Postpartum myocardial infarction: association with primary coronary artery dissection

LISA I. MANSUR, MD; GAROLD O. MINNS, MD; RICHARD A. STECKLEY, MD

A 36-year-old woman presented with an acute myocardial infarction 2 weeks after the birth of her first child. The patient had smoked two packs of cigarettes a day for 12 years and had been taking bromocriptine to suppress lactation. While in the emergency room, the patient went into ventricular fibrillation, but defibrillation successfully restored sinus rhythm. Coronary angiography revealed several atherosclerotic lesions. The patient refused to undergo coronary artery bypass grafting, and she was discharged receiving medical therapy.

Forty-eight cases of postpartum myocardial infarction have previously been reported; the present case makes 49. In 41 cases a cardiac examination was performed, either on necroscopy or by angiography. Twenty-two (54%) of the 41 patients had occlusion related to primary coronary artery dissection, 11 (27%) had normal coronary arteries and presumed spasm, and only 6 (15%) had atherosclerosis-related coronary occlusion. The mortality rate was 39%, and surviving patients had significant cardiac limitation.

Postpartum myocardial infarction and coronary occlusion, when they do occur, are frequently caused by primary coronary artery dissection. Immediate recognition of this association may significantly reduce morbidity and mortality for these patients.

INDEX TERMS: Puerperal disorders; Myocardial infarction; Aneurysm, dissecting; Coronary vasospasm

From the University of Kansas School of Medicine, Wichita.
Address reprint requests to L.I.M., 1993 W. Champagne Avenue, Taylorsville, UT 84118.
to the right arm and neck; it had begun 2 hours previously while she was carrying packages. Her initial electrocardiogram demonstrated ST elevation in the anterior and lateral leads. Soon after her arrival she went into ventricular fibrillation, but defibrillation successfully restored normal sinus rhythm. The patient was transferred to a tertiary-care hospital for cardiac catheterization.

Two weeks previously, the patient had given birth to her first child in an uneventful, normal vaginal delivery. Her pregnancy had been entirely uncomplicated, and she denied having any chest discomfort during the pregnancy or delivery. After delivery, she was given propoxyphene for pain and bromocriptine 2.5 mg twice a day to suppress lactation. She had smoked two packs of cigarettes a day for 12 years. She had no family history of coronary artery disease, and she denied using cocaine, amphetamines, or excessive amounts of alcohol.

The patient's initial creatine phosphokinase (CPK) concentration, drawn before her cardiac arrest, was 1.95 μkat/L, and her lactate dehydrogenase (LDH) concentration was 3.7 μkat/L. Her subsequent CPK concentrations, drawn at 8-hour intervals, were 8.57 μkat/L (19% MB fraction), 30.91 μkat/L (23% MB fraction), 52.07 μkat/L (15% MB fraction), and 37.87 μkat/L (15% MB fraction).

Left ventriculography demonstrated anterolateral hypokinesis and apical dyskinesis. The calculated left ventricular ejection fraction was 34%. Coronary arteriography revealed several atherosclerotic lesions, including a 60% left main artery stenosis, a 90% intermediate diagonal stenosis, and a total left anterior descending artery occlusion distal to the intermediate diagonal branch. The circumflex artery had a 90% elongated stenosis. The right coronary artery was free of obstruction.

Coronary artery bypass grafting was recommended, but the patient declined this procedure and was discharged receiving medical therapy.

The independent risk factor most associated with myocardial infarction in young women is cigarette smoking (especially more than 15 cigarettes per day).1,2 Other risk factors include a family history of coronary artery disease, as well as diabetes, hypertension, and hyperlipidemia.2 The effects of oral contraceptives are controversial.

