

STATE-OF-THE-ART PAPER

Acute Myocardial Infarction Associated With Pregnancy

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Acute myocardial infarction (AMI) during pregnancy or the early post-partum period is rare but has been shown to be associated with poor maternal as well as fetal outcome. Major changes in both diagnosis and treatment of AMI in the nonpregnant patient have led to improved outcome which may also affect pregnant patients. The purpose of this paper is to review available information related to the pathophysiology and clinical profile and provide recommendations for the diagnosis and management of AMI occurring during pregnancy and the early post-partum period. (J Am Coll Cardiol 2008;52:171-80) © 2008 by the American College of Cardiology Foundation

Acute myocardial infarction (AMI) in women during child-bearing age is rare. Pregnancy, however, has been shown to increase the risk of AMI 3- to 4-fold (1-5). With the continuing trend of childbearing at older ages and advances in reproductive technology enabling many older women to conceive (6), it may be expected that its occurrence will increase.

Our previous review more than a decade ago indicated high maternal mortality and fetal loss associated with pregnancy-related AMI (1). The last decade has witnessed a major change in both the diagnostic and therapeutic approaches to patients with AMI, which has led to improvement in outcome; these changes may have affected pregnant patients as well. The purpose of this article is to review new information on AMI related to pregnancy and provide recommendations for the diagnosis and management of this condition.

Methods

A literature search for AMI during or following pregnancy and related topics was performed using MEDLINE. All original articles were obtained from the Universities of Tel Aviv or Southern California libraries, interlibrary communications, or authors of the articles. Medical translators were used to translate all original articles written in languages other than English. Only cases of AMI documented by chest pain, standard electrocardiographic criteria, typical enzymatic changes, or histologic changes in those who died were selected for review. Ninety-five cases that appeared in the literature from 1995 until December 2005 (7-93) and

were not included in our previous review (1) were analyzed. In addition, 8 cases that were treated or consulted on by the authors were included (A. Roth, U. Elkayam, unpublished data).

Epidemiologic data were compared in patients who had AMI in the antepartum (≤ 24 h before labor), peripartum (within 24 h before or after delivery), and post-partum (24 h to 3 months after delivery) periods. Fisher's test was used to compare selected demographic and outcome parameters among patients diagnosed earlier and included in our previous review (1) and the current review. Recommendations were made on the basis of available information, with the understanding that the cases reviewed do not represent all patients who have sustained an AMI associated with pregnancy and that reporting may be biased.

Epidemiology. Our current review shows that AMI occurs at all stages of pregnancy and more commonly in multigravidas (66%). Patient ages ranged from 19 to 44 years, but the majority of patients (72%) were older than 30 years. Myocardial infarction (MI) location was mostly (78%) in the anterior wall (Table 1).

INCIDENCE. Ladner et al. (2) reviewed hospital discharge records for deliveries in California between 1991 and 2000 and reported an incidence of 1 AMI in 35,700 deliveries. James et al. (3) queried a nationwide inpatient sample for all pregnancy-related discharges in 2000 to 2002 and found a total of 859 cases of AMI, giving an incidence of 1 in 16,129 deliveries. The higher incidence reported by James et al. (3) may reflect improvements in diagnostic capability or a recent increase in the number of cases. The latter assumption is supported by the increase in the rate of AMI over the 10-year study period reported by Ladner et al. (2) (1 in 24,000 in the final year compared with 1 in 73,400 initially).

