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Cardiovascular Problems in Pregnant Women With Marfan Syndrome

Sorel Goland, MD; Uri Elkayam, MD

Case presentation: A 34-year-old Korean woman with Marfan syndrome (MFS) was referred for cardiac evaluation in the 24th week of her first pregnancy. Although she was diagnosed with MFS at the age of 7 years, the patient did not have cardiac evaluations before her pregnancy. An echocardiogram demonstrated mildly dilated left ventricle with normal systolic function, moderately dilated left atrium, severe dilation of the aortic root with maximum diameter of 64 mm, and moderate aortic regurgitation. Magnetic resonance imaging showed a 62×54-mm aortic root aneurysm with no evidence of aortic dissection. The patient was started on metoprolol 50 mg BID, which was increased to 100 mg BID, and she was advised to have an elective surgical aortic repair. She decided to delay her surgery to allow fetal maturity. The patient was hospitalized for 2 weeks for close monitoring and underwent a successful cesarean section at 28 weeks' gestation followed by a successful Bentall procedure to repair her aortic aneurysm and replace her aortic valve.

Diagnosis of MFS

The diagnosis is based on the Ghent criteria (Table) and relies on history,

physical examination, and a molecular genetic test.¹ MFS often remains undiagnosed before pregnancy and is recognized only after the development of complications. Because pregnancy-associated complications may be life threatening, health providers caring for women at childbearing ages should be familiar with the diagnostic criteria of MFS. The syndrome involves multiple organ systems, and the diagnosis is at times challenging² and requires a multidisciplinary approach by specialists in cardiology, ophthalmology, radiology, and clinical genetics.

Cardiovascular Risk of Pregnancy

Risk for the Mother

Pregnancy is associated with increased risk of aortic dissection,^{3,4} probably caused by hemodynamic changes⁵ and by hormonally mediated decrease in the amount of mucopolysaccharides and loss of elastic fibers in the aortic wall.⁶ Reviewing the English literature in the last decade, we found 39 cases that provide information regarding potential pregnancy-related complications in women with MFS.^{7–28} The mean age of these patients was 30±4 years; 18 patients had dissection of the

ascending aorta, 9 of the descending aorta, and 2 of both. In 19 patients aortic dilatation was diagnosed before 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 between weeks 13 and 20, 18 between weeks 24 and 40, and 6 after the delivery (between day of delivery to 3 months postpartum). In addition, 5 patients developed progressive dilatation of the ascending aorta, which required surgery during pregnancy, and 2 patients had intracranial hemorrhage postpartum (30 minutes and 6 weeks after the delivery). Two other patients with distal dissection diagnosed at initial evaluations remained stable during pregnancy. Fetal loss was reported in 4 cases with aortic dissection, 2 as a result of maternal death. The majority of patients who developed dissection during pregnancy (n=23) delivered by cesarean section. Timing of surgery (28 cases) was before delivery in 6 women, after delivery in 15, and immediately after cesarean section in 7. Although the majority of patients who were evaluated before or early in pregnancy had dilated aortic root, aortic

From the Department of Medicine and Obstetrics and Gynecology, University of Southern California Keck School of Medicine, Los Angeles (U.E.), and Kaplan Medical Center, Rehovot, Israel (S.G.).

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

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**Table. Ghent Diagnostic Nosology**

System	Major Criteria	Minor Criteria
Skeletal	At least 4 of the following features: <ul style="list-style-type: none"> ● Pectus carinatum ● Pectus excavatum requiring surgery ● Upper-to-lower segment ratio <0.86 or span:height >1.05 ● Wrist and thumb signs ● Scoliosis >20° or spondylolisthesis ● Reduced elbow extension (<170°) ● Pes planus ● Acetabular protrusion 	Two of the major features, or 1 major feature and 2 of the following: <ul style="list-style-type: none"> ● 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, aged <40 y Calcified mitral annulus, aged <40 y 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 MFS Inheritance of DNA marker haplotype linked to MFS in the family	None

Having 1 of the features listed constitutes a major criterion or minor criterion for all systems except the skeletal system, where >1 feature is needed. The diagnosis of MFS requires major criteria in 1 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 a third are required for diagnosis.

dissection also occurred in 2 patients with aortic diameter <40 mm.

