A review of cardiovascular complications of pregnancy

Przegląd chorób układu krążenia w ciąży

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Abstract

With recent advances in prenatal care, the incidence of direct causes of maternal death has declined and indirect causes have gained significant importance. Thromboembolism, hypertension and cardiovascular diseases are the most common indirect causes of maternal death. Acute myocardial infarction, stroke, venous thromboembolism, peripartum cardiomyopathy, aortic dissection and amniotic fluid emboli are responsible for the majority of the maternal deaths from cardiovascular causes.

The issue of pregnancy of heart transplant – and Turner syndrome – patients requires extensive research. Obstetricians should possess good knowledge of cardiovascular complications of pregnancy because a high index of suspicion and early diagnosis, together with timely and appropriate interventions may save the life of the fetus and the mother.

Key words: pregnancy / complication - cardiovascular /

Streszczenie


Słowa kluczowe: ciąża / powiklania ciąży - choroby układu krążenia /
With recent advances in prenatal care, the incidence of direct maternal deaths (due to obstetric complications or interventions during pregnancy) has declined and indirect causes (due to unrelated diseases aggravated by physiological effects of pregnancy) have gained more importance. The leading indirect causes of maternal death are pulmonary embolism and cardiac diseases. Successful surgical management of congenital cardiac anomalies opened a new era in the management of pregnancies of these women. Pregnancy in patients with cardiac diseases is a separate issue which the following article does not attempt to describe.

In this review we aimed at presenting some information which might be useful for obstetricians concerning cardiovascular complications of patients who are not considered to be at risk. However, we also included two more topics on patients who are commonly known to be at risk: pregnancies in heart transplant and Turner syndrome patients.

**Acute myocardial infarction**

During pregnancy the incidence of acute myocardial infarction (MI) increases 3–4 fold and is 3–10 per 100,000 deliveries [1]. Acute MI is usually encountered during the third trimester or the puerperium and the average age is 32 years [2]. The mortality of acute MI in pregnancy is 5.1%-7.3%, and rises to 45% during the first two weeks of puerperium [3].

The fact that pregnancy constitutes a risk factor for developing hypertension, ischemic and degenerative heart diseases and cerebrovascular diseases is suggested by vital statistics data collected in England and Wales which showed that parous women had a higher mortality from hypertension, ischemic and degenerative heart diseases and cerebrovascular diseases than nulliparous women [4].

Risk factors for acute MI include chronic hypertension, pregestational diabetes, smoking, thrombophilia, advanced maternal age, preeclampsia, postpartum hemorrhage, postpartum infection, multiparity and genetic basis [5,6].

British Heart Foundation Study revealed the genetic basis for coronary artery disease and MI, stating that the fact of having first degree relatives who had acute MI before they were 55 constitutes a risk factor for MI [5]. The programming of genetic basis for vascular heart diseases starts in utero. Lawrence et al. reported that prenatal nicotine exposure causes in utero programming of the gene expression patterns in the developing rat heart and increases heart susceptibility to ischemia reperfusion injury in adult offspring [6].

Factor V Leiden heterozygosity or activated protein C resistance, when combined with smoking, increase the myocardial infarction rate in young obese women [7].

Acute MI outside pregnancy is usually associated with atherosclerotic disease. However, only 10% of pregnant women who experience acute MI have in fact atherosclerotic disease. The most common cause of acute MI during pregnancy is spontaneous coronary artery dissection [8]. Changes in the collagenolytic system and shear stress of pregnancy predispose coronary vessels to dissection and initiate an intimal rupture with subsequent hemorrhage into the vessel wall. Coronary artery spasm may lead to dissection. Movsesian and Wray suggested that after MI, the coronary arteries which look anatomically normal in angiography may in fact be healed dissections [9].

Certain drugs should be used with caution during pregnancy. Intravenous ergometrine reduces the coronary artery lumen by 20% and is especially dangerous for hypertensive patients [10]. Nifedipine causes sudden hypotension and reflex tachycardia [11]. When Calcium channel blockers were used in hypertensive and diabetic patients, they have proven to increase the fatal and non-fatal MI [12]. Postpartum MI associated with the use of oxytocin and bromocriptine has also been reported [11, 13].

Acute MI can be associated with severe obstetric hemorrhage. This may occur due to a hypercoagulability, response to blood loss, transfusion or methylergonovine maleate used administered to treat uterine atony [14,15].