RISK FACTORS. Our review revealed a relatively high incidence of known risk factors for AMI in the patients

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Abbreviations and Acronyms

- ACE** = angiotensin-converting enzyme
- AMI** = acute myocardial infarction
- ARB** = angiotensin receptor agonist
- CABG** = coronary artery bypass graft
- CCB** = calcium-channel blocker
- LMWH** = low-molecular-weight heparin
- MI** = myocardial infarction
- PCI** = percutaneous coronary intervention
- RCA** = right coronary artery
- TT** = thrombolytic therapy
- UFH** = unfractionated heparin

reported despite their young ages. Forty-five percent were smokers, 24% had hyperlipidemia, 22% had family histories of myocardial infarction (MI), 15% had hypertension, and 11% had diabetes. In comparison with our early report (1), the incidence of risk factors was higher in the current group (Table 2), which may reflect the increased incidence of smoking among young women as well as better reporting. In addition, 72% of the patients were older than 30 years and 38% were older than 35 years. Lander et al. (2) identified chronic hypertension, diabetes, advanced maternal age, pre-eclampsia, and eclampsia as independent risk factors for pregnancy-related AMI, and James et al. (3) also found

thrombophilia, transfusion, and post-partum infections to be significant risk predictors for AMI.

MORTALITY. Our review identified 11 cases of maternal fatality for a mortality rate of 11%. With the exception of 1 patient who died following cardiac surgery (30) and another who died during cardiac catheterization (A. Roth, U.

Elkayam, unpublished data), maternal death occurred at the time of infarction. The incidence of mortality was twice as high in women diagnosed with AMI during the peripartum period compared with the antepartum or post-partum periods (Table 1); similar findings were reported by Ladner et al. (2). One case was associated with the administration of terbutaline to stop early uterine contractions during pregnancy (49), 2 cases were associated with the administration of bromocriptine to suppress post-partum lactation (52,62), and 1 case was associated with the administration of ergotamine shortly after delivery (82). Coronary angiography 2 days after an antero-septal AMI at the end of the second trimester (A. Roth, U. Elkayam, unpublished data) resulted in extensive coronary dissection and led to both maternal and fetal death. The mortality rate was higher in the peripartum period (18%) compared with the antepartum and post-partum periods (both 9%) (Table 1).

The maternal mortality rate of 11% found in the present review is considerably lower than the rate of 21% reported in our previous review (1) and 38% reported by others (27), but it is supported by a mortality rate of 7.3% recently reported by Ladner et al. (2) and 5.1% reported by James et al. (3) and probably indicates a significant improvement in the outcome of pregnancy-related AMI in the last decade.

The incidence of fetal mortality was 9% (6 of 68), and most fetal deaths were associated with maternal mortality. In 2 cases, pregnancy was terminated electively because of a concern regarding potential drug teratogenicity (59,87).

Table 1 Select Data in 103 Pregnancies Complicated by MIs

Variable	Antepartum Group (n = 46)	Peripartum Group (n = 22)	Post-Partum Group (n = 35)	All Groups (n = 103)
Mean age ± SD, yrs	33 ± 6	32 ± 5	34 ± 5	33 ± 5
Age range, yrs	19-45	24-44	22-43	19-44
Anterior MI location, n/n (%)	30/41 (73)	16/22 (73)	27/31 (87)	73/94 (78)
Multiparous, n/n (%)	27/37 (73)	6/13 (46)	19/29 (66)	53/80 (66)
Hypertension, %	18	15	11	15
Diabetes mellitus, %	13	10	11	11
Smoking, %	62	15	43	45
Family history of MI, %	33	5	18	22
Hyperlipidemia, %	23	15	32	24
Pre-eclampsia, %	2	7	9	6
Congestive heart failure or cardiogenic shock after MI, n (%)	2 (4)	3 (14)	4 (11)	9 (9)
Coronary anatomy available, n (%)	41 (89)	21 (95)	34 (97)	96 (93)
Stenosis	25 (54)	6 (27)	10 (29)	41 (40)
Dissection	5 (11)	11 (50)	12 (34)	28 (27)
Thrombus	2 (4)	1 (5)	5 (14)	8 (8)
Spasm	1 (2)	0	1 (3)	2 (2)
Embolus	2 (4)	0	0	2 (2)
Normal	6 (13)	3 (14)	4 (11)	13 (13)
Deaths, n (%)				
Mother	4 (9)	4 (18)	3 (9)	11 (11)
Infant	5 (11)	1 (5)	—	6 (9)*

*6 of 66 patients with acute MI either during the antepartum or peripartum period.
MI = myocardial infarction.

