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Coronary Artery Disease and Pregnancy

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1. Introduction

Although an acute coronary syndrome (ACS) in women of childbearing age is rare, consequences are considerable, especially in pregnant women. In this chapter we will give an overview of the current literature regarding pregnancy and ACS. Acute coronary syndrome prior to pregnancy, acute coronary syndrome in the antepartum, peripartum and post partum period and heart failure during pregnancy will be described using patient cases, followed by an overview of literature and recommendations. Epidemiology, pathophysiology, counselling, use of medication, treatment possibilities, delivery, maternal and fetal outcome will be discussed.

2. Epidemiology

Acute coronary syndrome is rare in women of childbearing age (16 to 45 years of age). During these years pregnancy has shown to increase the risk of ACS three- to fourfold. (James et al., 2006) Between 1991-2000 the overall incidence of pregnancy related acute coronary syndrome was reported 2,7 per 100.000 deliveries. (Ladner et al., 2005) A decade later James published on risk factors of ACS during pregnancy in a population based study in the United States, he reported an incidence of 6,2 per 100.000 deliveries between 2000-2002. (James et al., 2006) The higher incidence can be explained by three causes: First of all with the improved diagnostic tests, especially troponin assessment, more women with acute chest pain have been diagnosed with ACS; secondly, an increase of known cardiovascular risk factors is seen in the pregnant population; and finally, maternal age increased in the western world. (Ventura., 2004)

Cardiovascular risk factors specific for ACS during pregnancy are very similar to the risk factors of non-pregnant patients. The main risk factors for ACS in women are smoking, lipid metabolism disorders, hypertension and diabetes. But in pregnant patients also thrombophilia and anaemia are risk factors for ACS. In the last decades lifestyle has changed in the western world. (Ogden et al., 2006) As a consequence of high calorie intake and little exercise the incidence of obesity and diabetes has increased drastically. (Cecchine et al., 2010)

In addition to cardiovascular risk factors, a few obstetric risk factors have been discovered. The most important being multiparity, but also a history of preeclampsia, post-partum

haemorrhage, transfusions and post-partum infections are risk factors for ACS during pregnancy. (Ladner et al., 2005) In addition, obstetric complications may elevate the risk of developing ACS later in life. Still birth, preeclampsia and recurrent miscarriage are a risk factor for ACS later in life in the general population. Endothelial dysfunction is hypothesised to be the link between hypertension in the pregnancy and cardiovascular disease later in life. (Pina, 2011)

Maternal age is one of the most important risk factor for ACS during pregnancy. Over the age of 30 women have an odds ratio of 9.5. This is even higher in women over 40, with an odds ratio of 31.6. (James et al., 2006) There is a continuing trend of childbearing at older ages, caused by carrier choices of highly educated women. The advances in reproductive technology enable many older women to conceive, leading to more women with a high risk for ACS during pregnancy. Therefore it may be expected that the incidence of ACS during pregnancy will increase further in the coming years.

3. Changes during pregnancy

Knowledge of the normal physiological changes during pregnancy, labour and the postpartum period is essential for doctors looking after pregnant women with heart disease. In the following section we will give an overview of the most important physiological changes in pregnancy.

The majority of the cardiovascular changes occur in the first twenty weeks of gestation. The first hemodynamic change is a decline in total peripheral vascular resistance (TPVR) of 40-70%. The decline in TPVR is a response to circulating gestational hormones. The drop in TPVR results in a relatively underfilled vascular state reflected by a fall in blood pressure. The blood volume increases with 1-1,5 litre (30-50%) as a response to the low blood pressure. The increase in plasma volume is relatively higher than the increase in red blood cells resulting in a physiological haemodilution. The combined changes result in a fifty percent increase in circulating blood volume during pregnancy. (Robson et al., 1989)

Cardiac afterload decreases with the fall in TPVR and cardiac preload increases with the rise of blood volume. These changes result in an increase in cardiac output of 30-50% from the 20th week of gestation as shown in figure 1. During pregnancy heart rate increases by 10-20 beats per minute, this mainly happens in the third trimester. Pregnancy is associated with changes in cardiac structure secondary to the increase in cardiac output, with left ventricular dimensions increasing from between 10-30%; ejection fraction and fractional shortening also increase. (Hunter & Robson, 1992)

The vascular system changes with the increase in stroke volume. Arterial stiffness decreases during the first trimester, but slightly rises from the second trimester and vascular distensibility is increased. (Ulusoy et al., 2006) These changes are partially mediated by gestational hormones, for example estrogen has favourable effects on the endothelium and vascular smooth muscle cells and increases vasodilatation (Mendelsohn & Karas, 1999), but progestins reduce estradiol-induced endothelium-mediated vascular relaxation. (Skafar et al., 1997)

Delivery increases the stroke volume by 20%, which contributes to the 25% increase in cardiac output. This is initiated by the greater maternal oxygen consumption caused by the

increase in uterine contractions in combination with maternal stress and pain, which in turn stimulates higher epinephrine levels.