What is the expected rate of complications in unselected women with MFS during pregnancy? A number of recent studies^{8,9,16,28} have provided information on >350 unselected pregnancies in patients with MFS and suggested an expected rate of aortic dissection of ≈3% with an estimated 1% in women with aortic diameter <40 mm and 10% in high-risk patients (aortic root diameter >40 mm, rapid dilatation, or previous dissection of the ascending aorta).²⁹ It should be noted, however, that although uncommon, aortic dissections have been reported in women with normal-size aorta,^{8,30} and therefore an event-free pregnancy cannot be guaranteed to women with MFS even in the presence of normal aortic diameter.^{8,9,18}

Long-Term Outcome After Pregnancy

Information regarding expected morbidity and mortality after pregnancy should be provided to a woman with MFS who is considering pregnancy. A study³¹ of 125 patients with mean age of 21±15 years who did not present with aortic root dissection as a first sign of the disease reported 5- and 10-year survival after diagnosis of 95% and 88% and complication-free survival of 78% and 66%, respectively. Ten percent of the patients developed dissection, and 24% underwent prophylactic repair. Similar results were reported by Svensson et al³² and Gott et al³³ in a total of 393 patients who underwent aortic surgery for aortic root replacement. The rate of death was higher in patients who had urgent or emergency operation. Major

complications included arrhythmias, dissection or rupture of residual aorta, heart failure due to mitral valve disease, endocarditis, and intercerebral or spinal hemorrhage. These data clearly indicate that despite effective medical and surgical therapy, MFS is associated with increased likelihood of major morbidity and even premature death in women after successful delivery. The likelihood of complications is especially high in patients with a history of acute type A dissection, but unexpected fatal complications may also occur after prophylactic aortic root surgery²⁸ or mitral valve surgery.³⁴

Risk for the Fetus

The risk of transmission of MFS to the offspring is at least 50%.¹⁶ Because of the variability in the clinical presentation, severe expression of the syn-

drome can occur in an offspring of a mother with a relatively mild presentation. It should also be noted that development of aortic dissection in the mother carries a substantial risk to the fetus.^{4,8,11,15,30} In addition, MFS is associated with a high rate (40%) of obstetric complications such as premature delivery mainly due to premature rupture of membranes and increased mortality in the offspring.²⁸

Prenatal Diagnosis

Mutation or linkage analysis can be used for prenatal diagnosis,^{35,36} which can also be accomplished by chorionic villus sampling or amniocentesis (cell culture) in informative families.^{36,37} Because >500 mutations have been reported in FBN1, almost every patient has a unique mutation, and no efficient diagnostic test yet exists.³⁸ Recently, mutation detection has become available with thorough screening methods, but $\approx 10\%$ of mutations that cause MFS can still be missed.³⁸ Moreover, as indicated above, molecular diagnosis cannot predict the clinical severity of the disease.³⁷ In addition to the genetic linkage that can be done in early gestation, echocardiography may be used in the third trimester for the diagnosis of cardiac manifestations of MFS in the fetus such as atrioventricular valve regurgitation and dilatation of aortic root and pulmonary artery.³⁹

Preconception Evaluation and Counseling

The management of patients with MFS ideally should start before conception. The patient should undergo a careful cardiovascular evaluation, including assessment of proximal and distal aortic diameter as well as valvular and cardiac function by echocardiogram, computed tomography, or magnetic resonance imaging. Holter monitoring should be performed in patients with ventricular dilatation for detection of ventricular arrhythmias.⁴⁰ Patients should be informed about potential pregnancy-related maternal complications and the high risk of transmitting the syndrome to the offspring with the possibility of more severe expression

of the disease.³⁵ The woman and her family should also be informed of the need for close follow-up during pregnancy as well as the use of β -blockers and possibly other cardiac medications and the potential side effects to the fetus. Women with a history of aortic valve replacement with a mechanical prosthesis should be informed of the complexity and risk of anticoagulation in pregnancy.⁴¹ The possibility and limitations of prenatal diagnosis with the use of both genetic linkage and fetal echocardiography³⁹ should be explained. In addition, the patient should be informed about the likelihood of morbidity and possibly reduced longevity³¹ even after successful pregnancy.

Risk of Arrhythmias and Sudden Death

Yetman et al⁴⁰ reported sudden arrhythmic death despite β -blocker therapy in 3 of 70 patients with MFS who had mitral valve prolapse and left ventricular dilatation as well as ventricular couplets or tachycardia on routine 24-hour Holter monitoring. Because of the increased incidence of arrhythmias during pregnancy,⁴² implantation of an internal defibrillator should be considered in high-risk patients before conception.

