Cardiovascular Problems in Pregnant Women with the Marfan Syndrome
Uri Elkayam, MD; Enrique Ostrzega, MD; Avraham Shota, MD; and Anilkumar Mehra, MD

Purpose: To review the available information on the diagnostic, prognostic, and therapeutic aspects of cardiac complications in women with the Marfan syndrome during the peripartum period and to develop guidelines for the approach to these patients on the basis of this information.

Data Sources: A MEDLINE search and a manual search of bibliographies from reviewed articles.

Study Selection and Data Extraction: Articles that reported on pregnancy in patients with the Marfan syndrome or that discussed potentially relevant aspects of the syndrome.

Results: Pregnancy in the Marfan syndrome is associated with two primary problems: potential catastrophic aortic dissection and the risk for having a child with the syndrome. The risk for peripartum aortic dissection is especially high in women in whom aortic root dilatation is diagnosed before pregnancy. Gestation seems to be safer in women without preexisting cardiovascular disease; however, an event-free pregnancy cannot be guaranteed. The Marfan syndrome is inherited in an autosomal dominant manner, and the fetus has a 50% risk for inheriting the mutant gene.

Conclusions: Women with the syndrome should be counseled before conception about the risks of pregnancy to both mother and fetus. Because preconceptual dilatation of the ascending aorta seems to be an important predictor for aortic dissection, it should be excluded before pregnancy. Transesophageal echocardiography seems to be preferable for noninvasive assessment of aortic dilatation before and during pregnancy. Prophylactic use of β-blockers may be useful in preventing aortic dilatation. Surgery should be considered during gestation in patients with progressive aortic dilatation when or before the aortic root reaches 5.5 cm. Because of the potential risk of ionizing radiation to the fetus, noninvasive methods such as transesophageal echocardiography and magnetic resonance imaging are preferred to contrast aortography for the diagnosis of aortic dissection during pregnancy. Vaginal delivery can be done in patients with the Marfan syndrome who do not have cardiovascular system abnormalities. In patients with aortic dilatation, aortic dissection, or other important cardiac abnormalities, cesarean section should be the preferred method of delivery.

The Marfan syndrome is a hereditary disorder of the connective tissue (1–5) with an estimated prevalence of 4 to 6 cases per 10,000 persons; prevalence does not differ according to sex, race, or ethnicity (4). The syndrome is caused by abnormalities in the relation between fibrillin and fibers that are caused by an abnormal gene for fibrillin (1, 2) on chromosome 15 (3). A family history of the disease is present in 65% to 75% of patients and is sporadic in the rest. Cardiovascular involvement, including mitral and tricuspid valve prolapse with or without valvular regurgitation, dilatation of the aorta (primarily of the ascending portion), and aortic regurgitation, is a common feature of the disease (4, 6). Life expectancy is greatly reduced in patients with this syndrome, predominantly because of cardiac complications (aortic dilatation, dissection, and rupture) (7).

Cardiovascular Risk of Pregnancy

Pregnancy in women with the Marfan syndrome poses two problems: a potential catastrophic and often lethal acute aortic dissection and the risk for having a child who will inherit the syndrome. In a review of the literature published up to 1980, Pyeritz (8) found reports of 32 women with the Marfan syndrome who had had at least one pregnancy. Acute aortic dissection was diagnosed in 20 of these women, of whom 16 died during or shortly after pregnancy and 4 died later in the postpartum period because of aortic rupture or regurgitation. Most of these patients had had preexisting cardiovascular abnormalities, including aortic dilatation, aortic regurgitation, coarctation of the aorta, hypertension, cardiomegaly, and ductus arteriosus.

A review of the literature since 1980 shows the description of 15 additional cases of pregnancy in women with the Marfan syndrome. Most of these reports describe cardiovascular complications during pregnancy (Table 1), including 1) dilatation of the ascending aorta with the development of aortic regurgitation and congestive heart failure and 2) proximal and distal dissections of the aorta with the occasional involvement of the iliac (9, 11) and coronary arteries (13). Most women developed cardiac complications in the second and third trimesters, although aortic dissection occurred in isolated patients a few days after conception (15), during labor (9), and 8 days after delivery (16). Aortic dissections occurring in the 14th, 28th, and 32nd gestational weeks each resulted in maternal death (10, 14). Live babies were delivered before surgery by cesarean sections at the 36th week in two patients (11, 12) and at the 38th week in one patient (13). In all three of these patients, surgical repair was done successfully 3 days to 6 weeks after delivery. In two other patients, surgery was done during pregnancy. In one of these patients (15), aortic arch replacement and triple

From the University of Southern California School of Medicine, Los Angeles, California. For current author addresses, see end of text.

