Cardiovascular Management in Pregnancy

Pregnancy-Associated Acute Myocardial Infarction
A Review of Contemporary Experience in 150 Cases Between 2006 and 2011

Uri Elkayam, MD; Sawan Jalnapurkar, MD; Mohamad N. Barakkat, MD; Nudrat Khatri, MD; Angela J. Kealey, MD; Anil Mehra, MD; Arie Roth, MD

The incidence of coronary artery disease (CAD) in women of child-bearing age is low, and acute myocardial infarction (AMI) is uncommon. Pregnancy, however, has been shown to increase the risk of AMI 3-fold compared with the risk in non-pregnant women of similar age. Although previous studies have provided some data related to the incidence of pregnancy-associated MI (PAMI), clinical characteristics, risk factors, and outcome more information is needed on the mechanisms of AMI, the efficacy and safety of standard therapy, and the applicability of guideline recommendations designed for the general AMI population, to women with PAMI.

The aim of this study was therefore to review contemporary data on PAMI in an attempt to provide recommendations for the management of this condition.

Methods

A literature search for cases with AMI related to pregnancy was performed using PubMed and Google Scholar. References from these studies were cross-checked to obtain additional studies that may have been missed by the original search.

All original articles were obtained online or by interlibrary communication. Articles published in languages other than English were translated by medical translators. A total of 134 cases published in the literature from 2006 to 2011 not included in a previous review were included in this study. In addition, 7 cases presented at the First International Congress on Cardiac Problems in Pregnancy in 2010 (Valencia, Spain) and 9 patients treated or consulted by the authors were also included in the analysis. Recommendations were made on the basis of available clinical information, with the understanding that the cases published in the literature and reviewed by us do not represent all the patients who developed PAMI during the period of the study and that reporting may therefore be incomplete and biased.

Results

One hundred fifty patients with PAMI were included in the study (Table 1). The age ranged from 17 to 52 years; the mean age was 34 ± 6 years; 75% of the patients were >30 years of age; and 43% were >35 years. Reported risk factors for CAD included smoking in 25% of the patients, dyslipidemia in 20%, hypertension in 15%, and diabetes mellitus and a family history of CAD in 9% each.

The type and timing of AMI are shown in Figure 1. Data on the type of AMI were available in 139 of the patients. Of these, 105 (75%) presented with ST-segment–elevation MI (STEMI) and the rest with non-STEMI (NSTEMI). The majority of the patients developed AMI during either the third trimester of pregnancy (STEMI, 25%; NSTEMI, 32%) or the postpartum period (STEMI, 45%; NSTEMI, 55%). The myocardial infarct involved the anterior wall of the left ventricle (LV) in 69% of the patients, the inferior wall in 27%, and the lateral wall in 4%.

Table 2 shows the mechanisms of AMI. Coronary angiography was performed in 129 patients and demonstrated coronary dissection (CD) in 56 patients (43%), atherosclerotic disease in 27%, a clot without angiographic evidence for atherosclerotic disease in 22 patients (17%), and normal coronary anatomy in 14 patients (11%). Three of these patients were diagnosed with takotsubo cardiomyopathy, and noniatrogenic coronary spasm was documented in 2 patients. The majority of patients who developed CD presented in the postpartum period (73%) and the third trimester (21%); similarly, most patients (78%) who were found to have normal coronary anatomy presented in late pregnancy or the postpartum period, whereas women with atherosclerotic disease presented equally throughout the 3 gestational trimesters and the postpartum period. One of the patients with AMI resulting from documented spasm and the 3 patients with Takotsubo cardiomyopathy presented during the postpartum period. CD involved the left anterior descending artery (LAD) in 39 patients, the left main (LM) segment in 24 patients, the left circumflex artery (LCx) in 14 patients, and the right coronary artery (RCA) in 12 patients. Thirty-four patients had dissection limited to 1 coronary artery (LAD, 19; LM, 9; LCx, 1; and RCA 5); 14 women had dissection involving 2 vessels (LM, 9; LAD, 12; LCx, 5; and RCA, 2); and 8 women had involvement of ≥3 vessels (LM, 6; LAD, 8; LCx, 8; and RCA, 5).