Surgical Treatment and Pregnancy

Current recommendations call for prophylactic surgery in cases of ascending aortic dilatation >50 mm for patients with MFS.^{43,44} In patients with aortic diameter <50 mm, surgical intervention can be considered in cases with rapid growth, a family history of premature aortic dissection, and the presence of more than mild aortic regurgitation. Because of the increased risk associated with urgent surgery for dissection during gestation, a prophylactic elective repair is preferred in women who contemplate pregnancy. Recent guidelines have suggested an elective surgery before pregnancy for women with aortic root >47 mm.²⁹ Valve-sparing aortic root replacement has been advocated in young patients with MFS to prevent the need for

anticoagulation associated with valve replacement.^{44–47} Although excellent long-term survival and a low rate of complications have been described,^{45,46} the durability of this procedure may be somewhat limited.⁴⁷ Because the risk associated with emergency operation for aortic dissection or rupture is high,⁴⁸ a progressive, >10-mm dilatation of the aorta during pregnancy requires an elective surgery either after a therapeutic abortion (up to 20 weeks) or during pregnancy.

Successful surgeries during gestation or shortly after delivery^{4,5,10,21,30,33} have been reported in a number of women with MFS. A review of 40 pregnant women with surgery due to type A dissection prepartum reported 15% maternal death rate; however, death rates decreased from 30% in 1990–1994 to 0% in 2002–2004, and fetal death rates decreased from 50% to 10%, respectively.³⁰ Because cardiac surgery continues to be associated with increased fetal loss,^{18,30,48} cesarean section should be performed before or concomitantly with thoracic surgery if fetal maturity can be confirmed.^{12,13,18}

Medical Therapy

β -Blockers have been shown in nonpregnant patients to slow the growth of the aortic root and significantly reduce rate of aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure, and death.^{49–51} β -Blockers have been used extensively during pregnancy for various medical conditions with overall favorable results.⁵² Anecdotal reports of side effects include fetal growth retardation, bradycardia, hypoglycemia, hyperbilirubinemia, and apnea at birth in the newborn. Such side effects should therefore be anticipated by the clinician.

The use of propranolol, a nonselective β_1 receptor blocker that was successfully used in nonpregnant patients,⁵⁰ is not ideal in pregnancy because it blocks the inhibitory effects of epinephrine on myometrial activity and may therefore facilitate uterine

activity. The use of selective β_1 receptor blockers may therefore be preferred during pregnancy.⁵² Because lower birth weight with atenolol during gestation has been reported,^{53,54} metoprolol may be preferred. It is recommended in the nonpregnant patient that dosage be titrated to a resting heart rate of <60 bpm.⁴⁹ Because of increased sympathetic output during pregnancy, heart rate is increased, and a higher dose of β -blockers may be needed to achieve adequate heart rate control.^{55,56} When initiated during pregnancy, the dose of β -blockers should be titrated to reduce resting heart rate by $\geq 20\%$. β -Blocking agents are excreted in breast milk,⁵⁷ and nursing infants should therefore be monitored for adverse effects.

A recent study⁵⁸ has reported a favorable effect of angiotensin receptor blockers on the rate of progressive aortic root dilation. The use of angiotensin receptor blockers in pregnancy, however, is contraindicated because of potential toxicity to the fetus.⁵⁹

Follow-Up During Pregnancy

Patients with MFS should be followed during pregnancy jointly by their obstetrician and cardiologist. For patients with normal-size aorta, antenatal visits should be scheduled every month, and an echocardiogram should be scheduled during each trimester and before the delivery. In patients with aortic diameter ≥ 40 mm, progressive dilation, or a history of aortic surgery for aortic dilatation or dissection, an echocardiographic examination should be performed every 4 to 6 weeks.

