Chest Pain Syndromes in Pregnancy

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KEYWORDS

• Pregnancy • Acute myocardial infarction • Aortic dissection • Coronary dissection
• Pulmonary embolism • Venous thromboembolism • Amniotic fluid embolism

KEY POINTS

- Chest pain syndromes in pregnancy include acute myocardial infarction (AMI), aortic dissection and aortic syndromes, pulmonary embolism, and amniotic fluid embolism.
- The main risk factors associated with AMI in pregnancy are older maternal age(>35 years), hypertension, and diabetes mellitus.
- Most cases of aortic dissection and aortic syndromes occur in patients with Marfan syndrome, aneurysms associated with bicuspid valve, and other aortopathies that may get unmasked during pregnancy because of the accelerated aortic dilatation that occurs during pregnancy.
- The age-adjusted incidence of venous thromboembolism ranges from 4 to 50 times higher in pregnant compared with nonpregnant women, with most cases occurring postpartum versus peripartum.
- The basis of the management of amniotic fluid embolism, a rare but lethal condition, is support of the airway, tissue oxygenation, breathing, and circulation.

ACUTE MYOCARDIAL INFARCTION IN PREGNANCY

Introduction

Acute coronary syndromes and acute myocardial infarction (AMI) are rare in pregnancy (1–2 per 35,000 deliveries).[1] However, pregnancy has been shown to increase the risk of myocardial infarction (MI) 3- to 4-fold.[2] As the trend of child-bearing at older ages and advances in reproductive technology increase, so also does the incidence of AMI from atherosclerotic heart disease. The causes of acute coronary syndromes in pregnancy range from coronary dissection, to vasospasm, to acute plaque rupture. AMI can occur during any stage of pregnancy but is most common in the third trimester and in the 6-week period after delivery, occurring mostly in multigravidas (66%), most patients being older than 30 years (72%).[1,2] Location of the AMI is mostly the anterior wall, largely because of the greater susceptibility of the territory of the left anterior descending artery (LAD) for coronary dissection.

Incidence

In the past decade in the United States there has been a higher incidence of detection of AMI in pregnancy, largely reflecting the changing epidemiology of increasing age of pregnancy as well as improvements in diagnostic capability. The average incidence varies from 1 in 24,000 according to Ladner and colleagues[2] to 1 in 16,129 deliveries as per James and colleagues.[3–5] The higher incidence reported by James and colleagues likely reflects improvements in diagnostic capability or a recent increase in the number of reported cases in several of these studies.[1–3]

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Risk Factors

The main risk factors associated with AMI in pregnancy are[1–3,6]:

- Maternal age greater than 35 years
- Hypertension
- Diabetes mellitus.

The magnitude of the increase in risk was evaluated in the series of 859 cases from the Nationwide Inpatient Sample.[3] In a multivariable regression model, the odds ratio was 21.7 for hypertension, 3.6 for diabetes, 6.7 for maternal age between 30 and 34 years, and 15 to 16 for maternal age 35 years and older.

Other independent risk factors in this report were smoking (odds ratio 8.4), thrombophilia, including a history of thrombosis and antiphospholipid syndrome (odds ratio 25.6), severe postpartum hemorrhage (odds ratio 5), migraine headaches (odds ratio 4.2) as a possible marker of vasospastic disease, and postpartum infection (odds ratio 2–3). The marked increase in risk with thrombophilia may reflect an interaction with the hypercoagulable state induced by pregnancy.[2,3]

It is not clear whether pregnancy itself is a risk factor for MI. In a report that had 3.6 million woman-years of observation, the incidence of a first-ever MI not related to pregnancy was 5.0 per 100,000 woman-years in women of childbearing age, with the risk increasing dramatically after age 35.[7] Because pregnancy lasts three-quarters of a year, this rate of MI is not different from the rates in the 2 large epidemiologic studies cited above (2.8–6.2 per 100,000 pregnancies).[2,3]

Mortality

Maternal mortality with AMI has significantly lowered in current reviews,[1–3] ranging from as low as 5.1% reported by James and colleagues[3] to 11% as reported by Roth and colleagues,[1] compared with the mortality of as high as 38% reported in studies from decades before the year 2000.[8] This improving mortality has been largely due to use of percutaneous coronary intervention (PCI) in acute coronary syndromes in pregnancy. The mortality rate is higher in the peripartum period (18%) than in the antepartum and postpartum periods (both 9%).[1] The incidence of fetal mortality was 9% (6 of 68), and most fetal deaths were associated with maternal mortality.[1]

Etiology

In a review of 103 pregnant patients presenting with acute coronary syndrome from 1995 to 2005, coronary artery morphology was evaluated in 96 by angiography or autopsy.[1] Coronary atherosclerosis with or without intracoronary thrombus was present in only 40% of patients. The remaining cases consisted of thrombus in a normal coronary artery (8%), coronary artery dissection (27%), spasm in (2%), emboli (2%), and normal coronary arteries (13%).

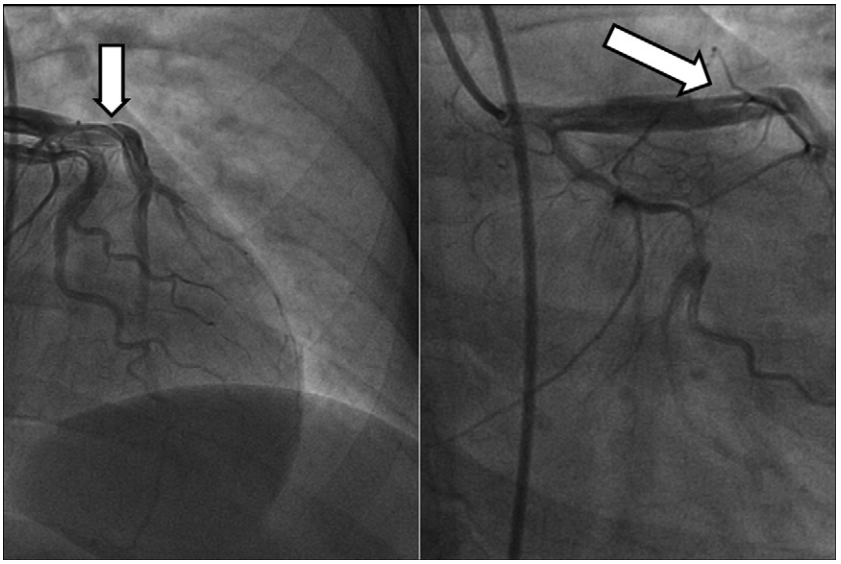

Fig. 1. Left coronary angiogram in a postpartum woman showing extensive coronary dissection (*arrows*). (*From* Alsleibi S, Dweik M, Afifi M, et al. Postpartum multivessel coronary artery dissection treated with coronary artery bypass grafting. J Cardiol Cases 2012;5(1):e23–7. doi: 10.1016/j.jccase.2011.11.003; with permission.)

Atherosclerotic disease was more prevalent in the pregnant women presenting with AMI in the antepartum period (54%) than in the peripartum (27%) or postpartum periods (29%).

Coronary dissection, which is a rare cause of AMI in the nonpregnant population, is the main cause of AMI in the peripartum period (50%) or postpartum period (34%), and rare in the antepartum period (11%).[7,9] The most commonly affected artery is the LAD,[1] followed by the right coronary artery (RCA), left circumflex artery (LCirc), and left main coronary artery (LM). The most common multivessel dissections involve the LM, LAD, and LCirc (**Fig. 1**).[1,8–11]

The timing of arterial dissection during or early after pregnancy is related to structural changes in the intima and media of the arterial wall produced by the effect of hormones such as progesterone, which produces loss of normal corrugation in elastic fibers, fragmentation of reticular fibers, and a decrease in the amount of acid mucopolysaccharides.[8,12,13] Other hypotheses include lytic action of proteases from eosinophils.[14–16] The hemodynamic changes of increase in blood volume and cardiac output magnify shear forces of blood in the large vessels, also resulting in a greater propensity for dissection.[17,18] The fact that coronary dissection occurs frequently in more than one vessel points toward generalized rather than localized pathogenesis.