Table 2 Comparison Between Select Data From 1922 to 1995 Versus 1995* to 2005

Variable	1922–1995 (n = 125)	1995–2005 (n = 103)	p Value
Mean age ± SD, yrs	33 ± 6	33 ± 5	1.0
Age range, yrs	16–45	19–44	—
Anterior MI location, n/n (%)	89/122 (73)	73/94 (78)	0.75
Multiparous, n/n (%)	93/111 (84)	53/80 (66)	<0.01
Hypertension, %	19	15	0.35
Diabetes mellitus, %	5	11	0.93
Smoking, %	26	45	<0.01
Family history of MI, %	8	22	<0.01
Hyperlipidemia, %	2	24	<0.01
Preeclampsia, %	11	6	0.15
Cesarean section, %	26	38	<0.005
Heart failure or cardiogenic shock after MI, n (%)	25 (19)	9 (9)	0.02
Coronary anatomy available, n (%)	68 (54)	96 (93)	<0.01
Stenosis	29 (43)	41 (40)	1.0
Thrombus	14 (21)	8 (8)	0.38
Dissection	11 (16)	28 (27)	<0.001
Spasm	1 (1)	2 (2)	0.45
Embolus	—	2 (2)	0.47
Normal	20 (29)	13 (13)	<0.001
Intracoronary/systemic thrombolytic drug treatment for coronary thrombosis, n (%)	1 (1)	10 (10)	<0.001
Percutaneous coronary angioplasty ± stenting, n/n (%)	1/58 (2)	38/90 (42)	<0.05
Deaths, n (%)			
Mother	26 (20)	11 (11)	0.08
Infant	16 (12)	6 (9)	

*Patients diagnosed in 1995 that were not included in the previous review.
 MI = myocardial infarction.

CORONARY ANATOMY. Coronary artery morphology was studied (angiographically or at autopsy) in 96 (93%) of the women included in this review (Table 1). Atherosclerosis with or without intracoronary thrombus was found in 41 cases (40%), and definite or probable coronary thrombus without evidence of atherosclerotic disease was present in 8%. Atherosclerotic disease was more prevalent in the antepartum period (54%) than the peripartum (27%) or post-partum (29%) period.

Coronary dissection, a rare cause of AMI in the nonpregnant population, was reported in 28 patients (27%) who had 41 dissected coronary arteries. In 9 women, dissection was limited to 1 vessel (3 to the left main artery, 4 to the left anterior descending artery [LAD], 1 to the circumflex artery [CX], and 1 to the right coronary artery [RCA]). When more than 1 vessel was involved, the dissection included the left main coronary artery in 3 patients, LAD in 17, and the CX and RCA in 6 each. Coronary dissection was the primary cause of infarction in the peripartum period (50%) and was found more commonly in post-partum compared with antepartum cases (34% vs. 11%) (Table 1).

Pregnancy-related spontaneous coronary dissection is thought to be related to an excess of progesterone, leading to biochemical and structural changes to the vessel wall (e.g., loss of normal corrugation in elastic fibers, fragmentation of reticular fibers, and decreases in the amount of acid

mucopolysaccharides) (94,95). Other hypotheses include an association among eosinophils (probably lytic action of proteases released from them) (96) and a lack of prostacyclin synthesis—stimulating plasma factor and elevated lipoprotein(a) (22).

The physiologic increase in blood volume and cardiac output may magnify shear forces of the blood column in large vessels, resulting in a greater propensity for dissection. The fact that coronary dissection frequently occurs in more than 1 vessel points toward generalized rather than localized disease.