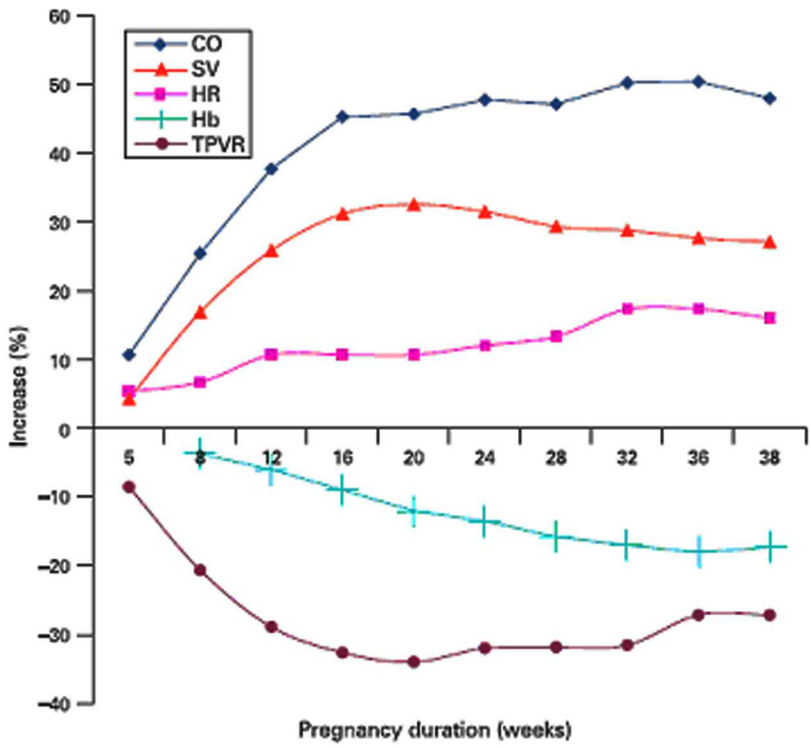

Fig. 1. Hemodynamic changes in the normal pregnancy: CO cardiac output, SV stroke volume, HR heart rate, Hb haemoglobin concentration and TPVR total peripheral vascular resistance. Reproduced from: "Karamermer Y, Roos-Hesselink JW. Pregnancy and adult congenital heart disease. Expert Rev Cardiovasc Ther 2007; 5: 859-869" with permission of Expert Reviews Ltd .

Major hemodynamic changes also occur during the puerperium, (from birth until 6 to 8 weeks after delivery). Decompression of the inferior cava and the return of uterine blood to the circulation (auto-transfusion) cause a period of overfilling. In women with impaired cardiac function this may result in cardiac decompensation. All gestational hemodynamic changes return to prepregnancy levels 3-12 months after pregnancy.

Pregnancy is a hypercoagulable state, probably an evolutionary adaptation to reduce the risk of severe haemorrhage after labour. There is a decrease in releasable tissue plasminogen activator (tPA), an increase in fast-acting tPA inhibitor and an increase in factors V, VII, VIII, IX, X, XII and von Willebrand factor. (Fletcher et al., 1979) Protein S is increased throughout pregnancy, while increased resistance to activated protein C is only seen during the second and third trimesters. (Coolman et al., 2006) The hypercoagulable state is partially reversed

by haemodilution and the activation of the fibrinolytic system. During delivery the placenta and myometrium release tPA inhibitors further increasing the hypercoagulable state (Yoshima et al., 1992); but by around 6 weeks after pregnancy the coagulation and fibrinolytic systems return to normal.

In summary pregnancy is a hypercoagulable state and an increase of 30-50% in cardiac output is seen as a result of decrease of vascular resistance and increased blood volume, stroke volume and heart rate.

4. Medication during pregnancy

The food and drug administration (FDA) made a classification system for the use of drugs in pregnant women:

Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

In table 1 an oversight is given on the safety during pregnancy and breast feeding of drugs which are commonly prescribed by cardiologist.

Medication	**Indication**	**FDA**	**Safe during pregnancy**	**Extra information**	**Safe during breast feeding**	**Extra information**
Atenolol	Hypertension, Arrhythmias,	D	Yes	IUGR and premature birth	No	A case report of adverse effects
Other beta blockers	Hypertension, Arrhythmias, Marfan disease ACS	C	Yes	Low birth weight, hypoglycemia and bradycardia in the fetus	Yes	Careful monitoring of the neonatal heart rate
ACE inhibitors	Hypertension, Heart failure	D	No	High incidence fetal death and fetotoxic effect: renal failure, renal dysplasia	Yes	Traces are detected in breast milk, fetal monitoring is advisable

ARB	Hypertension, Heart failure	D	No	High incidence fetal death and fetal anuria	No data	
Spironolactone	Hypertension, Heart failure	D	No	Potential anti-androgenic effects on the developing male fetus	Yes	
Thiazide diuretics	Hypertension, Heart failure	C	No	Hypovolemia can lead to reduced uterine perfusion	Yes	May suppress lactation
Loop diuretics	Hypertension, Heart failure	C	Yes	Hypovolemia can lead to reduced uterine perfusion	Yes	
Digoxin	Arrhythmias	C	Yes	No reports of congenital defects	Yes	Neonatal heart rate should be monitored after delivery
Nitrates	Hypertension, Angina	B	Yes	Careful titration is advised to avoid maternal hypotension	No data	
Calcium channel antagonists	Hypertension, Preeclampsia	C	Yes	Diltiazem: an increase in major birth defects have been reported	Yes	Excreted in breast milk
Statins	Lipid disorders	X	No	Animal studies demonstrated increased skeletal abnormalities, fetal and neonatal mortality	No	Probably appears in breast milk, there are some concerns with disruption of infant lipid metabolism
Aspirin	ACS, Arrhythmias	C	Yes	Low dose aspirin is safe	Yes	No adverse effects have been reported in low dose
Clopidogrel	ACS	B	No data	The benefits of using clopidogrel in some high risk pregnancies may outweigh the potential fetal risks	No	
LMWH and UFH	Arrhythmias Diminished ventricular function Thrombosis	C	Yes	Factor Xa should by measured to monitor the therapeutic levels of LMWH, which may fluctuate during pregnancy	Yes	

Table 1. Medication. ACE: Angiotensin-converting enzyme inhibitors. ARB: Angiotentin receptor antagonists.