The finding of spontaneous coronary artery dissection should also trigger the search for a previously undiagnosed connective tissue disease, such as Ehlers-Danlos syndrome or vasculitic syndromes such as Takayasu arteritis. Moreover, conventional risk factors such as hypertension also remain a risk factor for AMI related to spontaneous coronary artery dissection in the Nationwide Inpatient Sample.[3]

Normal coronaries were described in about 13% of recently reported cases, with almost equitable distribution throughout the 3 periods of pregnancy.[1] A transient coronary spasm is a possible explanation for these, caused by increased vascular reactivity to angiotensin II[19] or norephinephrine,[20] endothelial dysfunction,[21] increased renin-angiotensin production due to decreased uterine perfusion in supine position,[17] ergot derivatives used to control postpartum hemorrhage or to suppress lactation,[22–26] pheochromocytoma,[27] or cocaine abuse.[28,29]

Coronary thrombosis without atherosclerotic coronary artery disease, seen in approximately 8% of cases,[1] are likely due to a hypercoagulable state of pregnancy caused by alterations in the coagulation and fibrinolytic systems, which include decreased levels of tissue plasminogen activator (tPA),[16,30] increased levels of tPA inhibitor,[31,32] increases in levels of coagulation factors,[33] and decreased levels of functional protein S.[34–36] Smoking in pregnant women further increases platelet aggregability.[37]

Diagnosis

AMI in pregnant women is diagnosed in the same way as in nonpregnant patients, including the constellation of symptoms, electrocardiographic changes, and cardiac markers.[38] At the same time, however, the diagnostic approach is also influenced by fetal safety and normal changes during pregnancy.

Electrocardiograms (ECGs) done during normal pregnancy frequently show a left or right axis deviation, a small Q in lead III, nonspecific T-wave inversions, or an increased R/S ratio in leads V1 and V2, which can make the ECG diagnosis of ischemia in acute coronary syndromes more challenging. ECGs showing ST-segment depression mimicking myocardial ischemia have been observed in healthy women after the induction of anesthesia for cesarean section, and this result can be misleading.[1,39–41] One such study[40] reported significant ST-segment changes by Holter monitoring in 42% of 26 patients undergoing elective cesarean sections and in 38.5% of patients postoperatively.

Echocardiography 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.[42] 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 and colleagues,[42] and is probably related to the uterus and placenta, which embody substantial amounts of these enzymes. Mean creatine kinase-MB levels continued to increase and reached a maximum at 24 hours after delivery. By contrast, use of troponin I levels has been validated for the diagnosis of AMI in pregnancy.[43] Troponin levels may show a small increase after normal delivery and remain below the upper limit of normal,[42–45] except in women with preeclampsia and gestational hypertension, in whom it may show a mild elevation.[44,45]

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.[46,47] Because of these findings, the use of a submaximal

protocol (70% of maximal predicted heart rate) with fetal monitoring, if possible, is preferred.[48,49] The use of stress echocardiography may increase the sensitivity of the test for detection of myocardial ischemia and viability.[48] The use of radiation during pregnancy should be kept to a minimum, and nuclear imaging should be avoided because radionuclide imaging using ^{99m}technetium-labeled sestamibi or ^{201}thallium is expected to yield 1 rad of radiation to the conceptus,[48] which is teratogenic in the first trimester and if used in the second and third trimesters still poses a risk of intrauterine growth retardation, central nervous system abnormalities, and perhaps even malignancy.

Cardiac catheterization and interventional procedures also result in an approximate fetal exposure of 1 rad despite abdominal shielding, because of intra-abdominal scatter, and the more difficult and lengthier procedures could easily result in fetal exposure of 5 to 10 rad. Termination of pregnancy is not recommended for fetal doses of less than 5 rad because most researchers agree that it represents no measurable noncancer risk to the embryo or fetus at any stage of gestation.[50] However, congenital defects in the fetus and death of the human embryo are possible on exposure to greater than 10 rad, and termination of pregnancy is recommended for such exposure.[50,51] Using the radial or brachial approaches, appropriate abdominal shielding, minimizing fluoroscopy time, and so forth are important in reducing fetal risk.

Cardiac catheterization was reported in 386 (45%) of 859 patients with AMI in pregnancy postpartum by James and colleagues.[3] Of these, 81% needed angioplasty, stent placement, or coronary bypass. The procedure resulted in fatal coronary dissection in one patient and coronary dissection leading to bypass surgery in another. Because of the possible increased risk of coronary dissection, noninvasive risk stratification may be preferred during pregnancy or the early postpartum period in stable and low-risk patients.[38]

The technology of coronary computed tomographic angiography (CCTA) is also being applied to noninvasive imaging of acute coronary syndromes in pregnancy as a viable alternative to invasive catheterization, although it does preclude any intervention if a coronary abnormality is found. Besides being noninvasive, CCTA has the added advantage of identifying abnormalities such as intramural hematomas associated with coronary dissections in the tunica media (**Fig. 2**), aortic dissection, or pulmonary embolism (PE).

Treatment

The treatment of pregnant women with AMI and its complications should in general follow the usual standard of care,[52,53] although both maternal and fetal considerations should affect the choice of therapy. Therefore the treatment plan should be carefully concerted 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 a 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 (**Table 1**).

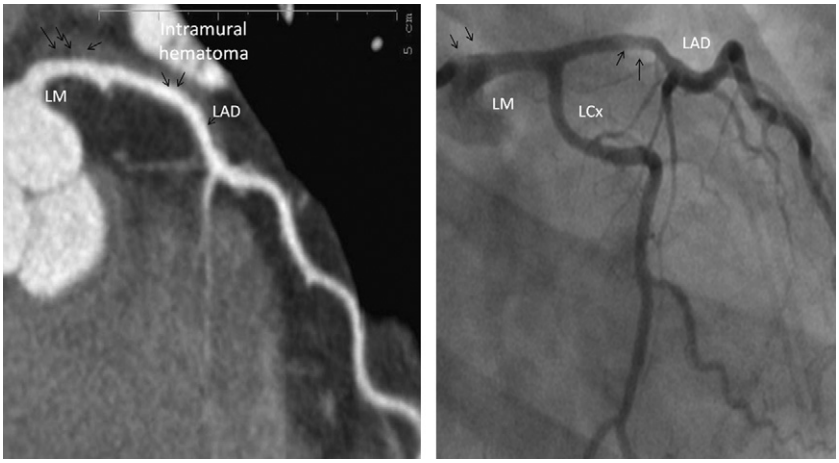

Fig. 2. Cardiac computed tomographic angiogram (CTA) (*left*) showing coronary intramural hematoma (*arrows*) in the left main (LM) and left anterior descending (LAD) artery resulting from a coronary dissection in the tunica media in a woman 2 weeks postpartum. The relatively unremarkable angiogram (*right*) done a few days before the CTA missed the diagnosis of coronary dissection. LCx, left circumflex artery. (*Courtesy of* Harvey Hecht, MD, Mount Sinai Medical Center, New York.)

Table 1
Recommendations for the management of coronary artery disease in pregnancy (European Society of Cardiology)

Recommendations	Class[a]	Level[b]
ECG and troponin levels should be performed in the case of chest pain in a pregnant woman	I	C
Coronary angioplasty is the preferred reperfusion therapy for STEMI during pregnancy	I	C
A conservative management should be considered for non–ST-elevation ACS without risk criteria	IIa	C
An invasive management should be considered for non–ST-elevation ACS with risk criteria (including NSTEMI)	IIa	C

Abbreviations: ACS, acute coronary syndrome; ECG, electrocardiogram; NSTEMI, non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.
[a] Class of recommendation.
[b] Level of evidence.
Data from The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2011;32:3147–97.

Revascularization

Percutaneous coronary intervention PCI has been well documented during pregnancy, and is considered safe for maternal and fetal survival.[1,3,54–57] In most cases PCI is preferred over thrombolysis because of the decreased risk of hemorrhage in pregnancy and because coronary dissection is a significant cause of AMI in pregnancy. The cardiovascular risks of angioplasty in pregnancy are similar to those in the nonpregnant patient. As in coronary angiography, the bleeding and radiation risks can be minimized by use of a radial approach,[58] appropriate abdominal shielding, and reducing fluoroscopy time. The use of an intra-aortic balloon pump to improve left ventricular output and coronary perfusion is also considered safe,[59,60] although the patient should be positioned in the left lateral recumbent position to reduce compression of the inferior vena cava.

James and colleagues[3] reported PCI in 135 patients with stenting in 127 of these. Roth and colleagues[1] reported PCI in 38 of 92 patients (41%) in their series with 23 antepartum, 6 peripartum, and 9 postpartum. All reported stenting during the acute phase of MI during pregnancy was performed with bare-metal stents; the safety of drug-eluting stents in pregnant women is currently still unknown. Because drug-eluting stents require prolonged antiplatelet therapy with clopidogrel and the incidence of cesarean deliveries in patients with heart disease is relatively high, the use of a drug-eluting stent during pregnancy may be problematic and should be avoided if possible.[38]

Coronary artery bypass graft surgery Hundreds of cases of cardiopulmonary bypass have been reported in literature since it was first used in pregnancy in 1959. Over time there have been significant improvements in maternal and fetal outcomes. At present, maternal mortality in coronary artery bypass grafting (CABG) is the same as that in the general population, at 1.7% to 3%, with a fetal mortality rate of 9.5% to 19%.[61–64] In a systematic review of cardiovascular surgery cases published between 1984 and 1996, Weiss and colleagues[65] reported a higher mortality of 6% in pregnant compared with nonpregnant patients. However, most these deaths occurred in patients with aortic dissection or PE, and there were no deaths in women undergoing CABG.