Coronary arteries were described as normal in 13% of the current cases with almost equal distribution throughout the 3 periods (Table 1). A transient coronary spasm is a possible explanation for this finding and may be caused by previously described enhanced vascular reactivity to angiotensin II (97) and norepinephrine (98) and due to endothelial dysfunction (99). Other possible causes of coronary spasm include: 1) renin release and angiotensin production due to decreased uterine perfusion in the supine position (100); and 2) ergot derivatives that are used to control post-partum or post-abortion hemorrhage or to suppress lactation (101).

Coronary thrombosis without evidence of atherosclerotic disease in 8% of the cases may be explained by the hypercoagulable state of pregnancy due to alterations in the coagulation and fibrinolytic systems, which include a de-

creased releasable tissue plasminogen activator (tPA) (102,103), increased fast-acting tPA inhibitor (104,105), change in the level of coagulation factors (103,106), and reduction in functional protein S levels (107-109). Cigarette smoking during pregnancy reported in 45% of the patients may further increase risk of thrombosis due to enhanced platelet aggregability (110).

Enhanced stroke volume and heart rate during pregnancy (111) can increase myocardial oxygen demand. At the same time, physiologic anemia and decreased diastolic blood pressure may reduce myocardial oxygen supply and contribute to the development of myocardial ischemia when coronary blood supply is compromised. Anxiety, pain, and uterine contraction during labor and delivery may increase oxygen consumption up to 3-fold and can further aggravate myocardial ischemia. In the puerperium, heightened hemodynamic load may be further increased by augmented return of venous blood to the heart, with relief of caval compression and shift of blood from the contracting emptied uterus into the systemic circulation.

Diagnosis. Criteria for diagnosis of AMI in pregnant women are in general the same as in nonpregnant patients and consist primarily of symptoms, electrocardiographic changes, and cardiac markers. At the same time, however, the diagnostic approach is also influenced by fetal safety and normal changes during pregnancy (112). ST-segment depression mimicking myocardial ischemia has been observed in healthy women after the induction of anesthesia for cesarean section, and this result can be misleading (1,113,114). A recent study (114) reported significant ST-segment changes by Holter monitoring in 42% of 26 patients undergoing elective cesarean sections and in 38.5% of patients postoperatively. Forty-two percent of the patients experienced chest pain requiring opioid analgesia; the majority of the patients had normal troponin levels.

Echocardiogram is safe during pregnancy and can be used to evaluate the presence of wall-motion abnormalities. Interpretation of biochemical markers is somewhat complicated by changes that may occur during normal labor and delivery (115). An increase in the concentration of creatine kinase and its MB fraction by nearly 2-fold within 30 minutes after delivery was reported by Shivvers et al. (115) and is probably related to the uterus and placenta, which embody substantial amounts of these enzymes. Mean creatine kinase-MB levels continued to rise and reached a maximum at 24 h after delivery. In contrast, troponin I levels demonstrated only a small increase after delivery and remain below the upper limit of normal (115-117), except in women with preeclampsia and gestational hypertension, in whom it may show a mild elevation (116,117).

Exercise testing can be performed during pregnancy for the diagnosis of myocardial ischemia or risk stratification following AMI. Fetal bradycardia, reduction of fetal heart rate variation, and absence of body movement have been described during moderate to heavy maternal exercise (112,118,119). Because of these findings, the use of a

submaximal protocol ($\leq 70\%$ of maximal predicted heart rate) with fetal monitoring, if possible, is preferred (112). The use of stress echocardiography may increase the sensitivity of the test for detection of myocardial ischemia and viability (120).

The use of radiation during pregnancy should be kept to a minimum (121). The amount of fetal exposure to radiation during chest radiography is extremely small and should probably be considered safe for use when necessary. Radioisotope imaging using ^{99m}Tc -labeled sestamibi or ^{201}Tl is expected to yield <1 rad of radiation to the conceptus. Cardiac catheterization and interventional procedures may also result in fetal exposure of <1 rad. Difficult procedures requiring longer fluoroscopy time and several cine views, however, could easily yield a fetal radiation exposure of 5 to 10 rads. Although termination of pregnancy is not generally recommended for fetal doses of radiation <5 rads, it may be considered when the dose exceeds 10 rads (121).

