

Pregnancy in Marfan Syndrome

Maternal and Fetal Risk and Recommendations for Patient Assessment and Management

Sorel Goland, MD,* Mohamad Barakat, MD,†‡ Nudrat Khatri, MBBS,†‡ and Uri Elkayam, MD†‡

Abstract: Pregnancy in women with the Marfan syndrome (MFS) is associated with the potential for a catastrophic and even fatal acute aortic dissection and the risk of having a child who will inherit the syndrome. The approach to pregnancy in patients with MFS is therefore challenging and deserves special considerations. This article presents an extensive review of available clinical information and provides recommendations for the management of patients with MFS during pregnancy.

Key Words: Marfan syndrome, pregnancy, aortic dissection, aortic dilatation, aortic surgery

(*Cardiology in Review* 2009;17: 253–262)

Marfan syndrome (MFS) is an autosomal dominant hereditary disorder of the connective tissue^{1–4} in which involvement of the cardiovascular, skeletal, ocular and other systems may be present. Pregnancy in MFS presents challenges to the clinician because of the increased incidence of maternal cardiovascular complications and the involvement of the fetus. The purpose of the article is to present an update on available information relevant to pregnancy in women with MFS, and to provide recommendations for clinical management.

EPIDEMIOLOGY AND ETIOLOGY OF MARFAN SYNDROME

In the United States, the estimated prevalence of this disease is 4 to 6 cases per 10,000 persons, affecting both genders equally.³ Eighty percent of patients have some cardiovascular involvement, which includes aortic dilatation (mainly of the ascending part), aortic regurgitation, and mitral and tricuspid valve prolapse with or without regurgitation.^{3–5} In the past, life expectancy in patients with MFS was reported to be greatly reduced (2/3 that of unaffected individuals).⁶ Recent studies, however, have described significantly better life expectancy because of improved medical and surgical treatment.⁷ Causes of death are predominantly cardiovascular and include aortic dissection and rupture.⁶

MFS is caused by a mutation in the gene for MFS (FBN1) on chromosome 15q21^{1–3} encoding the extracellular matrix protein called fibrillin-1.^{1,2} Recently, heterozygous mutations have also

been identified in the gene encoding tissue growth factor- β receptor 2 (TGFB2) on chromosome 3p24.2–25.⁸ Whereas the disorder segregates as a dominant trait in 65% to 75% of families, the rest of cases are sporadic and caused by a de novo mutation. Although MFS results from mutations in the FBN1 gene, molecular testing for the FBN1 mutation is neither sensitive nor specific for MFS and the diagnosis therefore is still based on clinical criteria.⁹ The recognition that many individuals with MFS do not have the FBN1 mutation led in 1996 to a revision of the diagnostic criteria for the Marfan syndrome (Table 1).^{5,10} Major criteria are found infrequently in the general population, and therefore carry limited diagnostic sensitivity but high specificity. Because of multisystem involvement, evaluation of patients with possible MFS must involve a multidisciplinary approach by specialists in cardiology, ophthalmology, radiology, and clinical genetics.

CARDIOVASCULAR RISK OF PREGNANCY IN MARFAN SYNDROME

Risk for the Mother

The most serious complication in patients with MFS is aortic dissection, and pregnancy has been shown to be associated with a substantial increase in the risk of this complication.^{11–13} This increased risk is caused by the maternal cardiovascular changes of pregnancy such as an increase in blood volume, heart rate, and stroke volume.¹⁴ In addition, hormonally mediated histologic changes occur in the aorta, including a decrease in the amount of mucopolysaccharides and the loss of elastic fibers in the aortic wall.¹⁵ The increased risk of complications of MFS associated with pregnancy were initially described by Pyeritz in 1981 in a review which included 32 women with both the Marfan syndrome and at least 1 pregnancy.¹⁶ Of these women, 20 developed acute dissection or rupture and died during pregnancy or during the peripartum and postpartum periods. Most of these patients had pre-existing cardiovascular abnormalities, including aortic dilatation, aortic regurgitation, coarctation of the aorta, hypertension, cardiomegaly, and patent ductus arteriosus. In a more recent review of the literature, we reported on 15 additional cases of pregnancy in women with MFS.¹² Among these cases, 10 were reported to have cardiovascular complications during pregnancy, including proximal and distal dissections of the aorta with the occasional involvement of the iliac and coronary arteries, as well as dilatation of the ascending aorta leading to the development of aortic regurgitation and congestive heart failure. Most women developed cardiac complications in the second and third trimesters, although aortic dissection occurred in isolated patients a few days after conception as well as during labor and after delivery and resulted in 2 maternal deaths. Uncomplicated C-section delivery was performed prior to surgery in 3 women in whom surgical repair was performed successfully 3 days to 6 weeks after delivery, whereas in 2 patients surgery was done during pregnancy. Another review reporting on cases of aortic dissection in pregnant women with MFS and bicuspid aortic valve disease described 16 Marfan cases with type A dissection.¹⁷ In this report, the mean age

From the *Kaplan Medical Center, Rehovot, Israel; Departments of †Medicine and ‡Obstetrics and Gynecology, University of Southern California Keck School of Medicine, Los Angeles, CA.

This review was modified and reproduced with permission from Wolters Kluwer/Lippincott Williams & Wilkins who published Goland S, Elkayam U. Cardiovascular problems in pregnant women with Marfan syndrome. *Circulation*. 2009; 119:619–623.

Correspondence: Uri Elkayam, MD, Departments of Medicine, Obstetrics and Gynecology, LAC+USC Medical Center, 1200 N. State St, Los Angeles, CA 90033. E-mail: Elkayam@usc.edu.

