Peripartum Cardiomyopathy

NASOM, 9/20/13

Providence RI

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32 yo G2P1 DOE at 36 weeks

Physical examination:

140/100, 90, 28, 94% RA

S1S2 nml, 3/6 HSM

JVP=6 cm

Bibasilar rales

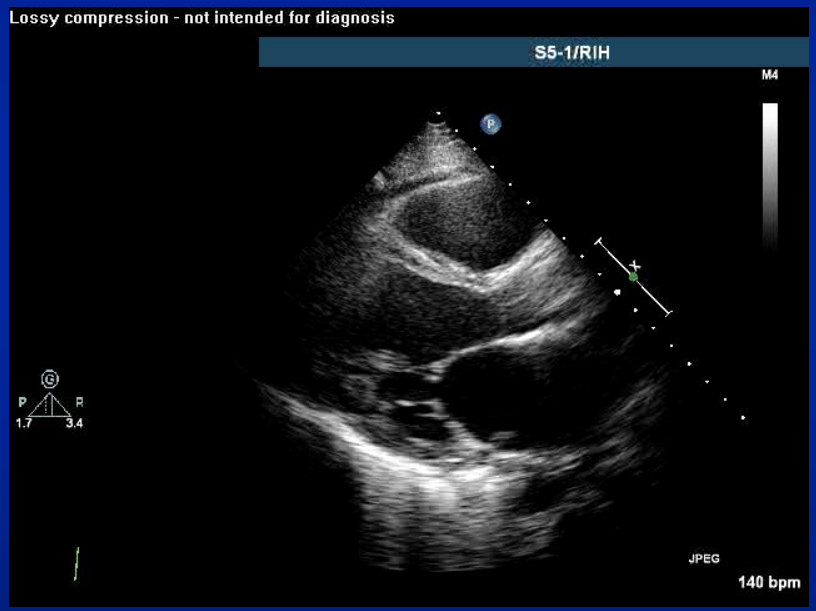
Gravid uterus

2+ pitting edema to knees

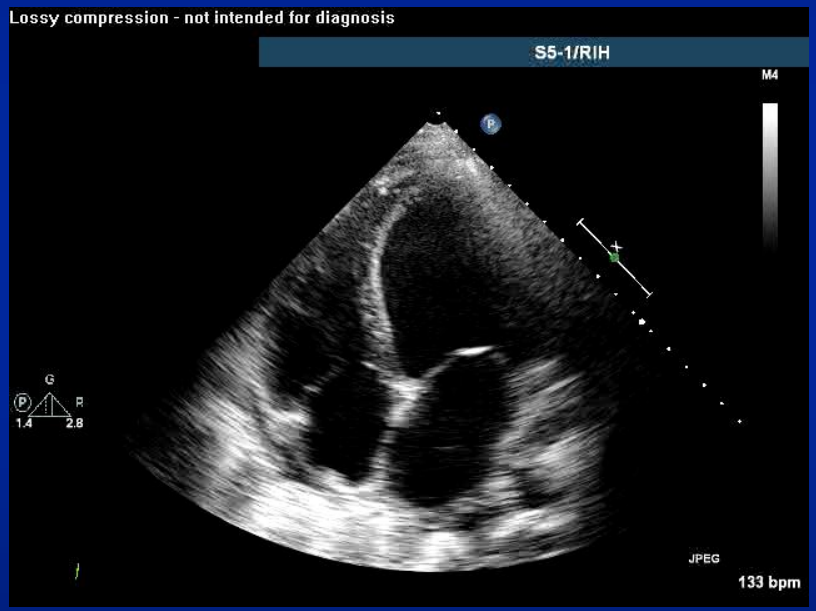
ECG: unremarkable CXR: pulmonary edema

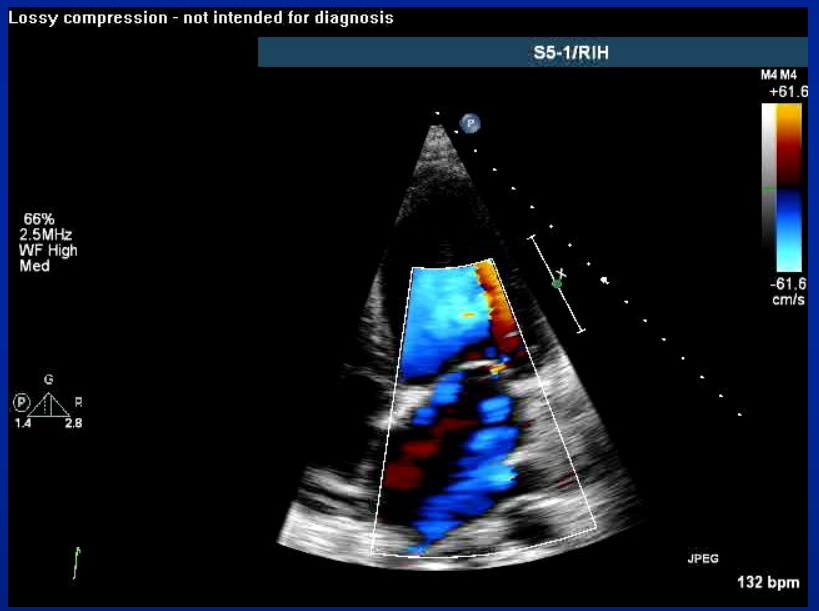
LABS: WNL (negative for preeclampsia)

Echocardiogram



Echocardiogram





Peripartum Cardiomyopathy
Diagnostic Criteria

- Onset 1 mo before or 5 mos after delivery
- No identifiable cause of heart failure
