

Acute Myocardial Infarction in Pregnant Women

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Abstract

Acute myocardial infarction (AMI) in pregnant women is a rare but potentially lethal occurrence that should be carefully managed, especially in consideration of cardiac conditions being a rising cause of maternal deaths. Risk factors for AMI occurrence, in addition to typical cardiac-related risk factors, include medical conditions such as (pre) eclampsia, blood transfusions, thrombophilia and postpartum infections. Being older, multigravida or in the third trimester of pregnancy is also associated with an increased risk. The pathophysiological causes underlying AMI in pregnancy are diverse but generally associated with the coagulative and physiological changes related to the pregnancy. The selection of diagnostic modality and treatment options require careful consideration for pregnancy-related changes as well as risk of harm to the patient and fetus. This paper serves to review available literature regarding an extensive range of management issues that directly impact on maternal and fetal outcomes.

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Introduction

Acute myocardial infarction (AMI) is an important cause of mortality and morbidity worldwide. It typically occurs in middle-aged or elderly people with cardiovascular risk factors, such as cigarette smoking and diabetes mellitus. Although uncommon, AMI does occur in pregnant women. From the physiological perspective, pregnancy has been shown to result in a 3 to 4 fold increase in the risk of AMI.¹⁻³ In western countries, the estimated incidence of AMI in pregnancy or during the early postpartum period is 1 in 10,000.⁴ A recently published report studying maternal deaths in the United Kingdom revealed that heart disease, including acquired heart disease, cardiomyopathy and AMI, is rising as a leading cause of maternal death.⁵

AMI in pregnancy is associated with poor maternal and fetal outcomes. A recent report revealed a maternal mortality rate of 11%, mostly occurring at the time of infarction or within 2 weeks.⁶ The mortality was twice as high when AMI occurred during peripartum, in comparison to the mortality observed during antepartum and postpartum periods. A fetal mortality of 9%, mainly associated with maternal mortality, was documented in the same report. Causes of fetal deaths include spontaneous abortion, unexplained stillbirth and elective termination of pregnancy due to concerns about

potential drug teratogenicity. Little systematic data is available due to the exclusion of pregnant women from almost all clinical trials in the diagnosis and management of AMI. In this review article, we seek to present an overview of the current knowledge of AMI in pregnancy. We refer to AMI as ST-segment elevation myocardial infarction (STEMI) whenever appropriate. Discussion on non-STEMI is beyond the scope of this article.

Demographic and Risk Factors

Pregnancy-associated AMI is found to occur in pregnant women of all child-bearing ages, ranging from 19 to 44 years. Yet, the highest incidence occurs in pregnant women over the age of 30, which is found to be associated with an odds ratio (OR) of 6.7.³ This is important, given the increasing number of late marriages and older childbearing ages, as well as advances in reproductive technology making conception in older women feasible. In addition, AMI tends to occur in multigravidas and during the third trimester. It has also been observed that patients suffering AMI in the postpartum period (24 hours to 3 months after delivery) are significantly younger than those having an AMI during the antepartum (>24 hours before delivery) or peripartum period (within 24 hours before and after delivery).⁷

Like AMI in non-pregnant individuals, conventional risk

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factors also play an important role for AMI in pregnant women. These include existing hypertension (OR = 21.7), diabetes mellitus (OR = 3.6) and smoking (OR = 8.4). The occurrence of pre-eclampsia and eclampsia, receiving transfusions, existing thrombophilia and postpartum infections have also been recognised as contributory factors for pregnancy-related AMI.^{1,3}

Pathophysiology

In the case of non-pregnant patients, sudden rupture and erosion of unstable atherosclerotic plaque, leading to partial or complete thrombotic occlusion of coronary artery, are the predominant causes of AMI. However, the underlying pathophysiology of AMI in pregnant women is more diverse and relates to the stage of pregnancy. Overall, the occurrence of atherosclerotic changes in the coronary artery remains the primary cause of pregnancy-related AMI, especially in patients presented at antepartum period.⁶ A list of possible causes of AMI during pregnancy is presented in Table 1.