Cardiac catheterization was reported in 386 patients by James et al. (3); no information, however, was provided regarding the outcome of these procedures. Cardiac catheterization was also performed in 92 (89%) of the patients reviewed with equal distribution among patients presented antepartum, peripartum, or post-partum. The procedure resulted in fatal coronary dissection in 1 patient, who was studied during the second gestational trimester, and coronary dissection leading to bypass surgery in another patient, who was studied post-partum and had balloon angioplasty without stenting. Because of the possible increased risk of coronary dissection, noninvasive risk stratification may be preferred during pregnancy or the early post-partum period in stable and low-risk patients.

Treatment. The treatment of pregnant women with AMI and its complications should in general follow the usual standard of care (122,123), although both maternal and fetal considerations should affect the choice of therapy. The treatment plan should therefore be established by both the cardiologist and obstetrician. If possible, the patient should be treated in an intensive care unit that can also provide maternal monitoring and comprehensive obstetric service. A plan should be established for urgent delivery of a potentially viable fetus in the case of clinical deterioration of the mother.

Revascularization. PERCUTANEOUS CORONARY INTERVENTION (PCI). James et al. (3) reported PCI in 135 patients with stenting in 127 of them. No information, however, was provided on the timing of these procedures or their outcome. Coronary angiography was performed in 92 of 103 patients included in our review; 49 of these procedures were done antepartum and 43 post-partum. PCI was performed in 38 of 92 (41%) subjects (23 antepartum, 6 peripartum, and 9 post-partum) with stent placement in 55% of these patients. Duration of pregnancy in 23 patients who underwent the procedure in the antepartum period (mostly in the third trimester) ranged from 6 to 38 weeks. One patient

who had a balloon angioplasty post-partum developed an extensive coronary dissection that resulted in coronary bypass surgery (A. Roth, U. Elkayam, unpublished data). All reported stenting during the acute phase of MI during pregnancy were performed with bare metal stents; the safety of drug-eluting stents in pregnant woman is therefore still unknown. Because drug-eluting stents require prolonged antiplatelet therapy with clopidogrel and the incidence of cesarean section deliveries in patients with heart disease is relatively high, the use of drug-eluting stent during pregnancy may be problematic and should be avoided if possible.

CORONARY ARTERY BYPASS GRAFT (CABG) SURGERY. The limited available information precludes reaching definite conclusions regarding the safety of CABG surgery during pregnancy. Surgical revascularization was reported in 61 women with AMI during pregnancy by James et al. (3). No information, however, was provided on the outcome of these surgeries. Ten women included in our review underwent CABG (13,14,26,29,30,32,33,54,65,67), 7 due to coronary dissection. Surgery was completed in the antepartum period in 5 patients (usually after the second week of pregnancy), of whom 1 had Turner syndrome and underwent the operation for aortic dissection with occlusion of the ostium of the RCA. The latter patient died 3 months post-surgery due to continuous deterioration and cardiac failure, but her fetus was delivered alive through a planned elective cesarean section (30). One intrauterine fetal death was reported in a patient undergoing CABG surgery due to dissection of the left main coronary artery subsequent to PCI (78).

THROMBOLYTIC THERAPY (TT). Thrombolytic therapy is considered to be relatively contraindicated in pregnancy, and because pregnant patients have been traditionally excluded from clinical trials, the information available is anecdotal (14,21,38,42,43,49,55). Recent clinical experience with the use of TT in pregnancy has been mostly with tPA and primarily in patients with stroke, prosthetic heart valve thrombosis, pulmonary embolism, or deep vein thrombosis (124,125). Several studies have demonstrated that placental transfer of streptokinase (126) and tPA (127) is too low to cause fibrinolytic effects in the fetus. Both urokinase and rtPA were not found to be teratogenic in rats or mice (125,128), and available reports do not support such an effect in humans. Although maternal and fetal outcomes were favorable in most cases (125), some reports have documented complications such as maternal hemorrhage, preterm delivery, fetal loss, spontaneous abortion, minor vaginal bleeding, massive subchorionic hematomas, abruptio placenta, uterine bleeding requiring emergency cesarean section, and post-partum hemorrhage requiring transfusion (124–129). Occasional fetal loss did not seem to be related to this therapy, although such a relation could not always be ruled out (124,125).