**Hemodynamic changes during pregnancy**

During pregnancy, the maternal cardiovascular system undergoes remarkable changes.3-18 The intravascular volume (plasma and red blood cell mass) increases 40% to 50%,4-8 the heart rate increases by 10 to 15 beats per minute, and the stroke volume increases 30%.9 Because of these changes, the cardiac output increases by 1.5 L/minute above baseline, reaching a peak at the beginning of the second trimester.9 Owing to increased filling volume secondary to increased intravascular volume, the heart undergoes concentric hypertrophy.10 However, systemic vascular resistance decreases, and arterial blood pressure therefore remains stable or decreases during a normal pregnancy.9,11,12

The cardiac output increases an additional 25% during the first stage of labor, 50% during the second stage, and 80% at delivery (less if conduction anesthesia is used).13 In addition, every uterine contraction adds up to 500 mL of blood into the central circulation, compounding cardiovascular stress with increased arterial pressure and stroke volume.13,15 During a vaginal delivery, blood loss of 300 to 500 mL is not uncommon; during a cesarean section, 1000 mL.16 Further, the use of oxytocin to induce labor likely decreases coronary blood flow.17 The cardiovascular system usually returns to a baseline state over the 7 to 10 days after delivery.18

**Myocardial infarction during or after pregnancy**

Despite these remarkable cardiovascular changes (which could alter coronary blood flow), myocardial ischemia and infarction during pregnancy, parturition, and the puerperium are rare, with a frequently cited incidence of 1 in 10 000 pregnancies.3 Over 100 cases of myocardial infarction and coronary occlusion during pregnancy, delivery, and the puerperium have been reported since 1922; 48 of these cases occurred during the puerperium.3,19-59 Reports of myocardial infarction during the puerperium are scant because the problem is uncommon and because all cases are not reported. By definition,
the puerperium is the period of "confinement" during and just after birth. However, this period is traditionally recognized as the time after delivery in which the reproductive system resumes a nonpregnant state (approximately 6 weeks).

A coronary artery examination was performed either by coronary angiography or at necropsy in 41 of the 49 postpartum cases (including the present one). Coronary atherosclerosis was documented as the primary cause of coronary occlusion in 40% to 50% of the reported cases occurring during pregnancy and delivery, but only 15% of the postpartum cases (Table). In contrast, primary coronary artery dissection was documented in 22 of the 41 postpartum cases in which coronary examination was performed. Coronary artery spasm was assumed to be the cause of occlusion in 11 cases in which the coronary arteries were normal on angiography. Additional possible causes include the same conditions that cause myocardial infarction in patients of similar age (congenital coronary atresia or malformation, hypercoagulable states, vasculitis, and coronary artery aneurysms).

The average age of the patients with postpartum myocardial infarction was 31.5 years (range 17 to 42 years). Over 75% were multigravid or multiparous or both, and virtually all had been previously healthy. Excluding the six cases that were diagnosed after 6 weeks, an average of 12 days elapsed between parturition and the cardiac event (range 3.5 hours to 42 days).

The mortality rate in myocardial infarction during pregnancy and parturition is as high as 45%. Nineteen (39%) of the 49 patients with postpartum coronary occlusion died as an immediate result of the cardiac event. Three additional patients were successfully resuscitated after cardiopulmonary arrest. Many of the surviving patients suffered severely limiting cardiac damage. The cardiac debilitation was likely related to involvement of the anterior or anterolateral wall in 85% of the postpartum cases.

**Coronary artery dissection**

Primary coronary artery dissection is ordinarily a rare cause of coronary occlusion. Recent reviews of the nearly 100 reported cases, dating back to 1933, revealed that almost 75% occurred in women. Of the 49 cases of postpartum coronary artery occlusion and infarction, 22 were related to primary coronary artery dissection. The dissection involved the anterior descending artery alone, both the anterior descending and the left main artery, or the left main artery and both its branches in 21 of the 22 cases. The mean age of the postpartum patients with coronary dissection was 33.8 years (range 26 to 42 years). An average of 24 days elapsed between parturition and the dissection (range 1 to 80 days). Thirteen cases were diagnosed at necropsy. Nine of the women underwent coronary angiography; eight demonstrated a thin radiolucent line indicating separation of the intima and filling of the dissection sac with dye, but one demonstrated stenosis only. All nine patients who underwent angiography survived the acute event.