During peripartum period, coronary artery dissection is the primary cause of infarction in patients, being responsible for 50% of the cases presenting at this stage of pregnancy. It has been suggested that angiographically normal coronary arteries in patients presenting at peripartum may be the result of spontaneously repaired coronary dissections, suggesting that this condition may have been under-diagnosed.⁸ The marked haemodynamic changes associated with pregnancy cause an increase in myocardial oxygen demand. This leads to the development of myocardial ischaemia, which worsens during gestation, accompanied by significant blood loss and physiological anaemia. Anxiety, pain and uterine contractions further aggravate the situation, being associated with an up to 3-fold increase in oxygen consumption during labour.⁷ With successful delivery, the sudden relief of prolonged caval compression and enhanced venous return from the contracting uterus to the heart adds further strain to the coronary vasculature, hence supporting the higher incidence of coronary dissection immediately after delivery. Other hypothesised causes of coronary dissection

include progesterone-mediated changes to the structural and biochemical properties of vessel wall, increased lytic activity of eosinophil proteases, absent prostacyclin synthesis stimulating plasma factor and elevated lipoprotein (a) levels.⁶

Coronary spasm is another possible cause of AMI in pregnancy.⁶ Coronary spasm is characterised by rapid reversal of coronary stenosis after intracoronary administration of nitroglycerin. The diagnosis of coronary spasm is more difficult if the spasm has been resolved, resulting in normal coronary patency, during diagnostic coronary angiography. A provocative test with acetylcholine chloride is seldom performed as it entails the risk of causing acute coronary occlusion and malignant arrhythmia. The underlying causes of coronary spasm include endothelial dysfunction and enhanced vascular reactivity to angiotensin II and noradrenaline, both of which are associated with pregnancy-induced hypertension and pre-eclampsia, as well as renin release (and subsequent angiotensin production) responding to decreased uterine perfusion in the supine position.⁹⁻¹² Ergot derivatives and bromocriptine, which are used to control postpartum or postabortion haemorrhage, or to suppress lactation, are similarly potential triggers of coronary spasm.^{13,14}

Coronary thrombosis without underlying atherosclerosis is detected in a small percentage of pregnant women with AMI.⁶ This may be explained by the hypercoagulable state associated with pregnancy. It is the result of an altered fibrinolytic and coagulation state caused by decreased tissue plasminogen activator (tPA) activity, with an increase in fast-acting tPA inhibitor, altered levels of coagulation factors and reduced levels of functional protein S.⁸ Hypercoagulation is further induced at the time of placental separation, the placenta being a major source of tPA. Cigarette smoking leads to additional release of tPA inhibitor, further increasing platelet aggregability.¹⁵

Diagnosis of AMI in Pregnancy

Prompt diagnosis of AMI during pregnancy is often difficult due to the rarity of the condition and because physicians frequently associate presentations of AMI with normal pregnancy manifestations. The diagnostic criteria in the case of pregnant women are identical to those for non-pregnant patients. The criteria include symptoms, elevated cardiac enzyme concentrations in blood and electrocardiogram (ECG) changes such as development of Q waves or ST segment changes.⁸ However, the selection of diagnostic modality and interpretation of results need to encompass consideration for normal pregnancy-related changes and fetal wellbeing. Pregnancy-related changes that affect the diagnostic markers of cardiac disease are summarised in Table 2.