©1995 American College of Physicians 117
Table 1. A Summary of Cases Reported since 1980 in Which Peripartum Cardiovascular Complications Occurred in Women with the Marfan Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient's Age, y</th>
<th>Previous Cardiovascular Disease</th>
<th>Maternal Complications</th>
<th>Fetal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferguson et al. (9)</td>
<td>42</td>
<td>Mild gestational hypertension; cardiac evaluation including M-mode echocardiography 2 years before admission reported to be normal</td>
<td>Proximal and distal aortic dissection extending to the iliac bifurcation; aortic insufficiency</td>
<td>Fetal bradycardia</td>
</tr>
<tr>
<td>Baltazar et al. (10)</td>
<td>31</td>
<td>Heart murmur present since the age of 2 years</td>
<td>Proximal and distal aortic dissection extending to abdominal aorta below the renal arteries; aortic regurgitation; ventricular tachycardia</td>
<td>Congestive heart failure starting at 28th week</td>
</tr>
<tr>
<td>Mor-Yosef et al. (11)</td>
<td>35</td>
<td>Aortic aneurysm; aortic and mitral insufficiency diagnosed 2 years before admission</td>
<td>Distal aortic dissection distal to origin of left subclavian artery to iliac arteries</td>
<td></td>
</tr>
<tr>
<td>Mor-Yosef et al. (11)</td>
<td>26</td>
<td>None; normal-sized aorta by echocardiography before and during pregnancy</td>
<td>Distal aortic dissection distal to origin of left subclavian artery</td>
<td></td>
</tr>
<tr>
<td>Rosenblum et al. (12)</td>
<td>28</td>
<td>Mitral valve prolapse; normal aortic root diameter by echocardiography at 13, 20, and 28 weeks</td>
<td>Distal aortic dissection distal to origin of left subclavian artery</td>
<td></td>
</tr>
<tr>
<td>Shime et al. (13)</td>
<td>NR (NR)</td>
<td>Hypertension</td>
<td>Aortic dissection with extension to the coronary arteries followed by cardiac arrest</td>
<td></td>
</tr>
<tr>
<td>Metcalfe et al. (14)</td>
<td>31</td>
<td>Hypertension</td>
<td>Distal aortic dissection extending the length of the thoracic and abdominal aorta; cardiogenic shock</td>
<td></td>
</tr>
<tr>
<td>Cola et al. (15)</td>
<td>34</td>
<td></td>
<td>Proximal and distal aortic dissection on the 1 to 8 days after conception</td>
<td></td>
</tr>
<tr>
<td>Barker et al. (10)</td>
<td>40</td>
<td>Severe retrosternal chest pain radiating to the back for 10 days during first pregnancy 6 years before admission</td>
<td>Dissection of abdominal aorta</td>
<td></td>
</tr>
<tr>
<td>Smith et al. (17)</td>
<td>19</td>
<td>Dilatation of aortic annulus to 5.5 cm 2 years before admission</td>
<td>Sinus of Valsalva aneurysm; mild aortic insufficiency; continued severe chest pain</td>
<td></td>
</tr>
</tbody>
</table>

* NR = Not reported.

Although most reports describe severe complications related to pregnancy in women with the Marfan syndrome, these reports are probably an overrepresentation of pregnancy-related complications caused by a bias toward reporting complicated rather than uncomplicated cases. Such an assumption is supported by Pyeritz (8), whose retrospective analysis of 105 pregnancies in 26 patients with the Marfan syndrome and prospective follow-up of 10 patients with the syndrome who had minimal or no preexisting cardiovascular disease showed only a low risk for maternal complications and death. In addition, two recent reports (20, 21) have described successful pregnancies in 3 patients despite mild to moderate aortic root enlargement and mitral valve prolapse in all 3 patients and a moderate degree of left ventricular systolic dysfunction in 1 patient.

