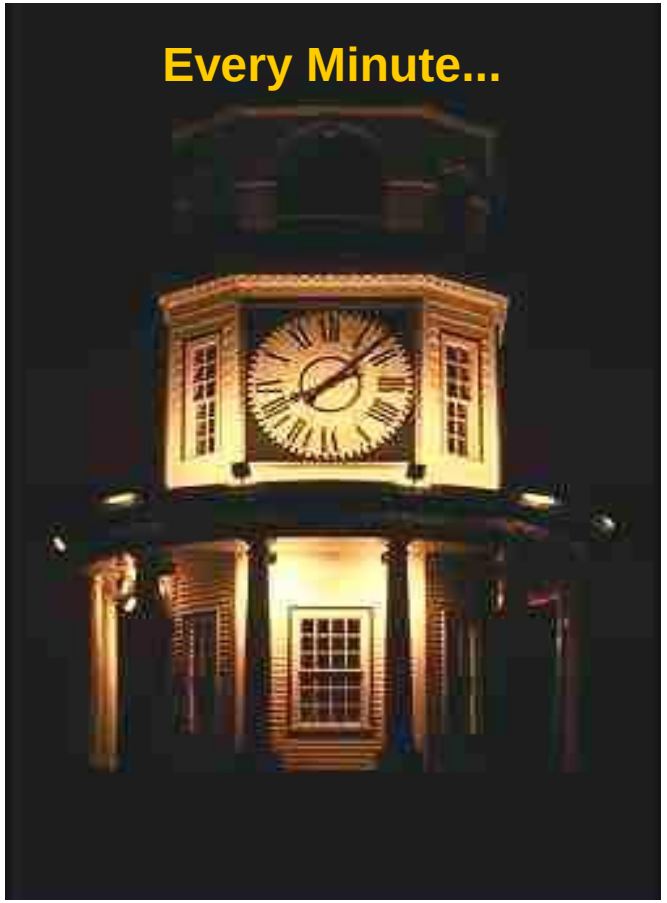
Cardiomiopatia peripartum

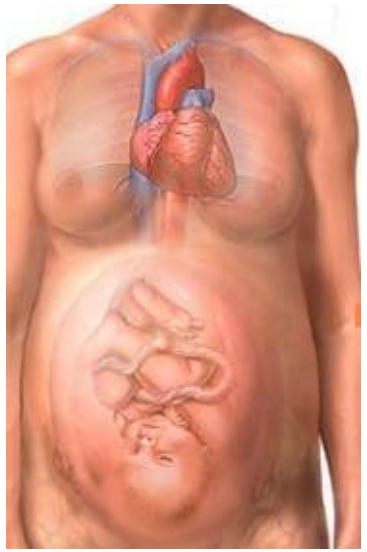
Dott. Mara Piccoli

Maternal Death Watch



- 380 women become pregnant
- 190 women face unplanned or unwanted pregnancy
- 110 women experience a pregnancy related complication
- 40 women have an unsafe abortion
- **1 woman dies from a pregnancy-related complication**

Cardiovascular Disease In Pregnancy



It is a relatively common in women of child bearing age, complicate about **4%** of pregnancies

Maternal mortality related to heart disease has decreased remarkably over the past 50 years

(**from 5.6 to 0.3/100 000** live birth)

Heart disease are still the **second** most common non obstetrical cause of maternal **mortality**

1) ESC Guidelines on the management of cardiovascular diseases during pregnancy European Heart Journal (2011) 32, 3147–3197

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Peripartum Cardiomyopathy

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PERIPARTUM CARDIOMYOPATHY, a disorder of heart muscle, presents clinically with the onset of cardiac failure in the last month of pregnancy or in the first 5 postpartum months. The first description of idiopathic myocardial failure with onset in the puerperium has been attributed to Ritchie in 1849.[1] Postpartum cardiomyopathy was again recognized in 1937 by Hull and Hafkesbring and by Gouley et al.[2, 3] Since some of the reported patients developed cardiac failure in the last month of pregnancy it is probably more appropriate [redacted]m "peripartum cardiomyopathy" (PPCM)[4] rather than postpartum cardiomyopathy.