Table 1. Causes of Pregnancy-related Acute Myocardial Infarction

• Atherosclerosis
• Coronary artery dissection
• Coronary artery spasm
• Aortic valve stenosis
• Aortic prosthetic valve thrombosis
• Sick cell disease
• Cocaine usage
• Pheochromocytoma

Table 2. A Summary of the Pregnancy-Induced Effects on Diagnostic Markers that Affect the Diagnosis of Acute Myocardial Infarction in Pregnant Patients

Diagnostic marker	Effect of pregnancy on marker
Signs and symptoms commonly associated with cardiac disease	Could be either diagnostic of cardiac disease or normal pregnancy manifestation
Cardiac markers:	
- Serum Creatinine Kinase MB	Significantly elevated with uterine contraction activity
- Troponin I	Not affected by labour, anaesthesia or surgery
	Elevated in pre-eclampsia and gestational hypertension
Electrocardiography (ECG)	Associated with ST-elevations with anaesthesia, as well as left axis deviation, in the third trimester

Signs and Symptoms

The signs and symptoms of a normal uncomplicated pregnancy may sometimes mimic those unique to cardiac disease, making it a challenge to determine whether they are significant markers of ongoing pathology. Examples of such cardinal cardiac symptoms include dyspnoea, tachypnoea, fatigue, decreased exercise capacity, dizziness, palpitations and syncope.

Pregnancy-related physiological changes such as increased heart rate, stroke volume or a twin pregnancy result in a significantly greater cardiac output. This, in addition to oestrogen-mediated effects on the renin-angiotensin system, produces an elevated plasma volume, resulting in symptoms such as lower extremity oedema, which is commonly associated with right heart failure. An increasing uterus size forces the diaphragm upwards, resulting in a smaller pulmonary volume and vital capacity, thus explaining the dyspnoea often experienced in pregnancy.¹⁶

Other findings of a physical examination that could present as clinical manifestations of cardiac disease, as well as a normal pregnancy, include mild elevation of jugular venous pressure, apex displacement, parasternal lift, increased intensity of the first heart sound, increased prominence of the second heart sound, an extra (third) heart sound, a systolic ejection murmur, as well as venous hums and mammary soufflés, which could be mistaken as cardiac murmurs.¹⁷

Biomarkers

The elevation of cardiac biomarkers, namely, creatinine kinase MB and/or troponin provides confirmatory evidence of myocardial necrosis. Cardiac troponin, specifically, has emerged as the preferred diagnostic marker for the past 10 years. It is crucial to be aware that in pregnant women, uterine contraction activity may increase the serum level

of creatinine kinase MB. In contrast, the serum level of troponin does not increase above the upper normal limit in healthy pregnant women even immediately after delivery. The serum troponin level is also unaffected by anaesthesia or surgical birth and is only elevated in patients with pre-eclampsia and gestational hypertension.⁸ As a result, troponin is the recommended diagnostic marker for AMI in pregnant women, especially after delivery.

Twelve-lead Electrocardiography

Diagnosing AMI using ECG requires an understanding of the pregnancy-associated changes that could be observed. Firstly, the induction of anaesthesia for caesarean sections frequently results in misleading ST-segment depressions. A study reported significant ST-segment changes in 42% of the 26 patients undergoing elective caesarean sections and in 38.5% of these patients after the operation.¹⁸ The physiological changes during pregnancy may also affect ECG presentations. In the third trimester, the diaphragm is commonly displaced upwards by the fetus, causing a left axis deviation. Other possible ECG changes include Q waves in lead III and augmented vector foot (aVF) and mildly inverted T waves in lead III.¹⁹

Transthoracic Echocardiography

Echocardiogram is a safe option during pregnancy but is not definitive in diagnosing myocardial ischaemia. In non-pregnant women, transthoracic echocardiography is often used as an adjunctive technique to examine left ventricular function and wall motion abnormalities, especially when the results from other diagnostic tests are conflicting or inconclusive. During pregnancy, the diagnostic role of transthoracic echocardiogram for AMI is particularly important because of the non-invasive nature of the test and absence of radiation. This test can also be used to exclude other conditions that might mimic AMI, such as aortic dissection or aortic valvular conditions.