5. Pre-existing coronary disease

A 39 year old woman was seen at the out patient clinic of a referral hospital for counselling. Three month earlier she had suffered a non ST elevation myocardial infarction (NSTEMI). On coronary angiogram (CAG) a thrombotic occlusion of an atherosclerotic lesion of the left coronary artery was seen and treated with a drug eluting stent. She had never been pregnant, had recently stopped smoking, was a non diabetic and normotensive. Her family history did not reveal any cardiovascular disease. Her left ventricular function was assessed with echocardiography and the estimated ejection fraction was 48%. She was prescribed aspirin, clopidogrel, simvastatine, perindopril and nifedipine.

5.1 Counselling prior to pregnancy

Ideally all women of reproductive age with cardiac disease should undergo thorough evaluation before becoming pregnant. This evaluation should focus on identifying and quantifying risk to the mother and the unborn child. During pre pregnancy counselling life expectancy and ethical aspects of parenthood should also be discussed. An exercise test and echocardiogram should be performed. Risk stratification is made to inform the patient of possible complications during pregnancy. The influence of pregnancy on the cardiac condition has to be considered, but also the cardiac condition may influence pregnancy outcome, especially the incidence of hypertension, preeclampsia, arrhythmias and thrombotic complications may be higher.

Low dose aspirin, beta blockade and nitrates should be continued during pregnancy. The safety of clopidogrel is unknown. In individual cases with recent drug eluting stent placement, continuation should be considered. ACE inhibitors and ARBs should be stopped in all patients or in the pre-conception clinic or immediately when pregnancy is diagnosed. Generally, statins should be stopped, however, in an individual patient with very high cholesterol, continuation may be considered.

5.2 Recurrence rate

Only limited data on recurrence risks have been published. Badui et al described 18 women in the literature with previous ACS, the mothers were 1 or 2 years after ACS and none of these patients had a recurrent ACS. (Badui & Enciso, 1996) One of the reasons for this lack of data is the fact that many women are advised against pregnancy after ACS. Doctors advise against pregnancy for a number of reasons, first it is suggested that the hypercoagulable state of pregnancy raises the chance of recurrence of thrombotic obstruction of the coronary arteries. Second the increase in left ventricular mass and heart rate lead to a high cardiac oxygen demand. The increased cardiac oxygen demand can lead to relative coronary flow mismatch in patients with pre-existing coronary artery disease. Finally, fear of complications may make them conservative.

The first patient was advised to wait for at least 3 more months before trying to become pregnant to make sure that she was cardiovascularly stable. Before conception perindopril, statin and clopidogrel are advised to be discontinued until after delivery. If pregnancy occurred, then the plan was made for outpatient review at 6, 12, 20 and 32 weeks of gestation.

5.3 Impaired left ventricular function

A 41 year old patient presented to the out patient department of a referral hospital with a desire for pregnancy. She had not been pregnant before. One year earlier she had suffered from a STEMI, CAG

at that time revealed atherosclerosis and thrombosis of the LAD and she was treated with thrombosuction and a drug-eluting stent. Six month after the ACS her left ventricular function was measured with echocardiography, ejection fraction was 35 %.

In 2000 Siu published predictors of cardiac events, mainly heart failure and arrhythmias. Prior cardiac events, left ventricular outflow obstruction, NYHA class > II, cyanosis and systemic ventricular dysfunction (ejection fraction >40%) were predictor for adverse maternal outcome. If one predictor was present, cardiac event rate was 27%. (Siu et al., 2001) However, the patient population consisted of patients with congenital or valvular disease and a diminished systemic ventricular function was mainly found in patients with transposition of the great arteries after atrial repair. To use these results to predict cardiac events in ischemic cardiomyopathy patients is at least questionable.

Generally women are advised against pregnancy if they have a left ventricular dysfunction with an ejection fraction under 40% and have a dilated left ventricle. (Prebitero et al., 2009) In a study on pregnancy in patients with dilated cardiomyopathy, an OR of 43 was found for moderate or severe left ventricular dysfunction and 39% of the pregnancies where complicated. (Grewal et al., 2009) Risk factors for adverse events were moderate (EF 30%-44%) or severe (EF<30%) ventricular dysfunction and NYHA class III or IV at baseline or prior cardiac event. Compared with non-pregnant patients with dilated cardiomyopathy, pregnant patients needed more medication and adverse cardiac events were more common. Pregnancy seemed to have a negative impact on the short-term clinical course for women with dilated cardiomyopathy. (Grewal et al., 2010) We need similar data for women with ischemic left ventricular dysfunction.