Clinical Characteristics of PPCM in the USA: Diagnosis, Prognosis, and Management

Elkayam U., J Am Coll Cardiol. 2011;58(7):659-670

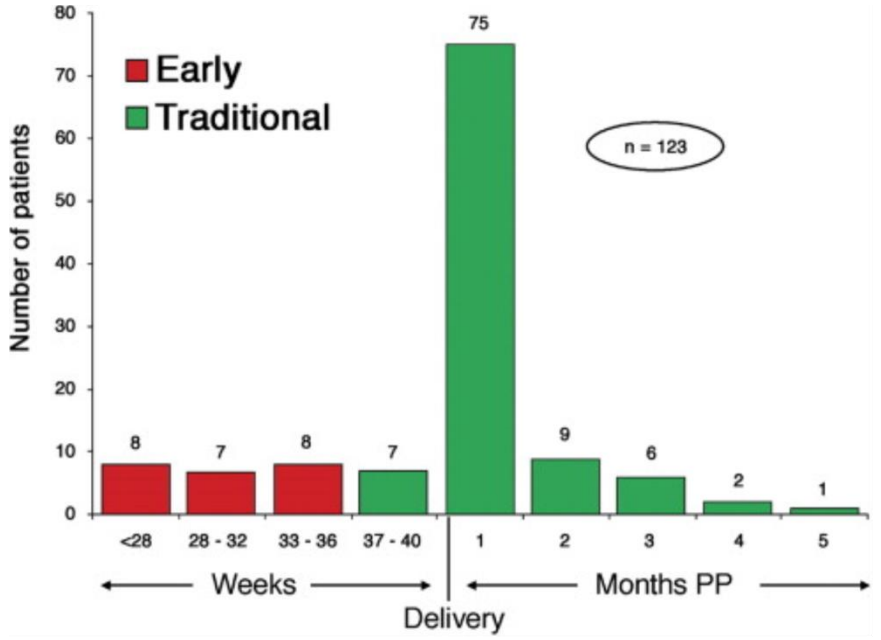

Figure Legend:

Time of Diagnosis of PPCM in 123 Patients

Red bars represent 23 patients with diagnosis before the last month of pregnancy. Green bars represent 100 patients diagnosed in the last month of pregnancy or the 5-month postpartum. PP = postpartum; PPCM = peripartum cardiomyopathy.

Peripartum Cardiomyopathy: definition

- A idiopathic cardiomyopathy, as distinct entity, presenting with heart failure secondary to LV systolic dysfunction from **1** month antepartum, up to **5** months after delivery, when no other causes of heart failure is found

	Definition of PPCM
European Society of Cardiology on the classification of cardiomyopathies[49]	A non-familial, non-genetic form of dilated cardiomyopathy associated with pregnancy
AHA Scientific Statement on contemporary definitions and classifications of the cardiomyopathies[7]	A rare and dilated acquired primary cardiomyopathy associated LV dysfunction and heart failure
Workshop held by the National Heart Lung and Blood Institute and the Office of Rare Diseases[2]	The development of heart failure in the last month of pregnancy or within 5 months post-partum The absence of an identifiable cause of heart failure The absence of recognizable heart disease prior to the last month of pregnancy LV systolic dysfunction demonstrated by classical echocardiographic criteria. The latter may be characterized as an LV ejection fraction $<45\%$, fractional shortening $<30\%$, or both, with or without an LV end-diastolic dimension >2.7 cm/m^2 body surface area
Heart Failure Association of the European Society of Cardiology Working Group on PPCM 2010	PPCM is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%.

3) Elliott P, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on myocardial and pericardial diseases. Eur Heart J 2008; 29: 270-276

4) Fett JD et al. Five year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc 2005; 80 (12): 1602-1606

5) Pearson G et al. National Heart, Lung and Blood Institute and Office of Rare Diseases (National Institute of Health) Workshop Recommendations and review. JAMA. 2000; 283 (9): 1183-1188

6) Sliwa K et al. Peripartum Cardiomyopathy. Lancet. 2006; 368 (9536): 687-693

7) Demakis JG et al. Natural course of peripartum cardiomyopathy. Circulation. 1971; 44 (6): 238-244

Peripartum Cardiomyopathy: Pathophysiology

- Incidence of 1:3000 to **1:4000** pregnancies USA, 1 in 1000 in South Africa, and 1 in 300 in Haiti, 1 in 100 in Nigeria

- But prospective, population-based, well-conducted, epidemiological studies are required

4) Fett JD et al. Five year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc 2005; 80 (12): 1602-1606

5) Pearson G et al. National Heart, Lung and Blood Institute and Office of Rare Diseases (National Institute of Health) Workshop Recommendations and review. JAMA. 2000; 283 (9): 1183-1188

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7) Demakis JG et al. Natural course of peripartum cardiomyopathy. Circulation. 1971; 44 (6): 238-244

Peripartum Cardiomyopathy: Pathophysiology

- Predisposing factors:
  - > Multiparity
  - > Multiple births
  - > Smoking, diabetes, tocolytic agents
  - ➢ Pregnancy complicated by pre-eclampsia, eclampsia or hypertension
  - ➢ Advanced age or teenage pregnancy
  - ➢ Environmental & Genetic variants