Coronary Angiography

Coronary angiography is helpful in the diagnosis of AMI, as well as offering the option of concurrent interventional therapy. The main concern for diagnostic coronary angiography is radiation exposure of the fetus. Before embarking on coronary angiography, it is necessary to acknowledge the detrimental effects of radiation to the growing fetus. Increased radiation exposure is associated with the induction of various tissue defects, ranging from isolated cellular and molecular damage to growth impairment, structural abnormalities and neoplasia. The correlation between receiving radiation in utero and increased risk of malignancy has been demonstrated by Bithell and Stewart,²⁰ who reported a relative risk of 1.47 for the development of subsequent malignancies in children

of mothers who underwent radiographs during pregnancy. The relative risk increased progressively from 1.26 for a single exposure to 2.32 for 5 or more exposures. A first trimester exposure was associated with a relative risk of 8.95, which fell to 1.25 and 1.41 for the second and third trimesters, respectively.

Owing to the invasive nature and risk of radiation exposure associated with coronary angiography, this test should only be performed when the results of other diagnostic tests are highly suggestive of AMI, and treatment with primary percutaneous coronary intervention (see below) is contemplated. Nonetheless, the risk of radiation from coronary angiography is deemed negligible when the abdomen is properly shielded.²¹ It usually causes a fetal radiation exposure of <1 rad unless the procedure is exceptionally challenging. Termination of pregnancy is usually recommended only when radiation exposure exceeds 10 rads.²²

Treatment

Urgent Reperfusion Therapy

Urgent reperfusion therapy remains the most important therapeutic intervention for all patients presenting with AMI, including pregnant women. However, pregnant women were almost always excluded in clinical trials that compared various reperfusion approaches. Extremely limited data, mostly anecdotal experiences, on different reperfusion strategies are available for pregnant women. In general, treatment of pregnant women suffering an AMI should adhere to the therapeutic recommendations as is the case for non-pregnant patients. The importance of a collaborative effort between the cardiologist and the obstetrician in implementing the most appropriate care cannot be overemphasised. Arrangements should be made for an emergency delivery to be performed in case of marked deterioration in the mother's condition

Percutaneous Coronary Intervention

Primary percutaneous coronary intervention (PCI) has been proven to be superior to thrombolytic therapy in randomised trials and meta-analysis. Provided it can be performed in a timely manner, primary PCI ought to be the preferred reperfusion treatment. The main concerns when PCI is performed in pregnancy include the need for prolonged antiplatelet therapy after coronary stent implantation, as well as the adverse effects associated with radiation. In a population-based study conducted in the United States, only 16% of the 859 pregnant women suffered from AMI.³ Roth et al⁶ reported that PCI was performed in 38 of the 92 pregnant women, with stent placement in more than half of the cohort. It was observed that after bare-metal stent implantation, dual antiplatelet therapy for 1 month followed by life-long aspirin becomes

mandatory. The duration of dual antiplatelet therapy would be even longer, at least 6 to 12 months after drug-eluting stent implantation.²³ Apart from the presently controversial benefits of implanting drug-eluting stent in STEMI, the need for prolonged dual antiplatelet therapy makes drug-eluting stent implantation a particularly less favourable choice in pregnant women due to the high proportion of caesarean section deliveries. It would also contraindicate the use of epidural anaesthesia during labour due to an associated increase in risk of epidural haematoma.²⁴

The undeniably detrimental effects of radiation, as mentioned above, may serve as a further deterrent to the implementation of primary PCI for some clinicians. However, it is important that the therapeutic benefits for the mother are not neglected while considering fetal wellbeing. Other possible complications associated with stent implantation are similar to that for non-pregnant patients; they include arterial embolisation, contrast renal toxicity and vascular injury.⁸