In case of heart failure during pregnancy diuretics are considered to be first choice, but diuretics could result in hypovolemia, leading to reduced uterine perfusion and so should be used with caution. Nitrates can be used safely and digoxin can be considered, especially if the patients has atrial fibrillation. Such patients should be treated in hospital and bed rest is advisable.

In the study of Grewal et al, the neonatal complication rate was high, especially in women with severe dilated cardiomyopathy, suggesting that in the context of severe left ventricular dysfunction, the heart may not be able perfuse the utero-placental circulation sufficiently. Therefore, regular growth scans to indentify fetal growth restriction and frequent review in a combined clinic with an obstetrician and cardiologist is advised. (Signore et al., 2010)

The second patient was informed about the high maternal and fetal risks associated with pregnancy in women with impaired left ventricular function as well as the lack of information on the recurrence rates of ACS during pregnancy. She decided not to take the risk.

5.4 Delivery

Planning delivery should be done in a multidisciplinary team consisting of an obstetrician, anaesthesiologist and cardiologist. The patient should be informed about the considerations prior to delivery, since patients preference has to be taken into account. Timing of delivery is individualized, according to the cardiac and obstetric status of the mother and fetal well being. In patients with heart failure delivery at 34 weeks can be considered to allow early optimisation of treatment modalities for the mother.

The mode of delivery depends on the maternal hemodynamic situation and obstetric factors. Women with adequate cardiac output may tolerate induction of labour and vaginal delivery. Vaginal delivery can lead to fluctuations in blood pressure, especially in prolonged labour. Assisted vaginal delivery (by vacuum or forceps extraction) is recommended in some women to avoid excessive maternal efforts and prolonged labour. (Roth & Elkayam, 2008) Adequate pain relief is very important, but epidural anaesthesia is contraindicated when the patient is on antithrombotic or anticoagulant treatment.

During caesarean section blood pressure can be controlled, stress and pain can be relieved and a stable environment can be created. However, caesarean section has been associated with a higher risk of venous thrombo-embolism, infection and peripartum haemorrhage. In some cases general anaesthesia will be necessary with some risk of complication. (Deneux-Tharax et al., 2006) In addition, blood loss during caesarean section has been shown to be greater than during vaginal delivery.

5.5 Post partum period

The volume shifts caused by auto-transfusion can be dangerous in patients with diminished left ventricular function. Close monitoring on a medium care unit may be advisable for the first 3 days after delivery. Early recognition of heart failure and immediate treatment with diuretics can be achieved by close monitoring of the patients and measurement of the central venous pressure. Some cardiologists advise prophylaxic diuretics in patients with severe systemic ventricular dysfunction. Ideally monitoring should be done in a unit with neonatal care, since early bonding of mother and child is very important. In patients with normal ventricular function after ACS prior to pregnancy close monitoring in-hospital for at least three days after delivery is advisable. The main risk during this period consists of thrombo-embolic events cause by the hypercoagulable state of pregnancy exacerbated by even higher tPA inhibitor levels immediately after delivery.

5.6 Breast feeding

The effects of breast feeding on maternal cardiovascular function are caused by circulating hormones. High levels of oxytocin circulate through the body. In the study of Mezzacappa cardiac output during breastfeeding was found to be higher than in bottle feeding mothers. They describe a decrease in heart rate and a slight increase in systolic blood pressure during the first minutes of breast feeding. (Mezzacappa et al., 2001) Light et al described a lower blood pressure in breast feeding mothers one hour after breast feeding. (Light et al., 2000) In the first weeks of breast feeding, women produce around 800 millilitres of milk daily. With the production of breast milk large volume shifts take place, these may cause a problem in patients with reduced left ventricular function.

The fluctuations in blood pressure may be harmful in severely symptomatic patients and bottle feeding should be considered. Lactation is also associated with a risk of bacteraemia secondary to mastitis.

6. Angina in the pregnant patient

A 41 year old patient presented to the emergency department with acute chest pain. There was a myocardial infarction at young age in her family history. She was 18 weeks pregnant with her first

child. She did not take any alcohol or medication during pregnancy. But she was continuing smoking during pregnancy. She had a blood pressure of 135/85mmHg, a pulse of 95 beats per minute and auscultation of the chest revealed normal breath sounds without rales. The ECG was normal. Transthoracic echocardiography revealed no wall abnormalities. Troponine levels were normal. During exercise testing she performed 92% of expected and during testing a down sloping ST depression of 2-3 mm was found in lead II, III and aVf.

6.1 Signs and symptoms

Evaluating chest pain in pregnant women can be challenging, since chest pain in pregnancy is common and can be caused by various conditions. Most often chest pain is caused by gastro-oesophageal reflux which is benign in most cases. Chest pain should never be ignored as it may also represent possible life threatening disease such as pericarditis, myocarditis, aortic dissection, hypertensive crisis, pulmonary thrombo-embolism or acute coronary syndrome. Urgent complete cardiac review is always appropriate if a pregnant woman presents with chest pain.

Physical examination can be misleading, hypotension and tachycardia are physiological responses to normal pregnancy (as describe in sub-chapter 3). In this case normal lung examination and oxygen saturation made pneumonic disease less likely, but pulmonary thrombo-embolism remained a possibility. Measuring blood pressure in both arms is important since aortic dissection is a part of the differential diagnosis.