Copyright © 2009 by Lippincott Williams & Wilkins

ISSN: 1061-5377/09/1706-0253

DOI: 10.1097/CRD.0b013e3181bb83d3

TABLE 1. Ghent Diagnostic Nosology

| System | Major Criteria | Minor Criteria |
|------------------|---|---|
| Skeletal | At least 4 of the following features: Pectus carinatum Pectus excavatum requiring surgery ULSR <0.86 or span: height >1.05 Wrist and thumb signs Scoliosis >20° or spondylolisthesis Reduced elbow extension (<170°) Pes planus Protrusion acetabulae | 2 of the major features, or 1 major feature and 2 of the following: Pectus excavatum Joint hypermobility High palate with dental crowding Characteristic face |
| Ocular | Lens dislocation (ectopia lentis) | Flat cornea Increased axial length of globe (causing myopia) Hypoplastic iris or ciliary muscle (causing decreased miosis) |
| Cardiovascular | Dilatation of aortic root | Mitral valve prolapse Dilatation of the pulmonary artery, below age 40 Calcified mitral annulus, below age 40 Other dilatation or dissection of the aorta |
| Pulmonary | None | Spontaneous pneumothorax Apical blebs |
| Skin/integument | None | Striae atrophicae Recurrent or incisional hernia |
| Dura | Lumbosacral dural ectasia | None |
| Genetic findings | Parent, child or sibling meets these criteria independently Fibrillin 1 mutation known to cause Marfan syndrome Inheritance of DNA marker haplotype linked to Marfan syndrome in the family | None |

Having one of the features listed constitutes a major criterion or minor criterion for all systems except the skeletal system, where more than one feature is needed.

The diagnosis of MFS requires major criteria in one organ and minor criteria (involvement) of another when a positive family history or genetic testing for FBN1 is present. In the absence of family history, major criteria in 2 organ systems and the involvement of 3rd are required for diagnosis.

ULSR indicates upper to lower segment ratio.

De Paepe et al: Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996;6:417–426.

was 30 ± 4 years, mean gestational week was 31 ± 6 weeks, and the mean aortic root diameter was 4.8 ± 0.8 cm, and all but 2 women delivered by C-section. There was no maternal death, however fetal deaths were reported in 3 cases, poor outcome in 1, and intracranial hemorrhage was reported in 2 patients (30 minutes and 6 weeks after delivery).

In reviewing the recent English literature of the last decade, we found an additional 39 cases of women with MFS who experienced pregnancy-related complications (Table 2). The individual characteristics of this population are presented in Table 3.^{18–36} The mean age was 30 ± 4 years, 29 women had an acute aortic dissection involving the ascending aorta in 19 of the cases, descending aorta in 8, and both in 2. In 19 patients, dilatation of aorta was diagnosed prior to pregnancy and 4 had a history of aortic surgery. Eight women were diagnosed with MFS only after the occurrence of complications. Five patients developed acute dissection before week 20 of gestation (13–20 weeks), 18 patients between 24 and 40 weeks, and 6 patients after delivery (between the day of delivery to 3 months post partum). In addition, 5 patients developed progressive dilatation of the ascending aorta requiring surgery during pregnancy, 2 patients had a chronic distal dissection which remained stable during pregnancy, and 1 showed an extension of distal dissection, 1 week postpartum. In addition 2 patients had intracranial hemorrhage postpartum (30 minutes and 6 weeks after delivery).

TABLE 2. Women With MFS Who Experienced Pregnancy Related Complications Published Between 1995 and 2007

| | |
|------------------------------------|------------|
| Number | 39 |
| Mean age (yr) | 30 ± 4 |
| Acute aortic dissection | 29 |
| Type A | 19 |
| Type B | 8 |
| Type A and B | 2 |
| Timing of dissection | |
| Weeks 13–20 | 5 |
| Weeks 24–40 | 18 |
| After delivery | 6 |
| Progressive aortic dilatation | 5 |
| Intracranial hemorrhage postpartum | 2 |
| Prior distal aortic dissection | |
| Stable during pregnancy | 2 |
| Extension 1 wk post partum | 1 |

Maternal and fetal mortality was reported in 2 patients, whereas in 2 cases aortic dissection resulted in fetal loss in spite of maternal survival. In the majority of patients who developed dissection during pregnancy, delivery was done by C-section. Information regarding the time of surgery was available in 28

TABLE 3. Cases of Women With MFS With Pregnancy-Related Complications Published Between 1995 and 2007

| Case | Author | Year | Age/OB Hx | Prior CV Disease | Complications | | | Mode and Time of Delivery | | Outcome | |
|------|------------------------------|------|-----------|--|---|----------------|----------------|---|--|---------|---------|
| | | | | | Maternal | Fetal | Maternal | Maternal | Fetal | | |
| 1 | Jayaram et al ¹⁸ | 1995 | 33/G6/P0 | Not reported | Type B aortic dissection, distal to left subclavian artery at 26 wk | None | None | C-section at 36 wk | Repair of distal aorta after delivery | Healthy | Healthy |
| 2 | Rossiter et al ¹⁹ | 1995 | 29/NA | Dilated aortic root (42 mm) | Rapid aortic dilatation: 3rd trimester, 52 mm and postpartum, 68 mm, moderate AR | None | None | Not reported, at full term | Aortic root replacement with a composite graft | Healthy | Healthy |
| 3 | Rossiter et al ¹⁹ | 1995 | 26/NA | Dilated aortic root (42 mm), MVP, moderate AR | Aortic dilatation to 48 mm and type B dissection of the aorta to the bifurcation at 17 wk | None | None | Pregnancy termination by hysterectomy at 17 wk | Repair of the thoracic aorta 1 yr later for extension of the dissection. | Death | Death |
| 4 | Rossiter et al ¹⁹ | 1995 | 26/NA | s/p aortic graft replacement for acute proximal aortic dissection 6 mo prior to pregnancy, and chronic descending aorta dissection | Chronic dissection of the descending thoracic aorta remained stable during pregnancy. Extension of dissection to the abdominal aorta 1 wk post partum | None | None | Not reported, at full term | Repair of thoraco-abdominal aorta 3 mo after delivery. Patient died 2 yr later from endocarditis | Healthy | Healthy |
| 5 | Lipscomb et al ²⁰ | 1997 | 29/G2P1 | Dilated ascending aorta (42 mm) | Proximal and distal aortic dissection during prostaglandin induction at 20 wk | Death | Death | Induced vaginal delivery due to intrauterine fetal death at 20 wk | Aortic root repair with a composite graft, 2 further episodes of dissection and death at age 37 | Death | Death |
| 6 | Lipscomb et al ²⁰ | 1997 | 30/NA | Not evaluated, MFS diagnosed during pregnancy | Proximal aortic dissection at 38 wk (aortic diameter-86 mm). LV dilatation, severe AR, pulmonary edema | None | None | C-section at 38 wk | Ascending aorta replacement with composite graft at the time of C-section. Patient died 2 yr later from sub-arachnoid hemorrhage | Healthy | Healthy |
| 7 | Lipscomb et al ²⁰ | 1997 | 35/NA | Not evaluated, MFS diagnosed during pregnancy | Uncontrolled HTN at 25 wk. Type A aortic root dissection 14 d postpartum with rupture of the aorta | Fetal distress | Fetal distress | C-section for fetal distress and uncontrolled HTN at 38 wk | Death | Death | Healthy |
| 8 | Lipscomb et al ²⁰ | 1997 | 30/G1P0 | Diagnosis of MFS during pregnancy. Dilated aortic root (40 mm) at 20 wk | Type B aorta dissection at 16 d postpartum | None | None | C-section at 38 wk | Managed medically for 18 mo then required surgery for aneurismal dilatation of thoraco-abdominal aorta | Healthy | Healthy |