Thrombolytic Therapy

Haemorrhagic complication remains the most troubling complication in administering thrombolytic therapy to pregnant women, most often occurring within the first 8 hours postdelivery. Thrombolytic therapy has routinely been contraindicated in pregnancy. This is, however, purely theoretical due to the routine exclusion of pregnant patients in past clinical trials. Studies have illustrated that placental transfer of streptokinase and tPA is minimal and hence unable to induce fetal harm.^{25,26} Teratogenic effects have not been reported till date. However, thrombolytic therapy is associated with an 8% risk of maternal haemorrhage and 6% risk of fetal mortality. The risk of haemorrhagic complications is more prevalent when thrombolytic therapy is administered at the time of delivery.⁸ Other concerns of using thrombolytic therapy include allergic reactions, activated plasminogen that triggers preterm labour and the development of reperfusion arrhythmias.²⁷ If thrombolytic therapy is employed in the presence of a coronary dissection, it could cause increased haemorrhage and further progression of the dissection.²⁸ Owing to these potential complications and inferior reperfusion efficacy, thrombolytic therapy should only be considered in pregnant women when primary PCI is unavailable or cannot be performed in a timely manner.

Coronary Artery Bypass Grafting

In contemporary primary PCI procedure, the need for emergency coronary artery bypass grafting (CABG) is exceedingly rare. CABG is only considered when primary PCI is unsuccessful or when complications such as coronary dissection arise during the procedure. Maternal mortality with CABG is 1.5%, as with the non-pregnant population.²⁹

Continuous fetal monitoring should be done during the surgery, as an indicator of placental perfusion, so as to guide the intraoperative pump flow.³⁰ Hypothermia or inadequate bypass pump flow could induce fetal bradycardia or sinusoidal fetal heart rate patterns.⁸

Pharmacological Treatment

Recommended drug therapy for a non-pregnant patient with AMI includes administration of beta-blockers, nitrates, calcium channel blockers, angiotensin-converting enzyme inhibitors, anticoagulant and antiplatelet therapy.³¹ However, research regarding the safety of these drugs in pregnancy is limited.

Beta-blockers have been extensively administered in pregnancy for the management of hypertension, arrhythmias, mitral stenosis and AMI. However, the use of beta-blockers has been associated with side effects such as bradycardia, hypoglycaemia, hyperbilirubinaemia and apnoea at birth.⁶ The levels of teratogenicity of each beta-blocker varies with differing lipid solubility and receptor specificity, with labetalol being accepted as the safest option in pregnancy.³² Beta-1 selective agents are preferred, as non-selective beta-blockers could increase uterine activity, consequently affecting the fetus.³³ Moreover, beta-blockers accumulate in breast milk and hence, breastfeeding should be avoided.⁶ Organic nitrates have been widely used in pregnant women for the treatment of AMI and hypertension, as well as for non-cardiovascular conditions, such as to arrest preterm labour or induce relaxation of the uterus postpartum with placental retention.³⁴ However, the dosage administered should be carefully titrated to avoid maternal hypotension which would affect uterine perfusion.

Information regarding the safety of calcium channel blockers is generally limited, with only nifedipine having sufficient evidence of past usage during pregnancy to demonstrate its safety in this specialised category of patients.³⁵ A surveillance study demonstrated the possible teratogenic effects related to diltiazem use. Calcium channel blockers are excreted in human milk and hence, breastfeeding is also discouraged.³⁶

Angiotensin-converting enzyme (ACE) inhibitors are administered to reduce afterload so as to minimise postAMI remodelling. However, ACE inhibitors being fetotoxic, their use is contraindicated in pregnant patients. Decreased levels of angiotensin II could affect uteroplacental blood flow due to a reduced production of vasodilator prostaglandins.³⁷ ACE inhibitors also severely disrupt the normal development of fetal kidneys.³⁸ Angiotensin-receptor antagonists have an effect similar to that of ACE inhibitors on angiotensin II and hence, they should also be avoided in pregnant patients.