6.2 Diagnostic testing

Criteria for ACS in pregnancy are the same as in non pregnant women, consisting of a combination of symptoms, ECG changes and positive cardiac markers. Normal diagnostic tests can be used in pregnancy, but outcome has to be evaluated against normal pregnancy values, since abnormal values can be normal in pregnancy. Table (2) gives a brief summary of the changes most often seen in diagnostic tests.

Diagnostic test	**Effect of normal pregnancy**
Electrocardiogram	Left axis deviation and Q waves in lead III and aVF, inverted T waves in lead III
Exercise test	Decreased exercise tolerance
Echocardiogram	Increase in left ventricular mass, mild mitral regurgitation
Serum creatinine kinase	Elevated during labour
Troponin	Not affected during normal pregnancy

Table 2. The changes in diagnostic tests in normal pregnancy.

The electrocardiogram (ECG) changes as a result of the upward shift of the diaphragm with the growing uterus. A left axis deviation with Q waves in lead III and aVF is seen in the third trimester. T waves can be inverted in lead III, V1 and V2. In case of a caesarean section with general anaesthesia ST depression is seen often. (Prebitero et al., 2009)

The use of echocardiography is safe in pregnancy because echocardiography does not involve radiation. Detection of wall motion abnormalities can be used as a sign of possible acute coronary syndrome. In normal patients exercise tests are used to confirm the diagnosis

of coronary artery disease or after ACS to establish exercise capacity and exclude residual ischemia. In pregnancy it is advisable to use submaximal exercise (<70% of the maximum predicted heart rate) testing, since fetal bradycardia and absence of body movement have been described after heavy maternal exercise. (Elkayam et al., 1998) There is no evidence of increased risk of spontaneous abortion after exercise testing.

Biomarkers are used in the cardiological practice to confirm the diagnosis of acute coronary syndrome. During labour elevated creatinine kinase (CK) and CK MB are found due to uterine contractions. These levels normalize during the second day after labour. (Poh & Lee, 2010) Troponine I is not elevated in normal pregnancy, as a result troponin I is the recommended biomarker in pregnancy. However, troponin I serum levels can be elevated in patients with pre-eclampsia and hypertensive crisis. It is not totally clear whether this is a sign of cardiac ischemia in these partients.

Chest radiography is only used in pregnancy during emergency medical conditions. If proper shielding of the abdomen is used radiation of chest radiography is considered relatively safe (especially in the third trimester). (Hirshfeld et al., 2005)

6.3 Treatment choices in patients with chest pain

The choice of treatment is dependent on the diagnosis and the presence of ECG changes. In patients without any ECG changes, other causes of chest pain should be considered; troponin should be measured in all patients. In women with ACS, conservative treatment (bed)rest, nitrates and beta blockers is advised. In NSTEMI patients a careful assessment should be made. Troponin levels, hemodynamic state and relief of pain determine whether the patient should have a coronary angiogram. A coronary angiogram will reveal the origin of the problem, eg dissection, thrombus. But a conservative treatment may be best in the majority of patients. STEMI patients need immediate treatment and PCI as first choice treatment should be performed as soon as possible.

In patients with angina catherization should be considered. If proper shielding of the abdomen is used, radiation dose is low. An interventional procedure may result in a fetal exposure of <1 rad. Termination of pregnancy is generally not recommended, although it may be considered when the fetal radiation dose exceeds 10 rad. (Roth & Elkayam, 2008)

The patient became pain free after the use of nitroglycerine and was treated with beta blockade. Further pregnancy was uneventful and she delivered a healthy baby boy at 39 weeks after spontaneous vaginal delivery.

7. Acute coronary syndrome during the first or second trimester of pregnancy

A 38 year old patient came to the emergency department with acute chest pain. She was 25 weeks pregnant with her second child. The first pregnancy was complicated by preeclampsia. She has no dyspnoea, syncope, cough or fever. She did not smoke nor use any alcohol or medication during pregnancy. She had a blood pressure of 100/60mmHg, a pulse of 105 beats per minute and was tachypnoeic at 24 breath per minute. Oxygen saturation by pulse oximetry was 99%. Auscultation of the chest revealed normal breath sounds without rales. The heart sounds were normal, no murmur or gallop was heard. Abdominal examination did not reveal any abnormalities and there was no oedema.

The results of the ECG were consistent with STEMI of the anterior wall with ST elevation in V1-V3 and ST depression in lead II, III and aVF. Transthoracic echocardiography revealed a dyskenetic left anterior wall. The patient underwent coronary angiography three hours after onset of complaints and revealed a thrombotic obstruction of the left main artery with TIMI flow grade 1.

