Myocarditis in Pregnancy

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Myocarditis – Definition

An *inflammatory* disease of the myocardium
diagnosed by established histological, immunological
and immunohistochemical criteria

Myocarditis – Etiology

Causes of Myocarditis

Infectious
- Viral
- Bacterial
- Spirochetal
- Fungal
- Protozoal
- Parasitic
- Rickettsial

Immune-Mediated
- Allergens
- Autoallergens
- Autoantigens
- Tetanus toxoid, vaccines
- Serum sickness, drugs
- Heart transplant rejection
- Infection-negative lymphocytic,
- Infection negative giant cell
- Associated with autoimmune or immune oriented disorders

Toxic
- Drugs
- Heavy Metals
- Hormones, e.g. catecholamines (pheochromocytoma)
- Physical agents

Myocarditis – Etiology

• Earliest evidence of virus infection during outbreaks of influenza, poliomyelitis, measles, rubella, mumps, and pleurodynia associated with enterovirus infection

• Currently parvovirus (PV) B19 and human herpes virus type 6 (HHV-6) are the most frequent viruses, while enteroviruses, like coxsackie B were in the past

• Viruses commonly tested are PVB19, adenovirus, cytomegalovirus, enterovirus, Epstein- Barr, hepatitis C, herpes simplex 1, 2, and 6 and influenza viruses A and B

• In Latin America Trypanosoma cruzi infection – Chagas disease
Lymphocytic and giant cell myocarditis are presumed idiopathic or autoimmune.

Autoimmune myocarditis may occur with exclusive cardiac involvement or in the context of autoimmune disorders with extra-cardiac manifestations, most frequently in sarcoidosis, hypereosinophilic syndrome, scleroderma, and systemic lupus erythematosus.
Myocarditis – Pathogenesis

The causative organism, usually viral, or the non-infectious insulting process evokes immune responses. Two major pathways are responsible for myocardial damage:

1. Direct cytopathic effects of the cardiotropic viruses
2. Virus-induced anticardiac immune response

Myocytolysis liberates cardiac antigens, evoking anticardiac autoimmunity, which may persist even after complete viral elimination.

Viral persistence perpetuates the anti-cardiac immune response.

Genetic predisposition – an important contributing factor for cardiac pathogenicity of these viruses.
Myocarditis – Pathogenesis cont’

Histologically there is an active inflammatory cellular infiltrate within the myocardium, associated with myocyte necrosis (Dallas Criteria 1984).

The inflammatory infiltrate is predominantly lymphocytic in >90% of cases. Eosinophilic infiltration, or giant cell formation may occasionally be seen.
Myocarditis – Pathogenesis cont’

- In a majority of cases the inflammatory process resolves with minimal or no damage or remodeling.
- Ongoing myocardial inflammation may result in dilated cardiomyopathy or restrictive cardiomyopathy.
- If the host immune response is overwhelming or inappropriate, the inflammation may acutely destroy the heart tissue leading to LV failure frequently even without dilatation (fulminant myocarditis) and death.
Myocarditis – Clinical Features

- A recent systemic illness with viral symptomatology: fever, sore throat, cough, arthralgia, myalgia, abdominal pain, nausea, vomiting, diarrhea, and skin rash.

- Cardiac involvement usually becomes apparent only a few days to a few weeks later. Usually manifested as fatigue, decreased exercise tolerance, dyspnea, palpitations, and precordial discomfort.

- Plueropericardial chest pain is not infrequent, especially when there is associated pericarditis.

- However, chest pain may occur without inflammatory involvement of the pericardium as was proven by MRI.
Myocarditis – Clinical Features

New physical findings depends on the severity of the disease. They include: persistent fever, excessive tachycardia, hypotension, and narrow pulse pressure. Clinical findings of HF with mitral and tricuspid regurgitation may occur in more severe cases.

Neck veins distention in HF, pericardial effusion, or both.

In the acute phase there is no cardiac dilatation, which after occurs days to weeks, and is associated with a diffuse and displaced PMI and RV heave.