4) Fett JD et al. Five year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc 2005; 80 (12): 1602-1606

5) Pearson G et al. National Heart, Lung and Blood Institute and Office of Rare Diseases (National Institute of Health) Workshop Recommendations and review. JAMA. 2000; 283 (9): 1183-1188

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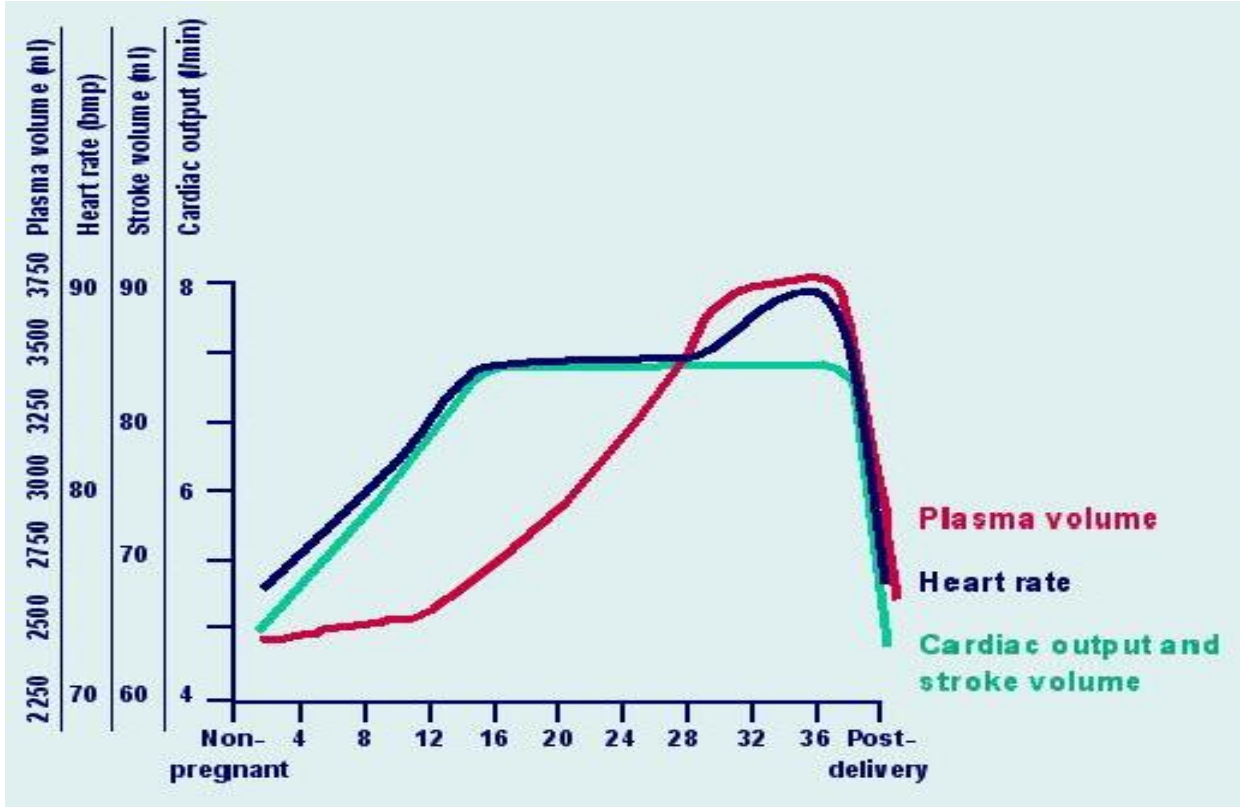
Cardiovascular Changes in Pregnancy

- To meet the increased metabolic demands of both the mother and fetus (evident by 5th to 8th wk, peak by late 2nd trimester)

  > Increased blood volume (40%)
  > Increased CO (30-50%) → 80% early postpartum
  > Decreased SVR & BP (active vasodilatation)
  > Increased LV size (30%, dilatation)

- Hypercoagulopathy
  - ➢ Increased coagulation factors, fibrinogen & platelet adhesiveness
  > Risk for thrombo-embolism from venous stasis due to obstructing uterus



1) ESC Guidelines on the management of cardiovascular diseases during pregnancy European Heart Journal (2011) 32, 3147–3197

2) ESC Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: European Journal of Heart Failure (2010) 12, 767–778

Peripartum Cardiomyopathy: Pathophysiology

Etiology (**Plausible etiologic mechanisms**):

- Viral Myocarditis **(Gouley et al 1937)**
  - > 8.8-78% prevalence of myocarditis in PPCM
  - > Endomyocardial biopsy shows lymphocytic infiltrates w/ myocytic edema, necrosis & fibrosis
- Apoptosis & inflammation
  - > programmed cell death
  - > Increased concentration of plasma cytokines: tumor necrosis factor a, CRP and Fas/Apo-1 (cell surface protein ligand role in apoptosis)
  - > no significant correlation has been demonstrated to LV function

