

Unstable angina during pregnancy in two patients with premature coronary atherosclerosis and aortic stenosis in association with familial hypercholesterolemia

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Obstructive atherosclerotic coronary artery disease is uncommon in women during childbearing age, and the occurrence of myocardial ischemia during pregnancy has therefore been anecdotal. Two young patients with premature coronary artery disease in association with familial hypercholesterolemia had unstable angina in the second trimester of pregnancy. Workup revealed coronary artery disease and aortic stenosis. One patient opted for abortion at the twentieth week of gestation, and the other decided to continue pregnancy and was delivered by cesarean at 28 weeks' gestation. Coronary artery bypass grafting was performed after pregnancy in both patients. In addition, one of the patients underwent aortic valve replacement, and the other had replacement of the narrowed ascending aorta with uneventful recovery. Our report describes an uncommon presentation of unstable angina during pregnancy in 2 young women with premature coronary artery disease and aortic valvular and supra-aortic stenosis as a result of familial hypercholesterolemia. The management of these conditions during pregnancy is influenced by the effects of available therapeutic modalities on both maternal and fetal outcome. (*Am J Obstet Gynecol* 2000;182:1152-5.)

Key words: Coronary artery disease, familial hypercholesterolemia, aortic stenosis, angina

Obstructive atherosclerotic coronary artery disease is uncommon in women during childbearing age,¹ and the occurrence of myocardial ischemia during pregnancy has therefore been anecdotal.^{2, 3} Familial hypercholesterolemia is a rare genetic disorder characterized by a substantial elevation of low-density lipoprotein early in childhood and can lead to coronary artery disease in women during childbearing age.⁴

We describe 2 patients with premature coronary atherosclerotic disease and aortic stenosis in association with familial hypercholesterolemia who had unstable angina during pregnancy.

Case report

Case 1. A 26-year-old African American woman, gravida 5, para 4, was admitted to the hospital during the 20th gestational week because of complaints of chest pain increasing in frequency and severity, occurring during mild

exertion and occasionally at rest, radiating to the neck and both arms, in addition to 3-pillow orthopnea and paroxysmal nocturnal dyspnea for the previous 12 weeks. The patient was diagnosed with hypercholesterolemia 3 years before this hospital admission. At that time she had hypertension and exertional chest discomfort provoked by walking 3 to 4 blocks in association with dyspnea and orthopnea. Cardiac catheterization showed atherosclerotic coronary artery disease with irregularities in all 3 major coronary arteries, aortic stenosis with an aortic valve area of 1.1 cm², and mild aortic regurgitation. The patient was treated medically with long-acting diltiazem, hydrochlorothiazide, and organic nitrates and was advised against pregnancy.

Family history revealed hypercholesterolemia involving her grandmother and a maternal aunt who was diagnosed with heart disease at age 31. During this admission to the hospital, physical examination was significant for tendon xanthomas over the Achilles tendons and antecubital areas and xanthelasmas at the lateral canthi of both eyes. Cardiovascular examination revealed systolic hypertension, bilaterally diminished carotid pulses with delayed upstroke, a sustained left ventricular point of maximal impulse, a grade III/VI systolic crescendo/decrecendo murmur in the second right intercostal space radiating to both carotids, and a grade II/VI diastolic aortic regurgitation murmur. Abdominal examination was consistent with intrauterine pregnancy at 20 weeks of gestation. Lipid profile revealed a total serum cholesterol level of 714 mg/dL, low-density lipoprotein

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fraction of 647 mg/dL, and a normal triglyceride level. All other laboratory values were within the normal range. Twelve-lead electrocardiogram showed evidence of left ventricular hypertrophy, and the echocardiogram showed thickened, calcified, tricuspid-appearing aortic valve with decreased cusp motion and mild regurgitation; both mitral and tricuspid valves were normal. The patient was started on an antianginal treatment with the β -adrenergic receptor blocker atenolol.