(Continued)

TABLE 3. (Continued)

| Case | Author | Year | Age/OB Hx | Prior CV Disease | Complications | | Fetal | Mode and Time of Delivery | Outcome | |
|------|-----------------------------------|------|-----------|--|--|-------------------|---|---|--------------------------|-------|
| | | | | | Maternal | Fetal | | | Maternal | Fetal |
| 9 | Lipscomb et al ²⁰ | 1997 | 28/NA | Diagnosis of MFS during pregnancy. Dilated aortic root (43 mm) | Progressive dilatation of aorta to 49 mm | None | C-section at 36 wk | Rapid dilatation of the aorta to 70 mm postpartum. Successful aortic root repair with composite graft at 18 wk postpartum | Healthy | |
| 10 | Lipscomb et al ²⁰ | 1997 | 28/G2P0 | Dilated aortic root (49 mm) diagnosed in previous pregnancy | Progressive dilatation of aorta to 56 mm at 17 wk | Not reported | Elective abortion at 17 wk | Aortic root replacement after elective termination of pregnancy | Aborted at 17 wk | |
| 11 | Zeebregts et al ²¹ | 1997 | 24/G2/P1 | HTN, severe AR | Type A dissection at 32 wk | Not reported | C-section at 5 d after aortic surgery | Bentall operation during pregnancy | Alive | |
| 12 | Zeebregts et al ²¹ | 1997 | 28/G2P1 | Not reported | Type B dissection at 35 wk | Not reported | Vaginal delivery of a dead fetus at 35 wk | Conservative treatment, multiorgan failure, sepsis | Fetal death intrauterine | |
| 13 | Mul et al ²² | 1998 | 32/G2P1 | Not reported | Type A dissection at 29 wk | Not reported | Delivery at 38 wk | Aortic root replacement at 29 wk | Fetal brain atrophy | |
| 14 | Akashi et al ²³ | 2000 | 25/NA | None | Proximal aortic dilatation (aortic root 60 mm), and dissection Type A at 37 wk | Fetal distress | C-section at 37 wk for fetal distress | Replacement of the aortic root and the ascending aorta 1 d after C-section | Healthy | |
| 15 | Jondeau et al ²⁴ | 2000 | 31/NA | Dilated aortic root (55–60 mm) in the beginning of pregnancy | Progressive dilatation to 62–65 mm and acute Type A dissection at 34 wk | None | C-section at 34 wk | Bentall operation and C-section at the same session | Healthy | |
| 16 | Fabricius et al ²⁵ | 2001 | 32/G1P0 | None | Type A dissection, AR and cardiogenic shock at 39 wk | Fetal tachycardia | C-section at 39 wk | Composite graft of aortic root and AVR. ECMO for 4 d | Healthy | |
| 17 | Fabricius et al ²⁵ | 2001 | 31/G1P0 | None | Type A and B dissection at 34 wk, celiac ischemia, lower limb paraplegia | None | C-section, 34 wk | Ascending aorta, aortic arch, and descending aorta replaced with Hemashield prosthesis. Ascending colon resection | Healthy | |
| 18 | Preiss et al ²⁶ | 2005 | 37/NA | Dilated aortic root (42 mm) before pregnancy | Type A dissection at 34 wk | NA | C-section and hysterectomy at 34 wk | Surgery of the ascending aorta and C-section at the same session | NA | |
| 19 | Lind and Wallenburg ²⁷ | 2001 | 28/G4P1A2 | None | Type A dissection at 24 wk | None | C-section, full term | Aortic root replacement then continued pregnancy till full term | Healthy | |
| 20 | Lind and Wallenburg ²⁷ | 2001 | 24/G1P0 | Dilated aortic root (40 mm) before pregnancy | Type A dissection at 39 wk during labor | None | C-section at 39 wk | Aortic repair and C-section at the same session | Healthy | |

(Continued)

TABLE 3. (Continued)