The safety and efficacy of TT in the treatment of AMI secondary to coronary dissection have not been clearly established, and such therapy may be a double-edged sword (4) and may increase the risk of hemorrhage and further progression of the dissection (27). For these reasons, TT should be considered a second choice to primary PCI in patients with ST-segment elevation acute myocardial infarction (STEMI) during pregnancy and especially during the peripartum and early post-partum periods when the incidence of coronary dissection is high.

In summary, available information is limited and not sufficient to drive conclusive recommendations for the use of TT in pregnant patients with AMI. At the same time, however, a favorable outcome in most cases does not support withholding this form of therapy from pregnant patients if an alternative effective therapy is not available. Considering the limited information related to the efficacy and safety of TT during pregnancy and the relatively high incidence of normal coronary anatomy and coronary dissection found in these patients, an invasive strategy may be preferred in women presenting with STEMI during pregnancy or the puerperium.

Drug therapy. Recent recommendations for drug therapy in the nonpregnant patient with AMI include the potential use of several drugs, including morphine sulfate; beta-blockers; nitroglycerin; calcium channel blockers; heparin; and antiplatelet therapy including aspirin, clopidogrel, and glycoprotein IIb/IIIa receptor inhibitors (122,123). Only limited information is available regarding the safety of many of these drugs when used in pregnancy. Drugs are categorized based on the level of risk to the fetus as follows (130): Category A: Controlled studies in women fail to demonstrate a risk to the fetus, and the possibility of fetal harm appears remote; Category B: Either animal reproduction studies have not demonstrated a fetal risk and there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters); Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available; drugs should be given only if the potential benefit justifies the potential risk to the fetus; Category D: There is positive evidence of a human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective); and Category X: Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit.

MORPHINE SULFATE (RISK CATEGORY C). One report of 448 exposures during pregnancy showed no evidence of teratogenic effects. Placental transfer of morphine is very rapid and may cause neonatal respiratory depression when it is given shortly before delivery. Morphine enters breast milk only in trace amounts unless it is given in high and repeated doses, and the drug is considered compatible with breast-feeding (131).

ORGANIC NITRATES (RISK CATEGORY B: NITROGLYCERIN; RISK CATEGORY C: ISOSORBIDE DINITRATE). In addition to their use in MI and ischemia, intravenous or oral nitrates have been used during pregnancy to treat hypertension (132), to treat acute tocolysis (133), and for relaxation of the uterus in post-partum patients with retained placenta (134). Use of transdermal nitroglycerin for the treatment of preterm labor was not associated with any affect on fetal or uterine perfusion (135). Careful titration however, is recommended to avoid maternal hypotension and reduced uterine perfusion (136). No data are available on breastfeeding in women treated with these drugs.

BETA-ADRENERGIC BLOCKING AGENTS (RISK CATEGORY B: METOPROLOL; RISK CATEGORY C: ATENOLOL). Beta-blocking agents have been extensively used in pregnancy for the management of hypertension, arrhythmias, mitral stenosis, Marfan syndrome, and myocardial ischemia (137). There have been no reports of teratogenic effects, but side effects such as bradycardia, hypoglycemia, hyperbilirubinemia, and apnea at birth have been anecdotally reported. In addition, a possible increase in the rate of fetal growth retardation was linked to the use of atenolol (138), especially when it is used in the first trimester (139). Because nonselective beta-blockers may facilitate increases in uterine activity, use of beta-1 selective agents may be preferred (137). Nursing infants should be monitored for adverse effects because all beta-blockers accumulate in greater concentrations in breast milk than in plasma.