Surgical revascularization was reported in 61 women of 859 with AMI during pregnancy by James and colleagues.[3] No information, however, was provided on the outcome of these surgeries. The review by Roth and colleagues[1] reported 10 women of 92 patients who underwent CABG, 7 of which were to treat 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. One intrauterine fetal death was reported in a patient undergoing CABG surgery for dissection of the LM subsequent to PCI.

Surgery in the first trimester is associated with more fetal congenital malformations but does not affect fetal mortality.[62,63] The timing of the CABG does affect fetal mortality, and if the fetus is of more than 28 weeks' gestation, consideration must be given to deliver the child immediately before or during the same cardiac surgery.[63] A first consideration that can improve fetal outcomes is to position the patient in the left lateral recumbent position during surgery to prevent aortic and caval compression. Second, high-flow extracorporeal circuits (2.5–2.7 L/m^2/min) and normothermic or mildly hypothermic conditions should be used because these techniques have been shown to improve fetoplacental perfusion.[61,62] Third,

continuous fetal monitoring should be used throughout surgery as an indirect means of assessing fetoplacental perfusion. Fetal bradycardia and loss of beat-to-beat variability suggest poor fetoplacental perfusion, and can be corrected by increasing the flow rate (5 L/min or greater) and maternal temperature. Fourth, an adequate mean arterial pressure must be maintained throughout surgery, as placental perfusion is dependent on mean arterial pressures of 70 mm Hg or greater in the relaxed uterus, and higher pressures in the contracting uterus.[63] Uterine activity should also be monitored because cardiopulmonary bypass and rewarming can place the patient at risk for early contractions.[61] Controlling contractions is crucial in avoiding placental insufficiency and secondary fetal hypoxia. Finally, hemodilution must be kept to a minimum to maximize oxygen-carrying capacity to the fetus, and the time necessary for cardiopulmonary bypass should be kept to a minimum.

Thrombolytic therapy Thrombolytic therapy (TT) is considered to be relatively contraindicated in pregnancy,[52] and because pregnant patients have been traditionally excluded from clinical trials, the available information is anecdotal.[66–68] Recent clinical experience with the use of TT in pregnancy has been mostly with tissue plasminogen activator (tPA) and primarily in patients with stroke, prosthetic heart valve thrombosis, PE, or deep vein thrombosis (DVT).[69,70] Several studies have demonstrated that placental transfer of streptokinase[71] and tPA[72] is too low to cause fibrinolytic effects in the fetus. Both urokinase and tPA were not found to be teratogenic in rats or mice,[70,73] and available reports do not support such an effect in humans. Although maternal and fetal outcomes were favorable in most cases,[70] 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 postpartum hemorrhage requiring transfusion.[69–74] Occasional fetal loss did not seem to be related to this therapy, although such a relation could not always be ruled out.[69,70]

Drug Therapy

Drugs that can be used with relative safety in pregnancy are discussed in detail in *Cardiovascular Drugs in Pregnancy* by William H. Frishman and colleagues. The most appropriate medication regimen for pregnant patients with ischemic heart disease or AMI is unknown. There is a significant amount of anecdotal evidence supporting the use of salicylates, β-blockers, nitroglycerin, calcium antagonists, and heparin during pregnancy, but little is known about the optimal combination of these medications.

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; facial and eye defects; and malformations of the central nervous system, viscera, and skeleton.[75] 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.[76,77] On the other hand, the safety of low-dose aspirin (<150 mg/d) has been suggested by a meta-analysis[77] and a large randomized trial[78] that enrolled more than 9000 patients during both the second and third trimesters. Although aspirin is secreted in breast milk in low concentrations, no adverse effects have been reported.[75] The American Academy of Pediatrics suggests cautious use of aspirin during lactation.[79]

Thienopyridine derivatives: risk category B

Information on the use of clopidogrel, prasugrel, or ticlopidine in pregnancy is very limited. Clopidogrel was administered in 6 patients[80–84] for a period of several weeks during weeks 6 to 37 of pregnancy. One case of intrauterine mortality was reported[81]; 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[83] described a patient with essential thrombocytopenia and a 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.[79] It is noteworthy that the newer antiplatelet drugs such as ticagrelor have been given a risk category of C.

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 breastfeeding.[79]

Nitrates: nitroglycerin (risk category B) and isosorbide dinitrate (risk category C)

Intravenous, transdermal, and oral nitrates have been used as antianginals in MI and acute coronary syndromes, to treat hypertension,[85] for acute tocolysis to avoid preterm labor,[86] and for relaxation of uterus in postpartum patients with retained placenta.[87] However, careful titration is required to avoid maternal hypotension and reduced uterine perfusion.[88] No data are available on breastfeeding, and nitrates are not recommended for use in nursing mothers.[76]

β-Blockers: risk category C

β-Blocking agents have been extensively used in pregnancy for the management of hypertension, arrhythmias, mitral stenosis, Marfan syndrome (MFS), and myocardial ischemia.[89] 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,[90] especially when it is used in the first trimester. Because nonselective β-blockers may facilitate increases in uterine activity, use of β1 selective agents may be preferred.[90] Nursing infants should be monitored for adverse effects because all β-blockers accumulate in greater concentrations in breast milk than in plasma, with the least transmission being that of metoprolol tartrate, the most widely studied β-blocker in pregnancy.

Calcium-channel blockers: risk category C

At present only nifedipine, a dihydropyridine calcium-channel blocker (CCB), which has been commonly used for the treatment of hypertension, preeclampsia, and tocolysis, has been shown to be safe during gestation.[91] Information regarding the use of verapamil and diltiazem during pregnancy is limited, and a surveillance study has suggested that diltiazem may have teratogenic effects and that verapamil in the third trimester may cause dysfunctional uterine bleeding.[75] Concurrent use of CCB and magnesium sulfate should be done cautiously because of the potential for synergistic effects.[92] Nifedipine, verapamil, and diltiazem are all excreted in human milk; therefore, breastfeeding has been recommended with caution in women taking these drugs, although the American Academy of Pediatrics considers their use to be compatible with breastfeeding.[79]

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: risk category C in first trimester and risk category D in second, third trimesters

The use of angiotensin-converting enzyme (ACE) inhibitors is contraindicated in pregnant patients[76] because of the fetotoxic effect predominately affecting the developing fetal kidneys. Other adverse events include oligohydramnios, intrauterine growth retardation, prematurity, bony malformations, limb contractures, patent ductus arteriosus, pulmonary hypoplasia, respiratory distress syndrome, hypotension, anuria, and neonatal death.[93] In 1992 the US Food and Drug Administration (FDA) warned against the use of ACE inhibitors in the second and third trimesters of pregnancy. Shotan and colleagues[93] in 1994 and, later, Cooper and colleagues[94] reported evidence for teratogenic effects and recommended avoiding these drugs during the first trimester as well. The effect of angiotensin receptor blockers (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.[95,96] ACE inhibitors are detected in breast milk (the least 1% with captopril); the use of the drug, however, is considered compatible with breastfeeding[75] after 4 weeks, once the neonatal kidney is less susceptible to the drug's nephrotoxic effects. It is not known whether ARBs are excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk.[97]

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 <40%) with clinical evidence of congestive heart failure or diabetes. Because of the lack of safety information in humans, eplerenone should be used in pregnancy only if the potential benefit justifies potential risks. No information is available regarding the concentration in human breast milk. Breastfeeding is therefore not recommended in women taking eplerenone.

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.[75,96] Information obtained from a worldwide postmarketing surveillance based on 137 reports to the manufacturer of inadvertent exposure to simvastatin or lovastatin during pregnancy did not show an adverse pregnancy outcome.[98] 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 heparin (risk category C) and low molecular weight heparin (risk category B)

Both unfractionated heparin (UFH) and low molecular weight heparin (LMWH) do not cross the placenta, and several reports have indicated a lack of fetal adverse effects.[99] LMWH has advantages over UFH because it has a longer half-life, greater bioavailability, decreased affinity for heparin-binding proteins,[100] and thus more predictable therapeutic effect. Numerous studies have shown its safety during pregnancy[101]; its use for long-term management is therefore convenient and feasible. Discontinuation of treatment with either form of heparin (6 hours with UFH and 24 hours with LMWH) is desirable before delivery. If indicated, treatment can be resumed after delivery as soon as hemostasis appears to be adequate.