HMG-CoA reductase inhibitors (statins) are commonly prescribed for their established efficacy in reducing low-

density lipoprotein levels. However, available research is inadequate in determining the safety of statin use in pregnancy. Previous animal studies have demonstrated an increased risk of skeletal abnormalities.⁶ Statins inhibit normal synthesis of mevalonic acid, which is essential for DNA replication as well as steroid and membrane synthesis in fetal development.⁶ It is, however, important to acknowledge the confounding influence of high proportion of patients requiring statins having comorbidities such as diabetes, obesity or both, all of which being associated with increased risk of birth defects.^{39,40}

Parenteral unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are the anticoagulants of choice in pregnancy as the large molecular weights of these anticoagulants prevent them from crossing the placenta, therefore preventing any teratogenic effects.⁴¹ LMWHs are associated with lower risk of bleeding as well as reduced incidence of heparin-induced thrombocytopenia.⁸ The lower affinity of LMWH with heparin-binding proteins results in more predictable therapeutic effects and a longer pharmacological half-life.⁴² The therapeutic effects may last up to 28 hours and hence, anticoagulants should be discontinued 24 hours before induction of labour. The effects of heparin may be reversed with protamine sulphate to reduce the risk of haemorrhagic complications, when necessary.⁸

Antiplatelet therapy is crucial in the prevention of subsequent cardiovascular events post-AMI. The use of aspirin in the first trimester is associated with possible birth defects such as skeletal, facial and eye deformities as well as malformations of the central nervous system or abnormal organogenesis.⁴³ However, a large randomised trial of 9000 patients showed that low-dose aspirin (60 to 150 mg/d) administered in the second or third trimester is safe for both mother and child.⁴⁴ High-dose aspirin use should be avoided as it may increase the risks of maternal and fetal haemorrhage, fetal mortality, intrauterine growth retardation and premature closure of ductus arteriosus.^{36,45} Aspirin is found in breast milk in low concentrations; however, no adverse effects associated with breastfeeding have been reported.³⁶

Information on the safety of thienopyridine derivatives such as clopidogrel or glycoprotein IIb/IIIa inhibitors during pregnancy remains scarce due to minimal research conducted on this target group. It is not yet known whether the above-mentioned drugs are excreted in breast milk; hence, breastfeeding is not recommended.⁴³

Labour

Delivery should be postponed for 2 to 3 weeks' postAMI to allow adequate healing of infarction.⁷ The mode of delivery should be selected based on obstetrical needs, as well as the mother's condition, since, as mentioned above,

no method of delivery is associated with a higher mortality.

Caesarean section avoids the haemodynamic fluctuations associated with a long, painful labour, which could result in myocardial ischaemia and cardiac decompensation. Vaginal delivery eliminates the potential risks associated with anaesthesia, as well as with surgery-induced haemodynamic fluctuations. It also reduces the total blood loss, as well as the risk of infection and respiratory complications.⁶ Techniques such as placing the patient in the left lateral position could be employed to optimise cardiac output while sustaining adequate placental perfusion.⁸ Shortening the second stage of labour with instrumental delivery could reduce maternal cardiac straining. If the patient has an ejection fraction of at least 40%, limited pushing is likely to be manageable.⁴⁶ Oxytocin infusions should be avoided to prevent induction of coronary spasm. Intravenous nitroglycerin, beta-blockers or calcium channel blockers may be administered for the prevention of labour-induced myocardial ischaemia.⁶

When adequate measures to lessen cardiac workload and oxygen demand are taken, most AMI patients are likely to tolerate vaginal delivery. Caesarean section should only be considered for patients who are haemodynamically unstable.⁷

Conclusion

In practice, the occurrence of AMI in pregnancy remains a rare event. Despite this situation, it is essential to maintain an adequate level of suspicion for the condition in light of the devastating long-term loss of cardiac function associated with delayed intervention. This review serves to provide a better understanding of the available diagnostic modalities, and the interventional and pharmacological treatment options specifically in the management of pregnant patients with AMI, so as to improve overall care provision and more importantly, ensure both maternal and fetal survival and well-being.

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