- No recognizable heart disease prior to the last month of pregnancy
- Echo: LV dysfunction
  - LVEF < 45% AND/OR FS < 30
  - LVEDD > 2.7 cm/m2

    - NHLBI workshop, Pearson GD JAMA 2000;283:1183

Peripartum Cardiomyopathy: Other Diagnostic Criteria?

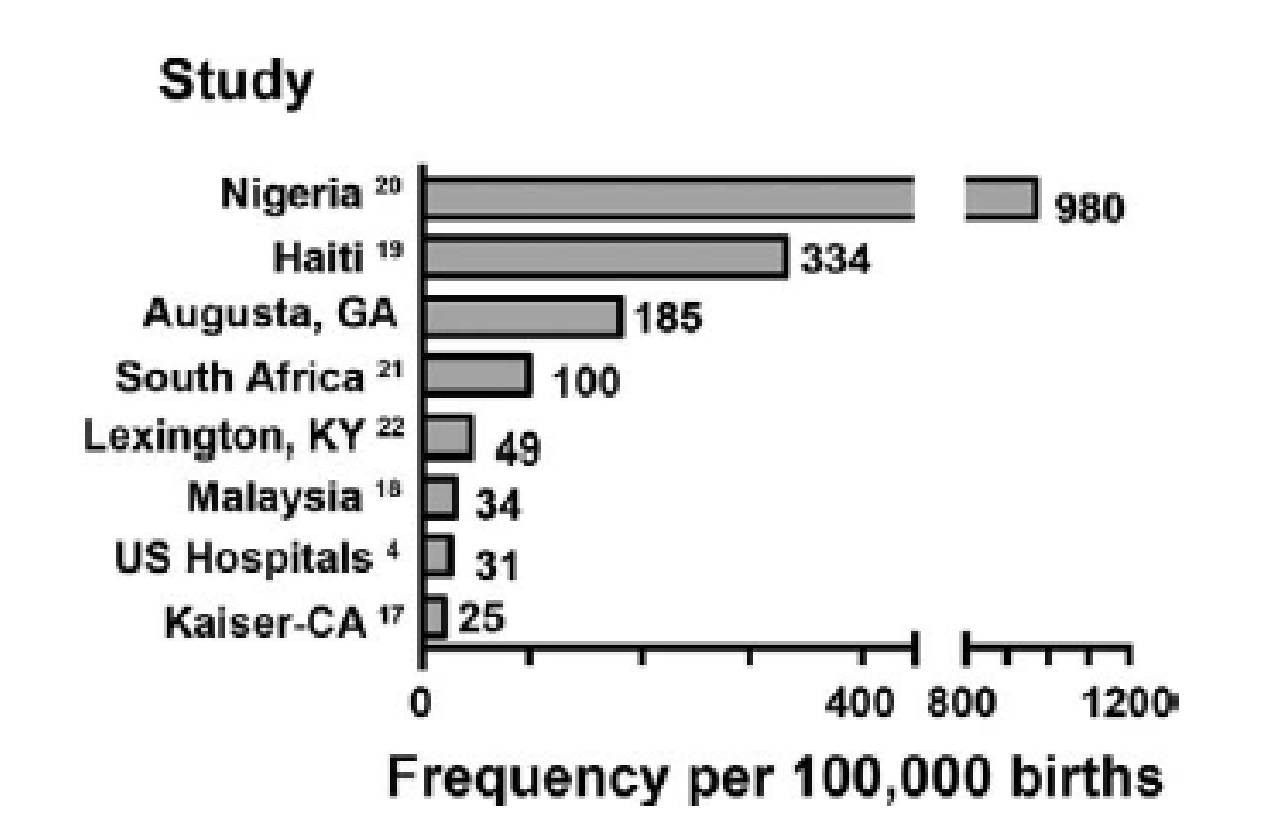
- Cardiomyopathy presenting BEFORE 36th week has similar presentation and prognosis
  - 23 presenting early (32 wks) vs 100 presenting late (38wks)
  - Age, HTN, LVEF and mortality equal
  - More twin pregnancy and preterm delivery
    - Elykam Circ 2005;111:2050
- ESC definition: does include ANY time during pregnancy