7.1 Cause of ACS

ACS in pregnancy has other causes than in the non-pregnant state. In the review of Roth and Elkayam only 40% (41 of the 103 patients) was caused by coronary artery stenosis. (Roth & Elkayam, 2008) Other causes were thrombus in 8%, coronary artery dissection in 27%, vascular spasm in 2% and normal coronary arteries were found in 13% of the patients. (Roth & Elkayam, 2008) ACS has been noted to occur more often in the anterior wall. (Iadanzo et al., 2007)

Coronary dissection is very rare in the non-pregnant population, but more frequently seen in pregnancy (27%) especially in patients with ACS in the peripartum period (50%). Excess of progesterone is thought to be one of the causes of coronary dissection, since it causes biochemical changes of collagen in the coronary vessel wall and weakens the media. The impact of increased blood volume and cardiac output may cause extra wall stress which is hypothesised to be an additional factor (Roth & Elkayam, 2008) also autoimmune conditions, such as systemic lupus erythromatosis and anti-phospolipid-antibody syndrome, have been linked to coronary artery dissection. (Nallamonthu et al., 2005)

Normal coronary artery morphology is found in 13% of patients, perhaps caused by transient coronary spasm or thrombus. Vascular spasm was found in 2% of the case reports described by Roth. (Roth & Elkayam, 2008) Spasm might be caused by enhanced vascular reactivity to angiotensin II, norepinephrine and endothelial dysfunction. (Nisell et al., 1985) Vascular spasm in combination with the hypercoagulable state of pregnancy may cause coronary thrombus leading to acute coronary syndrome. Patients who continue to smoke during pregnancy have an increased risk of coronary artery thrombosis due to enhanced platelet aggregability in smokers.

7.2 Treatment

When tests have confirmed the diagnosis of acute coronary syndrome, it is important to make a treatment plan and inform the patient about maternal and fetal risks of all possible treatment options.

There is only limited information available on PCI during pregnancy. Nowadays pregnancy is not a contraindication for PCI and since PCI is the primary treatment for non-pregnant STEMI patients, more and more cases of stenting during pregnancy are published. With PCI as a treatment modality during pregnancy mortality of ACS has dropped. James described PCI in 135 patients (of which 127 were with stenting), but no information on outcome was published. In the first review of Roth and Elkayam in 1996 only 3 of the 125 patients had PCI. (Roth & Elkayam, 1996) Whereas in their second review 38 patients had a PCI, all with bare metal stenting. In this review 92 patients had a coronary angiogram (of which 43 were postpartum). After PCI one patient needed CABG because of extensive coronary dissection. (Roth & Elkayam, 2008)

The preference for bare metal stenting is caused by the requirement of dual anti-platelet treatment around the delivery and the lack of experience. The use of drug eluting stents has been described in 2 case reports. One patient with STEMI at 27 weeks of gestation received a drug eluting stent, she delivered a healthy child by elective caesarean section at 35 weeks. Antiplatelet therapy was continued during delivery. However, post partum she had a haemoglobin drop of 5 g/dL and needed a blood transfusion. (Al-Aqeedi & Al-Nabti, 2008)

Since pregnant women are excluded from most clinical trials no randomised controlled trials have been preformed on thrombolytic therapy, PCI or CABG in the pregnancy. However, thrombotic therapy is considered to be relatively contraindicated in patient with acute coronary syndrome because of bleeding complications. In stroke, pulmonary embolism and mechanical heart valve thrombosis there is some clinical experience with several strategies such as tPA, urokinase and streptokinase. This medication does not cross the utero-placental barrier. (Leohardt et al., 2006) Maternal and fetal outcomes were favourable, but complications, as maternal haemorrhage, fetal loss, abruption placenta, preterm delivery and post partum haemorrhage have been reported in up to 10% and maternal mortality was 1.2 %. (Turrentine et al., 1995) The risk of haemorrhage is highest in the peripartum period (Murugappan et al,. 2006) and given the high incidence of coronary dissection in pregnancy, the use of thrombolytic therapy could lead to haemorrhage and further progression of the dissection. Thrombolytic therapy should be considered in case of thrombosis and possibly when primary PCI is not available. (Roth & Elkayam, 2008)

Very limited data is available on coronary artery bypass grafting (CABG) during pregnancy, no conclusion on safety for the mother or the unborn child can be made. In normal non-pregnant patients with ACS CABG is used when multiple vessels or the left main coronary artery are involved. (Nallamonthu et al., 2005) In the data by James 61 women underwent CABG, but there was no specific data on outcome in these patients. In the case study of Roth and Elkayam 10 patients were described who underwent CABG, of which were 7 due to coronary artery dissection, (Roth & Elkayam, 2008) in these cases one fetal death and one late maternal death were reported. (Garvey, 1998) Large differences in maternal mortality rates were found for ACS in pregnant women in the last decades, ranging from 5,1%(James et al., 2006) to 38%. (Koul et al., 2001) The decline in mortality rate could be explained by the detection of ACS in less severely ill patients as well as improvement in treatment options in the last decades. (Roth & Elkayam, 2008)

7.3 Delivery

Delivery should be postponed if possible for at least 2 or 3 weeks after the ACS to allow adequate healing. (Prebitero et al., 2009) Anti-platelet therapy should be continued in case of recent stent implantation, low dose aspirin is also advisable in patient with other forms of coronary artery disease, but doctors should be aware of a higher risk of post partum haemorrhage. Vaginal delivery with shortened second stage of labour and adequate pain relief can be safe. Caesarean section is the preferred mode of delivery in patients with cardiac instability.

7.4 Post partum period

Close monitoring on a medium care unit may be advisable for the first 3 days after delivery. With anticoagulant and anti-platelet therapy given during pregnancy, special attention

should be paid to major haemorrhage. Ideally monitoring should be done in a unit with neonatal monitoring.