LV function is shown in Figure 2. Information on LV ejection fraction measured by either echocardiography or contrast angiography was available in 97 patients and was reported to be ≤40% in 54% of the cases, ≤30% in 24% of cases, and ≤20% in 9% of cases.

Complications (Table 3) included heart failure or cardiogenic shock in 38% of the patients, ventricular arrhythmias in 12%, and recurrent angina or AMI in 20%. The incidence of maternal mortality was 7% (9 patients), and the causes were...
cardiogenic shock in 3 patients and sudden death, rupture of LV apex, ventricular fibrillation during cardiac catheterization, aortic dissection, heart failure and ventricular fibrillation, and rupture of right common iliac artery after percutaneous coronary intervention in 1 patient each. Fetal mortality was 5% (7 cases) and was the result of maternal mortality in 6 cases and coronary artery bypass graft surgery in 1 case.

Drugs and Invasive Procedures
The use of the following drugs was reported: aspirin (38 patients), β-blockers and heparin (38 patients each), clopidogrel (23 patients), nitroglycerin (20 patients), glycoprotein IIb/IIIa (18 patients), ACE inhibitors (9 patients), statins (7 patients), and fibrinolytic drugs (6 patients). No complications related to drug therapy including thrombolytic drugs were reported.

Coronary angiography was performed in 69 patients during pregnancy and in 60 patients during the postpartum period. Five of these patients developed acute CD during the procedure as a result of intracoronary contrast injection. The procedure was performed during the 36th week of gestation in 1 of these patients and during the first week after delivery in the rest of the patients. In all 5 patients, the dissection involved the LAD and LCx arteries, and it extended to the LM in 1 patient. Four of the patients had urgent coronary artery bypass graft surgery, and 2 patients, including 1 who had coronary artery bypass graft surgery required a left ventricular assist device. One of these patients, died of intracranial bleeding while awaiting cardiac transplantation.

Percutaneous coronary intervention was performed in 59 women, 21 of whom had CD; it was performed in 31 cases during pregnancy. Antepartum stenting involved the use of bare metal stents in 13 cases and drug-eluting stents in 2 patients; the type of stents was not reported in the rest of the patients. The procedure was associated with iatrogenic CD in 2 patients. The first developed propagation of a mid-LAD dissection to the proximal and distal parts of the artery at 3 days postpartum and required placement of 5 further stents. The second, who had the intervention 10 days postpartum, developed dissection of the proximal LAD with propagation into the first diagonal branch after stenting of the mid-LAD segment, which required further stenting.

Coronary artery bypass surgery was performed in 30 patients, including 14 patients during pregnancy. The procedure was associated with fetal loss in 1 case.

Discussion
Our study of 150 contemporary cases of AMI occurring during pregnancy or the postpartum period demonstrates that PAMI is different from MI occurring in the nonpregnant population and requires special consideration.

Seventy-five percent of the patients included in the present study were >30 years of age and 43% were >35 years of age. Age >35 years was also found to be strongly associated with

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Type and timing of acute myocardial infarction. NSTEMI indicates non-ST-segment-elevation myocardial infarction; and STEMI, ST-segment-elevation myocardial infarction.
The majority of the patients did not have traditional risk factors for CAD, and the prevalence was lower than that reported in nonpregnant young women with CAD. This finding is probably due to the relative young age of the patients and to the unusual mechanisms for PAMI. The most common cardiovascular risk factor was cigarette smoking (25%), followed by hyperlipidemia (20%), hypertension (15%), diabetes mellitus and family history (9% each). A very similar rate of cardiovascular risk factors was reported by Ladner et al in 151 women with PAMI (diabetes mellitus and hypertension in 19% each and lipid disorders in 7%). Despite the seemingly low rate of risk factors in the PAMI population, the incidence was found to be significantly higher compared with ≈5 million pregnancies without PAMI, suggesting a mechanistic importance of these risk factors in some women during pregnancy. This suggestion is supported by the report of James and associates, who found involvement of the anterior wall in only 25% of the cases. The difference between the 2 studies could be related to missing data on infarct location in more than half of the patients reported by James and coworkers.