- Preeclampsia: when severe includes pulmonary edema
  - Pulmonary vascular hydrostatic >plasma oncotic pressure
  - NORMAL LVEF

Peripartum Cardiomyopathy: Epidemiology

- 1:4000 US women
  - Pearson GD, JAMA 2000;283:1183
- 1:300 Haitian women
  - Mayo Clin Proc 2005
- 1:300 African American vs 1: 4000 Caucasian
  - Gentry MB. JACC 2010;55:654

Peripartum Cardiomyopathy: Epidemiology



Gentry MB. JACC 2010;55:654

Risk Factors for PPCM

- African American Descent
- Age > 30
- Pre-eclampsia and eclampsia
- Multigestations
- +/-Multiparity

– JAMA 2000;283:1183. Circ 2005;111:2050.
EHJ 2006;27:441 JACC 2010;55:654
EJHF 2010;12:767 JACC 2011;58:659

Peripartum Cardiomyopathy: Prognosis

- Pregnancy Mortality Surveillance System, 1991-1997
- 7.7% of pregnancy-related deaths due to CM
  - 245 CM deaths in US, 0.88/100,000 live births
  - 70% PPCM
    - Whitehead SJ. ObGyn 2003;102:1326.

- ICD codes in SoCA Kaiser, 1996-2005
  - 60 PPCM patients in 241,297 deliveries
  - 97% freedom from death at 4.7 year f/u
  - 1:1400 AA, 1:4000 C, 1:9800 H and A
    - Brar AJC 100: 302,2007.

Peripartum Cardiomyopathy: Prognosis

	N (% recover)	Mortality	Transplant	F/U
Witlin ‘97	28 (36%)	18%	11%	4yrs
Elkayam‘05	100 (54%)	9%	4%	2 yrs
Felker ’00	42	7%	7%	8.6 yrs
Amos ‘06	55 (64%)	0%	10%	2yrs
Fett ’05	98 (28%)	15%		2.2 yrs
Silwa ‘06	100 (28%)	15%		5 yrs
Goland* ‘09	182 (49%)	7%	6%	1.5 yrs

