CASE REPORT

Acute Coronary Syndrome in Pregnancy

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Abstract: Acute coronary syndrome (ACS) in pregnancy has traditionally been considered to be a rare event, but the combination of normal physiological changes of pregnancy and more prevalent cardiovascular risk factors are increasing its incidence in this population. The present report describes a 39 year-old woman that is seven weeks pregnant presenting with a non ST elevation myocardial infarction. The incidence, risk factors, pathophysiology and management of ACS in pregnancy are discussed.

Keywords: Acute coronary syndrome, pregnancy, risk factors, pathophysiology

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Case Report

A 39-year-old female who was seven weeks pregnant presented to a community hospital emergency department with a first episode of chest pain. She had a twenty pack per year smoking history and a significant family history of coronary artery disease (CAD) with her father developing CAD in his thirties. She had no known history of diabetes, dyslipidemia, or hypertension. The pain started after an episode of intense vomiting. She described the pain as a pressure sensation, retrosternal in location, with radiation down both arms. It was associated with intense nausea and vomiting, and she had some relief with aspirin. The pain continued at a high intensity for approximately five hours. Given the duration of discomfort and associated extreme weakness she sought medical attention.

In the emergency department, she denied recreational drug use, and did not have any constitutional symptoms. Clinically there was no evidence of deep vein thrombosis (DVT), pulmonary embolism (PE), or pericarditis. On physical examination she was afebrile and hemodynamically stable, with a heart rate of 69 and regular, equal blood pressures in both arms of 95/65 mmHg, and an oxygen saturation of 97% on room air. There were no signs of congestive heart failure with no pedal edema, clear lungs, and no jugular venous distension. The precordial exam was normal with no heaves, thrills, normal \( S_1 \) and \( S_2 \) with normal physiological splitting and no extra heart sounds, rubs or murmurs. A 12-lead electrocardiogram (ECG) was completed that showed normal sinus rhythm at a rate of 60 bpm, normal axis, normal intervals with no evidence of chamber enlargement with 1 mm ST segment depression in lead V\(_2\) and <1 mm depression in V\(_5\) (Fig. 1). Initial blood work showed a significant elevation of the cardiac markers with a Troponin T of 0.96 µg/L and a creatinine kinase (CK) level of 718 U/L, all of which decreased on serial measurements. Urine drug screen was negative. An echocardiogram demonstrated severe inferolateral wall hypokinesis with a preserved left ventricular systolic function and ejection fraction of 60% with no other abnormalities identified.

This presentation was complicated by a positive home pregnancy test. This was confirmed by a quantitative β-hCG of 20348 IU/L. The estimated gestational age was seven weeks and six days by last menstrual period. Her past obstetrical history included three pregnancies with one full term delivery, one preterm delivery, and one therapeutic abortion. The patient was transferred from a community hospital to our tertiary center for further management.

Discussion

Chest pain in pregnant women is rarely due to myocardial infarction. Pulmonary, gastrointestinal, psychiatric, neuromusculoskeletal, along with non-ischemic cardiac causes of chest pain must be considered in these patients. The incidence of myocardial infarction in pregnancy has been estimated to be 6.2 per 100,000 deliveries with a mortality rate of 5.1%–11% in recent reviews.\(^1,2\) Prior estimates of mortality have reported it as substantially higher at 37% and estimates of incidence substantially lower at 2.8 per 100,000 deliveries.\(^1,3\) This incidence is approximately 3–4 times higher than the estimated age associated risk for non-pregnant women.\(^2\) The decreased mortality and increased incidence in the recent literature is likely due to use of more sensitive and specific serum cardiac markers, such as troponins, identifying more cases of subendocardial myocardial injury as well as the increasing cardiovascular risks, such as advancing maternal age.\(^1\) In a nationwide US population based study of acute myocardial infarction (AMI) during pregnancy performed between 2000 and 2002, the anterior coronary circulation was found to be more commonly involved with 20% of reported infarctions occurring in this territory.\(^1\) Although not elaborated on within the original articles, the preponderance of anterior circulation culprit vessels in AMI may be due to the greater clinical presentation of these patients, while missing the smaller myocardial infarctions in the other vascular territories. The timing of MI in pregnancy varies. Ladner et al found that in pregnant women with AMI, 38% occurred in the antepartum, 21% occurred in the intrapartum, and 41% occurred in the 6-week postpartum period.\(^4\) Within pregnancy, Badui and colleagues identified that women in the third trimester had the highest risk of AMI.\(^5\) The increased stroke volume and heart rate during pregnancy causes an increased myocardial oxygen demand, while the decreased diastolic blood pressure and related physiologic anemia result in decreased myocardial perfusion that may contribute to the ischemia when coronary blood flow is compromised. With labour, myocardial ischemia may be precipitated by a further increase in
Figure 1. Twelve-lead electrocardiogram showing ST segment depression in leads V₄ and V₅.
myocardial oxygen demand driven by pain, uterine contraction, and anxiety. After delivery, caval compression is relieved and blood flow is shifted from the uterus back to the systemic circulation resulting in further stress on the myocardium and likely contributing to the increased incidence of myocardial infarction in the puerperium. With a compromise in the coronary blood flow, the high demand physiological state of normal pregnancy would precipitate myocardial ischemia and potentially infarction. James et al. reviewed the coronary anatomy through angiography and autopsy of pregnant women diagnosed with AMI and found that 40% had evidence of atherosclerosis with or without thrombosis, 8% had thrombosis without atherosclerosis, 27% had coronary artery dissections and 13% had normal coronaries. In the general population, nearly all cases of acute myocardial infarction are due to coronary atherosclerotic disease and acute plaque rupture resulting in coronary artery occlusion. Rarely, vasculitic syndromes, hypercoagulable states, coronary artery spasm, increased myocardial demand, coronary emboli, congenital coronary anomalies, trauma and aneurysm may cause AMI. The increased events associated with thrombosis without atherosclerosis, vasospasm and coronary artery dissection may be related to the physiological alterations associated with pregnancy. Pregnancy is a known hypercoagulable state. The association of thrombophilia with MI in pregnancy may be due to the increased testing for this in this particular population. In regards to vasospasm, the pregnant woman has more reactive vessels to norepinephrine and angiotensin II, has associated endothelial dysfunction and has an increased renin secretion and angiotensin activity associated with uterine malperfusion with the supine position and the use of ergot derivatives to control post-partum hemorrhage all may contribute. This vasospasm may also be the precipitating mechanism for thrombosis in coronary vessels that have no evidence of atherosclerosis, with the spasm impeding blood flow and the physiologic hypercoagulable state resulting in a thrombosis.

