05
Type A	50 (4.5)	4 (9.1)	3 (3.7)	.24
Type B	16 (1.4)	3 (6.8)	1 (1.2)	.12
Unspecified	22 (2.0)			
Rupture/tamponade	5 (0.5)			
Moderate-severe regurgitation	27 (2.4)			
MVP	11 (1.0)			
Dilation	60 (5.4)			

Of the 1112 pregnancies, there were 88 (7.9%) dissections reported, with 50 (4.5%) Type A, 16 (1.4%) Type B, and 22 (2.0%) unspecified dissections. The difference in proportion between patients with aortic diameter ≥40 and <40 mm who had a dissection, 16% vs 4.9%, was suggestive of a trend toward a significance (OR 3.64, 95% CI [1.044-11.55].

dissection (Fisher's exact test, $P = .0504$; OR 3.642, 95% CI 1.044-11.55). Of those whose aortic size was ≥40 mm, 4 of 44 (9.1%) had a Type A dissection whereas 3 of 81 (3.7%) whose aortic size was <40 mm had a Type A dissection (Fisher's exact test, $P = .24$). Of those whose aortic size was ≥40 mm, 3 (6.8%) of 44 had a Type B dissection whereas 1 of 81 (1.2%) whose aortic size was <40 mm had a Type B dissection (Fisher's exact test, $P = .12$) (Table 2).

3.4 | Delivery and fetal or neonatal outcome

Of the 1112 pregnancies, there were data for fetal outcome of 941 pregnancies. Of 941 pregnancies, there were 867 live births. There were 74 fetal deaths (0.085 fetal death per live birth), of which at least 6 were known to be deaths secondary to complications from dissection or from surgical management of dissection. There were two reported neonatal deaths, which were deaths related to prematurity. The number of neonatal deaths is limited by retrospective nature of many studies in this review, which some do not have or report neonatal records. Most births were from emergency or elective cesarean section, representing 262 of the 640 (41%) births with known type of delivery. Of the 262 cesarean sections, 96 were recorded a reason for the cesarean sections. Of the 96, 34 (35%) were emergency cesarean sections, of which 75% were secondary to cardiac emergency, 22% were secondary to OB emergency, which included cesarean delivery for footling presentation, placenta previa and accreta presentations, pre-eclampsia, breech presentation during early labor phase, and placental ablation, and 3% were secondary to other emergency, specifically emergency due to need for possibly starting anticoagulation for a preliminary diagnosis of embolic cerebrovascular accident.

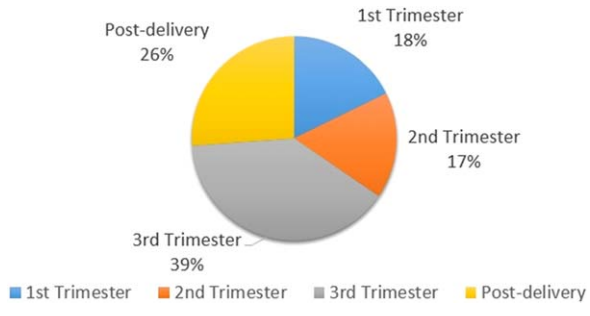

FIGURE 5 Timing of cardiac event. Cardiac complications were most frequent in the third trimester, followed by postdelivery

4 | DISCUSSION

Death due to cardiovascular disease as the cause of pregnancy related death has continued to increase and, in fact, has been the number one cause of death in pregnancy in the United States, surpassing obstetric related deaths, as reported by the CDC from 2006 to 2010.[20] MFS patients continue to provide a unique challenge to physicians because among those who have who have degeneration of the aortic media, one of the more feared complication during pregnancy is aortic dissection given its high mortality and morbidity.[21] Our literature review consisting of 1112 pregnancies, resulted in a dissection rate of 7.9%, in comparison to a dissection rate of 0.0004% reported in the general population, which suggests an almost 20 000-fold higher risk of dissection in this special population.[11] Our study had a comparable dissection risk in patients who had an initial aortic diameter of ≥40 mm, with 16% of MFS pregnant patients who had a dissection, comparable to the 10%, an often quoted, but without evidence, dissection risk in pregnant MFS population with aortic diameter ≥40 mm.[22]

Of those MFS patients who had a dissection, patients whose aortic diameter ≥40 mm showed a trend of greater rate of dissection than MFS patients whose aortic diameter <40 mm. The proportion between patients with aortic diameter ≥40 and <40 mm who had a dissection, 16% vs 4.9%, respectively, was suggestive of a trend towards a significance (OR 3.64, 95% CI [1.044-11.55], Fisher's exact test, $P = .0504$). This finding is important in that it is in agreement with 2010 ACCF/AHA (Class IIa, level C) guidelines which recommend prophylactically replacing the aortic root and ascending aorta prior to pregnancy if the aortic diameter was greater than 40 mm since aortic repair for those at