9) Midei MG et al. Peripartum myocarditis and cardiomyopathy. Circulation. 1990; 81: 922-928

10) Rizeq MN, et al. Incidence of myocarditis in peripartum cardiomyopathy. Am J Cardiol. 1994; 74: 474-477

11) Melvin K, et al. Peripartum cardiomyopathy due to myocarditis. N Engl J Med. 1982; 307 (12): 731-734

12) Sliwa K et al. Peripartum Cardiomyopathy: analysis of clinical outcome, LV function, plasma levels of cytokines and Fas/Apo-1. J Am Coll Cardiol. 2000; 35 (3): 701-705

13) van Hoeven KH, et al. Peripartum versus idiopathic cardiomyopathy in young women – a comparison of clinical, pathological and prognostic factors. Int J Cardiol 1993; 40 (1): 57-65

Peripartum Cardiomyopathy: Pathophysiology

Etiology (**Plausible etiologic mechanisms**):

- Abnormal immune response to pregnancy (chimerism)
  - > Fetal micro-chimerism (harboring) of fetal cells in maternal circulation
  - > Natural immuno-suppression lost after delivery & if the fetal cell happen to be on the cardiac tissues-> pathologic autoimmune response -> PPCM
- Maladaptive response to hemodynamic stress of pregnancy
  - > increased blood volume, increased CO, increased preload, decreased afterload → brief and reversible LV hypertrophy to meet the demands of pregnancy
  - > "transient LV dysfunction" during the 3rd trimester and early postpartum resolves shortly after birth
  - > There is an exaggerated decrease in LV function when these hemodynamic changes occur

5) Pearson G et al. National Heart, Lung and Blood Institute and Office of Rare Diseases (National Institute of Health) Workshop Recommendations and review. JAMA. 2000; 283 (9): 1183-1188

14) Ansari AA et al. Autoimmune mechanism as basis for human peripartum cardiomyopathy. Clin Rev Allergy Immunol. 2002; 23: 301-324

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Peripartum Cardiomyopathy: Pathophysiology

Etiology (**Plausible etiologic mechanisms**):

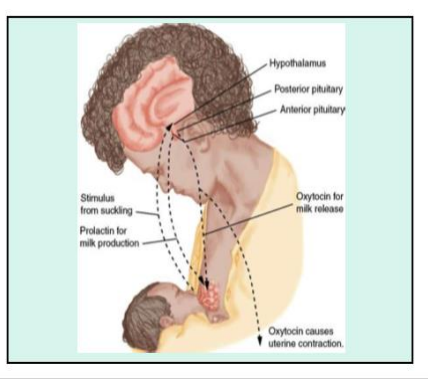
- Others: **Prolactin**

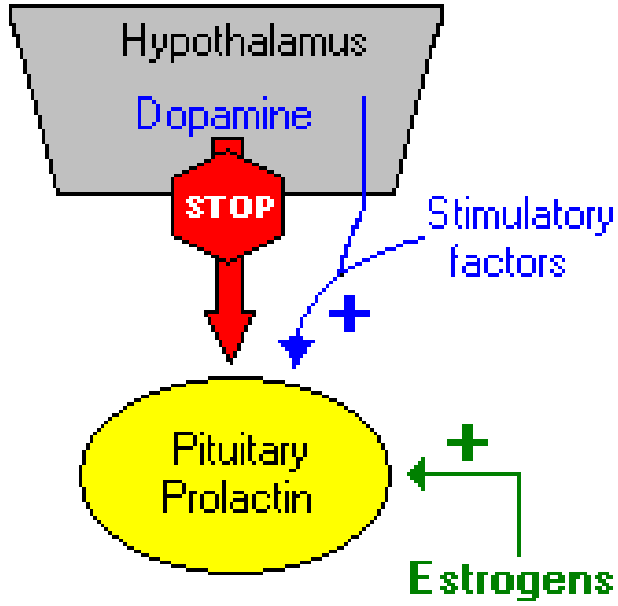
  > Increased mammary gland secretion

  > new proposed mechanism: excessive prolactin production

  > Increased Nursing Hormone Prolactin associated with:

  - **Increased blood volume**
  - **Decreased BP**
  - **Decreased angiotensin responsiveness**
  - **Decreased water, serum Na & K levels**
  - **Increased erythropoietin = increased Hct**





17) Hilfiker-Kleiner D et al. A cathepsin D-cleaved 16kDa form of prolactin mediates peripartum cardiomyopathy. Cell. 2007; 128 (3): 589-600