Auscultatory sounds may include a muffled first heart sound, a third heart sound, a friction rub, and murmurs due to mitral and tricuspid regurgitation.
Myocarditis – Laboratory Data

- **ESR** and **CRP** levels are often raised, but they do not confirm the diagnosis.
- **WBC** – slightly to moderately elevated, with ~50% neutrophilia
- **Eosinophilia** may indicate a *parasitic* etiology.
- Biomarkers are usually elevated, especially high sensitive **troponins**, which are more sensitive than CK, including CK-MB levels.
- They are **non-specific** and when normal do not exclude myocarditis.
- In comparison to acute MI **CRP** values are relatively much more elevated than high sensitive **troponin** values.
- Other biomarkers such as **BNP/Pro-BNP**, circulating **cytokines**, markers of extracellular matrix degradation, **pentraxin 3**, **galectin 3**, and **growth differentiation factor 15** that are frequently elevated.
C-reactive protein to troponin ratio for the differentiation of perimyocarditis from myocardial infarction

Myocarditis – Laboratory Data

- **Antibodies** are usually not found until about **1 week** after the illness onset.

- **IgM** antibody levels peak in **2-3 weeks** and are **later undetectable**

- **IgG** antibody levels peak later and may remain elevated for **months** or **years**

- Positive viral serology does not imply **myocardial infection**, but rather indicates the **interaction** of the **peripheral immune system** with an **infectious agent**.

- **Viral serology** is **not diagnostic**, as the **prevalence** of circulatory **IgG** ABs to cardiotropic viruses in the **general population** is **high without heart disease**.

- **Viral serology** has, therefore, a **low clinical value** and is currently not routinely recommended, as it did **not correlate** with **endomyocardial biopsy** viral findings.
The **diagnostic** cardiac magnetic resonance **criteria** for myocarditis in the setting of **clinically suspected myocarditis** (**Lake Louise criteria**) are:

1. **Regional** or global **myocardial signal intensity** increase in T2-weighted **edema** images.

2. Increased global myocardial **early gadolinium enhancement** ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images.

3. There is at least one **focal lesion** with **non-ischemic regional distribution** in inversion recovery-prepared gadolinium-enhanced T1-weighted images (**LGE**).

A CMR study is consistent with:

**Myocardial inflammation**, if $\geq 2$ **criteria** are present

**Myocyte injury** and/or **scar** caused by myocardial inflammation if **criterion 3** is present.
Myocarditis – Cardiovascular magnetic resonance (CMR) imaging

- CMR does not replace endomyocardial biopsy.
- It is unable to differentiate between infectious and immune-mediated forms.
- Does not provide information on the type of inflammation including special types of myocarditis, which may require special therapies (like giant cell, eosinophilic myocarditis or sarcoidosis).
- Does not provide information on the type of virus and non-diagnostic in milder cases.
- CMR supports the clinical suspicion of myocarditis and for noninvasive follow-up.
- Particularly important in patients with minor symptoms, e.g., young patients with unexplained arrhythmia, or troponin positive patients with normal coronary arteries.
Since the Dallas criteria (1984), endomyocardial biopsy has become the "gold standard" for the diagnosis of myocarditis.

Endomyocardial biopsy confirms the diagnosis of myocarditis and identifies the underlying etiology, especially specific type of inflammation (giant cell, eosinophilic myocarditis, sarcoidosis) which imply different treatments and prognosis.

However, the negative results of the multicenter Myocarditis Treatment Trial that used the Dallas criteria to recruit myocarditis patients to 6 mths immunosuppression had a negative effect in the next decade on the use of endomyocardial biopsy.
Myocarditis – Endomyocardial Biopsy

- Cell-specific immunehistological staining for surface antigens: such as anti-CD3 (T-cells), anti-CD4 (T-helper cells), anti-CD20 (B-cells), anti-CD68 (macrophages), and anti–human leukocyte antigen (HLA).

- This technique is associated with less sampling error, therefore is more sensitive than histopathology and has better prognostic value.

- The diagnostic contribution of EMB is enhanced by molecular analysis with DNA–RNA extraction and RT-PCR amplification of viral genome.

- In order to exclude systemic infection, peripheral blood should be investigated in parallel with EMB.

- Viral isolation from biopsy culture is complementary to histopathology and mandatory for identification & characterization of the inflammatory infiltrate.
Myocarditis – Endomyocardial Biopsy

❤ The ability to perform endomyocardial biopsy is somewhat limited during pregnancy, because the use of fluoroscopy is undesirable.