Glycoprotein IIb/IIIa inhibitors: eptifibatide and tirofiban (risk category B), abciximab (risk category C)

Because pregnant patients have been excluded from randomized trials, available information is limited to a few isolated reports.[56,102,103] 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.

Management of Labor and Delivery

- Because of the increased hemodynamic stress associated with labor, it has been recommended that induction of labor or scheduled cesarean delivery should be delayed, if possible, for at least 2 to 3 weeks after an AMI[1] if there is no obstetric indication or evidence of any fetal compromise.
- Mode of delivery in gestational MI should be decided by obstetric indications and the clinical status of the mother. In most cases it is advisable to proceed with vaginal delivery over elective cesarean section, because this eliminates the potential risks associated with anesthesia and a major surgical procedure that includes hemodynamic fluctuations, greater 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).[104] An elective cesarean section, on the other hand, is useful for avoiding long or stressful labor, and allows better control of the time of delivery to allow the planned presence of a multidisciplinary team including an experienced obstetrician, obstetric anesthesiologist, cardiologist, and pediatrician. In the study by Roth and colleagues,[1] 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. These data therefore suggest that vaginal delivery can be accomplished relatively safely in the stable patient with pregnancy-associated AMI as long as measures aimed to reduce cardiac workload and oxygen demands are taken.
- Instrumental vaginal delivery and other methods to shorten the second stage of labor are recommended to avoid excessive maternal effort and the catecholamine surges and increased shear forces associated with it.
- The patient should be positioned in the left lateral position 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 an increase in myocardial oxygen demand, should be prevented and treated with early epidural anesthesia.
- Vital signs as well as oxygen saturation, ECG, and fetal heart rate should be monitored continuously. For prevention or treatment of myocardial ischemia during labor, intravenous nitroglycerin, β-blockers, and calcium antagonists can be used with caution regarding the tocolytic effects of nitroglycerin and the CCBs.
- Tachycardia and hypotension should be promptly corrected to prevent placental hypoperfusion. Ephedrine is usually the vasopressor agent of choice for hypotension associated with regional anesthesia, because it helps maintain placental perfusion.[105]
- Ergot alkaloids immediately after delivery should be avoided because of the risk of coronary artery spasm. After initial recovery, the patient should be monitored for 48 hours postpartum in a coronary intensive care or general intensive care unit, because of the significant hemodynamic changes that occur during this time.

AORTIC DISSECTION AND AORTIC SYNDROMES

Incidence

The overall incidence of aortic dissection is 0.4 case per 100,000 person-years within the female population aged between 15 and 45 years. The incidence in the general population of aortic dissection is 2.6 to 3.5 cases per 100,000 person-years across all ages.[106] The majority of the dissections and/or ruptures occur in the third trimester (50%) and the peripartum period (30%). Most of the cases occur in patients with MFS, aneurysms associated with bicuspid valve, and other aortopathies that may be unmasked during pregnancy because of the accelerated aortic dilatation that occurs during pregnancy.

Mortality

Type A aortic dissection is a life-threatening event to both mother and baby, and accounted for 14% of maternal cardiac deaths in the 2006-2008 UK Confidential Enquiries into Maternal Deaths.[107] Prehospital mortality rates could be as high as 53% in some studies.[108] The mortality from untreated proximal aortic dissections increases by 1% to 3% per hour after presentation and is approximately 25% during the first 24 hours, 70% at 1 week, and 80% at 2 weeks[109,110]; the early recognition of this entity during pregnancy is therefore of prime importance. A study over a 27-year period found that misdiagnosis occurred in 85% of patients presenting with acute aortic dissection.[109] Several case reports describe how the diagnosis was initially missed in the peripartum period.

Pathophysiology and Risk Factors

The physiologic changes in pregnancy include increased maternal blood volume, stroke volume, and cardiac output.[18,111] Moreover, the effect of maternal hormones on remodeling the tunica media and intima of the arterial wall[12,112] cause increased shear forces on the aortic wall. These combined changes begin in the first and second trimesters but are most notable in the third trimester and peripartum.

However, these hemodynamic stressors in pregnancy alone cannot account for the high incidence of aortic dissection and are likely secondary contributors. Several observational studies have identified preexisting risk factors such as premature atherosclerosis and arterial hypertension, hereditary connective tissue disease such as MFS and Ehlers-Danlos syndrome, previous aortic surgery, bicuspid aortic valve disease, coarctation, aortitis, surgical manipulation, cardiac catheterization, and cocaine exposure as the most common risk factors in aortic dissection occurring in women younger than 45 years.[106–108,111,113–117]

In one of the few prospective studies of pregnant patients with MFS, 4.4% of carefully monitored patients developed aortic dissection.[118,119] In unmonitored patients, the risk is likely higher, with 10% of patients with aortic root diameter greater than 40 mm presenting with aortic dissection during pregnancy. In fact about half of pregnant women with MFS and aortic root dilatation greater than 40 mm will have a dissection, rupture, prophylactic surgery, or life-threatening growth, although a normal dimension does not exclude the possibility of dissection.[111,114,115] Most of the dissections that occur are proximal or type A dissections.

Clinical Presentation

Arterial hypertension (93%), sudden onset of severe chest pain (73%), and neurologic symptoms, such as syncope (40%), are the leading symptoms of acute aortic dissection[106] in pregnancy. The presence of severe chest or interscapular pain requiring opioid analgesia, especially in the presence of systolic hypertension, should be investigated. However, 10% of dissections are painless at presentation, more often in chronic dissections or preexisting connective tissue diseases.[109,110,120] There could be differential peripheral pulses in both arms with a difference in blood pressure greater than 20 mm Hg taken in both arms. Congestive cardiac failure is a less common but well-described presentation of thoracic aortic dissection.[110,120,121] Hypotension in the presence of aortic dissection is an ominous sign indicating cardiac tamponade or hypovolemia from aortic rupture.

Diagnosis

As per the American College of Cardiology/American Heart Association/American Thoracic Society (ATS) guidelines[122] for imaging in pregnant patients suspected of having aortic dissection or aneurysm, magnetic resonance imaging (MRI) without gadolinium is recommended over computer tomographic (CT) imaging to avoid exposing both mother and fetus to ionizing radiation. Barring the risks of ionizing radiation, the sensitivity of CT in diagnosis of aortic dissection is equivalent to that of MRI and may be used if the patient is unstable, intolerant of MRI because of claustrophobia, or if MRI is not available (**Fig. 3**). Transesophageal echocardiogram is an

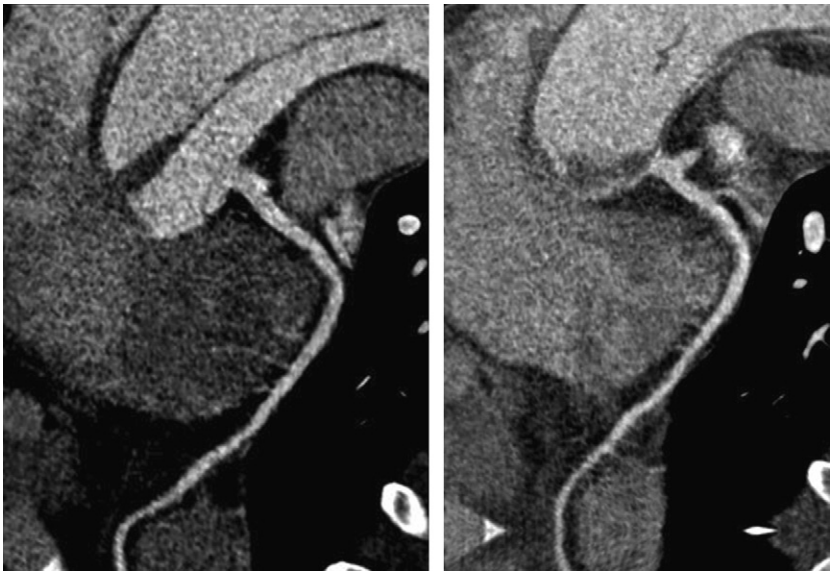

Fig. 3. Cardiac computed tomography in a patient in third trimester of pregnancy, showing a type A dissection involving aortic root and ascending aorta, with images in end diastole (*left*) and end systole (*right*) showing the dissection flap compressing the left main coronary ostium during systole. (*Courtesy of* Harvey Hecht MD, Mount Sinai Hospital, New York.)

alternative option (Class IC indication) if the patient is clinically unstable.