The risks and benefits of available possible therapeutic options, which included continuation of pregnancy with medical treatment of myocardial ischemia, aortic valve replacement with possible coronary artery bypass surgery during pregnancy, and therapeutic abortion, were discussed with the patient at length. The patient elected to terminate pregnancy at that time. Cardiac catheterization was then performed and demonstrated moderate pulmonary hypertension (pulmonary pressures, 46/32 mm Hg) and elevated pulmonary artery wedge pressure at 32 mm Hg. The systemic blood pressure was 198/74 mm Hg, the mean pressure gradient across the aortic valve was 24 mm Hg, and the aortic valve area was calculated at 0.8 cm². Left ventricular size and systolic functions were normal, and there was a mild aortic and mitral regurgitation. Aortogram demonstrated supraventricular narrowing of the ascending aorta. Coronary arteriogram showed diffuse nonobstructive coronary artery disease involving the left coronary circulation. The right coronary artery showed diffuse atherosclerotic irregularities and an 80% obstruction at the proximal part of the posterior descending branch. Abortion was performed by dilatation and evacuation after cervical dilatation with laminaria while the patient was under paracervical block anesthesia; the use of methergine was avoided, and the procedure was done without complications. The patient was treated with β -adrenergic receptor blockers and long-acting nitrates with improvement of symptoms, and she underwent cardiac surgery 3 weeks later. During surgery, the ascending aorta was found to be narrowed and heavily calcified. Surgical pathologic findings of the aortic valve showed degenerative and fibrotic changes along with atherosclerotic changes. Aortic valve replacement with a 19-mm St Jude mechanical valve was performed after widening of the ascending aorta with a Dacron polyester fiber graft. In addition, saphenous vein bypass grafting of the right coronary artery was performed.

Case 2. An 18-year-old primigravid Hispanic woman was examined at the high-risk obstetrics clinic at 27 weeks of gestation. The patient complained of progressively worsening chest pain that started 4 months before her visit. It was induced by walking 1 block and was accompanied by radiation to the left arm and dyspnea. In addition, the patient revealed a history of 2-pillow orthopnea and paroxysmal nocturnal dyspnea. The patient's father died of myocardial infarct at the age of 38 years, and her medical history was remarkable for severe hypercholesterolemia and mild symptoms of stable exertional angina. The patient underwent a cardiac evaluation at Children's Hospital approximately 3 years before her visit

to our clinic. Cardiac catheterization was performed and demonstrated mild supra-aortic narrowing and trace aortic regurgitation but did not include selective coronary angiography.

Physical examination was significant for xanthomas over both antecubital areas, the right achilles tendons, the right buttock, and the dorsal aspect of the right ring finger. The patient had similar lesions over both knees that had been removed. Cardiac examination revealed bilaterally diminished carotid arterial pulses with delayed upstroke and a grade III/VI crescendo/decrecendo systolic murmur at the second, right intercostal space radiating to both sides of the neck. Laboratory findings revealed a strikingly elevated cholesterol level of 540 mg/dL with a low-density lipoprotein level of 485 mg/dL and a normal triglyceride level.

The patient expressed a desire to continue with her pregnancy; therefore treatment with β -adrenergic receptor blockers and organic nitrates was initiated, and she was hospitalized for monitoring and optimization of medical therapy. A few days after hospitalization, the patient had an episode of resting chest pain associated with dramatic electrocardiogram changes. Both chest pain and electrocardiographic evidence for myocardial ischemia were relieved with sublingual and intravenous nitroglycerin. There was no evidence of fetal distress. Antianginal therapy with intravenous nitroglycerin, heparin, and oral β -adrenergic receptor blockers was started. Cardiac catheterization was performed urgently with appropriate fetal shielding and showed 90% ostial left main artery stenosis, 50% luminal narrowing at the midportion of the left anterior descending coronary artery, and 60% stenosis of the left circumflex artery. In addition, a supra-aortic narrowing was found. The mean pressure gradient across the aortic narrowing was 20 mm Hg. Because of the instability of the patient and the high-risk coronary anatomy, an intra-aortic balloon pump was placed. Because of the presence of stenosis of the left main segment, the patient was not thought to be a candidate for percutaneous transluminal coronary angioplasty, and it was decided to perform cardiac surgery. After consultation with the obstetric and cardiothoracic surgical services and discussion with the patient, it was decided to deliver the baby without delay by cesarean. After the administration of 2 doses of methasone given intramuscularly, the operation was performed by the obstetric team in the thoracic surgical suite. Before the cesarean delivery the patient was prepared for possible cardiac surgery, and a complete cardiac surgery team was present for emergent coronary artery bypass grafting if hemodynamic instability was encountered. A classical cesarean delivery was performed while the patient was under general anesthesia with continuous hemodynamic monitoring and no complications. A 1130-g male infant was delivered with Apgar scores of 9 and 9, but he required a stay of 2 weeks in the neonatal intensive care unit. Cardiac medications during delivery included continuous infusion of intravenous nitroglycerin and intravenous metoprolol. A 12-hour interval was allowed after delivery before the

performance of cardiac surgery to allow time for hemostasis and to reduce the likelihood of uterine bleeding as a result of the anticoagulation required for surgery. Coronary artery bypass graft surgery was performed with a left internal mammary artery graft to the left anterior descending artery and saphenous vein grafts to the distal right coronary artery, the obtuse marginal branch of the left circumflex artery, and the diagonal branch of the left anterior descending artery. In addition, replacement of the narrowed ascending aorta with a Dacron polyester fiber graft was performed. Inspection of the aortic segment removed during surgery showed a markedly thickened and calcified wall. In contrast, the aortic valve leaflets appeared to be normal. Postsurgical recovery was uneventful, and the patient was discharged home on the fifth day after surgery.