| Case | Author | Year | Age/OB Hx | Prior CV Disease | Complications | | | Mode and Time of Delivery | | Outcome | |
|------|-------------------------------------|------|-----------|--|---|-----------------------|-----------------------|--|---|-----------------------|-----------------------|
| | | | | | Maternal | Fetal | Fetal | Maternal | Fetal | Maternal | Fetal |
| 21 | Lind and Wallenburg ²⁷ | 2001 | 28/G1P0 | Dilated aortic root (45 mm) before pregnancy | Type A dissection on day 6 postpartum | None | None | Full term vaginal delivery | Aortic root replacement | Healthy | Healthy |
| 22 | Lind and Wallenburg ²⁷ | 2001 | 23/G1P0 | MFS diagnosed after occurrence of dissection | Type A dissection at 6 wk postpartum | None | None | Full term vaginal delivery | Aortic root replacement | Healthy | Healthy |
| 23 | Lind and Wallenburg ²⁷ | 2001 | 28/G1P0 | Dilated aortic root (41 mm) before pregnancy | Type B dissection immediately after delivery | None | None | Full term vaginal delivery | Aortic repair 2 wk after delivery | Healthy | Healthy |
| 24 | Lind and Wallenburg ²⁷ | 2001 | 24/G1P0 | Not evaluated, MFS diagnosed during pregnancy before the event | Intracranial hemorrhage, 30 min after delivery | None | None | Full term vaginal delivery | Left sided hemiparesis | Healthy | Healthy |
| 25 | Lind and Wallenburg ²⁷ | 2001 | 26/G3P2 | None | Intracranial hemorrhage with left paresis at 6 wk after delivery | None | None | Full term vaginal delivery | Recovered | Healthy | Healthy |
| 26 | Rahman et al ²⁸ | 2003 | 40/NA | MFS diagnosed after dissection | Type A aorta dissection at 40 wk | Severe fetal distress | Severe fetal distress | Vaginal delivery with forceps at 40 wk | Aortic root and aortic valve replacement | Healthy | Healthy |
| 27 | Rahman et al ²⁸ | 2003 | 38/G2P1 | Mild aortic root dilation with AR | Further aortic root dilatation during pregnancy up to 58 mm | None | None | C-section at 38 wk | Surgical repair of the aortic root and AVR 7 wk later | Healthy | Healthy |
| 28 | Sakaguchi et al ²⁹ | 2005 | 32/NA | Aortic root diameter 35 mm | Acute Type A aortic dissection at 33 wk | None | None | C-section at 33 wk | AVR, arch replacement. CABG and C-section at the same session | Healthy | Healthy |
| 29 | Sakaguchi et al ²⁹ | 2005 | 33/G1P1 | Dilated aortic root (55 mm) | Acute Type A dissection at 26 wk | Not reported | Not reported | Fetal loss due to maternal mortality | Aortic root and arch replacement has been performed with fetus in utero at 26 wk. Mother died from multiorgan failure | Death | Death |
| 30 | Sakaguchi et al ²⁹ | 2005 | 28/G1P0 | Dilated aortic root (85 mm) | Type A aortic dissection 30 wk | None | None | Spontaneous delivery at 30 wk | Aortic root replacement after delivery | Healthy | Healthy |
| 31 | Sakaguchi et al ²⁹ | 2005 | 34/G3P2 | Dilated aortic root (60 mm) | Type A aortic dissection at 34 wk | None | None | C-section at 34 wk | Aortic root and arch replacement and C-section at the same session | Healthy | Healthy |
| 32 | Tilak et al ³⁰ | 2005 | 29/G1P1 | HTN | Aortic dilatation (80 mm) and Type B dissection artery at 13 wk. Refused termination and chose elective operation | None | None | C-section at 32 wk | Partial repair of thoracic aneurysm at 14 wk. Extension of the dissection at 16 wk. Repair of descending aorta 5 mo later complicated by paraplegia | Healthy | Healthy |
| 33 | Ioscovich and Elstein ³¹ | 2005 | 29/G1P1 | Dilated aortic root (37 mm) | Aortic root 37 mm at 18 wk, type B aortic dissection at 30 wk | None | None | C-section at 30 wk | Conservative treatment | No major complication | No major complication |

(Continued)

TABLE 3. (Continued)

| Case | Author | Year | Age/OB/Hx | Prior CV Disease | Complications | | Mode and Time of Delivery | | Outcome | |
|------|------------------------------|------|-----------|---|--|-------|---------------------------|---|----------|-------|
| | | | | | Maternal | Fetal | Maternal | Fetal | Maternal | Fetal |
| 34 | Naito et al ³² | 2005 | 32/NA | Not reported | Type A aortic dissection at 20 wk | None | C-section at 33 wk | Bental operation during pregnancy at 24 wk | Healthy | |
| 35 | Chavanon et al ³³ | 2006 | 27/G1P1 | s/p Yacoub operation for aortic aneurysm, with diameter of 43 mm distal to the left subclavian artery | Aggravation of AR to 3+ during pregnancy and acute type B dissection 2 d after C-section | None | C-section | AVR and aortic root replacement and thoraco-abdominal aorta replacement | Healthy | |
| 36 | Matsuda et al ³⁴ | 2006 | 20/G1P1 | Dilated ascending aorta (78 mm) | Type A aortic dissection at 19 wk | None | Not reported (37 wk) | Hemi-arch replacement at 19 wk | Healthy | |
| 37 | Tomihara et al ³⁵ | 2006 | 24/G1P0 | Dilated aortic root (42 mm) | Abdominal aortic aneurysm (80 mm) 3 mo postpartum | None | C-section at 38 wk | Replacement of abdominal aorta | Healthy | |
| 38 | Elkayam (unpublished) | 2006 | 27/G1P1 | s/p Bental operation | Status post AVR chronic dissection of aortic arch and descending aorta. No change in aorta dissection during pregnancy | None | C-section at 31 wk | Conservative treatment | Healthy | |
| 39 | Tutarel et al ³⁶ | 2007 | 34/G1P1 | Dissection of aorta with ascending aorta replacement and aortic valve repair. Chronic dissection of distal arch and abdominal aorta | No changes in aortic dissection during pregnancy | None | C-section at full term | No intervention during pregnancy | Healthy | |

AR indicates aortic regurgitation; AVR, aortic valve replacement; CABG, coronary artery by pass graft surgery; ECMO, extracorporeal membrane oxygenation; HTN, hypertension; Hx, history; L.V, left ventricular; MVP, mitral valve prolapse; NA, not available.

patients and was prior to delivery in 6 women, after the delivery in 15, and immediately after C-section in 7.

What is the expected rate of complications in women with MFS during pregnancy? Although most of the published reports have described severe complications in women with MFS during pregnancy, this information probably provides an overrepresentation of pregnancy-related complications in a high-risk population caused by a bias toward reporting complicated rather than uncomplicated cases. Such an assumption is supported by a number of publications, which demonstrate a significantly lower rate of complications. Pyeritz¹⁶ showed only a low risk for maternal complications and death in a retrospective analysis of 105 pregnancies in 26 patients with MFS and prospective follow-up of 10 patients who had minimal or no pre-existing cardiovascular disease. Rossiter et al¹⁹ prospectively evaluated 45 pregnancies in 21 women with MFS; aortic dissection occurred in only 2 cases and the rest of patients with aortic diameter <4.0 cm tolerated pregnancy well. More recently, Libscomb et al²⁰ reported the outcome of 91 pregnancies in 36 women with MFS and described the occurrence of aortic dissections in 6 of these patients. In a prospective study of 127 women with MFS, 23 were followed by measurement of their aortic root diameter during 33 pregnancies and were compared with 22 matched childless women.³⁷ During 6.4 years of follow-up, no significant difference in growth of the aortic root was obtained and only 1 woman with previous type A dissection developed type B dissection during her second pregnancy. The authors concluded that pregnancy is relatively safe in women with an aortic root diameter of <4.0 cm.