The risk factors for AMI are also commonly seen in pregnancy, including diabetes mellitus, smoking, advanced maternal age, dyslipidemia, significant family history and hypertension. In addition novel risk factors such as black race, pre-eclampsia, eclampsia, anemia, migraine headaches and thrombophilia have been identified. The associated risk with migraines may be due to overall “vasospastic” disorder of the woman or due to heightened awareness of the physician for possible ACS events in these patients. The association of pre-eclampsia and eclampsia may be due to endothelial dysfunction that has been shown to persist up to one year post partum. The increased incidence of coronary dissection is thought to be due to the changes in progesterone resulting in several structural and biochemical changes within the vessel wall; however, other theories include changes in eosinophil activity and decreased prostacyclin activity have been postulated. It is these systemic changes in conjunction with the physiological changes of increased blood volume and cardiac output that likely result in increased shear forces that result in dissection occurring not only in single vessels, but frequently in multiple coronary arteries.

The treatment of ACS has been well established for the non-pregnant patient, but many uncertainties remain in the management of pregnant patient which may delay treatment. A classification scheme has been established to identify the associated risks with certain medications in pregnancy (Table 1). Nitroglycerine (Class B) is widely used for ischemic pain, however there are concerns about maternal hypotension and uterine malperfusion. Studies are required to fully elucidate the effect of nitrates in pregnancy. Heparin (unfractionated heparin Class C, low-molecular weight heparin LMWH Class B) has been proven to be safe in pregnancy in numerous studies, however it is recommended to stop heparin prior to delivery and monitoring anti-Xa levels if LMWH is used due to the pregnancy associated pharmacokinetic changes. Beta-blockers (Metoprolol Class B, Atenolol Class C) have been used successfully; however there are anecdotal reports of fetal bradycardia, hypoglycemia, hyperbilirubinemia, and apnea. A Cochrane review looking at oral beta blockers for use in treatment of mild to moderate hypertension in pregnant women found that there was a trend toward small for gestational age infants, but the results were skewed by a small outlier trial. There was insufficient data to comment on perinatal mortality or preterm delivery. Atenolol has been linked to a possible increase in fetal growth restriction, especially when used in the first trimester. ASA (Class C) is debateable for use during pregnancy because animal
studies have shown increased incidence of fissure of spine and skull, facial and eye defects, and malformations of the central nervous system (CNS), viscera, and skeleton. Chronic use of high dose ASA during pregnancy should be avoided because of increased fetal hemorrhage, increased perinatal mortality, intrauterine growth restriction and teratogenic effects. A meta-analysis looking at antiplatelet agents found that low dose ASA is safe in pregnancy. Clopidogrel (Class B) has very limited data for its use in pregnancy. It is recommended that Clopidogrel be stopped 1 week prior to any regional anesthesia procedures. Glycoprotein IIb/IIIa inhibitors (Eptifibatide and Tirofiban Class B, Abciximab Class C) have not been studied in pregnant patients as all randomized trials of these agents excluded pregnant patients. These drugs cannot be recommended in pregnant patients, however if they are used a C-section delivery is recommended to decrease the potential for fetal intracranial hemorrhage. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated in pregnancy due to teratogenic side effects. Many animal and human studies have found that ACE inhibitors and ARBs cause multiple birth defects including renal dysgenesis, oligohydramnios, IUGR, prematurity, bone malformations, limb contractures, death and multiple others. A recent retrospective analysis of fetuses exposed to ACE inhibitors in the first trimester identified ACE inhibitors as an independent risk factor for developing malformations of the cardiovascular and CNS. Statins (Class X) are not recommended in pregnancy as information on use in pregnancy is limited. Although laboratory models show potential placental growth disruption and animal studies have shown skeletal abnormalities and increases in mortality, a recent systematic review found that most data of human teratogenicity were only case reports and that the overall risk is likely minimal. The authors stated that statin exposure did not warrant termination of pregnancy as a sole reason. A prospective cohort of 134 women inadvertently exposed to lovastatin and simvastatin found no difference in the incidence of adverse pregnancy outcomes. The use of invasive catheter procedures for management of AMI in pregnancy is also not clearly identified. Numerous case studies have been published that describe results of both invasive and conservative management. In one report a patient was managed conservatively with ASA and beta-blockers, while waiting for the post-partum period to undergo cardiac catheterization. Other reports have described treating pregnant women with early percutaneous coronary intervention (PCI) and stent placement. Both reported favorable fetal and maternal outcomes. Bare metal stents have been used with success in the literature; however, there is limited data for the use of drug eluting stents and its necessary long-term clopidogrel treatment.