Comment

Pregnancy in women with ischemic heart disease is uncommon, and reports of unstable angina in pregnant women are rare.^{2, 3} Risk factors for coronary artery disease in premenopausal women include cigarette smoking, diabetes mellitus, hypertension, a family history of premature coronary artery disease, toxemia of pregnancy, the use of contraceptives, and hypercholesterolemia.¹ Our report describes the development of unstable angina during pregnancy in association with the development of premature obstructive coronary artery disease and left ventricular outflow obstruction in 2 young women with familial hypercholesterolemia. Both patients had escalating symptoms of myocardial ischemia during gestation as a result of worsening symptoms and an unfavorable effect of pregnancy on the balance between myocardial oxygen supply and demand. Marked increase in blood volume, stroke volume, and heart rate occurring during pregnancy can result in a significant increase in myocardial oxygen consumption.⁵ At the same time gestational anemia and decreased diastolic blood pressure may reduce myocardial oxygen supply, resulting in myocardial ischemia in cases with compromised coronary blood flow.

Although both patients included in this report had similar clinical presentations that were mediated by a common cause, the approach to their management differed considerably, mainly because of the difference in gestational age at the time of presentation. Patient 1 had an abortion at 20 weeks 1 day's gestation followed by surgical replacement of the aortic valve and coronary artery bypass surgery. Continuation of pregnancy and the performance of cardiac surgery during gestation was an alternative treatment plan for this patient. Cardiac surgery has been performed successfully during pregnancy, and in general, it is not associated with increased maternal risk. A detrimental effect on the fetus, however, has been reported to be increased with a high incidence of fetal loss ranging between 17% and 33%.⁶⁻⁸ Although the per-

formance of surgery during gestation was considered, because of concern to fetal well-being and potential surgery-related fetal complications, the patient elected to terminate pregnancy before surgery.

Patient 2 had escalating symptoms of exertional angina during the twenty-seventh gestational week. Because of a high incidence of fetal morbidity and even mortality associated with delivery at such an early gestational age,⁹ an attempt was made to treat the patient medically with anti-ischemic therapy including β -adrenergic receptor blockade, organic nitrates, and low-dose aspirin. Because of the large clinical experience and their proven relative safety in pregnancy,¹⁰ β -adrenergic receptor blockers seem the most appropriate drugs of first choice for patients with myocardial ischemia during pregnancy. The use of organic nitrates during pregnancy has been described in a limited number of patients for the treatment of myocardial ischemia,¹¹ myocardial infarction,¹² pregnancy-induced hypertension,¹³ and tocolysis and seems to be safe.¹⁴ Although the use of high-dose aspirin in pregnancy has been reported to increase the incidence of bleeding, both in the neonate and in the mother, the use of low-dose aspirin has been shown to be without complications.¹⁵

Urgent surgery was required in the patient because of severe worsening of symptoms and the diagnosis of critical narrowing of the ostial part of the left main coronary segment. Although the risk of abdominal surgery in a patient with significant left main coronary segment disease¹⁶ was recognized and explained to the patient, because of concerns for fetal well-being during cardiac surgery, it was decided, after initial stabilization of myocardial ischemia, to deliver the baby before the heart surgery. Because of the high risk for a catastrophic myocardial event associated with a high-grade stenosis in the left main segment, it was decided to deliver the patient without delay. To minimize maternal risk, delivery was performed by cesarean in a surgical suite with standby personnel ready to perform cardiac surgery on an urgent basis if so required.

Replacement of a stenotic aortic valve with a mechanical prosthetic valve was performed in patient 1 in addition to coronary bypass graft surgery. Because of the desire to avoid anticoagulation during pregnancy, the use of a bioprosthetic valve is often recommended for young women of childbearing age.¹⁷ Such a choice, however, has a number of limitations, including an inferior hemodynamic profile and a limited long-term durability.¹⁸ Longevity of the bioprosthetic valve has been clearly shown to have a strongly reversed correlation with the patient's age. Furthermore, limited durability of bioprosthetic valves has been shown to be affected by pregnancy-related accelerated valve calcification and deterioration.¹⁹

In summary, our report describes an uncommon presentation of unstable angina pectoris during pregnancy in 2 young women with premature coronary atheroscle-

rosis and aortic valvular and supra-aortic stenosis as a result of familial hypercholesterolemia. The management of these conditions during pregnancy is influenced by the effects of available therapeutic modalities on both maternal and fetal outcomes.