Most cases of nontraumatic primary coronary artery dissection (dissection unrelated to aortic dissection) are idiopathic, though some cases are related to Marfan's syndrome, sarcoidosis, and hypersensitivity angiitis. Because of the incidence of primary coronary dissection in the third trimester and puerperium, some authors have suggested that it is related to hormonal changes of pregnancy, hemodynamic stress, or both. A report of a woman who suffered two myocardial infarctions due to coronary dissection at 2 and 4 months after delivery documented that collagen synthesis was abnormal in her cultured skin fibroblasts. This report suggested that altered synthesis also occurred in the media of the patient's coronary vessels, and the abnormality was related to hormonal changes of pregnancy.

Adventitial infiltration by inflammatory cells has been described in several cases of primary coronary dissection. A histologic examination was performed in 14 of the postpartum cases; 12 patients had adventitial inflammation with dissection of the outer third of the media, and eight of them had a significant amount of eosinophils within the infiltrate. The significance of the eosinophilic infiltration is

<table>
<thead>
<tr>
<th>Cause</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary coronary artery dissection</td>
<td>22</td>
<td>54</td>
</tr>
<tr>
<td>Presumed coronary artery spasm</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Thromboembolism or thrombosis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>100</td>
</tr>
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*Forty-one of the 49 reported cases included coronary artery examination*
not known. Some speculate that the eosinophils contain several enzymes and cytotoxic substances, including histaminase, arylsulfatase, phospholipase, fibrolysin, and major basic protein, that could contribute to lysis and damage of the arterial wall.\textsuperscript{66,67}

Other vascular-wall abnormalities have been documented in postpartum coronary artery dissection. Cystic medial necrosis without inflammation was described histologically in two patients who had no history of hypertension or features of Marfan's syndrome. Significant atherosclerosis is rarely found in association with coronary dissection,\textsuperscript{31} and atherosclerosis in addition to adventitial inflammation was reported in only two of the cases of postpartum dissection. Some investigators believe the intramural hemorrhages of dissection arise from the thin-walled vasculature within the atheromatous plaques.\textsuperscript{68} Others, citing the prevalence of variant angina and primary coronary artery dissection in Japan,\textsuperscript{36} believe coronary artery spasm to be the primary event in dissection. Hypertension does not appear to be necessary in the pathogenesis of postpartum coronary dissection, as none of the patients had essential or pregnancy-induced hypertension.

Aortic dissection has also been associated with pregnancy. Studies have demonstrated aortic microstructural changes during pregnancy, including disorganization and fragmentation of elastic and reticulum fibers in the tunica media, hypertrophy and hyperplasia of smooth muscle fibers, decreased amounts of interstitial acidic mucopolysaccharides, and changes in the ground substance of the connective tissue.\textsuperscript{69,70} Some investigators believe the alterations of the aortic and coronary walls are associated with the "softening" of tissues that occurs before delivery. However, other investigators have found no consistent alterations in aortic structure or tensile strength when they compared women of all trimesters of pregnancy with controls.\textsuperscript{11,72}

**Hypertension and eclampsia**

Nine women with postpartum myocardial infarction had pregnancy-induced hypertension or preeclampsia-eclampsia that developed during or after delivery. Five of these nine patients underwent coronary examination; only one had normal coronary arteries and no other possible contributing factors; atherosclerosis was documented in three. The causes of pregnancy-induced hypertension and preeclampsia-eclampsia are not completely understood, but generalized vasospasm is important.\textsuperscript{73} Whether pregnancy-induced hypertension or preeclampsia-eclampsia directly result in coronary occlusion is not known, but evidence supports a pathogenic role.\textsuperscript{71}

**Vasospasm**

Postpartum myocardial infarction in patients with normal coronary arteries poses an etiologic puzzle. Eleven patients with postpartum myocardial infarction who underwent coronary angiography had normal coronary arteries; vasospasm was the presumed mechanism of coronary occlusion. None of the patients had a history consistent with variant angina. Use of vasoconstrictive medications or nicot ine was documented in seven of these patients. As in all young patients with myocardial infarction, the surreptitious use of cocaine and amphetamines should be suspected if results of coronary angiography are normal and vasospasm is suspected.