The yield of a chest radiograph is low, as a widened mediastinum is not seen in 40% of cases and in 12% no abnormalities can be seen at all.[106]

Management

Medical therapy

β-Blockers should be started to minimize aortic dilatation, lower blood pressure, and limit shear forces of aortic dissection during pregnancy. Labetolol or metoprolol is the preferred β-blocker in pregnant women because atenolol may impair fetal growth. Propranolol blocks the inhibitory effects of epinephrine on myometrial activity and the nonselective β-blocking effect of propranolol may, therefore, facilitate an increase in uterine activity. Intravenous labetolol could be used for urgent lowering of blood pressure and heart rate, in addition to adequate opioid analgesia to reduce shear forces. It is recommended that in the nonpregnant patient, β-blockers be titrated up to a resting heart rate of less than 60 beats/min. Because heart rate is increased during gestation, the dose should be titrated to reduce resting heart rate by at least 20%.[111] Because of increased sympathetic output during pregnancy the heart rate is increased, and a higher dose of β-blockers may be needed to achieve adequate control of heart rate. β-Blocking agents are excreted in breast milk, and nursing infants should therefore be monitored for adverse effects.

In addition to β-blockade, vasodilators may be required to control blood pressure. Intravenous sodium nitroprusside is the most established agent and offers the advantage of being rapidly titratable. Intravenous hydralazine, nitroglycerine, or sodium nitroprusside have all been studied in pregnancy. Vasodilator therapy without prior β-blockade may cause reflex tachycardia and increased force of ventricular contraction, leading to greater aortic wall stress and potentially causing false-lumen propagation. ACE inhibitors and ARBs are teratogens and are thus contraindicated during pregnancy.

Surgical treatment

For type A proximal aortic dissections during the first or second trimester, urgent surgical repair with aggressive fetal monitoring is preferred. Fetal loss during hypothermia and cardiopulmonary bypass is common. Death rates during surgery decreased from 30% in 1990-1994 to 0% in 2002-2004 in one study and a similar 1.5% to 3% mortality rate in other series, while fetal death

rates decreased from 50% to 10% for the same periods.[123] Because cardiac surgery continues to be associated with increased fetal loss,[65,123,124] cesarean section should be performed before or concomitantly with thoracic surgery if fetal maturity can be confirmed.[125,126]

Measures to reduce fetal mortality during surgery if done before 30 weeks of gestation include the use of intraoperative cardiotocography (CTG) for monitoring the fetal heart, use of high-flow, high-pressure normothermic perfusion and a perfusion index of 3.0 during cardiopulmonary bypass, which is probably safest for the fetus, and measures to prevent hypothermia (which causes fetal bradycardia).[65,123,124]

For acute arch or type B dissection, medical therapy is preferred unless percutaneous stent grafting or open surgery is mandated by malperfusion, aortic rupture, or subacute aortic leaking.[121]

Prophylactic aortic root and ascending aorta repair is also indicated in pregnant patients with MFS if the size exceeds 50 mm or if there is rapidly progressive dilatation of more than 10 mm during surveillance in pregnancy or greater than 50 mm with bicuspid aortic valve, because of the high risk of rupture and dissection.[38] Successful surgeries during gestation or shortly after delivery[108,116,124,127] have been reported in several women with MFS.

Mode of delivery

Cesarean delivery is preferred in patients with an aortic diameter greater than 45 mm, or greater than 40 mm in MFS, aortic dissection, severe aortic regurgitation, or heart failure. Vaginal delivery is safe in patients with MFS with aortic diameter of less than 40 mm.[111,114–117] To minimize the stress of labor in vaginal delivery, epidural anesthesia should be used to reduce pain, and forceps or vacuum should be used to shorten the second stage of labor.

Because around 70% to 90% of patients with MFS present with lumbosacral dural ectasia, an anesthetist should be consulted before delivery.[128] Although dural ectasia is not an absolute contraindication for epidural anesthesia, the increased risk of dural puncture or inadequate anesthesia should be discussed with the patient.

Both systolic and diastolic blood pressures increase markedly during uterine contractions and with labor pains. These changes should be anticipated and prevented with epidural anesthesia, β-blockers, and vasodilatory agents. Postpartum hemorrhage of the uterine vasculature 3 days after cesarean section secondary to MFS has been reported, and should be anticipated.

Prevention and preconception counseling

It is difficult to identify aortic aneurysms associated with bicuspid aortic valve, coarctation, and other aortopathies that are usually asymptomatic until they manifest with acute aortic syndromes in pregnancy.

However, women with MFS should be counseled before conception about the risk for potential pregnancy-related cardiovascular and obstetric complications as well as the 50% probability of transmitting the syndrome to their offspring. The woman and her family should also be informed of the need for close follow-up during pregnancy as well as the use of β-blockers and possibly other cardiac medications, and the potential side effects to the fetus. The possibility and limitations of prenatal diagnosis with the use of both genetic linkage and fetal echocardiography[129] should be explained.

In addition, the patient should be informed about the likelihood of morbidity and possibly reduced longevity[114] even after successful pregnancy. Based on most series, aortic dissection occurred in MFS women in their third decade of life; therefore, it is advisable to plan a pregnancy at a younger age.[114,123]

MFS patients and those with bicuspid aortic valve who are considering pregnancy should be evaluated using echocardiography, MRI, CT, and/or abdominal ultrasonography to comprehensively assess the heart and the aorta, with particular attention paid to the aortic root. It has thus been recommended that transthoracic echocardiography be performed every 4 to 8 weeks in the antenatal monitoring of the MFS patient and be continued until 6 months postpartum.[38] Progressive aortic dilatation and/or an aortic root dimension of 40 mm or greater suggest increased gestational risk for aortic dissection, such that pregnancy should be discouraged or prepregnancy aortic repair should be undertaken. If such a patient is already pregnant, therapeutic abortion should be considered. For bicuspid aortic valve, prophylactic prepregnancy repair should be considered for aortic diameter greater than 50 mm.

All patients with MFS or bicuspid aortic valve with dilated aorta should be administered β-blockers with close fetal monitoring, and this should continue until 3 months postpartum, as dissection (type A or B) can occur during this period.

PULMONARY EMBOLISM

Epidemiology

PE is a leading cause of pregnancy-related mortality in the developed world, accounting for 20% of maternal deaths in the United States.[130]

Pregnancy and the puerperium are associated with an increased incidence of venous thromboembolism (VTE), occurring in 1 in 500 to 1 in 2000 pregnancies (0.05%–0.20%).[131–136] The age-adjusted incidence of VTE ranges from 4 to 50 times higher in pregnant women than in nonpregnant women, with most cases occurring postpartum versus peripartum.

The incidence of pregnancy-associated DVT is about 3 times higher than that of pregnancy-associated PE.[131]

Risk Factors

Pregnancy and the postpartum period may be marked by the presence of all 3 components of Virchow's triad: venous stasis, endothelial injury, and a hypercoagulable state. Inherited or acquired thrombophilias such as factors unrelated to pregnancy further increase thromboembolic risk.[137,138] For example, the thrombotic risk for a woman with factor V Leiden mutation during pregnancy or the puerperium has been estimated at approximately 1 in 400 to 1 in 500, compared with 1 in 1400 in the general population.[139]

The most significant risk factors for VTE in pregnancy are a prior history of unprovoked DVT or PE (**Box 1**) and thrombophilias. Fifteen percent to 25% of VTEs are recurrent events, and 50% of the women who develop a thrombotic event during pregnancy have either a thrombophilic disorder or a previous idiopathic VTE.[140]

Diagnosis

Clinical examination

The clinical diagnosis of both DVT and PE is notoriously insensitive and nonspecific, especially during pregnancy when women often present with lower extremity swelling and discomfort, and dyspnea may occur in up to 70% of normal pregnancies. In a study of 38 pregnant women with confirmed PE, dyspnea (62%), pleuritic chest pain (55%), cough (24%), and perspiration (18%) were the 4 most common features at presentation[141]; Powrie and colleagues[142] reported an abnormal alveolar-arterial gradient (>15 mm Hg) in 8 of 17 (58%) pregnant women with confirmed PE. However, in most studies of pregnant women with clinical suspicion of PE, there was no significant risk association between any of these features and the presence of PE. Although there are some specific risk factors (see **Box 1**) that help to predict the pretest probability of VTE, at present VTE is ultimately confirmed in fewer than 10% of pregnant women who present with clinical features.[134] Although an array of diagnostic tests are currently available, clinicians are often uncertain as to the best diagnostic algorithm, which has now been suggested by the ATS Guidelines (**Fig. 4**) using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) System.