CALCIUM-CHANNEL BLOCKERS (CCBs): (RISK CATEGORY C: NIFEDIPINE, DILTIAZEM, VERAPAMIL). Currently only nifedipine, a dihydropyridine CCB, which has been commonly used for the treatment of hypertension, preeclampsia, and tocolysis, has been shown to be safe during gestation (140). Information regarding the use of verapamil and diltiazem during pregnancy is limited, and a surveillance study has suggested that diltiazem may have teratogenic effects (130). Concurrent use of CCB and magnesium sulfate should be done cautiously because of the potential for synergistic effects (141).

Nifedipine, verapamil, and diltiazem are all excreted in human milk; therefore, breastfeeding has not been recommended by some for women taking these drugs (126). The American Academy of Pediatrics considers the use of these drugs to be compatible with breastfeeding (125).

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS AND ANGIOTENSIN-RECEPTOR ANTAGONISTS (ARBs) (RISK CATEGORY C). The use of ACE inhibitors is contraindicated in pregnant patients (136) due to fetotoxic effect predominately affecting the developing fetal kidneys. Other adverse events include oligohydramnio, intrauterine growth retardation, prematurity, bony malformations, limb contractures, patent ductus arteriosus, pulmonary hypoplasia, respiratory distress syndrome, hypotension, anuria, and neonatal death (142).

In 1992 the U.S. Food and Drug Administration warned against the use of ACE inhibitors in the second and third trimesters of pregnancy. Shotan et al. (142) in 1994 reported evidence for teratogenic effects and recommended avoiding these drugs during the first trimester as well. A recent publication by Cooper et al. (143) confirmed these findings. The effect of ARBs is similar to that of ACE inhibitors, and the use of both groups of drugs should be avoided in all patients who develop AMI during pregnancy (144,145).

ACE inhibitors are detected in breast milk (1% with captopril); the use of the drug, however, is considered compatible with breastfeeding (130). It is not known if ARBs are excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk.

EPLERENONE (RISK CATEGORY B). Eplerenone is an aldosterone blocker indicated to improve survival in patients with AMI and left ventricular systolic dysfunction (left ventricular ejection fraction $\leq 40\%$) with clinical evidence of congestive heart failure or diabetes (146). Because of the lack of safety information in humans, eplerenone should be used in pregnancy only if potential benefit justifies potential risks (146). No information is available regarding the concentration in human breast milk. Breastfeeding is therefore not recommended in women taking eplerenone (146).

HMG-CoA REDUCTASE INHIBITORS (STATINS) (RISK CATEGORY X). Available information on the use of these drugs during pregnancy in humans is very limited. Animal studies have demonstrated increased incidence of skeletal abnormalities with lovastatin as well as maternal, fetal, and neonatal mortality with fluvastatin (135,147). Information obtained from a worldwide post-marketing surveillance based on 137 reports to the manufacturer of inadvertent exposure to simvastatin or lovastatin during pregnancy did not show an adverse pregnancy outcome (148). However, because these drugs inhibit the synthesis of mevalonic acid, which plays an important role in DNA replication and is essential for the synthesis of steroids and cell membranes in fetal development, and because information on the use of these drugs in pregnancy is limited, the use of HMG-CoA inhibitors is not recommended in pregnancy.

UNFRACTIONATED (UFH) AND LOW MOLECULAR WEIGHT HEPARIN (LMWH) (RISK CATEGORY B: LMWH; RISK CATEGORY C: UFH). Both UFH and LMWH do not cross the placenta, and several reports have indicated a lack of fetal

adverse effects (149). LMWH has advantages over UFH because it has a longer half-life, greater bioavailability, decreased affinity for heparin-binding proteins (150), and thus more predictable therapeutic effect. Numerous studies have shown its safety during pregnancy (151); its use for long-term management is therefore convenient and feasible. Discontinuation of treatment with either form of heparin (6 h with UFH and 24 h with LMWH) is desirable before delivery. If indicated, treatment can be resumed after delivery as soon as hemostasis appears to be adequate.