Risk for the Fetus

The risk of transmission of MFS to the offspring is at least 50%. Based on a report by Lind and Wallenburg²⁷ who also included infants with late diagnosis, 69% of infants of mothers with MFS were found to be affected. Because of the variability in clinical presentation of this disease, severe expression of the syndrome can occur in an offspring of a mother with a relatively mild presentation. It should be noted that development of aortic dissection in the mother carries a substantial risk to the fetus.^{12,17} Among the cases presented in the current review, intrauterine fetal death occurred in 4 patients with aortic dissection during pregnancy, and 1 case was reported to have fetal brain atrophy.^{19–22,26} In addition to the fetal complications described above, MFS has also been associated with a higher rate (40%) of obstetric complications, such as premature delivery, mainly because of premature rupture of membranes and increased mortality in the offsprings.³⁸

DIAGNOSIS OF MARFAN SYNDROME IN THE FETUS

Mutation or linkage analysis can be used for the prenatal diagnosis of MFS,^{39,40} which can also be accomplished by chorion villus sampling or amniocentesis (cell culture) in affected families.^{41,42} Because almost 400 mutations have been reported in FBN1, almost every patient has a unique mutation, and therefore there is still no reliable diagnostic test.⁹ In addition to the genetic linkage, which can be done in early gestation, echocardiography may be used in the 3rd trimester to diagnose cardiac manifestations of MFS in the fetus, such as atrioventricular valve regurgitation and dilatation of the aortic root and pulmonary artery.⁴³ Prenatal diagnosis has been performed until now in familial cases by linkage analysis. Recently, mutation detection has become available with thorough screening methods, however, about 10% of mutations that cause MFS can be still missed.⁴² Moreover, molecular diagnosis cannot predict the clinical severity of the disease.⁴¹

PRECONCEPTION COUNSELING

Unfortunately, based on previous published data, preconception counseling took place in only 25% of pregnant women with MFS and in no patient among 5 who had aortic dissection.²⁷

The management of pregnancy should be started, ideally, prior to conception. Preconception counseling has to draw attention to the risk of pregnancy in both the mother and the child. Women with MFS should be consulted before conception about potential pregnancy-related complications and the high risk of transmission of MFS to the offspring. Because of various clinical presentations of this disease, it must be noted that even in mildly affected women, a more severe expression of MFS can be expected.⁴ The patient should be also informed about the possibility of prenatal diagnosis, using both genetic linkage and fetal echocardiography.^{11,39–43} Mutation or linkage analysis can be used for prenatal diagnosis,⁴⁰ however, because almost every patient has a unique mutation, the diagnostic reliability of these tests are limited. Parents also have to know that because of the phenotypic variability, the molecular diagnosis cannot predict clinical severity of the disease. They also should be informed about 1% risk of fetal miscarriage because of sampling for genetic testing. During the preconception consultation, physicians should carefully counsel the woman and her family about possible morbidity during and after pregnancy. Women with MFS should be evaluated for cardiovascular abnormalities by both transthoracic and transesophageal echocardiogram,^{44,45} or by CT or MRI for assessment of both the ascending as well as the descending aorta before pregnancy.⁴⁶ These complications appear more likely in patients with aortic root dilatation (>4.0 cm) or rapid progression of the dilatation or previous dissection of the ascending aorta.^{17,19} However, dissection in pregnant women with normal size of the aorta has been reported,^{20,29} indicating that event-free pregnancy cannot be guaranteed to any patient with MFS. Thus, patients should be told about the 1% complication rate when the aortic root diameter is <4.0 cm and up to 10% in those with ascending aorta >4.0 cm.^{19,20} Based on most series, aortic dissection occurred in MFS women in their third decade of life, therefore it is advisable to plan a pregnancy at a younger age.^{7,17} It should also be emphasized that although the surgical techniques and surgical results have improved over the last decade, surgery during pregnancy still carries a risk for the mother and fetus. Elective aortic root replacement can be performed with low morbidity and mortality^{47–49}; for this reason, women with MFS who have an indication for elective surgery, should undergo aortic root replacement prior to pregnancy. The woman and her family should also be informed prior to pregnancy of the need for close follow-up during gestation as well as the need to use beta-blockers and possibly other cardiac medications and the potential side effects to the fetus. Women with prior aortic valve replacement with a mechanical prosthesis should be informed on the risk and the complexity of anticoagulation during pregnancy.⁵⁰

SURGICAL TREATMENT AND PREGNANCY

The leading cause of morbidity and mortality in MFS is aortic dissection, and prophylactic surgery is indicated to prevent this complication. Current recommendations call for surgical repair of the ascending aortic dilatation if it exceeds 5.5 cm in patients without MFS, and 5.0 cm in pts with MFS.^{49,51} In patients with aorta <5.0 cm, surgical intervention can be considered with rapid growth of the aortic diameter, a family history of premature aortic dissection, and the presence of more than mild aortic regurgitation.⁴⁸

Recently, new guidelines for pregnant women with MFS were established⁵² recommending that women with aortic diameter >4.0 cm be informed about the 10% risk of dissection, as well as recommending that elective preventive surgery be performed before pregnancy in patients with aortic root >4.7 cm, to reduce the

complication rates. Previous studies reported favorable maternal and fetal outcomes during pregnancy which were associated with minimal aortic enlargement (<4.0 cm).^{17,19,20} The more recent prospective study found that pregnancy is relatively safe with aortic root diameter <4.5 cm.³⁷

Outcomes of Surgery

Gott et al presented the outcomes of 675 patients with MFS who underwent surgery in 10 centers with special expertise in aortic surgery.⁴⁹ The 30-day mortality was 1.5% for elective surgery and 11.7% for an emergency operation, and the overall 5 year survival was 91%, however, 10% of patients required subsequent distal aortic surgery. Because of the young age of patients with MFS, a mechanical valve prosthesis was used, except for special cases, which include women planning pregnancy. A valve-sparing aortic root replacement has been advocated^{53,54} in patients with MFS, and the safety and long-term durability of this procedure has been reported.⁵⁵ Long-term survival has been excellent and the rate of complications low, however the durability of this procedure may be somewhat limited, with 17% of patients requiring reoperation by 10 years.⁵⁶ Thus, this technique can be a reasonable alternative for pregnant women and women of childbearing age who are planning a pregnancy and are willing to accept the risk of possible reoperation in the future.