REFERENCES

1. Rutherford J. Coronary artery disease in the childbearing age. In: Elkayam U, Gleicher N, editors. *Cardiac problems in pregnancy*. 3rd ed. New York: Wiley-Liss; 1998. p. 121-30.
2. Shalev Y, Ben-Hur H, Hagay Z, Blickstein I, Epstein M, Ayzenberg O, et al. Successful delivery following myocardial ischemia during the second trimester of pregnancy. *Clin Cardiol* 1993;16:754-6.
3. Cowan NC, deBelder MA, Rothman MT. Coronary angioplasty in pregnancy. *Br Heart J* 1988;59:588-92.
4. Farmer JA, Gotto AM. Atherosclerosis: pathogenesis and risk factors. In: Willerson JT, Cohn JN, editors. *Cardiovascular medicine*. New York: Churchill Livingstone; 1995. p. 1101-13.
5. Elkayam U, Gleicher N. Hemodynamics and cardiac function during normal pregnancy and the puerperium. In: Elkayam U, Gleicher N, editors. *Cardiac problems in pregnancy*. 3rd ed. New York: Wiley-Liss; 1998. p. 3-20.
6. Chambers CE, Clark SL. Cardiac surgery during pregnancy [review]. *Clin Obstet Gynecol* 1994;37:316-23.
7. Becker RM. Intracardiac surgery in pregnant women. *Ann Thorac Surg* 1983;36:453-8.
8. Born D, Massonetto JC, deAlmeida PA, Moron AF, Buffulo E, Gornes WJ, et al. Heart surgery with extracorporeal circulation in pregnant women. Analysis of materno-fetal outcome. *Arq Bras Cardiol* 1985;64:207-11.
9. Goodwin TM. Tocolytic therapy in the cardiac patient. In: Elkayam U, Gleicher N, editors. *Cardiac problems in pregnancy*. 3rd ed. New York: Wiley-Liss; 1998. p. 437-44.
10. Hurst AK, Hoffman K, Frishman WH, Elkayam U. The use of β -adrenergic blocking agents in pregnancy and lactation. In: Elkayam U, Gleicher N, editors. *Cardiac problems in pregnancy*. 3rd ed. New York: Wiley-Liss; 1998. p. 357-72.
11. Sheikh AU, Harper MA. Myocardial infarction during pregnancy: management and outcome of two pregnancies. *J Obstet Gynecol* 1993;169:279-84.
12. Offman EH, Gall SA. Myocardial infarction in the third trimester of pregnancy secondary to an aortic valve thrombus. *Obstet Gynecol* 1993;81:804-5.
13. Cotton DB, Jones MM, Longmire S, Dorman KF, Tessem J, Joyce TH III. Role of intravenous nitroglycerin in the treatment of severe pregnancy-induced hypertension complicated by pulmonary edema. *Am J Obstet Gynecol* 1986;154:91-3.
14. Lees C, Campbell S, Jauniaux E, Brown R, Ramsay B, Gibb D, et al. Arrest of preterm labour and prolongation of gestation with glyceryl trinitrate, a nitric oxide donor. *Lancet* 1994;343:1325-6.
15. Ginsberg JS, Hirsch J. Use of antithrombotic agents during pregnancy. *Chest* 1995;108(Suppl 4):305S-11S.
16. Goldman L. General anesthesia and noncardiac surgery in patients with heart disease. In: Braunwald E, editor. *Heart disease*. 5th ed. Philadelphia: WB Saunders; 1997. p. 1756-68.
17. Salazar E, Zajarías A, Guitierrez N, Itrube I. The problem of cardiac valve prosthesis, anticoagulants and pregnancy. *Circulation* 1984;70(Suppl 1):169-77.
18. Vongpatanasin W, Hills LD, Lange RA. Prosthetic heart valves. *N Engl J Med* 1996;335:407-16.
19. Cobanoglu A, Jamieson WRE, Miller DC, McKinley C, Grunkemeier GL, Floteu HS, et al. A tri-institutional comparison of tissue and mechanical valves using a patient-oriented definition of "treatment failure". *Ann Thorac Surg* 1987;43:245-53.