18) Forster O, et al. Reversal of IFN-gamma, oxLDL, and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. Eur J Heart Fail. 2008; 10: 861-868

Peripartum Cardiomyopathy: Pathophysiology

Etiology (**Plausible etiologic mechanisms**):

- Others: **Prolactin**
  - **Oxidative stress** → end of pregnancy
  - enhanced Cathepsin D activity and MM protease activity
  - Increased nursing hormone prolactin (23kDa)-a growth, differentiating and anti-apoptotic factor- cleavage in **16 kDa form of prolactin** in acute peripartum cardiomyopathy
  - Correlation between pro-BNP, prolactin, oxidized LDL and interferon-Y

Uncompensated oxidative stress mediated by cleavage of the nursing hormone prolactin into an **antiangiogenic and proapoptotic 16-kDa form** recently has been proposed to be a specific pathogenic mechanism of PPCM

Blockade of prolactin cleavage with Bromocriptine has shown therapeutic promise

17) Hilfiker-Kleiner D et al. A Cathepsin D-cleaved 16kDa form of prolactin mediates peripartum cardiomyopathy. Cell. 2007; 128 (3): 589-600

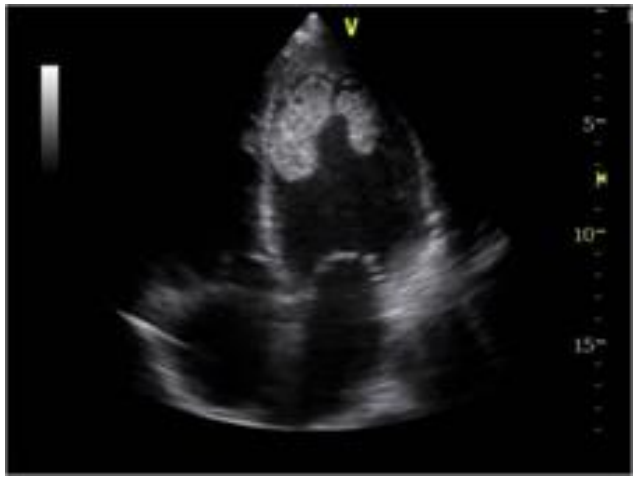
18) Forster O, et al. Reversal of IFN-gamma, oxLDL, and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. Eur J Heart Fail. 2008; 10: 861-868

Peripartum Cardiomyopathy:clinical examination

Clinical Manifestations:

- **H failure:** dyspnea, SOB, dizziness, EF, orthopnea
- chest pain, palpitations, cough , - BP (left lateral recumbent)
- Neck
  - NVE
  - Lungs
  - Rales (bibasal)
- Heart
  > Soft S1 - S3, S4 gallop
- Extremities
  > bipedal edema
- Abdomen > Hepatomegaly, hepato-jugular reflux

- **Arrhythmia i.e. AF**
- **Embolic events due to dysfunctional dilated LV**
- **Asymptomatic LV dysfunction**



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19) Ro A et al. Peripartum cardiomyopathy. Cardiac Rev 2006; 14 (1): 35-42

20) Ramaraj R et al. Peripartum cardiomyopathy: causes, diagnosis and treatment. Clev Clin J Med. 2009; 76 (5): 289-296

21) Williams J, et al. Critical Care in Obstetrics: pregnancy-specific conditions. Best Prac Res Clin Obstet Gynaecol. 2008; 22 (5): 825-846

Peripartum Cardiomyopathy: Diagnosis

Evaluation:

- Blood: CBC, electrolytes, BUN, creat, SGPT, SGOT, **cardiac enzymes** (troponin), urinalysis, + **BNP (pro-BNP)**
- CXR: **pulmonary edema**, pneumonia
- ECG > 5-20' L axis deviation, LVH, ST-T abnormalities
- TT Echocardiogram (serial **evaluation)**
  - > Assess cardiac function, structural integrity
  - > Chamber dimensions
  - > Valvular structure
  - ➢ Wall motion abnormalities → global hypokinesia
  - ➢ Pericardial evaluation
- Others: thyroid function test, CT scan
- **MRI** can be used to distinguish inflammatory from noninflammatory pathogenesis

8) Johnson-Coyle L, et al. Peripartum cardiomyopathy: Review and Practice Guidelines. Am J Critical Care 2012; 21 (2): 89-98

20) Ramaraj R et al. Peripartum cardiomyopathy: causes, diagnosis and treatment. Clev Clin J Med. 2009; 76 (5): 289-296