Successful surgery during gestation or shortly after delivery has been reported in a number of women for a marked dilatation of the aorta⁵⁷ and for aortic dissection.^{14,17,21,23,29,35}

A retrospective analysis¹⁷ of outcomes of 16 pregnant women with MFS complicated by aortic dissection has found that an enlarged aortic root >4.0 cm or an increase of aortic root diameter during pregnancy was associated with a risk of Type A dissection. Of note, an impressive decrease in maternal and fetal mortality over the years was described with maternal mortality decreasing from 30% in 1990–1994 to 0% in 2002–2004 and fetal mortality from 50% to 10%. It should be recognized, however, that cardiac surgery in general, and aortic surgery in particular, have been shown to result in increased fetal loss.^{17,29,58} For this reason, if fetal maturity can be confirmed, a C-section should be done before or concomitantly with thoracic surgery.^{16,17}

MEDICAL THERAPY

A number of studies have demonstrated that β -blockers, such as propranolol, atenolol, or metoprolol, increase aortic distensibility, and reduce aortic stiffness and pulse wave velocity, especially in young patients and in those with aortic root diameters <4.0 cm.^{59–62} Several preliminary studies^{59–64} have suggested that β -blocking agents may also have a beneficial effect on the rate of aortic root dilatation in children and adolescents. These initial results were supported in reports by Shores et al⁵⁹ and Rossi-Foulkes et al,⁶⁰ who showed that patients receiving β -blockers had slower aortic root absolute growth and a significantly reduced rate of complications, such as aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure, and death.

The applicability of these findings to pregnant patients needs to be studied in more detail, but on the basis of available information, the prophylactic use of β -blockers during pregnancy seems to make a good clinical sense. Beta blockers have been extensively used during pregnancy to treat various conditions,^{65–72} including hypertension, thyrotoxicosis, hypertrophic cardiomyopathy, and maternal and fetal supraventricular tachyarrhythmias. Although the overall experience with these drugs in pregnancy has been favorable, potential side effects, including fetal growth retardation, bradycardia, hypoglycemia, hyperbilirubinemia, and apnea at birth in the newborn, have been reported.^{67,71} Such side effects should be

anticipated by the clinician. It has been shown that propranolol given to pregnant women blocks the inhibitory effects of epinephrine on myometrial activity. The nonselective β -blocking effect of propranolol may, therefore, facilitate an increase in uterine activity. Although the clinical relevance of these findings is not clear, the use of β 1-adrenergic receptor-blocking agents, such as metoprolol and atenolol, may be preferred during pregnancy.^{72,73}

It is recommended that in the nonpregnant patient, β -blockers be up titrated to a resting heart rate of <60 bpm. Because heart rate is increased during gestation, the dose should be titrated to reduce resting heart rate by at least 20%.

β -Blocking agents are excreted in breast milk.⁷³ Although the use of these drugs has a potential adverse effect, the benefit of decreased mortality in mothers with MFS is likely to outweigh the risks for the baby. For this reason, and unless hepatic function is markedly impaired, breast-feeding should not be discouraged.

Standard medical therapy for acute aortic dissection includes the use of intravenous nitroprusside and β -blockers to control blood pressure and decrease left ventricular contractility, and thus reduce ejection velocity and minimize shear forces. The use of nitroprusside during pregnancy, however, may lead to thiocyanate toxicity to the fetus,⁷⁴ thus the gestational use of hydralazine to control blood pressure is preferred. Hydralazine has been used extensively to control blood pressure during pregnancy, and its safety has been well established.⁷⁴

Follow-Up During Pregnancy

Follow-up of women with MFS with no dilation of the aorta should be done on a monthly basis with echocardiographic evaluation of the size of the aorta each trimester and prior to delivery.⁷⁵ In patients with aortic root dilatation (>4.0 cm), progressive dilatation during pregnancy or a history of surgery for aortic dilatation or dissection prior to pregnancy, an echocardiographic examination should be performed every 4 to 6 weeks. MRI is considered safe during pregnancy, as magnetic energy has been shown not to be harmful for the developing fetus.^{76,77} For this reason MRI can be used for evaluation of the aorta during pregnancy in cases when echocardiography is not able to provide sufficient information.

LABOR AND DELIVERY

Vaginal delivery can be safely performed in patients with MFS who have no cardiovascular involvement or stable minimal aortic dilatation (<4.0 cm). In these patients, C-section should be reserved for obstetrical indications.²⁰ At the same time, however, to reduce the stress of labor, epidural anesthesia to minimize pain and forceps or vacuum to shorten the second stage of labor are recommended. Both systolic and diastolic blood pressures increase markedly during uterine contractions and pain,¹⁴ and these changes should be anticipated and prevented with epidural anesthesia and β -blocking or vasodilator agents. It should be noted that lumbosacral dural ectasia is present in about 70% of patients with MFS and therefore an anesthesiology consultation is advised to plan the appropriate anesthesia prior to delivery.¹¹ Patients with aortic dilatation \geq 4.0 cm or with progressive dilatation of aorta during pregnancy are at high risk for aortic dissection and elective C-section with epidural²⁰ or general anesthesia⁷⁸ is preferred to minimize the hemodynamic changes associated with vaginal delivery. If an aortic root \geq 5.0 cm is diagnosed in the later stage of pregnancy, surgery should be performed a few days after delivery, if possible. In the case of an urgent need for surgery (type A aortic dissection), to prevent an unfavorable fetal outcome, emergency delivery of the fetus by a C-section is recommended, followed by cardiac surgery.^{17,22,24,29,30}