In our patient thrombosuction was performed and a bare metal stent was inserted. She was treated with heparin for 24 hours and received aspirin, beta blockade and nitrates during the remainder of the pregnancy. Clopidogrel was not given during pregnancy. She delivered 12 weeks later at 37 weeks by the assisted vaginal route. Epidural pain medication was given to limit pain and stress. A healthy girl (3045 gram) was born. After delivery she was treated with a statin and an ACE inhibitor.

8. Acute coronary syndrome in the third trimester

A 34 year old patient presented to the emergency department with acute chest pain. She was 36 weeks pregnant. The results of the ECG were consistent with acute myocardial infarction of the anterior wall. The patient underwent cardiac catheterisation two hours after onset of symptoms, coronary angiogram revealed a coronary artery dissection of the left anterior descending artery.

8.1 ACS in the third trimester

Coronary artery disease in the peripartum period differs from ACS in the antepartum period in terms of coronary abnormality, cause, treatment options and mortality rate. Coronary dissection was the primary cause of coronary artery disease in the peripartum period (50%) and more commonly in post-partum period (34%) compared to antepartum period (11%). This is probably the result of hormonal changes and the stress on the walls of the coronary arteries during labour. In some cases an association with the administration of the medicine terbutaline (a medicine used to stop early uterine contractions) was found.

The mortality rate in patients with ACS in the peripartum period is 18% versus 9% in the antepartum and postpartum period. (Roth & Elkayam, 2008) This was also shown in the study of Ladner, who reprted a mortality rate of 19% in the peripartum period. No specific cause for the high maternal mortality in the peripartum period was given. Different causes for high mortality rates could be hypothesized. The symptoms could be misinterpreted during delivery and both patient delay as well as doctor delay could lead to late recognition of ACS. A second reason could be the complication and mortality rate is relatively higher in patients with coronary artery dissection compared to coronary arthrosclerosis. (Basso et al., 1996) A third reason is that major haemorrhage may result from anti-thrombotic therapy. And finally, cardiac failure after delivery caused by autotransfusion with stressing the injured myocytes could lead to maternal death. Moran et al described myocardial ischemia in normal patients during elective caesarean section. By using Holter monitoring and analysis of troponin I he showed ischemic changes in 8% of the patients and 81% had ST segment changes. None of these patients needed any form of treatment. This study showed that even normal healthy women experience ECG changes which may reflect some myocardial ischemia during caesarean section. (Moran et al., 2001)

8.2 Treatment in peripartum period

Treatment options are limited in the peripartum period, since anticoagulation and antithrombotic therapy should be discontinued 24 hours prior to delivery to avoid major bleeding complications. PCI is the treatment of choice in patients with STEMI. As pregnant patients have a substantial higher chance of coronary dissection and a high maternal

mortality, PCI should be preformed in a larger referral centre with cardiothoracic surgery standby.

8.3 Delivery and postpartum period

Caesarean section prior to CAG is a possible strategy in patients with ACS diagnosed after 32 to 34 weeks of gestation. (Hameed & Sklansky, 2007) At this point fetal outcome is generally good and maternal benefit is high because of reduced stress during the last weeks of pregnancy and the use of antithrombotic therapy after PCI. Close monitoring on a medium care unit may be advisable for the first 3 days after delivery.

It is very important to consider ACS in peripartum patients with acute chest pain. Early recognition and diagnosis can save lives. A healthy baby girl was born at 39 weeks. The patient stayed in the hospital until 3 days after delivery.

9. Acute coronary syndrome in the postpartum period

After delivery of a healthy girl, a 31 year old patient was treated with bromocriptine to suppress lactation. Four days after delivery she presented to the emergency department with acute severe chest pain. The ECG showed an acute anterior myocardial infarction with ST elevation in V1-V3. Coronary angiography revealed a dissection of the left anterior descending artery and she was treated with bare metal stenting. She remained in the hospital for 3 more days and was treated with betacblockade, aspirin and clopidogrel.

9.1 Post partum ACS

Coronary dissection was found in 34% of the coronary angiograms and this was the most frequent cause of ACS in the postpartum period as it was in the peripartum period. Postpartum, some cases of ACS are associated with the administration of medicine. There are nineteen cases reported of ACS after the administration of bromocriptine, which is used to suppress lactation. Bromocriptine has dopaminergic agonist properties and may have vasopastic effects which can lead to thrombus formation. (Hopp et al., 1996) This medication has been taken off the market as a lactation suppressant because of these reports. The second medicine associated with ACS is ergotamine, which is commonly used to prevent post partum haemorrhage by stimulating uterine contractions. Ergot derivatives are known to reduce the capacity of the intravascular lumen by 15-20% in normal coronary arteries. Eight cases of postpartum myocardial infarction have been described. (Eom, 2005) It is important to consider ACS as a possible complication before administration of this medicine in high risk patients (high age and cardiovascular risk factors).

9.2 Treatment post partum ACS

After delivery the treatment options are greater. Only maternal health determines the treatment, as is usual in "normal" cardiac patients PCI is the treatment of choice. Drug eluting stents can be used now. However, the uterine vascular bed has to be considered a large wound until one week after delivery.

Bromocriptin, ergotamine and terbutaline have been associated with post partum ACS.

