Heart failure in pregnant women. A difficult therapeutic approach

Abstract

Pregnant women have significant physiological hemodynamic changes that can decompensate a preexistent heart failure. Also, pregnant women without history of cardiovascular diseases can develop heart failure during pregnancy, due to cardiovascular diseases acquired during pregnancy, as peripartum cardiomyopathy. Pregnant women have not been adequately represented in randomized clinical trials of heart failure. Clinicians involved in managing pregnant women with heart failure must frequently make treatment decisions without adequate evidence or consensus expert opinion.

Keywords: *heart failure, pregnancy, therapeutics*

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1. Introduction

Pregnant women have significant physiological hemodynamic changes that can decompensate a preexistent heart failure. Also, pregnant women without history of cardiovascular diseases can develop heart failure during pregnancy, due to cardiovascular diseases acquired during pregnancy, as peripartum cardiomyopathy. Women with known preexisting cardiac lesions should be counseled in advance about the risk of pregnancy. In normal pregnancy, the blood volume increases by 35%, the cardiac output by 40-43%, stroke volume by 30% and heart rate by 15-17%[1]. The mean arterial pressure has no significant change. Systolic blood pressure decreases with 3-5 mm Hg; also, the diastolic blood pressure decreases with 5-10 mm Hg[1]. These hemodynamic changes during normal pregnancy set the scene for the development of some signs and symptoms that can mimic the signs and symptoms of heart disease. The physiological adaptations to pregnancy influence the diagnosis and interpretation of cardiac tests. Pregnant women usually have mild peripheral edema and jugular venous distension. Also, they can have audible physiologic systolic murmurs, due to increased blood flow. The electrocardiogram may show a leftward shift of the electrical axis, when the diaphragm is pushed upward by the uterus.

According to the guidelines of European Society of Cardiology, heart failure is an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures). Clinically, heart failure is defined as a syndrome in which patients have typical symptoms (dyspnea, ankle swelling, fatigue) and signs (elevated jugular venous pressure, pulmonary crackles and displaced apex beat) resulting from an abnormality of cardiac structure or function.

It is a well known fact that women population in randomized clinical trials of heart failure is smaller than men population, due to higher costs, more difficult enrollment and pregnancy. There are gender differences in pharmaceuticals effects[2] (Table 1).

2. The managing pregnant women

Clinicians involved in managing pregnant women with heart failure must frequently make treatment decisions without adequate evidence or consensus expert opinion. There is a need for further evaluation of treatment. Currently, management of heart failure in pregnant women is guided by observational studies. During pregnancy, many of these therapies are associated with an increased risk to the fetus; however, if the benefits for the mother are thought to outweigh the risks, these treatments are used. Physiological changes that occur during pregnancy can affect absorption, excretion and bioavailability of drugs.

Common causes of heart failure in women of childbearing age are congenital heart disease, valvular heart disease, idiopathic dilated cardiomyopathy, familial cardiomyopathies, drug-induced (adriamycin) cardiomyopathy, peripartum cardiomyopathy, ischemic cardiomyopathy, and hypertension-related cardiomyopathy. Four conditions are associated with a mortality risk of up to 50% during or after pregnancy: ongoing heart failure with left ventricle ejection fraction <35%, pulmonary hypertension, Eisenmenger syndrome, Marfan syndrome[3].

Women with new-onset or pre-existing left ventricular dysfunction may exhibit marked clinical deterioration during the course of pregnancy. Cardiac decompensation can occur at any time during pregnancy[3]. Generally, patients with NYHA class I or II symptoms pre-pregnancy tolerate pregnancy well (mortality <1%)[3]. The initial evaluation of a pregnant women with a history of heart failure that presents in a stable condition prior to or in the early stages of pregnancy should include a careful history and clinical examination, assessment of NYHA functional class (Table 2)[4], an electrocardiogram, an echocardiography and, in special cases, cardiac magnetic resonance imaging or other imaging studies[3].

Pregnant women with decompensated heart failure have progressive dyspnea or persistent cough, associated or not with chest discomfort. The initial evaluation of these patients should include a detailed history and clinical examination, an echocardiography, an electrocardiogram and laboratory tests. Usually, laboratory tests should include a complete blood count, seric ionogram and renal function tests. Additionally, other tests can be ordered: cardiac enzymes, serum B-type natriuretic

Received: *January 20, 2013*
Revised: *March 10, 2013*
Accepted: *April 14, 2013*

Table 1 Gender differences in pharmaceutical effects[2]

Drug	Gender-specific differences
Beta blockers	More side effects in women Same benefits in both sexes
Digitalis	Higher mortality in women
ACEI	More side effects in women
ARBs	Gynecomasty only in men Same safety profile in both sexes
Antiarrhythmics	More tachycardia in women Higher incidence of torsades des points
Aspirin	Effective in primary stroke prevention in women Not effective in primary MI prevention in women Effective in primary MI prevention in men Not effective in primary stroke prevention in men
Thrombolytic agents and anticoagulants	More frequent and severe side effects in women

peptide (BNP) or N-terminal pro-BNP. In nonpregnant patients, cardiac biomarkers BNP and NT-proBNP are very useful to detect and monitor heart failure. In pregnancy, there are no enough data on the value of these biomarkers in evaluating heart failure[5,6].

In pregnancy, the differential diagnosis of heart failure includes pneumonia, pulmonary embolism, myocardial infarction, severe preeclampsia, amniotic fluid embolism or acute lung injury, renal failure with volume overload.

Treatment of heart failure during pregnancy is different than in nonpregnant women. Each drug must be carefully considered in pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptors blockers (ARBs), which are standard therapy of systolic heart failure according to European guidelines, are contraindicated in pregnancy, due to high risk of adverse affects in the fetus (urogenital defects, intrauterin growth retardation, fetal renal failure, even neonatal death)[7].