REFERENCES

- Judge DP, Dietz HC. Marfan syndrome. *Lancet*. 2005;366:1965–1976.
- Dietz HC, Cutting GR, Pyeritz RE, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature*. 1991;352:337–339.
- Pyeritz RE, McKusick VA. The Marfan syndrome: diagnosis and management. *N Engl J Med*. 1979;300:772–777.
- Rossiter JP, Johnson TR. Management of genetic disorders during pregnancy. *Obstet Gynecol Clin North Am*. 1992;19:801–813.
- De Paepe A, Devereux RB, Dietz HC, et al. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet*. 1996;62:417–426.
- Murdoch JL, Walker BA, Halpern BL, et al. Life expectancy and causes of death in the Marfan syndrome. *N Engl J Med*. 1972;286:804–808.
- Silverman DI, Burton KJ, Gray J, et al. Life expectancy in the Marfan syndrome. *Am J Cardiol*. 1995;75:157–160.
- Mizuguchi T, Collod-Beroud G, Akiyama T, et al. Heterozygous TGFBR2 mutations in Marfan syndrome. *Nat Genet*. 2004;36:855–860.
- Loeys B, De Backer J, Van Acker P, et al. Comprehensive molecular screening of the FBN1 gene favors locus homogeneity of classical Marfan syndrome. *Hum Mutat*. 2004;24:140–146.
- Beighton P, de Paepe A, Danks D, et al. International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986. *Am J Med Genet*. 1988;29:581–594.
- Simpson LL, Athanassios AM, D'Alton ME. Marfan syndrome in pregnancy. *Curr Opin Obstet Gynecol*. 1997;9:337–341.
- Elkayam U, Ostrzega E, Shotan A, et al. Cardiovascular problems in pregnant women with the Marfan syndrome. *Ann Intern Med*. 1995;123:117–122.
- Elkayam U, Ostrzega E, Shotan A. Marfan's syndrome and pregnancy. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy*. New York, NY: Wiley-Liss; 1998:211–221.
- Elkayam U, Gleicher N. Hemodynamics and cardiac function during normal pregnancy and the puerperium. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy*. New York, NY: Wiley-Liss; 1995:23–32.
- Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol*. 1967;83:336–341.
- Pyeritz RE. Maternal and fetal complications of pregnancy in the Marfan syndrome. *Am J Med*. 1981;71:784–790.
- Immer FF, Bansal AG, Immer-Bansal AS, et al. Aortic dissection in pregnancy: analysis of risk factors and outcome. *Ann Thorac Surg*. 2003;76:309–314.
- Jayaram A, Carp HM, Davis L, et al. Pregnancy complicated by aortic dissection: caesarean delivery during extradural anaesthesia. *Br J Anaesth*. 1995;75:358–360.
- Rossiter JP, Repke JT, Morales AJ, et al. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol*. 1995;173:1599–1606.
- Lipscomb KJ, Smith JC, Clarke B, et al. Outcome of pregnancy in women with Marfan syndrome. *Br J Obstet Gynaecol*. 1997;104:201–206.
- Zeebregts CJ, Schepens MA, Hameeteeman TM, et al. Acute aortic dissection complicating pregnancy. *Ann Thorac Surg*. 1997;64:1345–1348.
- Mul TF, van Herwerden LA, Cohen-Overbeek TE, et al. Hypoxic-ischemic fetal insult resulting from maternal aortic root replacement, with normal fetal heart rate at term. *Am J Obstet Gynecol*. 1998;179:825–827.
- Akashi H, Tayama K, Fujino T, et al. Surgical treatment for acute type A aortic dissection in pregnancy: a case of aortic root replacement just after Cesarean section. *Jpn Circ J*. 2000;64:729–730.
- Jondeau G, Nataf P, Belarbi A, et al. Aortic dissection at 6 months gestation in a woman with Marfan syndrome. Simultaneous Bentall intervention and cesarean section [in French]. *Arch Mal Coeur Vaiss*. 2000;93:185–187.
- Fabricius AM, Autschbach R, Doll N, et al. Acute aortic dissection during pregnancy. *Thorac Cardiovasc Surg*. 2001;49:56–57.
- Preiss M, Hosli I, Holzgreve W, et al. Aortic dissection in pregnancy in Marfan syndrome: case report and treatment concept [in German]. *Z Geburtshilfe Neonatol*. 2001;205:110–113.
- Lind J, Wallenburg HC. The Marfan syndrome and pregnancy: a retrospective study in a Dutch population. *Eur J Obstet Gynecol Reprod Biol*. 2001;98:28–35.
- Rahman J, Rahman FZ, Rahman W, et al. Obstetric and gynecologic complications in women with Marfan syndrome. *J Reprod Med*. 2003;48:723–728.
- Sakaguchi M, Kitahara H, Seto T, et al. Surgery for acute type A aortic dissection in pregnant patients with Marfan syndrome. *Eur J Cardiothorac Surg*. 2005;28:280–283; discussion 283–285.
- Tilak M, Smith J, Rogers D, et al. Successful near-term pregnancy outcome after repair of a dissecting thoracic aortic aneurysm at 14 weeks gestation. *Can J Anaesth*. 2005;52:1071–1075.
- Ioscovic A, Elstein D. Images in anesthesia: transesophageal echocardiography during Cesarean section in a Marfan's patient with aortic dissection. *Can J Anaesth*. 2005;52:737–738.
- Naito H, Naito H, Tada K. Open heart operation for a pregnant patient with Marfan syndrome [in Japanese]. *Masui*. 2005;54:525–529.
- Chavanon O, Rama A, Leprince P, et al. Valve-sparing operation in a young woman with Marfan syndrome: a word of caution. *J Thorac Cardiovasc Surg*. 2006;132:683–684.
- Matsuda H, Ogino H, Neki R, et al. Hemiarch replacement during pregnancy (19 weeks) utilizing normothermic selective cerebral perfusion. *Eur J Cardiothorac Surg*. 2006;29:1061–1063.
- Tomihara A, Ashizawa N, Abe K, et al. Risk of development of abdominal aortic aneurysm and dissection of thoracic aorta in a postpartum woman with Marfan syndrome. *Intern Med*. 2006;45:1285–1289.
- Tutarel O, Lotz J, Roentgen P, et al. Pregnancy in a Marfan patient with pre-existing aortic dissection. *Int J Cardiol*. 2007;114:E36–E37.
- Meijboom LJ, Timmermans J, Zwinderman AH, et al. Aortic root growth in men and women with the Marfan syndrome. *Am J Cardiol*. 2005;96:1441–1444.
- Meijboom LJ, Drenthen W, Pieper PG, et al. Obstetric complications in Marfan syndrome. *Int J Cardiol*. 2006;110:53–59.
- Child AH. Marfan syndrome—current medical and genetic knowledge: how to treat and when. *J Card Surg*. 1997;12:131–135; discussion 135–136.
- Eldadah ZA, Grifo JA, Dietz HC. Marfan syndrome as a paradigm for transcript-targeted preimplantation diagnosis of heterozygous mutations. *Nat Med*. 1995;1:798–803.
- Godfrey M, Vandemark N, Wang M, et al. Prenatal diagnosis and a donor splice site mutation in fibrillin in a family with Marfan syndrome. *Am J Hum Genet*. 1993;53:472–480.
- Rantamaki T, Raghunath M, Karttunen L, et al. Prenatal diagnosis of Marfan syndrome: identification of a fibrillin-1 mutation in chorionic villus sample. *Prenat Diagn*. 1995;15:1176–1181.
- Ramaswamy P, Lytrivi ID, Nguyen K, et al. Neonatal Marfan syndrome: in utero presentation with aortic and pulmonary artery dilatation and successful repair of an acute flail mitral valve leaflet in infancy. *Pediatr Cardiol*. 2006;27:763–765.
- Penco M, Papani S, Dagianti A, et al. Usefulness of transesophageal echocardiography in the assessment of aortic dissection. *Am J Cardiol*. 2000;86:53G–56G.
- Cigarroa JE, Isselbacher EM, DeSanctis RW, et al. Diagnostic imaging in the evaluation of suspected aortic dissection: old standards and new directions. *N Engl J Med*. 1993;328:35–43.
- Milewicz DM, Dietz HC, Miller DC. Treatment of aortic disease in patients with Marfan syndrome. *Circulation*. 2005;111:e150–e157.
- Kouchoukos NT, Dougenis D. Surgery of the thoracic aorta. *N Engl J Med*. 1997;336:1876–1888.
- David TE. Aortic surgery in the Marfan syndrome. *Adv Card Surg*. 2001;13:61–75.
- Gott VL, Cameron DE, Alejo DE, et al. Aortic root replacement in 271 Marfan patients: a 24-year experience. *Ann Thorac Surg*. 2002;73:438–443.
- Elkayam U, Bitar F. Valvular heart disease and pregnancy. Part II: prosthetic valves. *J Am Coll Cardiol*. 2005;45:403–410.
- Davies RR, Goldstein LJ, Coady MA, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg*. 2002;73:17–27; discussion 27–28.
- Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2003;24:761–781.
- Sarsam MA, Yacoub M. Remodeling of the aortic valve annulus. *J Thorac Cardiovasc Surg*. 1993;105:435–438.
- David TE, Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. *J Thorac Cardiovasc Surg*. 1992;103:617–621;622.
- De Oliveira NC, David TE, Ivanov J, et al. Results of surgery for aortic root aneurysm in patients with Marfan syndrome. *J Thorac Cardiovasc Surg*. 2003;125:789–796.
- Birks EJ, Webb C, Child A, et al. Early and long-term results of a valve-sparing operation for Marfan syndrome. *Circulation*. 1999;100:II29–II35.
- Smith VC, Eckenbrecht PD, Hankins GD, et al. Marfan syndrome, pregnancy,