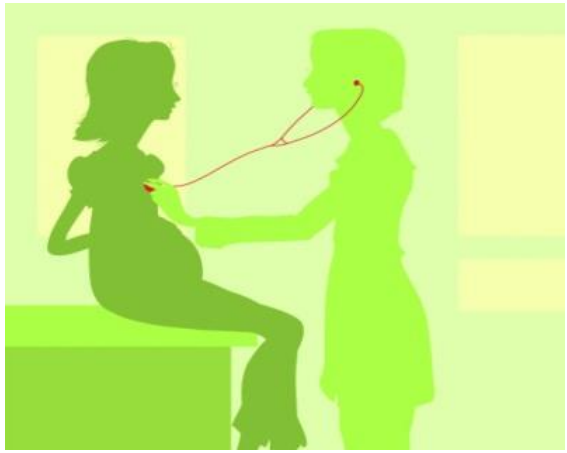
Peripartum Cardiomyopathy: Diagnosis

Is it Pregnancy **or** Heart Failure?

Evaluation: - **Diagnostic Criteria (4)**:

> **Timing:** Heart failure developing in the last month of pregnancy or within 5 months of delivery
> **no** identifiable cause of heart failure
> **no** recognizable heart disease before the last month of pregnancy
> **Echo** parameters:
- EF < 45% or
- FS <30% + LVEDD > 2.7 cm/m²

Diagnosis of exclusion



22) Hibbard JU, et al. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. Obstet Gynecol 1999; 94: 311-316

Peripartum Cardiomyopathy: Treatment

Peripartum Care:

- joint Obstetric and Cardiac care; perinat/neonat
- consider urgent termination of pregnancy in refractory HF
- vaginal delivery preferred, C/S as obstetrical indication
- lumbar epidural analgesia
- LL recumbent during labor, avoid to “push,” assisted by forceps delivery
- systemic arterial pressure monitoring,
- foetal monitoring, (Swan is rarely needed)

1) ESC Guidelines on the management of cardiovascular diseases during pregnancy
European Heart Journal (2011) 32, 3147–3197

Peripartum Cardiomyopathy: Treatment

Peripartum Care:

- **HF treatment as per guidelines,** similar to other forms of heart failure
- careful attention to a) foetal safety
  b) drug excretion
  c) drug metabolism
- Goals:
  > Improve hemodynamic status
  > Minimize signs & symptoms
  > Optimize long term outcome
- Focus:
  > reducing preload and afterload
  > increasing/improving cardiac inotropy

5) Pearson G et al. National Heart, Lung and Blood Institute and Office of Rare Diseases (National Institute of Health) Workshop Recommendations and review. JAMA. 2000; 283 (9): 1183-1188

21) Williams J, et al. Critical Care in Obstetrics: pregnancy-specific conditions. Best Prac Res Clin Obstet Gynaecol. 2008; 22 (5): 825-846

23) Tidswell M, et al. Peripartum cardiomyopathy. Critical Care Clin. 2004; 20: 777-788

Peripartum Cardiomyopathy: Treatment

Peripartum Care:

- Hospitalization due to a) hypotension
  b) worsening HF
  c) altered mental status
  d) pulmonary edema
- Management:
  > vasodilators/unloaders: nitrates, hydralazine, diuretics loop
  ACE-I/ARB & Aldosterone antagonist (Contra indication)
  > fluid restriction; Na restriction
  > positive inotropic agents: dopamine, milrinone

8) Johnson-Coyle L, et al. Peripartum cardiomyopathy: Review and Practice Guidelines. Am J Critical Care 2012; 21 (2): 89-98

Peripartum Cardiomyopathy: Treatment

Postpartum Care:

- Focus: > reducing preload and afterload
  > increasing/improving cardiac inotropy

- Medications:
  1) ACE-I/ARB –
  2) digoxin
  3) diuretics – furosemide/spironolactone
  4) BB – metoprolol, carvedilol
  5) Inotropes – dopamine, milrinone, levosimendan
  6) anticoagulation – LMWH/UFH/warfarin/ASA* (warcef)
  7) Others:

- Cardiac support options a) intra-aortic balloon pump
  b) LV assist device
  c) cardiac transplantation = 4% of PPCM

8) Johnson-Coyle L, et al. Peripartum cardiomyopathy: Review and Practice Guidelines. Am J Critical Care 2012; 21 (2): 89-98

24) Homma S et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012; 366 (20): 1859-1869

Peripartum Cardiomyopathy: Treatment

Postpartum Care:

- Medications:

7) Others: **in refractory heart failure**, limited data

a) **pentoxifylline** – improve outcomes, LV function/ S&S

b) IV immunoglobulin – improved EF, reduced levels of inflammatory cytokines

c) immunosuppressive therapy – no proven role but could be tried in proven viral myocarditis

d) **Bromocriptine**

e) others: monoclonal antibodies, interferon, therapeutic aphoresis, cardiomyoplasty