Compared with the general population, including young women in whom the majority of AMI occurs as a result of coronary atherosclerosis, this was found in fewer than a third of women included in our study, and the majority of the patients had other mechanisms for AMI. CD, a rare cause of AMI in the nonpregnant population (0.28% to 1.1% of cases), was the most common cause in our population, documented in 40% of the patients. AMI secondary to CD occurred mostly in late pregnancy or the early postpartum period and involved mostly the LAD and LM. Multivessel involvement in a large proportion of these cases in the present study and in previous studies supports generalized rather than localized vessel wall changes in pregnancy. Although the exact pathophysiology of CD related to pregnancy remains unclear, hormonal and hemodynamic changes have been proposed as potential causes. Excess levels of progesterone can lead to a loss of normal corrugation of elastic fibers and a decrease in acid mucopolysaccharide ground substance. Estrogen has also been shown to increase the release of matrix metalloproteinase, which can lead to cystic medial necrosis and lack of structural support of the vasa vasorum in the media-adventitia border. An unsupported vasa vasorum in the adventitial layer may rupture as a result of the increased hemodynamic stress of pregnancy or labor, leading to an intramural hematoma. The association between pregnancy-associated CD and hormonal changes may be supported by a relatively high incidence of hormonal therapy reported in nonpregnant women who developed CD. Other proposed etiologic factors for pregnancy-associated CD include matrix changes resulting from an inflammatory effect and release of proteolytic enzymes like collagenase, peroxidase, and acid phosphatase, which may cause excessive degradation of collagen matrix at the media-adventitia layers.

Table 2. Mechanisms of AMI (132 Patients)

<table>
<thead>
<tr>
<th>Cause of AMI</th>
<th>First Trimester, n</th>
<th>Second Trimester, n</th>
<th>Third Trimester, n</th>
<th>Postpartum, n</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary dissection</td>
<td>…</td>
<td>3</td>
<td>12</td>
<td>41</td>
<td>56 (43)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>35 (27)</td>
</tr>
<tr>
<td>Clot</td>
<td>3</td>
<td>10</td>
<td>3</td>
<td>6</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Spasm</td>
<td>…</td>
<td>…</td>
<td>1</td>
<td>1</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Takotsubo</td>
<td>…</td>
<td>…</td>
<td>3</td>
<td>3</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction.

Figure 2. Incidence of reduced left ventricular (LV) ejection fraction (EF) in 97 women with pregnancy-associated myocardial infarction who had data on LV function.
We found a preponderance of LAD and LM involvement in the cases with CD. A possible explanation may be related to the hemodynamic and anatomic differences between the right and left coronary arterial system. Although the RCA flow is more uniform during systole and diastole, the left coronary system experiences a significant decline in blood flow during systole, accompanied by a marked increase in diastolic pressure, leading to a significant rise in both oscillatory shear stress and wall stress. In addition, because of a higher number of branches, the LAD is subjected to increased torsion force during cardiac cycle compared with the RCA.

Coronary arteries were found to be anatomically normal in 18% of the cases in the present study and in a similar proportion of pregnant women in previous studies. The mechanism of AMI in such cases is not clear. Potential explanations may include transient coronary spasm potentially caused by the previously described increased release and enhancement of vascular reactivity to angiotensin II and catecholamines, endothelial dysfunction, and use of ergot derivatives prescribed for lactation suppression control or prevention of postpartum hemorrhage. In addition, both nonobstructive atherosclerotic lesions and CD leading to hematoma in the vessel wall between the media and adventitia may be interpreted on angiography as normal coronary anatomy. Similarly and because of the limitations of coronary angiography, intramural hematoma secondary to CD of a normal coronary artery may be misinterpreted as atherosclerotic disease.

Thrombosis without evidence of coronary atherosclerosis was found in 17% of the cases. This finding is most likely related to well-described changes in the coagulation and fibrinolytic systems and the resulting hypercoagulable state of pregnancy and the postpartum period.