The diagnosis of acute MI may be challenging during pregnancy because chest pain, dyspnea and exercise intolerance are then common. ECG is abnormal in 97% of the cases but only 40-60% of them follow a classic pattern. If the ECG is normal and there is a high suspicion of MI, ECG should be repeated every 5-10 minutes [16]. Serum markers of MI may also be increased. Troponin I is unaffected by pregnancy, labor and delivery therefore it is the only test which can be used reliably at that time.

After MI the patient should be monitored in an intensive care unit that can provide both cardiac and obstetric care. Blood pressure, tachycardia and arrhythmias should be controlled. Nitrates, beta-blockers, and calcium channel blockers have been reported to be safe during pregnancy.

When the diagnosis is made, cardiac catheterization should not be delayed. However, usually this method is not used out of a concern for the fetus and possible consequences of radiation exposure. Thus, medical treatment is preferred instead.

If a patient is not in labor and there is no dissection, thrombolytic treatment should be administered. Thrombolytic treatment should be withheld in later stages of pregnancy and 10 days after the labor. If thrombolytic treatment is administered in the first hour following MI the mortality is reduced by 50%. With every hour of delay the mortality rises by 1.6 per 1000 [17]. Primary stenting can be done but there is scarce data to recommend it. Risks should be weighed against possible benefits [18].

After the infarction aspirin alone reduces the mortality by 32% [18]. Beta blockers treat the arrhythmias and decrease the risk of cardiac rupture. ACE inhibitors are teratogenic and prolonged β-blocker use may cause intrauterine growth restriction so they should be used with caution in pregnant patients [19].

Following hemodynamic stabilization, the delivery should be delayed at least two weeks because the mortality is highest in the next two weeks following the MI.

Whether or not patients who had MI should become pregnant again remains a separate issue. Clearly, the probable outcome after myocardial infarction can be assessed only in individual cases. In each case, residual left ventricular function, severity of the underlying coronary disease and the interval between myocardial infarction and pregnancy should be considered. Among the 18 reported cases of pregnancy following prior myocardial infarction, no maternal deaths were documented [19].

**Stroke**

Stroke is an uncommon but potentially debilitating and even fatal complication of pregnancy. It accounts for 12% of maternal...
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deads and 8-15% of the stroke patients die [20]. Survivors may suffer permanent disability [21]. The risk of stroke in pregnant patients increases 3 times and the incidence of stroke is 3.42 per 100000 deliveries [22]. Ischemic and hemorrhagic strokes are seen in approximately equal proportions [23]. Eleven percent of strokes happen in the antepartum period and the remaining part in the intrapartum and postpartum periods equally [24].

Stroke usually appears in healthy women. Only one third of the cases have a risk factor. The reported risk factors are: over 35 years of age, black ethnicity, hypertension, smoking, diabetes, cesarean delivery, multiple gestation, greater parity, preeclampsia, eclampsia, DIC, thrombophilia, migraine headaches, systemic lupus erythematosus and heart disease.

During pregnancy most of the ischemic strokes are secondary to arterial occlusion. Hemorrhagic stroke is associated with preeclampsia, eclampsia, cerebral venous thrombosis (CVT), subarachnoid hemorrhage (SAH) and primary intracerebral hemorrhage (ICH).

The exact pathogenesis is not known, but high blood pressure is not the sole factor responsible for a stroke. Recent analysis has indicated that most patients never reach the diastolic blood pressure threshold of 105mmHg before cerebral hemorrhage occurs [25]. The most probable cause is endothelial dysfunction, which is common in both preeclampsia and atherosclerosis. Loss of cerebral autoregulation, activation of coagulation cascade and microthrombi formation, hemococoncentration as a result of loss of fluid to third space and hypoperfusion are other suggested mechanisms.

SAH is the third non-obstetric cause of maternal death. It is usually secondary to aneurismal rupture. Loss of elastic fiber alignment weakens the vessel wall and hemodynamic changes of pregnancy such as increased blood volume and cardiac output place further stress on the weakened vessel wall predisposing to aneurismal rupture [26]. Surgical treatment during pregnancy improves the maternal and fetal outcomes [27].

The treatment of stroke in puerperium is the same as that of non-pregnant patients. When pregnancy is still ongoing, treatment of stroke is limited. Thrombolytic therapy has been linked to abortion and hemorrhage and puts the fetus at risk for preterm labor and demise. However, considering that approximately half of the patients are left with a residual neurological deficit, the risk of thrombolytic therapy weighs against its benefit [28].