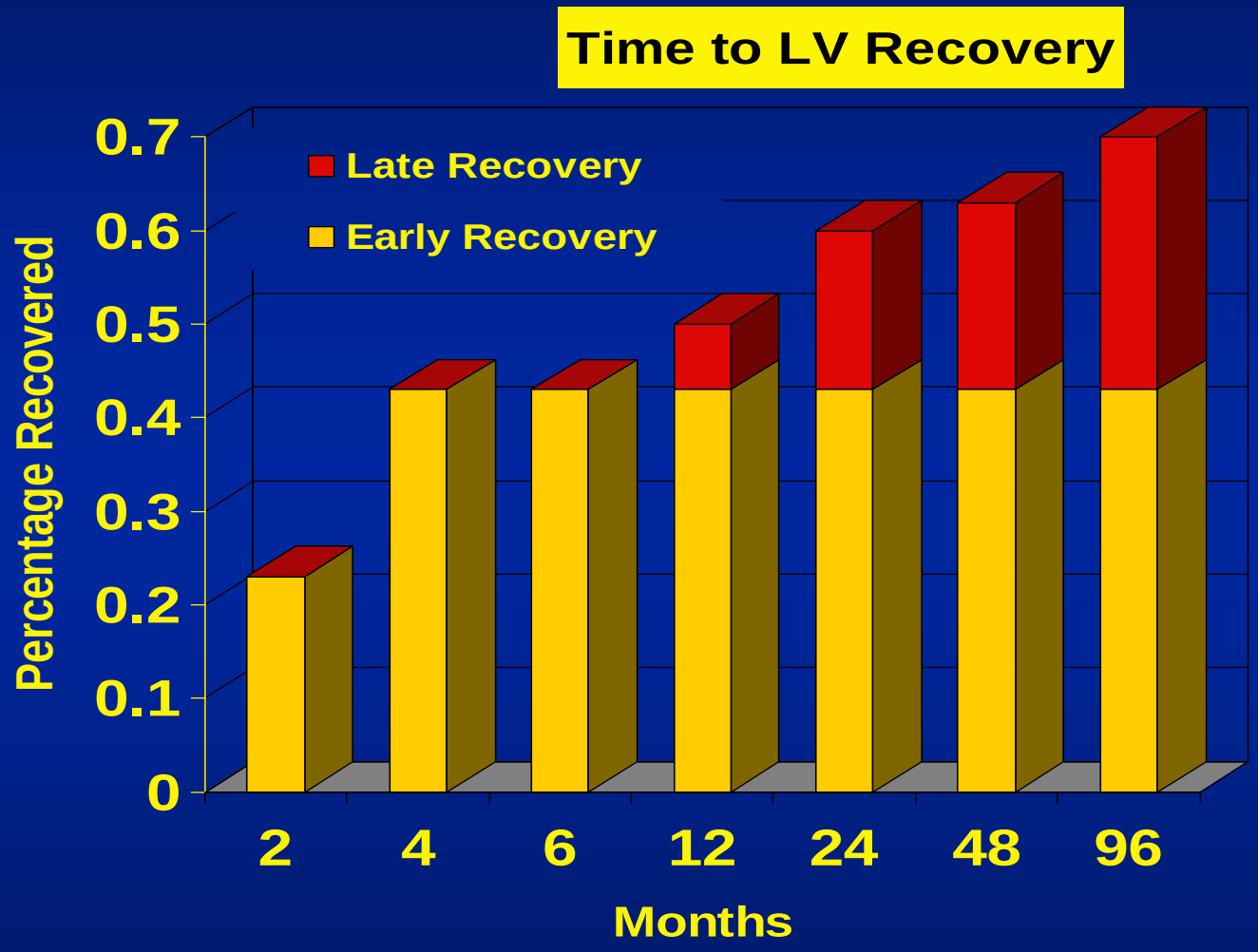
*87% deaths within first 6 months

Peripartum Cardiomyopathy: Prognosis

- 1990-2003 Duke CHF clinics/echo lab: 55 patients
  - 62% improved
  - 25% unchanged
  - 10% required transplant
  - No deaths
    - Amos AM AHJ 152:509,2006.
- 1997 survey of doctors:76/233 pts records +24 USC
  - 54% improvement
  - 4% transplant
  - 9% mortality (4 SCD, 2 tx comp)
    - Elkyam Circ 111;2050,2005.