❤ The procedure should, therefore, be performed under echocardiographic guidance.

❤ Viral persistence in the myocardium has been associated with ventricular dysfunction, and viral genome clearance with improvement of ventricular function and a better 10-year prognosis.

❤ In contrast, immunohistological evidence of inflammation, but not the presence of viral genome alone, was an independent predictor of survival.
Myocarditis – Treatment

♥ Acute myocarditis resolves within 2-4 weeks in 50% of cases, but about 25% will develop persistent cardiac dysfunction and 12–25% may acutely deteriorate and either die or progress to end-stage DCM.

♥ The treatment of many milder forms of myocarditis is symptomatic, care of arrhythmia and of heart failure and, where supported by evidence, etiology-targeted therapy.

♥ All pregnant women with suspected myocarditis should be hospitalized for clinical monitoring, until a definite diagnosis is established, since cardiopulmonary emergency, like severe heart block or life threatening arrhythmia, may occur even if systolic function is initially preserved.

♥ Patients with hemodynamic instability, HF, significant pericardial effusion, at risk of tamponade, and serious arrhythmias should be adequately monitored in ICCU.

♥ Exercise testing is contraindicated in the acute stage, as it can precipitate arrhythmia.
Myocarditis – Treatment

- HF should be treated with diuretics and beta blockers. The use of ACE-I, ARBs, MRAs and Sacubitril / Valsartan is contraindicated during pregnancy, due to their teratogenicity and/or lack of evidence.

- Digoxin, commonly used, increases proinflammatory cytokines and mortality in a murine model of viral myocarditis.

- As therapeutic levels of digoxin may be associated with toxicity in myocarditis, and serum digoxin levels cannot be accurately measured during pregnancy, it should be used with caution and only at low doses.

- In acute/fulminant cases with cardiogenic shock and severe ventricular dysfunction, besides inotropic agents and intraaortic counterpulsation, ventricular assist devices (VAD) or extracorporeal membrane oxygenation (ECMO) are needed early (sometimes within 12-24 hours) to provide a bridge to cardiac transplantation or to recovery.
Myocarditis – Treatment

- Important arrhythmias should be treated with beta blockers, lidocaine, quinidine, or procainamide, which are relatively safe in gestation, and if persistent, the implantation of a defibrillator should be considered. However, whenever clinically feasible, ICD implantation should be deferred until resolution of the acute episode.

- Temporary pacing should be inserted for high degree AV block. As conduction disturbances are transient in the majority of patients with myocarditis, a permanent pacemaker is usually not indicated.

- Cardiac electronic implantable device, either pacemaker or ICD/CRTD can be implanted during pregnancy using echocardiography with relatively minimal X-ray irradiation.

- In the last years there is an increased use of a wearable defibrillator (LifeVest) during pregnancy, awaiting cardiac recovery or internal ICD/CRTD implantation after delivery.
Wearable Defibrillator (LifeVest)
Myocarditis – Treatment

♥ NSAIDs, in particular acetylsalicylic acid, are a cornerstone of treatment for acute pericarditis, but have been associated with increased mortality in experimental models of myocarditis. Clinical data for their administration in myocarditis are inconclusive, and controlled trials are needed.

♥ Anticoagulation may be added, especially if patients have severe LV dysfunction, with or without evidence of a LV thrombus, to reduce the risk of emboli.

♥ Anti-viral therapies – Interferon beta treatment can eliminate enteroviral and adenoviral genomes in patients with LV dysfunction, is associated with improvement in NYHA class, and in enteroviral infection is associated with a better 10-year prognosis.

♥ However, Interferon beta was not effective against parvoviral B19 infection in the recently published BICC trial.
Myocarditis – Treatment

- High dose intravenous immunoglobulin (IVIG) has been associated with improved LVEF in chronic symptomatic HF of various causes.

- However, IVIG was ineffective in the IMAC trial of recent-onset DCM.

As IVIG has no major side effects it may be used in myocarditis refractory to conventional HF therapy, both viral and autoimmune forms, particularly if autoantibody-mediated.

- Immunosuppression should be started only after ruling out active infection on EMB by PCR. Most data have been obtained using steroids alone, azathioprine and steroids, or cyclosporine A.