Labor and Delivery

Vaginal delivery is safe in patients with MFS who have no significant cardiovascular involvement and normal aortic diameter (<40 mm).^{6,32} To minimize the stress of labor, epidural anesthesia should be used to reduce pain, and forceps or vacuum should be used to shorten the second stage of labor. Because $\approx 70\%$ of patients with MFS present with lumbosacral dural ectasia, an anesthetist should be consulted before delivery.⁴ Both systolic

and diastolic blood pressures increase markedly during uterine contractions and pain.⁵ These changes should be anticipated and prevented with epidural anesthesia, β -blockers, and vasodilator agents. Patients with aortic dilatation ≥ 40 mm, progressive dilatation of the aorta during pregnancy, or a history of aortic repair for prior dissection are at high risk for aortic dissection and should therefore have an elective cesarean section with epidural or general anesthesia to minimize hemodynamic changes associated with vaginal delivery. Postpartum hemorrhage of the uterine vasculature 3 days after cesarean section secondary to MFS has been reported¹¹ and should be anticipated. If elective aortic repair is indicated in the later stage of pregnancy, surgery should be performed after delivery, if possible. In case of an urgent need for surgery and to prevent unfavorable fetal outcome, an immediate cesarean section followed by cardiac surgery is recommended.^{11,13,18,19,30}

Summary

Our case scenario presents some of the challenges faced by the pregnant patient with MFS and her physicians. Although diagnosed at a young age, she was not treated with β -blockers and did not have a preconception evaluation and thus was exposed to a high risk of acute aortic dissection during pregnancy. A finding of a dilated aorta before pregnancy would have mandated surgery before conception. The case also demonstrates the dilemma faced by the patient of having surgery during pregnancy, which is associated with high rate of fetal loss and other fetal complications. Because of concern for her fetus, the patient preferred to assume the risk herself and delayed the surgery to allow fetal maturity and delivery of the baby before the operation. Because of an increased risk of aortic dissection due to the hemodynamic strain involved with vaginal delivery, the delivery was done by cesarean section.

Disclosures

None.

References

- De Paepe A, Devereux RB, Dietz, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet.* 1996;417–426.
- Summers KM, West JA, Peterson MM, Stark D, McGill JJ, West MJ. Challenges in the diagnosis of Marfan syndrome. *Med J Aust.* 2006;184:627–631.
- Elkayam U, Ostrzega E, Shotan A, Mehra A. Cardiovascular problems in pregnant women with Marfan syndrome. *Ann Intern Med.* 1995;123:117–122.
- Lachandani S, Wingfield M. Pregnancy in women with Marfan's syndrome. *Eur J Obstet Gynecol.* 2003;110:125–130.
- 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; 1998:23–32.
- Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol.* 1967;83:336–341.
- Jayaram A, Carp HM, Davis L, Jacobson SL. Pregnancy complicated by aortic dissection: caesarean delivery during extradural anaesthesia. *Br J Anaesth.* 1995;75:358–360.
- Rositer JP, Repke JT, Morales AJ, Murphy EA, Pyeritz RE. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol.* 1995;173:1599–1606.
- Lipscomb KJ, Smith JC, Clarke B, Donnai P, Harris R. Outcome of pregnancy in women with Marfan's syndrome. *Br J Obstet Gynaecol.* 1997;104:201–206.
- Zeebregts CJ, Schepens MA, Hameeteman TM, Morshuis WJ, de la Riviere AB. Acute aortic dissection complicating pregnancy. *Ann Thorac Surg.* 1997;64:1345–1348.
- Mul TF, van Herwerden LA, Cohen-Overbeek TE, Catsman-Berrevoets CE, Lotgering FK. 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, Onitsuka S, Sakashita H, Aoyagi S. 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, Farcot JC, Lung B, Delorme G, Gandjbakhch I, Boudarias JP. Aortic dissection at 6 months gestation in women with Marfan's syndrome: simultaneous Bentall intervention and cesarean section [in French]. *Arch Mal Coeur Vaiss.* 2000;93:185–187.
- Fabricius AM, Autschbach R, Doll N, Mohr W. Acute aortic dissection during pregnancy. *Thorac Cardiovasc Surg.* 2001;49:56–57.
- Preiss M, Hosli I, Holzgreve W, Zerkowski HR. Aortic dissection in pregnancy in Marfan syndrome: case report and treatment concept [in German]. *Z Geburtshilfe Neonatol.* 2001;205:110–113.