**Bromocriptine and postpartum vasospasm**

Bromocriptine, a semisynthetic hydrogenated ergot alkaloid derivative of alpha-ergocryptine, is a D2-dopamine receptor agonist.\textsuperscript{9,74} It was approved in 1980 by the Food and Drug Administration for postpartum lactation suppression at doses of 2.5 mg twice or three times a day. In low doses (less than 10 mg/day), it typically acts as a potent vasodilator, is well known for causing severe postural hypotension, and does not usually activate alpha-adrenergic receptors.\textsuperscript{59,75} However, bromocriptine in low doses has been implicated in cases of hypertension, cerebrovascular accident, Raynaud's phenomenon, vascular headaches, seizures, vasospasm, and myocardial infarction.\textsuperscript{16,71}

According to one theory, bromocriptine-induced vasospasm is a paradoxical response\textsuperscript{50}; according to another, the constrictive response is mediated by receptors that accept both nonhydrogenated and hydrogenated ergot alkaloids,\textsuperscript{48} or by abnormally positioned D2-dopamine receptors.\textsuperscript{76} Alternatively, a decreased sensitivity of peripheral dopaminergic receptors may unmask the vasoconstrictor effects of bromocriptine.\textsuperscript{78} Finally, up-regulation of dopamine receptors (similar to the up-regulation demonstrated with cocaine use) may occur, causing a dopamine-agonist supersensitivity response to bromocriptine.\textsuperscript{79}

Six case reports have suggested an association between postpartum use of bromocriptine and myocardial ischemia and infarction.\textsuperscript{46,53,56,58,59} Two of the pa-
tients had normal angiographic findings, one had a single stenosis (possibly caused by spasm) and no evidence of atherosclerosis, one had pregnancy-induced hypertension and used ergonovine, and two used other vasoconstrictive medications (isometheptene, benzquinamide, oxytocin) in addition to bromocriptine. Because bromocriptine has no known effects on coagulation, the presumed mechanism of occlusion is coronary vasospasm.

Some of these cases are confounded by the concomitant use of other potentially vasoconstricting or cardioactive agents (eg, ergonovine maleate for uterine atony and postpartum hemorrhage, isometheptene for migraine headache, benzquinamide for nausea and vomiting, and nicotine). Bromocriptine may have potentiated the vasoconstrictive activity of these agents by interfering with drug metabolism.8

Patients prone to vasospasm and the possible vasoconstrictive effects of bromocriptine include those who develop hypertension during pregnancy or after delivery and those with a history of vascular headaches, atherosclerotic disease, cocaine abuse, and Raynaud's phenomenon.80-82 In 1991, the Food and Drug Administration suggested that lactation suppression is safer without the use of drugs.83 The association of bromocriptine use with postpartum myocardial infarction is speculative but should be recognized as a possibility.

Atherosclerotic coronary artery disease

Myocardial infarction related to atherosclerotic coronary artery disease is rare in women younger than 35 years.1 In reported cases, atherosclerosis seems a less common cause of myocardial infarction during the puerperium than during pregnancy and delivery. Only six of the 41 postpartum patients who underwent coronary artery examinations had atherosclerosis-related occlusions. Two of these patients smoked cigarettes, three received bromocriptine or ergonovine after delivery, and four had essential or pregnancy-induced hypertension.

Thrombosis, thromboembolism

Finally, in two reported cases, postpartum myocardial infarction was caused by thrombosis or thromboembolism. Although embolization usually occurs in association with other conditions such as mitral stenosis, cardiomyopathy, atrial septal defect, endocarditis, or atrial fibrillation, these patients had no such history.