In addition to the maternal risk associated with pregnancy in the Marfan syndrome, there is a risk for transmitting the disease to the fetus. The Marfan syndrome is inherited as an autosomal dominant disorder (22), and the fetus has a 50% chance of inheriting the mutant gene (5).
Preconceptual Evaluation and Consultation

Because no large clinical trials of pregnancy in patients with the Marfan syndrome have been reported, our recommendations are made on the basis of general principles rather than trial data. Women with the Marfan syndrome should be counseled before conception about the risk for potential pregnancy-related complications and the risk for transmitting the syndrome to the offspring. Mildly affected patients should be informed about the different presentations of the disease and the possibility of more severe expression in the offspring (5). It should be noted that because of better understanding of the gene defect of the Marfan syndrome (2, 3, 23–26), prenatal diagnosis of this disease may be possible in some patients of informative families in which the disease cosegregates with marker alleles (5, 27). During preconceptual consultation, physicians should carefully counsel the patient and her family about the expected morbidity of the mother in years to come and the possibility of reduced life expectancy.

Many pregnancy-related complications described in patients with the Marfan syndrome emphasize the great potential for risk associated with gestation, especially in patients with cardiovascular involvement. Such cardiovascular abnormalities should be carefully evaluated before and frequently throughout pregnancy. Preconceptual dilation of the ascending aorta seems to be an important predictor of aortic dissection during gestation and should be excluded before pregnancy. Reports of aortic dissection in the Marfan syndrome in pregnant (12) and non-pregnant patients with normal aortic root diameter (28) show that event-free pregnancy cannot be guaranteed to any patient with this syndrome. Recently, Simpson and colleagues (29) showed that transesophageal echocardiography was superior to transthoracic echocardiography in the assessment of aortic diameter and the diagnosis of aortic dissection and other cardiovascular manifestations of the Marfan syndrome. The use of transesophageal echocardiography should, therefore, be preferred for preconceptual risk stratification in women with the Marfan syndrome.

Surgery during Pregnancy

If a pregnant patient with the Marfan syndrome has substantial dilatation of the aorta, therapeutic abortion or
surgical intervention should be considered. Surgery for marked dilatation of the aorta (17) and for aortic dissection (15) has been reported during gestation. Cola and Lawin (15) recently reported successful aortic arch replacement and coronary artery bypass grafting for aortic dissection in a patient with the Marfan syndrome; the surgery was done a few days after conception with normal fetal outcome. Smith and coworkers (17) reported successful replacement of the aortic valve and the ascending aorta during the 22nd week of gestation; this was done because of symptomatic dilatation of the aorta from 5.5 cm to 7.7 cm during pregnancy.

Gott and colleagues (30) showed a 5-year survival rate of 85% in 50 patients with the Marfan syndrome after composite graft repair of the ascending aorta. They recommended preventive replacement of the ascending aorta if the aorta reaches or exceeds 60 mm. A recent study by Murgatroyd and colleagues (28) reported aortic root dimension to be 5.1 ± 1.3 cm in 11 patients who developed aortic dissection. In contrast, the average aortic dimension in patients with uncomplicated courses was 3.7 ± 1.3. On the basis of these data, a recent editorial (31) recommended elective replacement of the aortic root when or before the root reaches 5.5 cm in patients with the Marfan syndrome who show progressive dilatation of the aortic root by serial echocardiographic assessment, in patients with a family history of aortic dissection, and in women who are planning pregnancy.

Successful surgery for aortic dissection during pregnancy has been reported in a few cases (32–34). It should be noted, however, that cardiac surgery in general has been shown to result in increased fetal loss (35). For this reason, if fetal maturity can be confirmed, a cesarean section should be done before or concomitantly with thoracic surgery (8, 10, 12).