Some ACE inhibitors (benazepril, captopril, and enalapril) have been sufficiently tested in breast-feeding women and use by mother is safe for babies[8].

3. Betabloskers

Betablockers (carvedilol, metoprolol) are mainstay therapy in patients with chronic heart failure due to systolic dysfunction. These drugs are generally safe during pregnancy. However, beta-blockers may decrease uteroplacental blood flow, may impair fetal response to hypoxic stress and may be asssociated with neonatal hypoglycemia at high doses. Atenolol is contraindicated[8,9]. Beta-1 selective betablockers are preferred, because they are less likely to interfere with beta-2 mediated uterine relaxation and peripheral vasodilation. Fetal growth should be monitored by ultrasound. Some betablockers, as propranolol, labetalol, nadolol and metoprolol, are excreted in breast milk. However, the American Academy of Pediatrics considers these agents

Table 2 New York Heart Association (NYHA) functional classification[4]

Class	NYHA functional class
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

compatible with breast-feeding with the recommendation that a pediatrician should monitor the newborn.

Digoxin is another drug included in the heart failure therapeutic regimens in nonpregnant patients. It is recommended for control of ventricular rate in heart failure patients with atrial fibrillation, who cannot achieve adequate control on betablockers alone, and also in heart failure patients that remain symptomatic despite treatment with standard therapies, including ACE inhibitors, betablockers and diuretics. In pregnancy, digoxin has no major fetal adverse effects and is generally safe, but patients may need higher doses. Digoxin passes through placenta and is also excreted in breast milk. However, American Academy of Pediatrics considers digoxin compatible with breast-feeding, because of very small quantity that is excreted in milk[8].

Diuretics are prescribed for symptomatic relief of exertional dyspnea and peripheral edema in pregnant women. In heart failure, diuretics are the cornerstones of treatment for volume overload. Loop diuretics are preferred in pregnant women with heart failure, together with sodium restriction. The side effects are similar in pregnant and nonpregnant women: hypokalemia, hyponatremia, hyperuricemia. The fetus can be affected by reduced placental perfusion. Thiazidic diuretics therapy in pregnant women is associated with hyponatremia and bleeding diathesis in neonates.

Vasodilators decrease afterload and improve cardiac output in heart failure patients. Hydralazine has been long time used as vasodilator therapy in pregnancy, being safety for both mother and fetus. Hydralazine is the vasodilator of choice for pregnant women with mild to moderate symptoms of heart failure. In patients with decompensated heart failure and arterial hypertension nitroglycerin can be used, but with caution. Afterload reduction increases the risk of deterioration of the fetal heart rate, because of rapid drop of maternal blood pressure.

Aldosterone antagonists are another class of drugs largely prescribed in heart failure. In selected groups of pregnant women with heart failure, spironolactone and eplerenone have been demonstrated to prolong survival. However, because there are no data about the safety of these drugs in pregnancy, they are contraindicated. Spironolactone has fetal antiandrogenic effects.

Intravenous inotropes are indicated in patients with acute decompensated heart failure with systolic dysfunction and arterial hypotension. In pregnancy, the administration of these drugs depends of the clinical situation, usually in critically ill patients. Dopamine and dobutamine have inotropic and vasodilator properties.

Vasopressors are avoided in heart failure patients, because peripheral vasoconstriction may further alter cardiac output. There are no data about the use of these agents in pregnancy.

Anticoagulation presents unique challenges in pregnancy, both antepartum and postpartum. Heart failure also is associated with an increased risk of venous thromboembolism. Despite the fact that studies about anticoagulation in pregnant women with heart failure are lacking, prophylactic anticoagulation of these patients is recommended[10]. Low molecular weight heparin has become the drug of choice for the prophylaxis and treatment of venous thromboembolism in pregnant patients. The dose is based on the patient's weight.

In women with severe heart failure, pregnancy is not recommended and termination should be advised. Mortality of these patients is between 8-35%[11]. The presence of heart failure NYHA class III or IV during pregnancy requires hospitalization and prompt treatment. If hemodynamic improvement is not obtained, the patient should be counseled about termination of pregnancy or delivery.

In conclusion, pregnancy may lead to deterioration of heart failure due to the rise in blood volume and increase in cardiac output, as well as the substantial increase in extravascular fluid. Cardiac decompensation can occur at any time during pregnancy; however, there are specific periods when the risk is increased. Clinical deterioration can occur late in the second trimester, during the third trimester or in the peripartum period, due to rapid hemodynamic changes that take place[3]. Many medications used in heart failure treatment are contraindicated during pregnancy. The risk of pregnancy is considered greater than the risks linked to contraceptive use. It is recommended that women with heart failure discuss contraceptives and plan pregnancy with the physician in order to take an informed decision based on assesment of potential risks. A multidisciplinary approach (cardiologists, gynecologists, neonatologists, anaesthesiologists) is needed.

Another problem regarding pregnant patients with heart failure is delivery. Early delivery is not required unless medical management is unsuccessful and the patient is hemodynamically deteriorating[3]. Vaginal delivery is preferable to caesarean[3]. Vaginal delivery is associated with less blood loss and infection risk compared with caesarean delivery, which also increases the risk of venous thrombosis and thromboembolism. Caesarean delivery is reserved for obstetric indications.

4. Conclusions

Monitoring of delivery should include blood pressure monitoring, continuous maternal electrocardiogram, pulse oximetry, tocodynamometry with fetal heart rate monitoring and should continue throughout labour and the early postpartum period. ■

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