The present study provides information not previously available on LV function in women with PAMI. More than half of the patients had a substantial reduction in LV systolic function with an ejection fraction <40%. These findings reflect a large myocardial insult related to involvement of the LV anterior wall in more than two thirds of the patients as a consequence of involvement of LAD artery and LM segment in many cases. The predominance of anterior AMI and the marked depression of LV ejection fraction in many of the patients explain the high incidence of complications, including heart failure, cardiogenic shock, ventricular arrhythmias, and death. The incidence of maternal mortality in this study was 7%. Causes of death were pump failure and cardiogenic shock in almost half of the patients and arrhythmias, LV myocardial rupture, or vascular complications in the remainder. The rate of maternal mortality in the present study is lower than that published in earlier series but similar to the incidence described in more recent reports. This apparent reduction in mortality is probably due to the continued improvement in the management strategies of AMI in the general population in the last 2 decades, which must also have affected the outcome of PAMI. It should be noted, however, that despite this apparent improvement, the incidence of mortality in women with PAMI is substantially higher than mortality expected in a nonpregnant women of similar age or even older. The rate of fetal mortality was also higher than reported in other cardiac conditions and was related mostly to maternal mortality.

Standard recommended drug therapy for the nonpregnant population of patients with AMI includes the potential use of morphine sulfate, angiotensin-converting enzyme inhibitors, β-blocker, nitroglycerin, heparin, calcium channel blockers, and antiplatelet therapy, including aspirin, clopidogrel, prasugrel (or newer antiplatelet drugs), glycoprotein IIb/IIIa receptor inhibitors, statins, and fibrinolytic drugs. Although the use of guideline-recommended drug therapy seems desirable for maternal protection even during pregnancy, only limited information is available on fetal safety for some of these drugs. Concern about safety is most likely the explanation for the failure to use standard cardiac medications in many of the patients in our study, a fact that could have contributed to the high rate of complications.

Although the use of angiotensin-converting enzyme inhibitors and statins is contraindicated during pregnancy, the safety of most of the other medications listed above has not been established. The reported uncomplicated use of clopidogrel and glycoprotein IIb/IIIa inhibitors during pregnancy in 23 and 18 patients, respectively, included in the study adds to the limited information published in the literature on the antenatal use of these medications. This information, however, is incomplete, and reports have been limited to acute events without appropriate follow-up information. Although most investigators have suggested the use of antiplatelet therapy in patients with AMI resulting from CD, such recommendations have come into question because of concerns that these drugs may prevent healing and promote the extension of the dissection.

Recent recommendations by the European Society of Cardiology have suggested using clopidogrel only when strictly needed (after stenting) and refraining from the use of glycoprotein IIb/IIIa inhibitors, bivalirudin, prasugrel, and ticagrelor. Because of the potential benefit of β-blockers in reducing shear stress and the relative safety during pregnancy, the use of these drugs seems advisable. Thrombolytic drugs were used in 6 of our cases without reported side effects. Such therapy is relatively contraindicated in pregnancy because of insufficient information and a potential risk of maternal hemorrhage and fetal loss. In patients with CD, fibrinolytic therapy is considered contraindicated because of the concern that it may act as a double-edged sword and facilitate the extension of the dissection. Because of the high incidence of CD as a mechanism for PAMI, blinded use of fibrinolytic therapy in this population is risky and should probably be avoided.

Primary percutaneous coronary intervention with the goal of early reperfusion is strongly recommended in nonpregnant patients with STEMI and in unstable patients with NSTEMI. These recommendations should also be applied to pregnant women with the same conditions. However, our data demonstrate