Ultrasound scanning

Direct evidence for the use of bilateral compression ultrasonography (CUS) of the lower extremities for diagnosis of PE in pregnancy currently does not exist. The benefit of using ultrasonography early in the diagnostic algorithm is potential avoidance of radiation-associated tests in the setting of a positive study (see **Fig. 4**). Selection of women with signs and symptoms of DVT could increase the positive yield of CUS. Chan and colleagues[143] have reported 3 objective variables ("LEFt": symptoms in the left leg [L]; calf circumference difference >2 cm [E]; and first-trimester presentation [Ft]) to be highly predictive of DVT in pregnancy; in their study of 194 pregnant women, the presence of 2 or 3 of these variables was associated with DVT in 58.3% of cases.

Chest radiography

In pregnant women with suspected PE, chest radiography (CXR) is the first radiation-associated procedure suggested by the ATS.[144] If the CXR is normal, ventilation/perfusion (V/Q) scan is the next imaging test recommended. If the CXR is abnormal, chest CT pulmonary angiogram (CTPA) is suggested. Use of chest radiographs to selectively triage only patients with normal CXR findings to undergo V/Q scan can increase the prevalence of definitive V/Q results.[145,146] Two studies (n = 105 and n = 24) performed in pregnant women with suspected PE have reported definitive V/Q results (normal and high probability) in 94% and 96% of cases when the presenting CXR is normal.[146,147]

Ventilation/perfusion scanning

Direct evidence for the use of lung scintigraphy for diagnosis of PE in pregnancy is derived from 4 retrospective management studies performed in the pregnant population that reported the prevalence of diagnostic V/Q scan results (high probability, very low probability, and normal) to range from 75% to 94%, with the upper value observed in a group selected by normal CXR and no prior history of asthma or chronic obstructive pulmonary disease.[146,148–150]

Box 1
Risk factors for venous thromboembolism in pregnancy

Hypercoagulable Risk Factors in Pregnancy

- Increase in coagulation factors, particularly factors I, II, VII, VIII, IX, and X
- Fibrinogen levels double in pregnancy
- Factors V, VII, and X increase in the first few days after delivery
- Decrease in levels of the endogenous anticoagulant Protein S
- Increase in resistance to the anticoagulant Protein C in second and third trimesters
- Fibrinolysis is suppressed through increases in plasminogen activator inhibitor type 2 produced from the placenta, and plasminogen activator inhibitor type 1 produced from the endothelium

Venous Stasis

- Compression of iliac veins by gravid uterus
- Hormonally mediated vein dilatation
- Immobilization

Obstetric Risk Factors

- Preeclampsia
- Dehydration/hyperemesis/ovarian hyperstimulation syndrome
- Multiple pregnancy or assisted reproductive therapy
- Emergency and elective cesarean section
- Midcavity or rotational forceps
- Prolonged labor longer than 24 hours
- Peripartum hemorrhage

Preexisting Risk Factors

- Previous VTE
- Family history of VTE
- Known thrombophilias such as factor V Leiden mutation, antithrombin III deficiency
- Antiphospholipid antibody syndrome
- Medical comorbidities such as heart, lung disease, systemic lupus erythematosus, cancer, sickle cell disease
- Age older than 35 years
- Parity greater than 3
- Body mass index greater than 30 kg/m^2
- Smoker
- Gross varicose veins

Transient Risk Factors

- Concomitant systemic infection (eg, pyelonephritis)
- Immobility
- Surgical procedure in pregnancy or less than 6 weeks postpartum

Dose-reduction techniques for lung scintigraphy include using one-half the usual administered activity of technetium-99m (Tc-99m) macroaggregated albumin for the perfusion scan and increasing the scan time to achieve adequate counts. When possible, a xenon-133 ventilation scan should be performed instead of a Tc-99m aerosol ventilation study, because the effective dose to the mother is lower. Although some experts recommend omitting the ventilation scan,

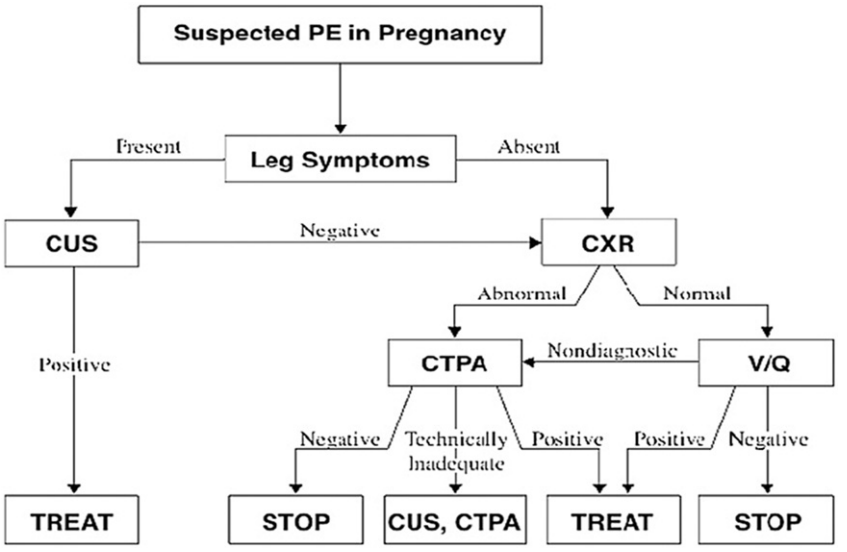

Fig. 4. Diagnostic algorithm for suspected pulmonary embolism in a pregnancy. CTPA, computed tomographic pulmonary angiography; CUS, compression ultrasonography; CXR, chest radiography; V/Q, ventilation/perfusion. (*Adapted from* Leung AN, Bull TM, Jaeschke R, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. ATS/STR Committee on Pulmonary Embolism in Pregnancy. Am J Respir Crit Care Med 2011;184(10):1200–8; with permission.)

this may decrease the diagnostic accuracy of the study. Further dose-reduction techniques include hydration to encourage frequent urinary voiding and reduction of fetal exposure.[144]

D-dimer

A degradation product of cross-linked thrombus, D-dimer levels have a high negative predictive value in the normal population. However, in pregnancy D-dimer levels become elevated as a result of physiologic changes in the coagulation system, and there is a 39% relative increase in D-dimer concentration for each trimester compared with the previous[151] and even more if there is a concomitant problem (eg, preeclampsia, threatened miscarriage, or antepartum hemorrhage). Direct data come from a retrospective study of 37 pregnant women[152] with suspected PE who had both V/Q scans and D -dimer testing. Sensitivity and specificity for suspected PE was calculated to be 73% and 15%, respectively, and the negative likelihood ratio was 1.8, suggesting that a negative D-dimer is inadequate to rule out PE in pregnancy. In addition, 2 case reports have documented negative D-dimer levels in the setting of acute PE in pregnancy.[153,154]

Computed tomographic pulmonary angiography

The main risk of iodinated contrast agents given during CTPA to rule out PE is related to the presence of free iodine with possible induction of neonatal hypothyroidism. A retrospective study of 344 pregnant women who underwent a CTPA examination for suspected PE found normal thyroxine levels in all neonates at time of birth.[155] No animal studies have demonstrated teratogenicity to the developing fetus from iodinated contrast. Iodinated contrast agents are classified as category B by the US FDA.[156] A recent retrospective management study comparing CTPA (n = 106) with V/Q scan (n = 99) in the diagnosis of PE in pregnancy has reported negative predictive values of 99% and 100%, respectively.[149] **Fig. 5** however, there is the consideration that CTPA exposes the fetus to lower radiation doses but has a higher maternal exposure in comparison with V/Q scanning (**Table 2**), keeping in mind that the mortality associated with untreated PE far outweighs the potential oncogenic and teratogenic risk incurred by fetal exposure to diagnostic imaging for PE. The European Society of Cardiology recommends CTPA over VQ scanning for the diagnosis of PE in pregnancy,[38] whereas the ATS is equivocal with the choice of imaging, depending on the initial CXR being normal or not.[144]

Magnetic resonance imaging

The main risk to the fetus from gadolinium administration for MRI is exposure to potentially free unchelated gadolinium in the amniotic fluid. Animal studies have demonstrated teratogenic effects,