Preeclampsia, myocardial infarction and stroke

Endothelial dysfunction, platelet aggregation and hypertension predispose especially the preeclamptic patients to acute MI [3]. Hannaford et al. reported that compared with parous women with no history of toxemia, those who had experienced toxemia had a significantly increased risk for hypertensive diseases, acute myocardial infarction, chronic ischemic heart disease, angina pectoris, all ischemic heart diseases, and venous thromboembolism. The rates for all cerebrovascular disease and peripheral vascular disease were also increased but not significantly (Table 1). Royal College of General Practitioners’ (RCGP) oral contraception study, and Rosenberg et al. found increased cardiovascular risk for women with history of preeclampsia. (30,31). The World Health Organization study of cardiovascular diseases in young women also found that a history of preeclampsia increased a woman’s chances of experiencing a venous thromboembolic event) or hemorrhagic stroke [32, 33].

The risk continues for lifelong. Therefore patients with history of preeclampsia should be followed up carefully, stop smoking, exercise regularly and have a healthy diet to minimize their cardiovascular risk. Further studies need to investigate the benefits of the change in the lifestyle.

Aortic aneurysm, dissection and pregnancy in Turner syndrome patients

Aortic dissection is rare in young adults and half of all aortic dissections in young women occur during pregnancy. Activation of collagenolytic system, remodeling of the large diameter collagen fibres to small ones, increased cardiac output, blood pressure and stress of labor damage the vessel wall. Patients with pre-existing collagen defects such as Marfan syndrome, Ehlers-Danlos syndrome, bicuspid aortic valve and coarctation of the aorta are especially prone to aortic dissection [34]. Although hypertension has not been definitely linked to the initiation of dissection, it is the major factor promoting the propagation.

The most prevalent symptom is knife-like or stabbing chest pain, usually of sudden onset. If migratory pain, following the path of dissection, deficits in peripheral pulses, chest pain and hypertension refractory continue despite treatment, it should raise the suspicion of aortic dissection. The diagnosis of aortic dissection is usually established with contrast-enhanced computed tomography (CT) or transesophageal echocardiography.

In cases of acute dissection reported fetal and maternal mortalities are 30% and 2-6% respectively. Rapid intervention is necessary because the mortality rate for untreated proximal aortic dissection increases by 1-3% per hour. Fatal complications include aortic rupture and occlusion of the coronary artery or severe aortic valve regurgitation as a result of proximal extension of the dissection [35].

Emergent surgery is required if the dissection is proximal to the origin of left subclavian artery. Medical treatment is preferred for the dissections distal to the left subclavian artery.

85 cases of aortic dissection in Turner syndrome patients have been reported so far [36]. Turner syndrome is associated with 100-fold increase in mortality during pregnancy and is a relative contraindication to pregnancy. The incidence of aortic dissection in patients with Turner syndrome increases from 1.4% to 2% when they are pregnant [37]. Seven aortic dissections during pregnancy in Turner syndrome patients are reported in the literature. Six of these patients died despite surgery. It is estimated that 25-50% of Turner syndrome patients have cardiovascular malformations [38]. Mortality is significantly higher among Turner syndrome patients with cardiovascular malformations, nonetheless aortic dissection in Turner syndrome patients with no cardiovascular malformations has also been reported. Patients with baseline or progressive aortic root dilatation constitute the highest risk group.

Specific recommendations for surveillance in women with Turner syndrome during pregnancy according to the 2008 guidelines of American Society of Reproductive Medicine include [39]:

- Treatment of hypertension.
- Periodic echocardiography and consultation with a cardiologist.
• Women in stable condition having an aortic root diameter less than 4 cm may attempt vaginal delivery under epidural anesthesia.
• Women exhibiting baseline or progressive aortic root dilation should have an elective cesarean delivery prior to the onset of labor under epidural anesthesia.

Boissonnas et al. reported a patient accepted in the oocyte donation programme according to the ASRM guidelines who had had a normal cardiac examination before pregnancy [40]. A repeated cardiac examination by another doctor at the 16th week revealed a bicuspid aortic valve with aortic root enlargement of 39 mm. The patient developed an aortic dissection at the 38th week of pregnancy and died despite surgery. Boissonnas et al. argue that aortic dissection is still possible in patients with aortic roots less than 4 cm and recommend normalization of aortic root diameter according to the body surface area. Matura et al. reported the critical aortic root to be more than 2.5 cm [41]. Bondy recommends these patients to be examined by experienced cardiologists [42].

Pregnancy after heart transplantation
The first pregnancy of a heart transplant patient was reported in 1988 by Lowenstein and colleagues [43]. At the beginning data about pregnancies in heart transplant patients was scarce and they were discouraged from pregnancy. When the number of pregnancies in these patients increased, the knowledge increased likewise.