10. Neonatal outcome

Neonatal outcome is strongly correlated with maternal outcome. In the first report of Roth and Elkayam 16 fetal deaths in 125 pregnancies (13%) were reported, of which 10 (62%) associated with maternal death. (Roth & Elkayam, 1996) In the second report only a 9% fetal death rate was reported, of which two were elective terminations because of potential drug teratogenicity. (Roth & Elkayam, 2008) Ladner et al described low birth weight and prematurity in patients with antenatal ACS and a 10% fetal death rate was reported in patients with intrapartum ACS. (Ladner et al., 2005)

Fetal mortality is high in cardiac surgery during pregnancy with rates as high as 30% (Parry & Westaby, 1996). Factors which predicted an adverse fetal outcome were severity of maternal illness, total operative time, emergency surgery, reoperation, advanced maternal age and gestational age. (Barth, 2009)

During cardiopulmonary bypass, continuous fetal monitoring should be performed. The fetal heart rate can be used as an indicator of placental perfusion to guide bypass pump flow. (Chandrasekhar et al., 2009) Uterine monitoring is essential to allow early control of these contractions as they are associated with significant fetal loss. (Parry & Westaby, 1996) Deleterious effects on the fetus are thought to be related to hypotension, hypothermia, embolic complications and inadequate placental flow. Caesarean delivery prior to CABG or PCI can be considered from 28 weeks of gestation. (Barth, 2009)

Fetal mortality in PCI compared to CABG is low. Proper shielding of the abdomen is essential in fetal protection. (Roth & Elkayam, 2008) Where chest radiography is considered relatively safe (especially in the third trimester). Cardiac catherization and intervention procedures may result higher fetal exposure with some chance of fetal abnormalities, especially when used in the first trimester.

11. Conclusion

Acute coronary syndrome in women of childbearing age is rare, but pregnancy has shown to increase the risk of ACS 3- to 4-fold. (James et al., 2006) The overall incidence of pregnancy related acute coronary syndrome was reported between 2.7 and 6.2 per 100,000 deliveries and seems to have been increased in the last decade. Maternal age is one of the most important risk factor for ACS during pregnancy. Mortality rate has declined over the last decades from 19% in 1922-1994 to 5,1% in 2001-2002, probably as a result of improvement in treatment modalities.

Evaluating chest pain in pregnant woman can be challenging, since chest pain in pregnancy is common and may be caused by benign as well as life threatening diseases. Physical examination and diagnostic tests can be misleading, since normal pregnancy changes the results of these tests. Coronary artery disease in pregnancy has different causes than seen in non-pregnant women, artherosclerosis is less frequently found, whereas thrombus, dissection, spasm and normal coronary arteries are more often reported. In table 3 an overview is given of the management and outcome in the different patient groups.

Not all medication is safe during pregnancy, fetal and maternal risks have to be taken into account when medication is given. Pregnancy is not a contraindication for PCI anymore and this is probably the main reason maternal mortality has fallen recently. Very limited data is

Patient group	Counselling	First treatment choice	Maternal outcome	Fetal outcome
Previous ACS	Check medication	Medication	No data	No data
ACS and impaired LV function	Risk stratification	Medication	No data, high risk	No data
ACS antepartum	Not applicable	PCI	9 % mortality	11 % mortality
ACS peripartum	Not applicable	PCI	18 % mortality	5 % mortality
ACS postpartum	Not applicable	PCI	9 % mortality	No fetal mortality

Table 3 Oversight of different patient groups in ACS in pregnancy.

available on CABG during pregnancy, and it should only be considered when all other therapeutic options have failed. Neonatal outcome is strongly correlated with maternal outcome; reported mortality was highest in the peripartum period.

The delivery should be planned by a multidisciplinary team consisting of an obstetrician, anaesthesiologist and cardiologist. Women with adequate cardiac output may tolerate induction of labour and vaginal delivery, but it is possible to create a potentially more stable environment during a caesarean section in high risk patients. Close monitoring in-hospital for at least one week after delivery is advised for patients with ACS in pregnancy.

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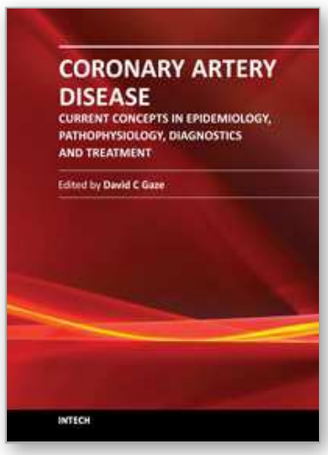

Coronary Artery Disease - Current Concepts in Epidemiology, Pathophysiology, Diagnostics and Treatment

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Cardiovascular disease is ranked as the leading cause of death world wide, responsible for 17.1 million deaths globally each year. Such numbers are often difficult to comprehend. Heart disease kills one person every 34 seconds in the USA alone. Although the leading killer, the incidence of cardiovascular disease has declined in recent years due to a better understanding of the pathology, implementation of lipid lowering therapy new drug regimens including low molecular weight heparin and antiplatelet drugs such as glycoprotein IIb/IIIa receptor inhibitors and acute surgical intervention. The disease burden has a great financial impact on global healthcare systems and major economic consequences for world economies. This text aims to deliver the current understanding of coronary artery disease and is split into three main sections: 1. Epidemiology and pathophysiology of coronary artery disease 2. Coronary artery disease diagnostics and 3. Treatment regimens for coronary artery disease

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