**Prophylactic Use of β-blockers**

Several preliminary studies (36–39) have suggested that β-blocking agents may have a beneficial effect on the rate of aortic root dilatation in children and adolescents. These initial results are strongly supported by a recent report by Shores and colleagues (40), who did a randomized study of the effect of propranolol (mean dose, 212 ± 68 mg/d) on the progression of aortic dilatation in adolescents and adults with the Marfan syndrome for approximately 10 years. These investigators showed a lower rate of aortic dilatation and a significantly reduced rate of aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure, and death in the patients treated with propranolol. The applicability of these data to pregnant patients needs to be further studied but, on the basis of available information, the prophylactic use of β-blockers during pregnancy seems to make good clinical sense. Propranolol has been extensively used during pregnancy to treat various conditions, including hypertension (41–44), thyrotoxicosis (45, 46), hypertrophic cardiomyopathy (47, 48), and maternal (43, 49, 50) and fetal supraventricular tachyarrhythmias (41, 50–54). Although the overall experience with this drug in pregnancy has been favorable (55), potential side effects, including fetal growth retardation (43), bradycardia, hypoglycemia, hyperbilirubinemia, and apnea at birth in the newborn, have been reported (56, 57). Such side effects should be anticipated by the clinician. Barden and Standen (58) have 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 β1-adrenergic receptor-blocking agents, such as metoprolol and atenolol, may be preferred during pregnancy. Several studies have shown these agents to be safe when used to treat hypertension during pregnancy (59–61). A few studies, however, have reported lower birth weight in association with exposure to atenolol during gestation (62). β-blocking agents are excreted in breast milk (63–65). However, unless hepatic function in the newborn is markedly impaired, breastfeeding should not be discouraged.

**Diagnosis of and Medical Therapy for Aortic Dissection during Pregnancy**

Transcatheter echocardiography has traditionally been used to assess the ascending aorta in patients with the Marfan syndrome. The recent introduction of transesophageal echocardiography has provided the clinician with a highly effective tool for the diagnosis of aortic dissection in both nonpregnant and pregnant patients (66, 67). Because aneurysm of the aorta in the patients with the syndrome can occasionally also involve the descending aorta (68), transesophageal echocardiography seems preferable to transcatheter echocardiography for both preconceptual assessment and periodic follow-up during pregnancy. This is further supported by a recent study by Simpson and coworkers (29), who report that this technique is superior to transcatheter echocardiography in the diagnosis of aortic dissection and dilation in patients with the Marfan syndrome. Magnetic resonance imaging may be equally effective in the stable patient, but the safety of this technique during pregnancy has not been completely established. No evidence suggests that short-term exposure to an electromagnetic field can harm the fetus, but prolonged or high-level exposure to electromagnetic radiation has been linked to unfavorable effects on embryogenesis and chromosomal structure (69, 70). Until conclusive information about the effect of magnetic resonance imaging on the fetus is established in many studies with long follow-up periods, echocardiography seems preferable (69). If contrast aortography is done, an attempt should be made to minimize the use of radiation and to adequately shield the fetus (71).

Standard medical therapy for aortic dissection includes the use of intravenous nitroprusside and β-blockers to control blood pressure and decrease left ventricular contractility, thereby reducing ejection velocity and minimizing shear forces (72). The use of nitroprusside during pregnancy, however, may lead to thiocyanate toxicity in the fetus (55). 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 (55).

**Labor and Delivery**

The available literature and our own experience show that vaginal delivery can be done in patients with the
Marfan syndrome who have normal results on cardiovascular examination and no evidence of aortic dilatation. In these patients, cesarean section should be reserved for obstetrical indications (20, 21, 73, 74). At the same time, however, to reduce the stress of labor, epidural anesthesia to minimize pain and forces or vacuum to shorten the second stage of labor are recommended. Both systolic and diastolic blood pressures increase markedly during uterine contractions (75). These changes should be anticipated and prevented with β-blocking or vasodilator agents. In patients with aortic dilatation, aortic dissection, or other important cardiac abnormalities, cesarean section should be the preferred method of delivery because it minimizes the hemodynamic changes associated with vaginal delivery. A recent report by Irons and Pollard (76) described postpartum hemorrhage of the uterine vasculature 3 days after cesarean section secondary to the Marfan syndrome. Similar postpartum hemorrhage was reported by Pyeritz (8) in 4 of 11 women with the Marfan syndrome and should be anticipated in such patients.

References
70. Beers GL. Biological effects of weak electromagnetic field from 0 Hz to 200 MHz: A survey of the literature with special emphasis on possible magnetic resonance effects. Magn Reson Imaging. 1989;7:391-41.