- Cardiac support options a) intra-aortic balloon pump

b) LV assist device

c) cardiac transplantation = 4% of PPCM

20) Ramaraj R et al. Peripartum cardiomyopathy: causes, diagnosis and treatment. Clev Clin J Med. 2009; 76 (5): 289-296

25) Sliwa K et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof of concept pilot study. Circulation. 2010; 121: 1465-1473

Peripartum Cardiomyopathy: Bromocriptine Study

- **Evaluation of Bromocriptine in the Treatment of Acute Severe Peripartum Cardiomyopathy** (A Proof of Concept Pilot Study)

- Hypothesis: Prolactin (mainly 16-Kda angiostatic and proapoptotic form) initiates and rives PPCM and that early pharmacologic blockade of prolactin with bromocriptine may improve the patients' condition before irreversible cell damage sets in, looked into as HF therapy to improve LVEF, functional class and survival in women with acute severe PPCM.

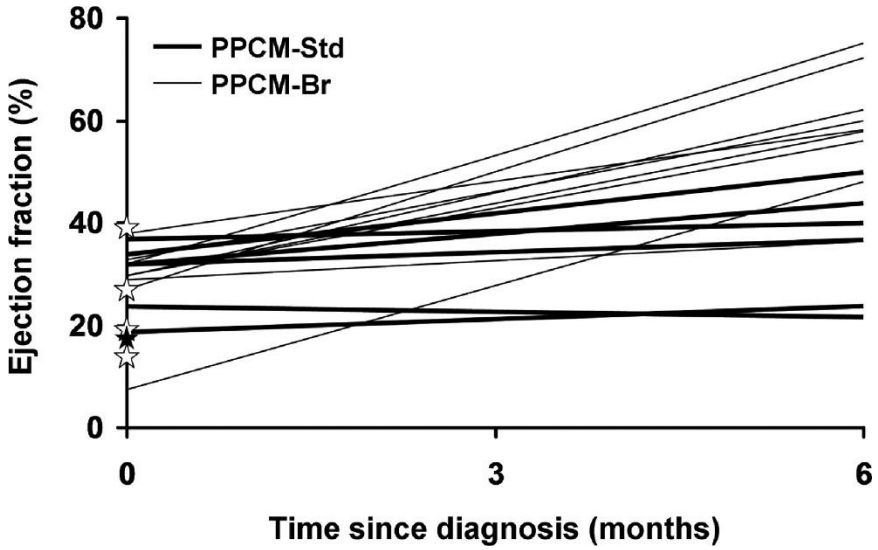
- P : **20** PPCM patients ≤ 35% with SBP >95 < 160 /or DBP < 105
  I : **PPCM-Std (10)** vs **PPCM-Br (10)**
  O : composite endpoint of death, NYHA Class 3 /4,
  LVEF <35% at 6months
  M : prospective randomized open-label clinical trial,
  PPCM-Std: Enalapril, carvedilol, furosemide, warfarin
  PPCM-Br: Std + 2.5mg BID X 2wks, 2.5mg OD X 6wks

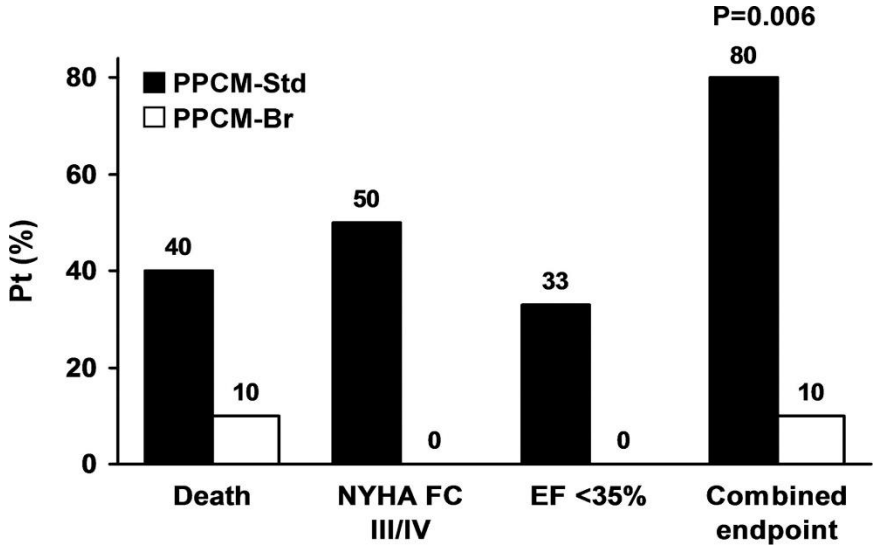
25) Sliwa K et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof of concept pilot study. Circulation. 2010; 121: 1465-1473