The teratogenic effects of radiation were first reported in 1929 when Goldstein and Murphy observed a high rate of micrencephaly and reduced cranial circumference in women who had undergone radiation treatment for uterine cancer during pregnancy.

| Category | Interpretation |
|----------|----------------|
| A        | Controlled studies show no risk Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus. |
| B        | No evidence of risk in humans Either animal findings show risk (but human findings do not) or, if no adequate human studies have been done, animal findings are negative. |
| C        | Risk cannot be ruled out Human studies are lacking and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk. |
| D        | Positive evidence of risk Investigational or post-marketing data show risk to fetus. Nevertheless, potential benefits may outweigh the risk. |
| X        | Contraindicated in pregnancy Studies in animals or humans, or investigational or post-marketing reports have shown fetal risk which clearly outweighs any possible benefit to the patient. |
While many studies have shown that a fetal dose of 5 rads is not related to teratogenicity at any period of gestation, the most vulnerable time for the fetus is 8–15 weeks of gestation. Coronary angiography exposes patients to 2.5–5.0 mSv (equivalent to 125–250 chest x-rays), and percutaneous coronary intervention exposes patients to 5.0–15.0 mSv (equivalent to 115–1000 chest x-rays), which are both below the threshold for teratogenicity at any gestational age. The amount of radiation that reaches the fetus is a percentage of the total amount delivered to the patient and depends on the body parts being irradiated and the type of protection used. No necessary radiodiagnostic examination that is clinically justifiable should be avoided due to pregnancy, and protective measures for the mother and fetus should be taken. Other diagnostic procedures that are equally as effective but not as dangerous to the fetus should be preferentially used.

A number of therapies ranging from multiple drugs to PCI are available for the pregnant patient presenting with ACS. It is important to weigh the risks and benefits of each potential therapy and tailor the management according to the clinical presentation.

Return to the Case
The patient was started on ASA, beta-blockers, and intravenous unfractionated heparin. Nitroglycerine spray was prescribed to be used as needed for chest pain relief. The obstetrics team was consulted to guide management. A quantitative β-hCG and pelvic ultrasound were arranged to verify the viability of the pregnancy. A quantitative β-hCG and pelvic ultrasound were arranged to verify the viability of the pregnancy prior to starting medications with known teratogenic side effects and unclear risk profiles. PCI was discussed however not pursued as she had a normal left ventricular ejection fraction, no recurrent chest pain, no electrical or mechanical complications. A pelvic ultrasound showed an intrauterine pregnancy with no fetal heartbeat, consistent with fetal demise. Expectant management of the fetus was chosen and follow-up ultrasound was arranged with the obstetrics team. The cardiology team arranged follow-up regarding long term medications and planning for further risk stratification.

Although ACS in pregnancy has been historically uncommon, the increasing prevalence of atherosclerotic risk factors in women of child bearing age combined with the normal physiological changes of pregnancy will cause the incidence of this presentation to increase in clinical practice. It is important that physicians are familiar with the clinical presentation, risk factors, potential management options and their interactions with both the pregnant female and the fetus.

Disclosures
The authors report no conflicts of interest.

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