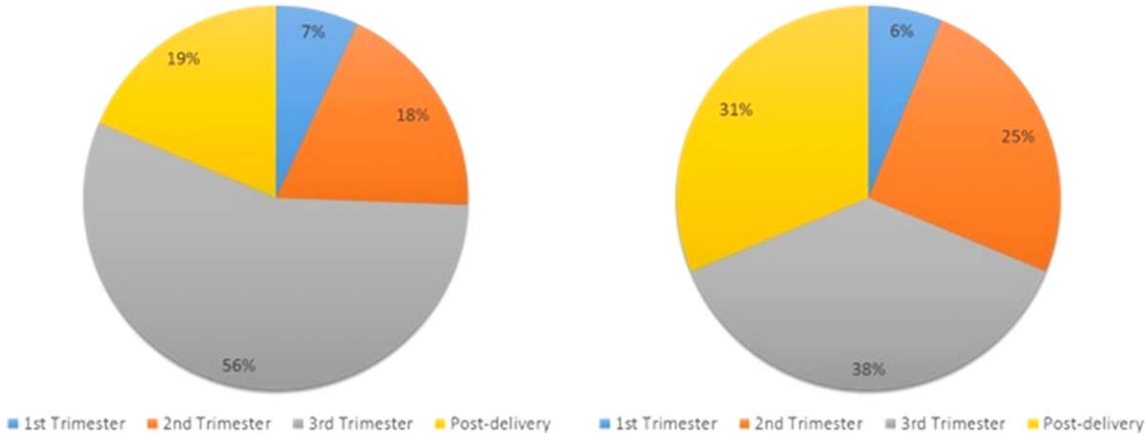

FIGURE 6 Type A (left pie chart) vs Type B dissection (right pie chart). Both Type A and Type B dissections were most frequent in the third trimester

greatest risk for dissection may improve morbidity and mortality.[11] The 2011 ESC guidelines (Class I, level C) recommend prophylactically replacing the aortic root and ascending aorta prior to pregnancy if the diameter was greater than 45 mm, but given the trend towards a difference in dissection rate is already observed at a cutoff of 40 mm, we recommend a more conservative approach.[23]

Aortic repair does not safeguard against future dissections during pregnancy or postpartum. In addition to prophylactic repair in patients whose diameter is greater than 40 mm, medical therapy with beta-blockers, such as metoprolol and labetolol, is considered first-line medication during MFS pregnancy.[24] Prior studies have shown that in nonpregnant MFS patients, beta-blockers were effective in slowing or blunting the rate of aortic dilation, when taking into consideration the initial aortic size at the initiation of beta-blockers, and is considered the gold standard with the dose recommended to be titrated to resting heart rate of 60 bpm.[25–27] In pregnant MFS patients, these medical therapies are not without risks since few studies have shown a possible association between taking beta-blockers, especially with atenolol, and intrauterine growth restriction (IUGR).[22,28–30] These possible associations between beta-blockers and IUGR in MFS patients were based on few small studies and the protective benefit of beta-blockers in reducing the shear force and wall tension of the aorta may outweigh the possible risk of IUGR. If patients are started on beta-blockers during pregnancy, continuous fetal growth monitoring is recommended. The efficacy of angiotensin-converting inhibitors (ACE-I) in nonpregnant MFS patients has also been studied and has been of debate. One study showed that enalapril was associated with improved aortic distensibility than propranolol or atenolol, while a more recent study with a longer length of follow-up showed that ACE-I has not shown to significantly decrease aortic growth velocity compared to beta-blockers.[26,31] Angiotensin receptor blockers (ARBs), have been shown in also smaller studies to decrease the rate of aortic root dilation, with one study showing similar effect when compared to beta-blockers.[25,32] The mechanism contributing to decrease in rate of aortic dilation in ARBs is inhibition of TGF-β signaling, in contrast to decrease in hemodynamic stressors with beta-blockers.[32] While much research in medical therapy in MFS patients are underway, the utility of ACE-I and ARBs in MFS pregnant patients are unknown since both medications should be avoided during pregnancy due to its teratogenicity, specifically its imposition on fetal renal function.

In general, more type A, affecting the ascending aorta and/or ascending aortic arch, than type B dissections, originating distal to the left subclavian artery, was observed in our literature review. However, of the dissections that were reviewed in our study, neither Type A ($P = .24$) nor Type B dissection ($P = .12$) was associated with aortic diameter. This conclusion is in contrast to one study that reported that a greater aortic diameter was more predictive of Type B dissection than Type A dissection.[33] Thus, physicians taking care of MFS patients should continuously monitor patients closely for both types of dissections when aortic diameter is large and be prepared to manage both types of dissections.