ANTIPLATELET THERAPY. Aspirin (Risk Category C). The safety of aspirin during the first trimester of pregnancy is questionable because animal studies have shown birth defects, including fissure of the spine and skull; fascial and eye defects; and malformations of the central nervous system, viscera, and skeleton (135). The safety of high-dose aspirin during pregnancy is also debatable, and its chronic use should be avoided because it may lead to increased maternal and fetal hemorrhage, increased perinatal mortality, intrauterine growth retardation, and premature closure of the ductus arteriosus (130,152). On the other hand, the safety of low-dose aspirin (≤ 150 mg/day) has been suggested by a meta-analysis (152) and a large randomized trial (153) that enrolled more than 9,000 patients during both the second and third trimesters. Although aspirin is secreted in breast milk in low concentrations, no adverse effects have been reported (130). The American Academy of Pediatrics suggests cautious use of aspirin during lactation (131).

Thienopyridine derivatives (Risk Category B). Information on the use of clopidogrel or ticlopidine in pregnancy is very limited. Clopidogrel was administered in 6 patients (54,78,154–157) for a period of several weeks during weeks 6 to 37 of pregnancy. One case of intrauterine mortality was reported (78); this patient's clinical condition was complicated by CABG, and thus no conclusion could be reached regarding the effects of the drug on the fetus. One report (155) described a patient with essential thrombocytopenia and a past history of AMI treated with clopidogrel throughout pregnancy without complications.

At least 1 week is needed for the elimination of clopidogrel for safe application of regional anesthesia. It is not known whether these drugs are excreted in human milk, and breastfeeding is therefore not recommended in women taking ticlopidine or clopidogrel (136).

Glycoprotein IIb/IIIa inhibitors (Risk Category B: *eptifibatide, tirofiban*; Risk Category C: *abciximab*). Because pregnant patients have been excluded from randomized trials, available information is limited to 3 isolated reports (20,70,157). Until more information on fetal safety becomes available, a cesarean section should be considered as the method of delivery to avoid the risk of fetal intracranial hemorrhage if delivery occurs while the antiplatelet effects of these agents are present.

Labor. The mode of delivery in a patient with gestational MI should be determined by obstetric considerations and

the clinical status of the mother. An elective cesarean section avoids a long or stressful labor and allows better control of the time of delivery and allows the presence of an appropriate medical team including an experienced obstetrician, obstetric anesthesiologist, cardiologist, and pediatrician. Vaginal delivery, on the other hand, eliminates the potential risks associated with anesthesia and a major surgical procedure that includes hemodynamic fluctuations, larger blood loss, pain, infection, respiratory complications, damage to pelvic organs, and potential unfavorable effects on future reproductive health (risks of miscarriage, ectopic gestation, placenta previa, and placenta accreta [158]).

Only 10 of the 103 reviewed patients with pregnancy-related AMI delivered by cesarean section, a rate lower than the contemporary rate of 30% in the general population (159). These data therefore suggest that vaginal delivery can be accomplished relatively safely in the stable patient with pregnancy-associated AMI when measures aimed to reduce cardiac workload and oxygen demands are taken. Instrumental vaginal delivery is recommended to avoid excessive maternal efforts and prolonged labor. Positioning the patient in the left lateral position can help to improve cardiac output during labor and delivery. In addition, the patient's pain, fear, and apprehension, which may lead to tachycardia and hypertension and thus to increase in myocardial oxygen demand, should be prevented and treated. Vital signs as well as oxygen saturation, electrocardiogram, and fetal heart rate should be monitored continuously. For prevention or treatment of myocardial ischemia during labor, intravenous nitroglycerin, beta-blockers, and calcium antagonists can be used. It should be noted that nitroglycerin and calcium antagonists have some tocolytic effects and may prolong labor.

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