Ideally these patients should be counseled on timing of conception and maternal and fetal risks before transplantation. The National Transplantation Pregnancy Registry (NTPR) and American Society of Transplantation (AST) consensus groups recommend that pregnancy should not be attempted sooner than one year after transplantation for the graft function to stabilize and immunosuppressants to reach basal levels [44, 45]. The graft function should be adequate, with no signs of acute rejection. Kidney functions should also be assessed because these patients usually have some degree of renal dysfunction. Contrarily to common concerns, hemodynamic changes of pregnancy have been proven to be well-tolerated by heart transplant patients in most cases. The denervated heart can still increase the cardiac output due to higher preload via the Frank-Starling mechanism. Heart rate and contractility increase in response to increased circulating catecholamines [46].

Maternal risks in pregnant heart transplant patients include rejection, infection, hypertension and preeclampsia. Armenti et al. reported a 21%-rejection rate, most of which were low-grade and did not require additional treatment. No graft loss within two years of pregnancy was reported. Thus, rejection rate seems to be comparable to non-pregnant patients [47]. Plasma volume increases during pregnancy and plasma levels of immunosuppressant drugs change. Hyperemesis may preclude adequate absorption of drugs. Drug concentrations should be followed and adjusted accordingly in order to minimize the risk of rejection.

Immunosuppressed patients are susceptible to infections. Due to 30% risk of progression to pyelonephritis, asymptomatic bacteriuria should be treated promptly, and the patients should be followed up by regular monthly urine cultures [48].

Hypertension and preeclampsia are more common in these patients. Armenti et al. reported the incidence of hypertension and preeclampsia to be 43% and 11% respectively [49]. High blood pressure should be treated to prevent organ damage and pregnancy complications. The differential diagnosis of preeclampsia and HELLP syndrome might be difficult as they may resemble acute rejection, drug toxicity or progressive disease. If the organ biopsy becomes necessary, as it might compromise the long term graft function, it should not be delayed until after pregnancy [50].

Diabetes and anemia are more common in transplant patients. Diabetes should be especially screened in patients using steroids and tacrolismus [51].

Preterm birth, low birth weight and stillbirth are also more common in these patients. The NTPR reported the rate of preterm delivery and low birth weight to be 32% and 32% respectively. Spontaneous labor was responsible for two-thirds of preterm deliveries, whereas pregnancy complications necessitating delivery made up the remaining one-third [52].

There had been some concern about the potential effects of immunosuppressants on the fetus. According to the AST’s Women’s Health Community of Practice Survey most transplantation professionals were comfortable with using cyclosporine, tacrolismus and steroids. However, malformations associated with mycophenolate mofetil exposure have been reported [53, 54].

All transplant patients should be screened for TORCH, parvovirus and hepatitis. All live vaccines are contraindicated in the immunosuppressed transplant patients so they should be administered before transplantation. Hepatitis, tetanus, influenza and pneumococcal vaccines may be given before or during pregnancy [55].

During pregnancy the graft function should be followed up by electrocardiogram and echocardiography. Cardiac biopsy rarely becomes necessary. Some cardiac diseases, like congenital cardiac malformations, mitochondrial myopathies and dilated cardiomyopathy have a genetic basis, thus posing a threat of developing in the offspring [56, 57, 58]. Therefore, during the pre-pregnancy counseling this information should be given to the patients.

The fetuses of these patients are at risk of congenital anomalies and cardiac diseases. Therefore a detailed scan and fetal echocardiography must be performed. Armenti et al. and Sibanda et al. reported a stillbirth rate of 2% and 6% respectively. When taking this numbers to account it seems reasonable to start antenatal testing at 32 weeks gestation [53, 54].

During labor heart transplant patients should be closely monitored for arrhythmias by ECG. Vaginal delivery is the preferred mode of delivery because cesarean section increases the infection rate in the immunocompromised patients [58]. Epidural anesthesia is beneficial in reducing the pain. In the postpartum period immunosuppressant levels should be monitored closely.

Successful pregnancies are reported in these patients. Nevertheless, these pregnancies should be regarded as high-risk and monitored by a team of transplant professionals, maternal – fetal specialists and cardiologists.
To conclude, cardiovascular complications are important causes of maternal mortality. Most of the patients who develop cardiovascular complications of pregnancy are not considered to be at risk. Obstetricians should be familiar with knowledge of cardiovascular complications of pregnancy. A high index of suspicion, early diagnosis and timely and appropriate interventions may save the life of the fetus and the mother.

Furthermore, it should be remembered that these patients carry higher risk for adverse cardiovascular events for the rest of their lives so they should be managed accordingly.

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