The diagnosis of myocardial ischemia and infarction in the postpartum population requires the same criteria as in any other patients, with a few caveats. Myocardial ischemia may be mistakenly identified as gastroesophageal reflux, a common cause of chest discomfort during and after pregnancy. Peripheral edema, distended neck veins, an S3 gallop, a systolic ejection murmur at the left sternal border, and increased splitting of the first and second heart sounds are not uncommon during pregnancy but usually resolve during the first weeks after delivery. The electrocardiogram may show nonspecific ST- and T-wave changes as well as left axis deviation. The serum LDH level during pregnancy is 18% to 100% higher than in nonpregnant women, and serum LDH and CPK levels increase during the muscular work of childbirth. However, the MB fraction of CPK should not increase during pregnancy and childbirth, and serial MB fractions should be followed for diagnosis.

Because of the apparent frequency of primary coronary artery dissection in postpartum coronary artery occlusion, early catheterization is necessary to determine the cause of occlusion. Typical angiographic findings for dissection confirm the diagnosis, but single stenotic lesions may be caused by dissection as well.

Reports in the medical literature on the treatment of postpartum myocardial infarction are limited. Treatment depends on the cause of coronary occlusion. A thorough drug and nicotine history should be taken, and a screen for drugs of abuse should be ordered. Medications should be evaluated and discontinued if a potential for vasoconstriction exists. Nitroglycerin (given intravenously) and analgesics (morphine) have been used without adverse consequences. Depending on the cause of occlusion, the length of time since delivery, and the risk of hemorrhage, aspirin may be used for its antiplatelet action and heparin for its anticoagulant effect. Beta blockers, if not contraindicated, may be used in an attempt to limit infarction size and prevent ventricular arrhythmias. However, beta-blocker use could potentiate spasm in patients with normal coronary arteries.84 Calcium antagonists
may be of benefit in coronary vasospasm and in dissection.

Thrombolytics are relatively contraindicated within 10 days of obstetric delivery because of the risk of bleeding. However, thrombolytics have been used successfully during the postpartum period to treat isolated thrombosis of a prosthetic mitral valve and superior sagittal sinus thrombosis, with few complications. Given the possibility of coronary artery dissection in this population, using thrombolytics without knowing the cause of coronary occlusion is not advised.

Percutaneous transluminal balloon coronary angioplasty was successful in two postpartum patients, including one with atherosclerotic disease and one with presumed spasm. Coronary artery bypass grafting may be indicated, especially given the frequent involvement of the left main and proximal anterior descending arteries.

Of the nine women who survived coronary artery dissection, one underwent thoracotomy and evacuation of a coronary artery hematoma, and three underwent bypass grafting (one with aneurysmectomy). The remaining five patients received medical therapy, including calcium antagonists, nitrates, and warfarin. One of these patients subsequently received a cardiac transplant.

Whether to perform surgery for dissection depends on the degree of stenosis, hemodynamic status, and myocardial viability. Past surgical experience indicates that internal mammary grafts are best, and that proximal ligation of the dissected artery is probably not necessary.

**SUMMARY**

Postpartum myocardial infarction, though rare, often results in severe morbidity or death. In reported cases, the most common cause of postpartum coronary occlusion was primary coronary artery dissection. Immediate recognition of this association is essential for appropriate decisions concerning diagnostic procedures and treatment.

Only 15% of the reported cases were attributed to atherosclerotic disease, though all cases of atherosclerosis-related occlusion were probably not reported because of the rarity of the disease. The 11 cases in which the coronary arteries were demonstrated normal on angiography pose an etiologic and therapeutic puzzle, though vasospasm is a likely mechanism of occlusion. Possible pathogenic roles of vasospasm caused by medications (bromocriptine and ergonovine) and of pregnancy-induced hypertension have been postulated.

Thrombolytics are relatively contraindicated within 10 days after delivery because of the risk of hemorrhage and should not be used until coronary dissection has been excluded.

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