Peripartum Cardiomyopathy: RI

- Women & Infant Hospital: 90% RI deliveries
  - RIH Heart Failure Center: 80% PPCM
- 35 patients/ 10 years
  - LVEF = 34% ± 10%
  - 65% white, age 32 ± 5yrs
- Prognosis
  - 69% recovered function
  - 3-6% mortality at presentation:
    - 1 SCD (survivor), 1 CHF death peri-delivery



Of those that recover:

- 60% at 6mos
- 75% at 1 year
- Additional 25% after 2years

Early vs. Late Recovery			
	Early (≤6mo) n=13	**Late (>6mo) n=8**	**P value**
Race			
Caucasion	85%	83%	0.704
Black	0%	0%	1.000
Hispanic	0%	16%	0.350
Other	15%	0%	0.456
Age (yr)	34.5	29.8	0.109
LVEF at presentation	34.5%	29.8%	0.085

Predictors of Recovery of Left Ventricular Function

- Most patients recover by 6 mos
- Predictors recovery based on baseline data:
  - LVEF>30%
  - LVEDD< 6cm
  - Cardiac Troponin T
  - Contractile reserve by DSE
    - Circ 2005;111:2050.
      Heart 2007;93:488.
      JCF 2011;17:426
      ObGyn 2005;105:1303.
      JASE 2005;18:45
      JACC 2011;58:659

Prognosis - Recovery

- Chart review of 33 patients, with follow up > 3 years

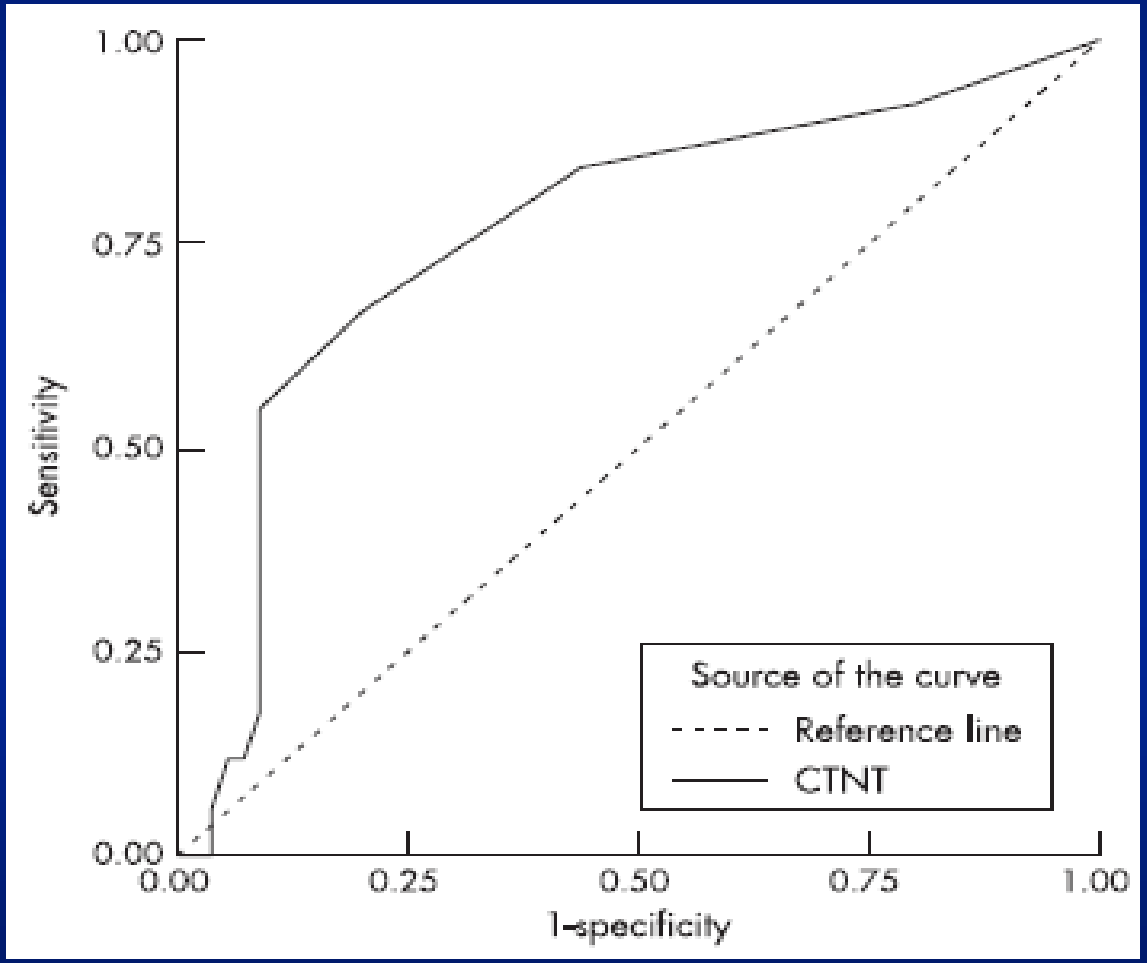
Table 2. Risk for Persistent Left Ventricular Dysfunction Based on Echocardiographic Parameters at Time of Initial Diagnosis