<table>
<thead>
<tr>
<th>Table 3. Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complication</td>
</tr>
<tr>
<td>Heart failure/cardiogenic shock</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>Recurrent angina/MI</td>
</tr>
<tr>
<td>Maternal mortality</td>
</tr>
<tr>
<td>Fetal mortality</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction.
a high incidence of iatrogenic CD related to either intracoronary angiography or coronary stenting, resulting in the need for multiple stents, urgent coronary bypass surgery, and even death. These findings, in addition to the limited technical success recently reported in nonpregnant patients with CD,\textsuperscript{1,3} suggest that a non-invasive approach to the management of stable, low-risk women with PAMI should be considered. When coronary angiography is performed, catheter entry into the coronary ostia should be done carefully, followed by a minimum number of low-pressure intracoronary contrast injections. Coronary revascularization should be used to relieve significant coronary obstruction in patients with CD, but treatment should be restricted to more severe obstructions of proximal segments, keeping in mind the possible propagation of the dissection. Although intravascular ultrasound is useful in the diagnosis of CD,\textsuperscript{120} its use in pregnancy may not be advisable and should be reserved for cases in which the benefit of the information obtained outweighs the increased risk. Computed tomographic coronary angiography during pregnancy may provide an alternative and safer method to obtain anatomic information, but it is limited by the risk of fetal radiation\textsuperscript{142} and the need for excessive doses of \(\beta\)-blockers for heart rate control with unknown risk to the fetus.

A recent report by James et al.\textsuperscript{2} described 61 women with PAMI who underwent surgery during pregnancy; however, no information was provided on outcome. A previous review of PAMI reported 1 fetal mortality in 5 women with AMI undergoing surgery during pregnancy.\textsuperscript{4} Surgical revascularization was performed in 30 of the patients described in the present study, 23 of them for CD. Eleven of the patients had surgery during pregnancy; the others had surgery in the postpartum period. There was no maternal mortality, and only 1 fetal loss was reported. Although this limited information does not allow assessment of the overall risk of coronary artery bypass graft surgery in women with PAMI, the rate of fetal mortality is lower than that reported in previous studies\textsuperscript{143} and may suggest lower risk of fetal loss with contemporary surgery. This assumption is supported by a report by Immer et al., who described a substantial decrease in maternal and fetal mortality associated with cardiac surgery for aortic dissection in women with Marfan syndrome operated on during pregnancy between 2002 and 2004 compared with 1990 and 1994, with fetal loss decreasing from 50% to only 10%.

**Study Limitations**

The results of this study have to be considered limited because of the retrospective collection of data mostly from reports of single cases or small case series. Data collected in this fashion may be incomplete and do not allow more robust information on maternal and offspring outcome. In addition, the data could be strongly influenced by selection and ascertainment bias, and it is possible that cases submitted and accepted for publication represent preferential selection of more complicated cases. At the same time, however, the results of this study are consistent with findings from our 2 previous surveys\textsuperscript{1,130} and are strongly supported by the results of 2 recent large population studies.\textsuperscript{1,2}

**Summary and Recommendations**

PAMI is different from AMI in nonpregnant patients in several important aspects that need to be taken into strong considerations in the management of women with this condition. Atherosclerotic CAD, the most common cause of AMI in the nonpregnant population, is responsible for only a third of PAMI cases; the majority of patients develop their AMI by other mechanisms. There is frequent involvement of the LAD and LM coronary arteries, and the location of PAMI is commonly the anterior wall, resulting in a high incidence of LV dysfunction, congestive heart failure, cardiogenic shock, and mortality. Because many women with PAMI have CD or normal coronary anatomy, the risk of thrombolytic therapy may outweigh a potential benefit, and blinded use of such therapy does not seem advisable. The high incidence of iatrogenic CD secondary to intracoronary contrast injection and mechanical interventions suggests that an invasive approach to PAMI should be limited to high-risk patients and that mechanical coronary manipulations should be limited to cases in which potential benefits clearly outweigh the risk. The use of guideline-recommended antiplatelet therapy may be desirable for maternal protection. At the same time, however, women should be informed about the paucity of information available on the safety of these drugs for their fetus.

**Disclosures**

None.

**References**


Duran JR 3rd, Raja ML. Myocardial infar 2006;332:643.


Kierman TJ, Rochford M. Postpartum spontaneous coronary artery dissection: an important clinical link with anticoagulidin antibody. Int J Cardiol. 2007;114:E75–E76.


KEY WORDS: myocardial infarction, pregnancy

Uri Elkayam, Sawan Jalnapurkar, Mohamad N. Barakkat, Nudrat Khatri, Angela J. Kealey, Anil Mehra and Arie Roth

_Circulation_. 2014;129:1695-1702
doi: 10.1161/CIRCULATIONAHA.113.002054

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/129/16/1695

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/