- and the cardiac surgeon. *Mil Med.* 1989;154:404–406.
58. Pomini F, Mercogliano D, Cavalletti C, et al. Cardiopulmonary bypass in pregnancy. *Ann Thorac Surg.* 1996;61:259–268.
59. Shores J, Berger KR, Murphy EA, et al. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med.* 1994;330:1335–1341.
60. Rossi-Foulkes R, Roman MJ, Rosen SE, et al. Phenotypic features and impact of beta blocker or calcium antagonist therapy on aortic lumen size in the Marfan syndrome. *Am J Cardiol.* 1999;83:1364–1368.
61. Groenink M, Lohuis TA, Tijssen JG, et al. Survival and complication free survival in Marfan's syndrome: implications of current guidelines. *Heart.* 1999;82:499–504.
62. Haouzi A, Berglund H, Pelikan PC, et al. Heterogeneous aortic response to acute beta-adrenergic blockade in Marfan syndrome. *Am Heart J.* 1997;133:60–63.
63. Rios AS, Silber EN, Bavishi N, et al. Effect of long-term beta-blockade on aortic root compliance in patients with Marfan syndrome. *Am Heart J.* 1999;137:1057–1061.
64. Zahka K, Hensley C, Glesby M, et al. The Impact of medical and surgical therapy on the cardiovascular prognosis of the Marfan syndrome in early childhood [abstract]. *J Am Coll Cardiol.* 1989;13:119A.
65. Pruyt SC, Phelan JP, Buchanan GC. Long-term propranolol therapy in pregnancy: maternal and fetal outcome. *Am J Obstet Gynecol.* 1979;135:485–489.
66. Bott-Kanner G, Schweitzer A, Reisner SH, et al. Propranolol and hydralazine in the management of essential hypertension in pregnancy. *Br J Obstet Gynaecol.* 1980;87:110–114.
67. Bullock JL, Harris RE, Young R. Treatment of thyrotoxicosis during pregnancy with propranolol. *Am J Obstet Gynecol.* 1975;121:242–245.
68. Oakley GD, McGarry K, Limb DG, et al. Management of pregnancy in patients with hypertrophic cardiomyopathy. *Br Med J.* 1979;1:1749–1750.
69. Kleinman CS, Copel JA, Weinstein EM, et al. Treatment of fetal supraventricular tachyarrhythmias. *J Clin Ultrasound.* 1985;13:265–273.
70. Teuscher A, Bossi E, Imhof P, et al. Effect of propranolol on fetal tachycardia in diabetic pregnancy. *Am J Cardiol.* 1978;42:304–307.
71. Widerhorn J, Widerhorn AL, Rahimtoola SH, et al. WPW syndrome during pregnancy: increased incidence of supraventricular arrhythmias. *Am Heart J.* 1992;123:796–798.
72. Hogstedt S, Lindeberg S, Axelsson O, et al. A prospective controlled trial of metoprolol-hydralazine treatment in hypertension during pregnancy. *Acta Obstet Gynecol Scand.* 1985;64:505–510.
73. Liedholm H, Melander A, Bitzen PO, et al. Accumulation of atenolol and metoprolol in human breast milk. *Eur J Clin Pharmacol.* 1981;20:229–231.
74. Calvin S. Use of vasodilators during pregnancy. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy.* New York, NY: Wiley-Liss; 1995:391–397.
75. Stoddard MF, Longaker RA, Vuocolo LM, et al. Transesophageal echocardiography in the pregnant patient. *Am Heart J.* 1992;124:785–787.
76. De Wilde JP, Rivers AW, Price DL. A review of the current use of magnetic resonance imaging in pregnancy and safety implications for the fetus. *Prog Biophys Mol Biol.* 2005;87:335–353.
77. Garcia-Bournissen F, Shrim A, et al. Safety of gadolinium during pregnancy. *Can Fam Physician.* 2006;52:309–310.
78. Tritapepe L, Voci P, Pinto G, et al. Anaesthesia for caesarean section in a Marfan patient with recurrent aortic dissection. *Can J Anaesth.* 1996;43:1153–1155.