Peripartum Cardiomyopathy: Bromocriptine Study

- **Results:** > Recovery of EF: 31% better for PPCM-BR (**27%->58%);**
PPCM-Std (**27%->36%),** p=0.012

> Primary Outcome: PPCM-Br patients better outcome, P=0.006





25) Sliwa K et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof of concept pilot study. Circulation. 2010; 121: 1465-1473

Peripartum Cardiomyopathy: Prognosis

Prognosis:

- Treatment duration: continued until recovery of LV function, 6-12 months or lifetime
- Usually return to normal heart size within 6 months
- 30-50% recover baseline LV function within 6 months
- Prognosis is positively related to recovery of LV function
- failure of LV size to return to N is associated w/ inc M & M
- **94% survival rate in 5 years**;
- Mortality vary: **0-9% -15%**

4) Fett JD et al. Five year prospective study of the incidence and prognosis of peripartum cardiomyopathy at a single institution. Mayo Clin Proc 2005; 80 (12): 1602-1606

5) Pearson G et al. National Heart, Lung and Blood Institute and Office of Rare Diseases (National Institute of Health) Workshop Recommendations and review. JAMA. 2000; 283 (9): 1183-1188

16) Ntusi NB, et al. Aetiology and risk factors of peripartum cardiomyopathy: a systematic review. Int J Cardiol. 2009; 131 (2): 168-179

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29) Felker GM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000; 342: 1077-1084

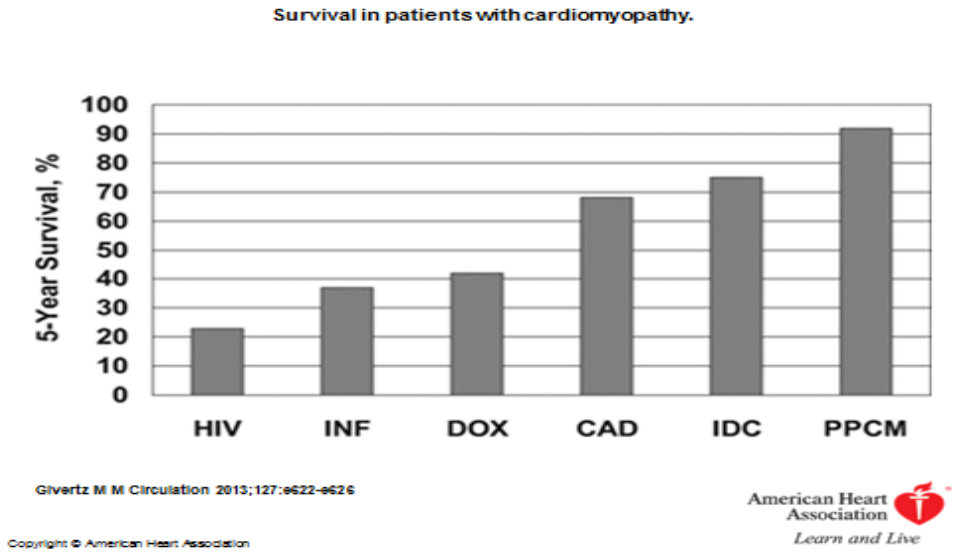
Peripartum Cardiomyopathy: Prognosis

Prognosis:

- Predictors for normalization:
  a) LVEDD ≤ 55mm
  b) LVEF ≥ 27%

- Predictors for persistent LV dysfunction:
  a) Trop T (measured 2 wks after onset) = inversely correlated with LV function at 6 months: > 0.04ng/ml (Sn=55%, Sp=91%)
  b) FS ≤ 20%
  c) LVEDD ≥ 56 – 60 mm

- EF is the strongest predictor of outcome



12) Sliwa K et al. Peripartum Cardiomyopathy: analysis of clinical outcome, LV function, plasma levels of cytokines and Fas/Apo-1. J Am Coll Cardiol. 2000; 35 (3): 701-705

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31) Duran N, et al. Predictors of prognosis in patients with peripartum cardiomyopathy. Int J Gynaecol Obstet 2008; 101: 137-140

32) Hu CL, etal. Troponin T measurement can predict persistent left ventricular dysfunction in peripartum cardiomyopathy. Heart 2007; 93: 488-490

Peripartum Cardiomyopathy: Summary

- Provide standard HF care
- ASA recommended, anticoagulant therapy considered
- **Bromocriptine is a new option for intractable HF**

- Mortality varies up **15%** but overall prognosis is good with more than **90% survival rate in 5 years**

- Predictors for prognosis should be used when counselling patients regarding **subsequent pregnancy** who are at high risk for recurrence (30-50%)

Grazie per l'attenzione