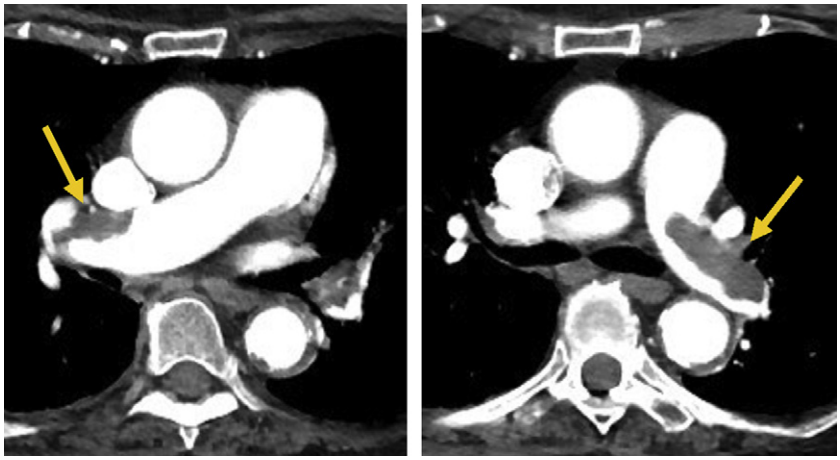

Fig. 5. Computed tomography scan showing massive bilateral pulmonary embolism (seen as filling defect denoted with *arrows*) in a patient presenting with sudden shortness of breath 2 days postpartum. (*Courtesy of* Partho Sengupta, MD, Mount Sinai Medical Center, New York.)

but only at markedly increased doses and/or for extensive periods of exposure,[157] and limited human observational studies have not documented any adverse fetal effects.[158] Gadolinium-based contrast agents are classified as category C by the FDA[156] and MRI with gadolinium is relatively contraindicated in pregnancy because of the uncertain long-term effects of gadolinium on the fetus.[159] Moreover, no accuracy or management studies that evaluate the performance of MRI for PE in pregnancy have been performed in the pregnant population. There are unenhanced MR techniques that have been described for the diagnosis of PE that require no use of gadolinium and with no risk of ionizing radiation to the fetus or mother, which could be a promising imaging modality for the future.[160]

Management

Detailed discussion of use of various anticoagulants and thrombolytics in pregnancy is outlined in a another article by Sorel Goland elsewhere in this issue, but here these are briefly discussed in the context of PE.

Table 2
Fetal and maternal radiation doses associated with diagnostic tests for PE

Diagnostic Test	Fetal Dose (mGy)	Maternal Dose (Whole-Body Effective Dose in mSv)
CXR	0.002	0.1
V/Q scan	0.32–0.74	1–2.5
CTPA	0.03–0.66	4–18

Low molecular weight heparins

LMWH has also become the drug of choice for the treatment of VTE in pregnancy and puerperium. LMWHs have been used in pregnancy since 1992, and the efficacy and safety of several LMWH preparations was shown in a review of 2777 pregnant women, treated for DVT or PE.[161] The risk of recurrent VTE with treatment doses of LMWH was 1.15%. The observed rate of major bleeding was 1.98%. Protamine sulfate reverses up to 60% of factor Xa inhibition versus 100% for UFH. Heparin-induced thrombocytopenia is markedly lower with LMWH than with UFH, as is heparin-induced osteoporosis (0.04%). LMWHs are not teratogenic or fetotoxic and do not cross the placenta, and are classified by the FDA as pregnancy category B, whereas UFH[156] is category C (**Table 3**). In clinically suspected DVT or PE, treatment with LMWH should be given until the diagnosis is excluded by objective testing.

Table 3
FDA pregnancy categories of anticoagulants and thrombolytics

Drug	FDA Category
Unfractionated heparin	C
Enoxaparin	B
Dalteparin	B
Danaparoid	B
Recombinant alteplase	C
Streptokinase	C
Urokinase	C
Warfarin	X

LMWH has also been shown to be effective in preventing pregnancy-related complications in women with thrombophilia and/or antiphospholipid antibody syndrome. Administration of enoxaparin, 20 mg daily, to women with primary early recurrent pregnancy loss and impaired fibrinolytic capacity produced up to 75% to 80% successful live births in different case series.[162,163] Similar results have been seen in patients with factor V Leiden mutation.[164]

Dosage The recommended therapeutic dose is calculated on body weight (eg, enoxaparin 1 mg/kg body weight twice daily; dalteparin 100 IU/kg body weight twice daily) aiming for 4- to 6-hour peak anti-Xa values of 0.6 to 1.2 IU/mL.[165]

Monitoring The necessity to monitor anti-Xa values regularly in patients with VTE is still controversial. Whereas it is considered necessary in patients with mechanical valves in whom LMWH is used (see section Anticoagulation in Pregnancy), this is not so clear in patients with VTE. Given the need for dose increase as pregnancy progresses to maintain a certain therapeutic anti-Xa level, it seems reasonable to also determine anti-Xa levels during pregnancy in patients with VTE.

Unfractionated heparin

UFH also does not cross the placenta, but is associated with more thrombocytopenia, osteoporosis, and more frequent dosing when given subcutaneously in comparison with LMWH. UFH is favored in patients with renal failure and when urgent reversal of anticoagulation by protamine is needed, as well as in the acute treatment of massive pulmonary emboli.

Dosage In patients with acute PE with hemodynamic compromise, intravenous administration of UFH is recommended (loading dose of 80 U/kg, followed by a continuous intravenous infusion of 18 U/kg/h).[165]

Monitoring The activated partial thromboplastin time (aPTT) has to be determined 4 to 6 hours after the loading dose, 6 hours after any dose change, and then at least daily when in the therapeutic range. The therapeutic target aPTT ratio is usually 1.5 to 2.5 times the average laboratory control value. The dose is then titrated to achieve a therapeutic aPTT, defined as the aPTT that corresponds to an anti-Xa level of 0.3 to 0.7 IU/mL. When hemodynamics are improved and the patient is stabilized, UFH can be switched to LMWH in therapeutic doses and maintained during pregnancy. LMWH should be switched to intravenous UFH at least 36 hours before the induction of labor or cesarean delivery. UFH should be discontinued 4 to 6 hours before anticipated delivery, and restarted 6 hours after delivery if there are no bleeding complications. Neither UFH nor LMWH is found in breast milk in any significant amount, and neither represents a contraindication to breastfeeding.

Thrombolytics

Thrombolytics are considered to be relatively contraindicated during pregnancy and peripartum, and should only be used in high-risk patients with severe hypotension or shock.[166] The risk of hemorrhage, mostly from the genital tract, is around 8%.[167] In 200 reported patients, streptokinase was mostly used and, more recently, recombinant tissue plasminogen activator. Neither of these thrombolytics crosses the placenta in significant amounts. Fetal loss of 6% and 6% preterm delivery were reported.[168] When thrombolysis has been given, the loading dose of UFH should be omitted and an infusion started at a rate of 18 U/kg/h. After stabilization of the patient, UFH can be switched to LMWH for the residual duration of pregnancy.

Bechtel and colleagues[169] reported the successful use of catheter-directed mechanical fragmentation and local thrombolytic infusion, with the theoretical advantage of rapid clot lysis and avoidance of hemorrhagic complications. Disadvantages are the need of sophisticated material, pulmonary artery catheterization, and radiation exposure. No conclusions can be made regarding the superiority of this method.

Embolectomy

Embolectomy, another treatment option when conservative treatment fails, is indicated to prevent death in patients who are hemodynamically unstable despite anticoagulation and treatment with vasopressors. Early experience with embolectomy was associated with a high incidence of mortality and neurologic sequelae, but technologic advances and extracorporeal bypass have significantly reduced the mortality associated with this procedure.[168] Pregnant women may be good candidates for surgery, as they tend to be younger and healthier than the average patient with VTE. Embolectomy has been associated with a 20% to 40% incidence of fetal loss,[168] however, so this treatment must be restricted to cases whereby woman's life is endangered.

Inferior vena cava filters

Inferior vena cava (IVC) filters have been used in pregnancy, and their indications are the same as for the nonpregnant population. Patients with such indications include: (1) patients with acute

VTE and contraindications to anticoagulation, (2) patients who have an episode of acute VTE while appropriately anticoagulated, and (3) patients who are critically ill and at risk for recurrent embolism whereby recurrent embolism is likely to be fatal.[168] In patients with hemodynamic compromise from PE, a repeat embolic event may be catastrophic. High risk for fatal recurrent embolism is an indication for the placement of an IVC filter, and retrievable filters are a valuable option in pregnancy.[170]

Management of delivery

Because of reports of spinal hematomas and cord compression during epidural anesthesia in nonpregnant women treated with LMWH, it is prudent to take measures to minimize the risk of hemorrhage when administering epidural anesthesia to women previously on LMWH. These measures include delaying epidural insertion until 10 to 12 hours after the last dose of LMWH and not restarting it until at least 6 to 8 hours after the epidural catheter has been removed.[101,161]

Prevention

Early mobilization and graduated compression stockings are mildly effective, safe, and noninvasive methods for prevention of VTE; they are probably all that is needed to prevent VTE in low-risk groups. Prospective, nonrandomized studies showed that in women with risk factors not receiving anticoagulation, the recurrence rate of VTE ranged from 2.4% to 12.2%, in comparison with 0% to 2.4% in patients who did receive anticoagulation.[171] LMWH has become the drug of choice for the prophylaxis and treatment of VTE in pregnant patients.[161] The dose of LMWH for thromboprophylaxis is based on the booking weight. There are no data to guide appropriate doses of LMWH for pregnant women who are obese or puerperal. It is agreed that women of higher weights should receive higher doses, but there are no studies available on the optimal dose and weight ranges. Patients at high risk for VTE (see **Table 2**) should receive the usual prophylactic dose of enoxaparin, 0.5 mg/kg body weight or dalteparin, 50 IU/kg body weight twice daily.