- Current recommendation of immunosuppression: proven autoimmune forms of myocarditis, with no contraindications, including giant cell myocarditis, cardiac sarcoidosis, eosinophilic myocarditis and myocarditis associated with known extra-cardiac autoimmune disease.
Myocarditis – Treatment

❤ Steroid therapy is indicated in cardiac sarcoidosis in the presence of ventricular dysfunction and/or arrhythmia, and in some forms of infection-negative eosinophilic or toxic myocarditis with HF and/or arrhythmia.

❤ Immunosuppression may be considered by a recent position statement in infection-negative lymphocytic myocarditis refractory to standard therapy in patients with no contraindications to immunosuppression.

❤ This approach is based on the positive results of the TIMIC randomized trial, and a recently published observational retrospective study. These studies included patients with inflammatory cardiomyopathy of at least 6 months duration. The use of immunosuppression in infection negative acute myocarditis unresponsive to supportive treatment had been documented only in sporadic cases.

❤ Strenuous activity may be deleterious and should be prohibited during the acute phase of myocarditis for at least 6 months both in athletes and nonathletes.
Myocarditis in Pregnancy

Only a few cases of myocarditis have been reported in pregnancy

- In an early review (1968) 4 of 22 pts with viral myocarditis – in the postpartum period

- Grimes (1980) reported 4 cases with fatal outcome following an abortion in early stage of gestation – autopsy evidence of myocarditis

- Gehrke (1994) reported a 28-year-old asthmatic female who developed postpartum acute HF accompanied by diarrhea, fever, and hypereosinophilia. During steroid treatment, cytomegalovirus-associated myocarditis developed

- Chen (1994) described a patient with repeated episodes of acute myocarditis who developed heart failure in the 36th week of gestation, with rapid deterioration and death
Ciccone (2016) reported a 40-year-old woman who developed, after childbirth, hyperthermia with neck and left arm pain, who died suddenly few days later. Autopsy disclosed normal sized heart with fulminant myocarditis, congested organs and negative microbiological tests.

Massengill A (2016) described a pregnant woman who developed infectious myocarditis presenting as acute respiratory distress.

Malhorta (2016) described a 38-year-old postpartum female who had a cesarean section due to preeclampsia, who developed acute pericarditis and myocarditis related to SLE, complicated by acute respiratory failure and cardiogenic shock with dramatic improvement within days under steroid therapy.
Myocarditis in Pregnancy

♥ Several reports have demonstrated a relatively high incidence histologically proven myocarditis in patients with PPCM, suggesting that myocarditis may be an important etiologic factor in PPCM.

♥ The incidence of active myocardial inflammation in PPCM varied:

♥ Rizeq (1994) reported a low incidence 3(9%) of myocarditis in 34 patients with PPCM, comparable to age- and sex-matched control population with idiopathic-dilated CMP.

♥ Bültmann (2005) studied 26 patients with PPCM in whom endomyocardial biopsy specimens revealed viral genomes: parvovirus B19, human herpes virus 6, Epstein-Barr virus, and human cytomegalovirus in 8 patients (31%)
Comparison of Myocarditis during pregnancy to PPCM/PAC

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<th>Age (years)</th>
<th>Myocarditis</th>
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<td></td>
<td>All</td>
<td>All, more frequent &gt;30</td>
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<th>Number of pregnancies</th>
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<table>
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Comparison of Myocarditis during pregnancy to PPCM/PAC  cont'

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<thead>
<tr>
<th></th>
<th>Myocarditis</th>
<th>PPCM / PAC</th>
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<tr>
<td>Flu-like preceding symptoms</td>
<td>Frequently</td>
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<tr>
<td>Diagnosis</td>
<td>Delayed (usually within few days unless severe)</td>
<td>delayed (on average 2 weeks unless severe)</td>
</tr>
<tr>
<td>Fever</td>
<td>Very frequently</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Pericardial pain</td>
<td>Quite frequently</td>
<td>Rarely</td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Endomyocardial biopsy</td>
<td>In clinical severe cases</td>
<td>Currently not recommended</td>
</tr>
<tr>
<td>Treatment</td>
<td>Myocarditis</td>
<td>PPCM / PAC</td>
</tr>
<tr>
<td>-----------------------------------</td>
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<td>------------</td>
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<tr>
<td>HFrEF Guidelines recommended</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Interferon beta</td>
<td>When viral persistence (not effective in parvovirus)</td>
<td>No</td>
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<tr>
<td>Immunosuppression</td>
<td>Yes - mostly biopsy guided</td>
<td>No</td>
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<tr>
<td>Bromocriptine</td>
<td>No</td>
<td>Yes (still debatable)</td>
</tr>
<tr>
<td>Subsequent pregnancy</td>
<td>Recurrence rate not reported. Probably low. When full recovery it may be safe</td>
<td>20-40% recurrence</td>
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Myocarditis during pregnancy is **rare**.