16. 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.
17. Rahman J, Rahman FZ, Rahman W, al-Suleiman SA, Rahman MS. Obstetric and gynecologic complications in women with Marfan syndrome. *J Reprod Med.* 2003;48:723–728.
18. Sakaguchi M, Kitahara H, Seto T, Furusawa T, Fukui D, Yanagiya N, Nishimura K, Amano J. Surgery for acute type A aortic dissection in pregnant patients with Marfan syndrome. *Eur J Cardiothorac Surg.* 2005;28:280–283.
19. Tilak M, Smith J, Rogers D, Fox P, Muntazar M, Peyton M. Successful near-term pregnancy outcome after repair of a dissecting thoracic aortic aneurysm at 14 weeks gestation. *Can J Anaesth.* 2005;52:1071–1075.
20. Ioscovich 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.
21. Naito H, Naito H, Tada K. Open heart operation for a pregnant patient with Marfan syndrome [in Japanese]. *Mastui.* 2005;54:525–529.
22. Chavanon O, Rama A, Leprince P, Bonnet N, Pavie A, Jondeau G, Gandjbakhch I. Valve-sparing operation in a young woman with Marfan syndrome: a word of caution. *J Thorac Cardiovasc Surg.* 2006;132:683–684.
23. Matsuda H, Ogino H, Neki R, Kitamura S. Hemiarth replacement during pregnancy (19 weeks) utilizing normothermic selective cerebral perfusion. *Eur J Cardiothorac Surg.* 2006;29:1061–1063.
24. Tutarel O, Lotz J, Roentgen P, Drexler H, Meyer GP, Westhoff-Bleck M. Pregnancy in a Marfan patient with pre-existing aortic dissection. *Int J Cardiol.* 2007;114:E36–E37.
25. Tomihara A, Ashizawa N, Abe K, Kinoshita N, Chihaya K, Yonekura T, Fukae S, Ashizawa K, Eishi K, Hayashi T, Yano K. Risk of development of abdominal aortic aneurysm and dissection of thoracic aorta in a postpartum woman with Marfan's syndrome. *Intern Med.* 2006;45:1285–1289.
26. Carrel T, Beyeler L, Schnyder A, Zurmuhle P, Berdat P, Schmidli J, Eckstein FS. Reoperations and late adverse outcome in Marfan patients following cardiovascular surgery. *Eur J Cardiothorac Surg.* 2004;25:671–675.
27. Meijboom LJ, Timmermans J, Zwinderman AH, Engelfriet PM, Mulder BJ. Aortic root growth in men and women with the Marfan's syndrome. *Am J Cardiol.* 2005;96:1441–1444.
28. Meijboom LJ, Drenthen W, Pieper PG, Groenink M, van der Post JA, Timmermans J, Voors AA, Roos-Hesselink JW, van Veldhuisen DJ, Mulder BJ. Obstetric complications in Marfan syndrome. *Int J Cardiol.* 2006;110:53–59.
29. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2003;24:761–781.
30. Immer FF, Bansi AG, Immer-Bansi AS, McDougall J, Zehr KJ, Schaff HV, Carrel TP. Aortic dissection in pregnancy: analysis of risk factors and outcome. *Ann Thorac Surg.* 2003;76:309–314.
31. Groenink M, Lohuis TAJ, Tijssen JGP, Naef MSJ, Hennekam RCM, van Der Wall EE, Mulder BJM. Survival and complication free survival in Marfan syndrome: implications of current guidelines. *Heart.* 1999;82:499–506.
32. Svensson LG, Blackstone EH, Feng J, de Oliveira D, Gillinov AM, Thamilarasan M, Grunn RA, Griffin B, Hammer D, Williams T, Gladish DH, Lyte BW. Are Marfan syndrome and Mafanoid patients distinguishable on long-term follow-up? *Ann Thorac Surg.* 2007;83:1067–1074.
33. Gott VL, Cameron DE, Alejo DE, Greene PS, Shake JG, Caparrelli DJ, Dietz HC. Aortic root replacement in 271 Marfan patients: a 24-year experience. *Ann Thorac Surg.* 2002;73:438–443.
34. Bhudia SK, Troighton R, Lam BK, Rajes Waran J, Mills WR, Gillinov AM, Griffen BP, Blackstone EH, Lytle BW, Svensson LG. Mitral valve surgery in the adult Marfan syndrome patient. *Ann Thorac Surg.* 2006;81:843–848.
35. Ho NC, Tran JR, Bektas A. Marfan's syndrome. *Lancet.* 2005;366:1978–1981.
36. Eldadah ZA, Grifo JA, Dietz HC. Marfan syndrome as a paradigm for transcript-targeted pre-implantation diagnosis of heterozygous mutations. *Nat Med.* 1995;1:798–803.