Of the 1112 cases, the greatest percentage of cardiac events occurred in the third trimester, which is consistent with the physiology of pregnancy, where hemodynamic stresses are greatest at the third trimester. Pregnancy increases cardiac output by 40%, stroke volume, blood volume by 30–40%, and heart rate by 10–20 beats/minute in the first and second trimesters and been reported to peak at 32 weeks, with an increase in intravascular volume up to 50%.[8] Because cardiovascular demand has reported to remain elevated as long as 12 weeks postpartum, it is important that physicians continue to monitor MFS patients for cardiovascular outcomes even after delivery and to make ED providers aware, which is also in agreement with our study that showed that the second largest group of cardiac events occurred in the postpartum period.[34] The importance of monitoring MFS patients especially towards the end of their pregnancy is demonstrated in the observation that dissections in patients whose aortic diameter was $<$40 mm all occurred at the latter half of their term of pregnancy, one in their 26th week, two patients in their 27th week, and another 4 months postpartum, periods when hemodynamic stresses are elevated.

In addition to the risk of dissection during pregnancy, MFS patients carry an additional high probability of cesarean delivery. Of the

emergency cesarean sections reported in this review, more than three times as many were secondary to cardiac emergencies, 75%, compared to 22%, which were secondary to obstetric related emergencies, most due to malpresentations of the fetus prior to or during labor. Cardiovascular reasons for cesarean delivery not only arise from dissections, but also included lumbar arthrodesis secondary to spinal correction surgery for MFS that impede regional anesthesia for vaginal delivery and complications of aortic root surgery. This suggests that the decision on the mode of delivery involves more than the absolute aortic diameter during labor and include factors that affect MFS patients in their lifetime such as prior surgeries for skeletal involvement of MFS.

Limitations in the study include that only 2 of the 57 studies were prospective studies. Included are registries in which the maternal mortality could be underestimated since one study looked at registries of MFS women with prior pregnancies who were living. Furthermore, the suggestive but not statistically significant rate of dissection between the groups, aortic size $\geq$40 mm and size $<$40 mm, may be attributed to the low rate of dissection in the retrospective and prospective studies. Thus, a larger prospective study is warranted. Finally, because this is a literature review, not all patients were exposed to the same protective factors such as beta-blockers, which are thought to decrease dissection risk, since many in several studies were not aware that patients had MFS. There were only two prospective studies in the review, in which in total, 2 dissections among 69, prospectively followed pregnancies combined, were observed, which implies that with good cardiac and obstetrical care and prophylaxis, the risk of dissection could be reduced.[22,28,35]

Overall, MFS pregnant patients would highly benefit from frequent visits at an interdisciplinary office. For example, Montefiore Medical Center provides a joint Maternal Fetal Medicine (MFM) Cardiology Program, which provides care by both MFM and Cardiology physicians for pregnant patients at high cardiovascular risk. During the first visit, we recommend a thorough cardiovascular and family history and an EKG, chest x-ray, and a transthoracic echocardiogram (TTE), evaluating for initial aortic root diameter, mitral valve prolapse and regurgitation, and aortic regurgitation, with follow-up TTEs every 6–8 weeks to monitor aortic diameter, and if aortic dissection is suspected, a transesophageal echocardiogram.

5 | CONCLUSIONS

Our literature review suggests that MFS pregnant patients have a moderate to high risk of dissection, with our review demonstrating 7.9% of the 1112 cases, which was 20 000-fold higher than the risk of dissection in the general population. A greater aortic size $\geq$40 mm was suggestive towards a trend for increased dissection risk, compared to aortic size $<$40 mm, supporting ACCF/AHA guidelines that recommend prophylactic aortic replacement surgery in pregnant patients whose aortic diameters are greater than 40 mm. Cardiac events were noted to be more common in the third trimester and postpartum periods, periods when hemodynamic stresses are the greatest and patients were observed to deliver more commonly through cesarean section, and for emergency cesarean sections, more than three times as many were secondary to cardiac emergencies than obstetric emergencies. The risk of dissection in pregnant MFS patients should be assessed as a whole, including the patient's family history of dissection, absolute aortic size, and previous aortic surgery. It is recommended that MFS patients be closely monitored with echocardiography every 6–8 weeks, and be on appropriate medical therapy with beta-blockers with careful fetal monitoring.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Concept/design, data collection/analysis/interpretation, drafting, statistics: Kim

Concept/design, data interpretation, drafting, critical revision: Taub

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