- Its **clinical presentation varies** from asymptomatic, mild non-specific symptoms to cardiogenic shock and/or life threatening arrhythmias.

- Its **diagnosis** is based on **combination** of clinical features, electrocardiographic, laboratory, echocardiographic and CMR findings.

- **Endomyocardial biopsy** confirms the diagnosis of myocarditis, identifies the underlying etiology and may reveal particular types of inflammation. (e.g. giant cell, eosinophilic myocarditis, sarcoidosis), which require specific immunosuppressive treatment.

- **Immunosuppressive** therapy may be considered in selected patients unresponsive to standard therapy, in whom inflammation was demonstrated and viral persistence was excluded by endomyocardial biopsy.

- Myocarditis **resolves** within few weeks. However, patients may develop **persistent** cardiac dysfunction and 12–25% of them may **deteriorate** to end-stage cardiomyopathy and even death.
Thank You
Myocarditis – Prevalence

• Affects individuals of all ages, but most frequent in the young

• Global prevalence – 22 / 100,000 pts per year

• Age-standardized death rate due to myocarditis & cardiomyopathies – 6.1 / 100,000 pts


Myocarditis – Prevalence

- Affects individuals of all ages, but most frequent in the **young**
- Global prevalence – **22 / 100,000** pts per **year**
- Age-standardized death rate due to myocarditis & cardiomyopathies – **6.1 / 100,000** pts

Myocarditis – Clinical Features

- Myocarditis may cause ventricular arrhythmias and heart block or mimic acute MI, especially when presents with localized electrocardiographic changes and wall motion abnormalities.
- Hemodynamic instability, and circulatory collapse, may develop with severe LV and/or RV dysfunction, a high degree AV block, ventricular arrhythmias, or cardiac tamponade.
- Myocarditis may be the cause of ~20% of cases of sudden, unexpected death in young adults, <40 years of age and in young athletes, secondary to tachyarrhythmias or complete AV block.
- In autopsies of young adults, myocarditis is responsible for 4-12% of sudden deaths, ranking as the 3rd cause after hypertrophic cardiomyopathy and congenital and atherosclerotic coronary artery disease.
- Systemic and pulmonary emboli have been reported and may be the presenting feature.
- Myocarditis resolves spontaneously in approximately 80% of patients, but in those who did not recover, prospective studies revealed a 10-year survival rate of only 45%, mostly due to manifestation of DCM and sudden cardiac death.
Myocarditis – Electrocardiogram

- In the acute stage, the electrocardiogram is usually abnormal, demonstrating ST segment elevation with inversion or flattening of the T wave and possible prolongation of the QT interval.
- ST-T segment elevation in myocarditis is typically concave (rather than convex as seen in myocardial infarction) and diffuse without reciprocal changes or limitation to a specific coronary territory.
- The ST segment changes usually return to baseline within a few days, whereas T-wave changes may persist for several weeks or months.
- Abnormal Q waves may sometimes develop and mimic acute myocardial infarction.
- Ventricular premature beats are common, and atrial and ventricular tachyarrhythmias are present in many patients.
- QRS prolongation may be an independent negative predictor for survival.
- Atrioventricular conduction disturbances of varying degrees associated with ventricular tachyarrhythmias should raise the suspicion of giant cell myocarditis, considered the most malignant form of myocarditis, which requires histopathologic confirmation and aggressive immunosuppressive therapy.
- A-V block in the presence of mild left ventricular dilatation may be also suggestive of Lyme disease or cardiac sarcoidosis.