	Relative Risk	95% Confidence Interval	*P*
Fractional shortening < 20%	3.06	1.31–7.16	.004
Left ventricular end diastolic dimension ≥ 6.0 cm	3.55	1.02–12.33	.01

Chapa et al. Obstet Gynecol 2005;105:1303

Prognosis - Recovery

- Prospective trial studying 106 newly diagnosed PPCM patients. TnT was measured < 2 weeks of onset of PPCM
- TnT>0.04 predicted persistent dysfunction with SN 55%, SP 91%



Hu et al. Heart, 2007;93:488

PPCM with HTN with rapid recovery

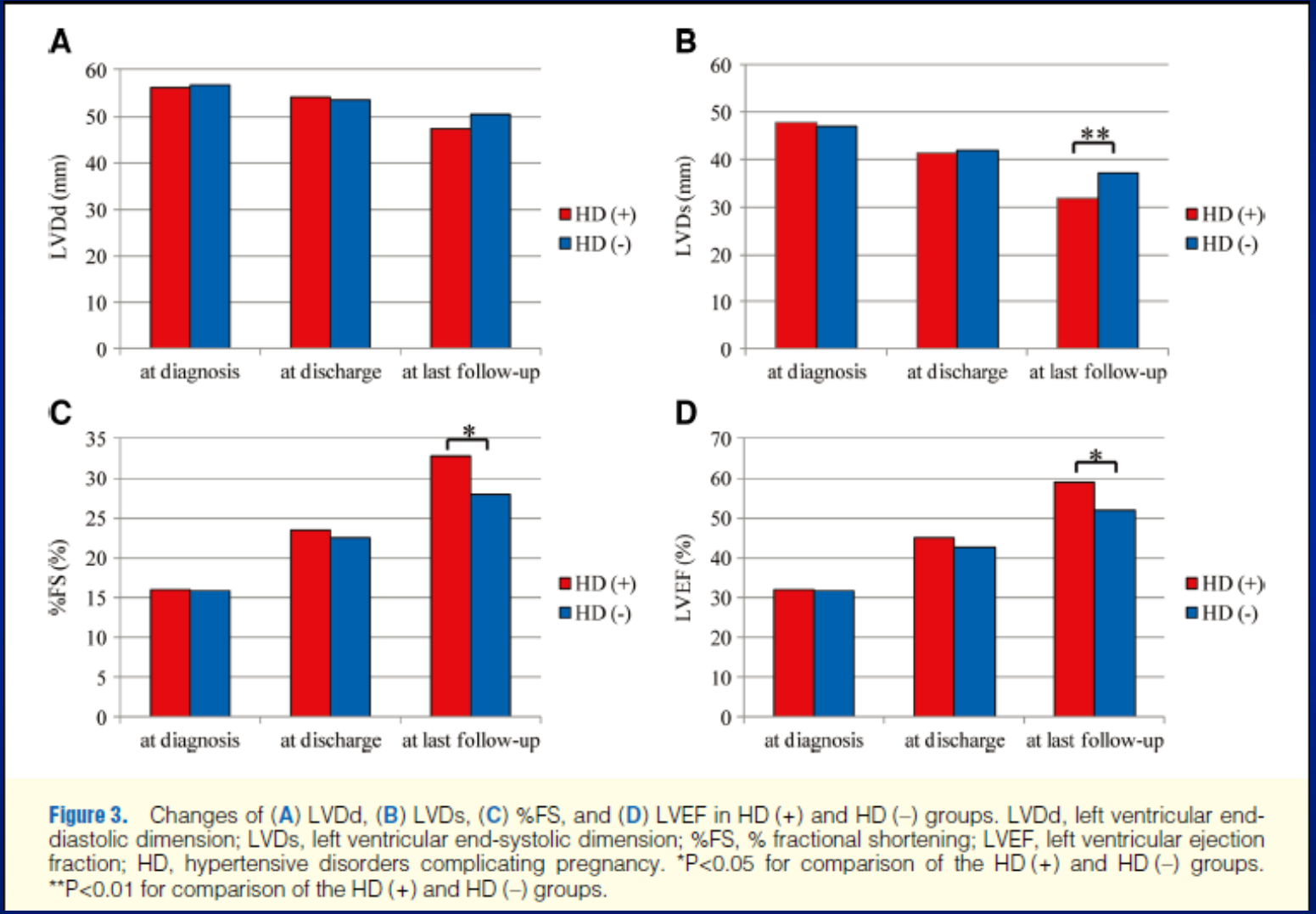


Figure 3. Changes of (**A**) LVDd, (**B**) LVDs, (**C**) %FS, and (**D**) LVEF in HD (+) and HD (–) groups. LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; %FS, % fractional shortening; LVEF, left ventricular ejection fraction; HD, hypertensive disorders complicating pregnancy. *P<0.05 for comparison of the HD (+) and HD (–) groups. **P<0.01 for comparison of the HD (+) and HD (–) groups.