AMNIOTIC FLUID EMBOLISM

Introduction

Amniotic fluid embolism (AFE) is a rare but lethal condition also known as anaphylactoid syndrome of pregnancy. It usually occurs during or soon after delivery but can occur at any time during pregnancy.[172–175] AFE has also been described with the following procedures: vacuum aspiration of the uterus in the first trimester, second-trimester termination of pregnancy, amniocentesis, amnioinfusion, and as late as 48 hours after a cesarean delivery.[172,173]

AFE was first described in a report by Meyer in 1926, who suggested that there was an occlusion of the pulmonary blood vessels by amniotic fluid or fetal cells,[174] but it was not widely recognized until 1941 when an autopsy series of 8 women who had died of sudden shock during labor reported squamous cells and mucin of fetal origin in the maternal pulmonary vasculature.[176,177] The modern concept of an anaphylactoid syndrome of pregnancy was suggested by Clark and colleagues.[178]

Outcomes

AFE has a high mortality rate of 61% to 85%,[172,179,180] although some recent reports found it to be as low as 16% to 37%[181,182] in United States and United Kingdom registries. Apart from the high mortality associated with AFE, the incidence of neurologic handicap is also significant, with reports quoting figures between 7%[172] and 85%.[180]

Incidence

The incidence of AFE is reported to be between 1 in 8000 and 1 in 80,000 live births.[172–174,179–181,183]

Risk Factors

AFE was associated with maternal age greater than 35 (odds ratio [OR] 2.2, 95% confidence interval [CI] 1.5–2.1), grand multiparity of more than 5 pregnancies (adjusted OR 10.9, 95% CI 2.81–42.7), placenta previa and abruptio placenta (OR 30.4, 95% CI 15.4–60.1), cesarean delivery (OR 5.7, 95% CI 3.7–8.7), medical induction of labor (OR 1.5, 95% CI 0.9–2.3), eclampsia and preeclampsia, and forceps and vacuum delivery.[181,184] Despite the associations, our current understanding of the pathogenesis suggests that these factors are probably not the cause of AFE syndrome, which at best is considered unpredictable and unpreventable.

Pathophysiology

Amniotic fluid probably enters the maternal circulation through the endocervical veins, the placental insertion site, or a site of uterine trauma. Once it reaches the maternal circulation it can precipitate cardiogenic shock, respiratory failure, and, possibly, an inflammatory response. Invasive hemodynamic measurements from women with AFE show a biphasic pattern of cardiogenic shock, with an initial phase of acute pulmonary hypertension due to diffuse vasospasm of the

pulmonary vasculature lasting 15 to 30 minutes followed by left ventricular dysfunction. The mechanism of left ventricular failure during the later phase is unclear. Animal data suggest that it may be due to hypoxic injury to the left ventricle, release of maternal inflammatory mediators, or a direct depressant effect of amniotic fluid on the myocardium.[185–188]

Clinical Presentation

80% of patients with AFE present with[172,173,179,180]:

- Hypotension due to cardiogenic shock
- Coagulopathy due to disseminated intravascular coagulation (DIC)
- Acute respiratory failure or adult respiratory distress syndrome.

Most patients present with rapid cardiorespiratory collapse caused by these symptoms. Nonspecific symptoms (eg, chills, nausea, vomiting, agitation, mental confusion) may precede the onset of dyspnea and hypotension. Tonic-clonic seizure activity may also occur. There also appears to be a less severe presentation of AFE whereby only some of the major symptoms and signs occur. Such patients generally present with the sudden onset of milder dyspnea and hypotension. The clinical course tends to be abbreviated and the prognosis is much better than in women who have the full syndrome.[189,190]

Differential Diagnosis

The aforementioned signs and symptoms may also be seen in the following conditions:

- Obstetric-related hemorrhage and hypovolemia
- Cardiogenic shock
- Massive thromboembolism
- Septic shock
- Eclampsia
- Incorrect drug administration
- Allergic reaction to a drug
- Transfusion reaction
- Peripartum cardiomyopathy
- Aspiration.

Diagnosis

- AFE is a clinical diagnosis that is based on the constellation of clinical findings, rather than isolated symptoms and signs. Clinicians should suspect AFE whenever shock and/or respiratory compromise develops during labor or immediately postpartum. Other causes of sudden intrapartum or postpartum cardiorespiratory failure must be excluded (see the differential diagnosis above).
- Amniotic fluid debris (squamous cells, trophoblastic cells, mucin, and lanugo) can sometimes be identified in blood samples drawn from the distal port of a pulmonary artery catheter. However, finding amniotic fluid debris should not be considered diagnostic of AFE because such debris is common in the maternal circulation of women without AFE.[191]
- Serologic assays of monoclonal antibodies to the mucin-like glycoprotein sialyl Tn and immunohistochemical staining that uses a monoclonal antibody (TKH-2) to detect a common fetal antigen in the mother's blood appear to have a high sensitivity for AFE.[192–194] However, these methods have not been fully validated and cannot be recommended for routine clinical practice.
- Other important tests to evaluate AFE should include a chest radiograph, ECG, full blood count and platelet count, coagulation profile, and arterial blood gas.
- Transesophageal echocardiography has been used to evaluate patients with suspected AFE, and shows the acute right ventricular overload with a D-shaped left ventricle on short-axis views, due to septal flattening from increased pulmonary pressures. Pulmonary trunks are dilated, with no other clinical conditions to explain the findings. During the later phase the left ventricular function is also globally depressed.[175,180,183]

Management

The basis of the management of AFE is support of the airway, tissue oxygenation, breathing, and circulation.[179]

- To maintain tissue oxygenation, 100% supplemental oxygen is indicated with intubation and ventilation to maintain positive end-respiratory pressure and to attempt to achieve a level of arterial oxygen partial pressure greater than 60 mm Hg with the saturation above 90%. The administration of diuretics is recommended.
- For circulatory support the Advanced Cardiac Life Support (ACLS) protocol should be initiated with the mother in the left lateral decubitus position. Colloids and crystalloids should be administered with inotropes such as dopamine, dobutamine, or phenylephrine. The aim is to improve the circulation and maintain a urine output of more than

25 mL/h with the mean arterial pressure higher than 65 mm Hg. Other treatment modalities include nitric oxide (a selective pulmonary vasodilator), cardiopulmonary bypass, extracorporeal membrane oxygenation, and intra-aortic balloon counterpulsation. Delivery of the fetus improves the survival of the fetus and helps with the maternal cardiopulmonary resuscitation. Intact fetal survival is possible if the fetus is delivered within 5 minutes. Improvement in maternal outcome is possible if the fetus is delivered within 4 minutes of developing malignant arrhythmia via a perimortem cesarean section.

- In cases where the mother develops convulsions or an altered level of consciousness, her hypoxia needs to be corrected and antiepileptic drugs may be used. Central venous pressure and pulmonary arterial lines are recommended in the fluid management of these patients.
- An important step in management is to correct the coagulopathy, which can be done using fresh-frozen plasma, packed red blood cells, and platelets. Cryoprecipitate is not the first-line therapy but has a role in volume-overloaded patients and also contains fibronectin, which assists the reticuloendothelial system with the filtration of antigenic and toxic substances. Recombinant factor VIIa may be useful to treat the DIC caused by AFE. Obstetric hemorrhage should be aggressively prevented by balloon tamponade of the uterus, and uterine artery embolization may be of help.
- Other treatment modalities such as high-dose steroids (500 mg hydrocortisone sodium succinate every 6 hours until improvement), antithrombin III infusion, leukotriene inhibitors, inhaled prostacyclines, hemofiltration, or exchange transfusion have been described anecdotally, and are unlikely to be tested scientifically.

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