37. Godfrey M, Vandemark N, Wang M, Velinov M, Wargowski D, Tsipouras P, Han J, Becker J, Robertson W, Droste S, Rao VH. Prenatal diagnosis and a donor splice site mutation in fibrillin in a family with Marfan syndrome. *Am J Hum Genet.* 1993;53:472–480.
38. Rantamaki T, Raghunath M, Karttunen L, Lonnqvist L, Child A, Peltonen L. Prenatal diagnosis of Marfan syndrome: identification of a fibrillin-1 mutation in chorionic villus sample. *Prenat Diagn.* 1995;15:1176–1181.
39. Ramaswamy P, Lytrivi ID, Nguyen K, Gelb BD. 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.
40. Yetman AT, Bornemeier RA, McCrindle BW. Long-term outcome in patients with Marfan syndrome: is aortic dissection the only cause of sudden death? *J Am Coll Cardiol.* 2003;41:329–332.
41. Elkayam U, Bitar F. Valvular heart disease and pregnancy, part II: prosthetic valves. *J Am Coll Cardiol.* 2005;45:403–410.
42. Shotan A, Ostrzega E, Mehra A, Johnson J, Elkayam U. Incidence of arrhythmias in normal pregnancy and reaction to palpitations, dizziness and syncope. *Am J Cardiol.* 1997;79:1061–1064.
43. Milewicz DM, Dietz HC, Miller DC. Treatment of aortic disease in patients with Marfan syndrome. *Circulation.* 2005;111:e150–e157.
44. Kouchoukos NT, Dougenis D. Surgery of the thoracic aorta. *N Engl J Med.* 1997;336:1876–1988.
45. David TE. Aortic surgery in the Marfan syndrome. *Adv Card Surg.* 2001;13:61–75.
46. De Oliveira NC, David TE, Ivanov J, Armstrong S, Eriksson MJ, Rakowski H, Webb G. Results of surgery for aortic root aneurysm in patients with Marfan syndrome. *J Thorac Cardiovasc Surg.* 2003;125:789–796.
47. Birks EJ, Webb C, Child A, Radley-Smith R, Yacoub MH. Early and long-term results of a valve-sparing operation for Marfan syndrome. *Circulation.* 1999;100:II29–II35.
48. Weiss BM, von Segesser LK, Alon E, Seifert B, Tulina M. Outcome of cardiovascular surgery and pregnancy: a systemic review of the period 1984–1996. *Am J Obstet Gynecol.* 1998;179:1643–1653.
49. Keame MG, Pyeritz RE. Medical management of Marfan syndrome. *Circulation.* 2008;117:2808–2813.
50. 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;330:1335–1341.
51. Rossi-Foulkes R, Roman MJ, Rosen SE, Kramer-Fox R, Ehlers KH, O'Loughlin JE, Davis JG, Devereux RB. 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.
52. Hurst AK, Hoffman K, Fushman WH, Elkayam U. The use of β -adrenergic blocking agents in pregnancy and lactation. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy.* New York, NY: Wiley-Liss; 1998:357–372.
53. Lydakis C, Lip GYH, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens.* 1999;12:541–547.
54. Lip GYH, Beevers M, Churchill D, Shatter LM, Beevers DG. Effect of atenolol on birth weight. *Am J Cardiol.* 1997;79:1436–1438.
55. Greenwood JP, Scott EM, Stoker JB, Walker JJ, Mary DASG. Sympathetic neural mechanisms in normal and hypertensive pregnancies in humans. *Circulation.* 2001;104:2200–2204.
56. Hurst AK, Shotan A, Hoffman K, Johnson J, Goodwin TM, Koda R, Elkayam U. Pharmacological and pharmacodynamic evaluation of atenolol during and after pregnancy. *Pharmacotherapy.* 1998;18:840–846.
57. Liedholm H, Melander A, Bitzen PO, Helm G, Lonnerholm G, Mattiasson I, Nilsson B, Wahlin-Boll E. Accumulation of atenolol and metoprolol in human breast milk. *Eur J Clin Pharmacol.* 1981;20:229–231.
58. Brooke BS, Habashi JP, Judge DP, Patel N, Loeys B, Dietz HC. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med.* 2008;358:2787–2790.
59. Alwan S, Polifka JE, Friedman JM. Angiotensin II receptor antagonist treatment during pregnancy. *Birth Defect Res.* 2005;73:123–130.