42/102 PPCM with HTN. Kamiya CA. Circ J 2011;75:1975

Risks of Repeat Pregnancy

- Haiti: 15/99 PPCM recurrent pregnancies
  - 8 (53%) increased CHF (1 death)
  - 7 no change & recovered
    - Fett JD Annals 145;330,2006.
- Retrospective survey of doctors: 44 pts
  - 16 (EF=36%) vs 28 nml EF
  - ALL showed reduced EF
  - CHF 44% vs 21%, Mortality 19% vs 0
    - Elkyam U. NEJM.2001;344:1567.
- Web-based 61 PPCM (26 EF<55%)
  - 30% worsened: 46% vs 17% recovered
    - Fett Int J wGyn Obst 2010;109:34

Why?

- Pathophysiology: _Hemodynamic stress worsens function and structure
- Proposed Mechanisms: cellular and genetic
- Risk factors: correlation does not prove causality

Pathophysiology: Hemodynamic stress worsens function and structure

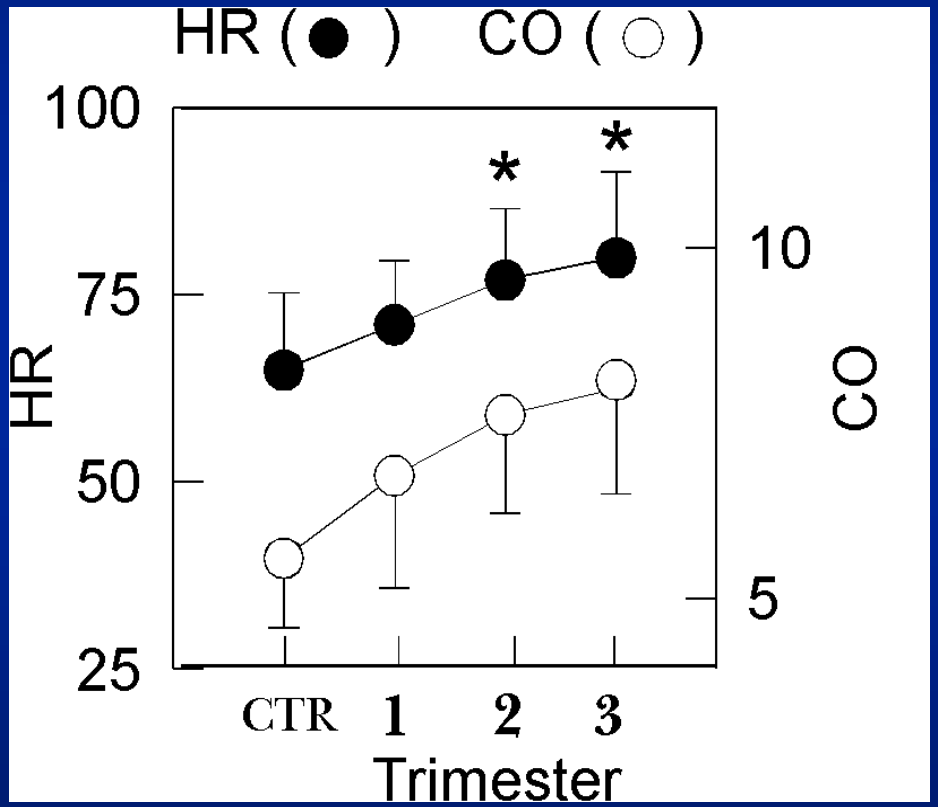
Dilated Cardiomyopathy:

- Increase in volume and chamber dilation worsens pre-existing function and symptoms

Normal Cardiovascular Alterations in Pregnancy

- Hemodynamic Changes
  - Preload and CO increased
- Structural changes
  - Ventricle and atria enlarged
  - Valves increase insufficiency
  - LV mass increased

Hemodynamic Changes During Normal Pregnancy



- 30-50% ⇧ CO
  - Increase SV early
- 10-20% ⇧ HR
  - 10-20 BPM
- 30% decrease in TPR
  - 600-800 dynes/sec/cm2

Poppas A.Circ.1997;95:2407

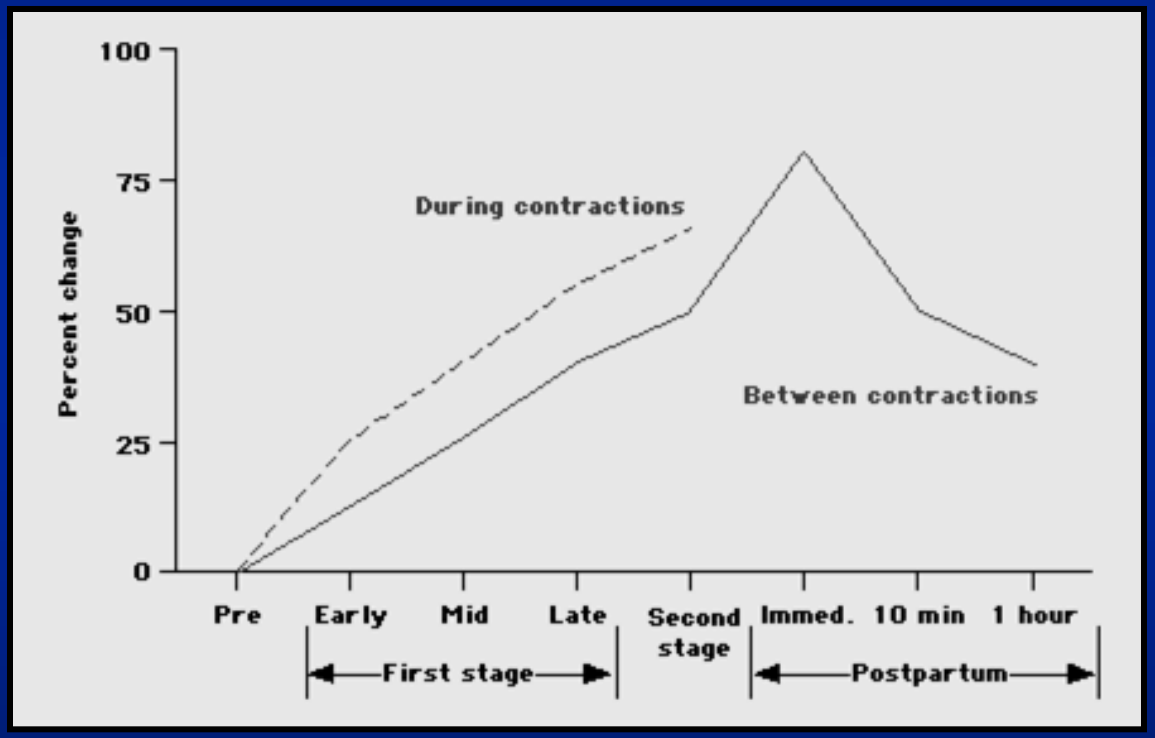
Hemodynamics of Labor and Delivery

- Increased cardiac output
  - 25% in first stage
  - 50% during contractions
  - 50% in second stage
  - 80% early postpartum
    - autotransfusion

23 women: CO by indocyanine

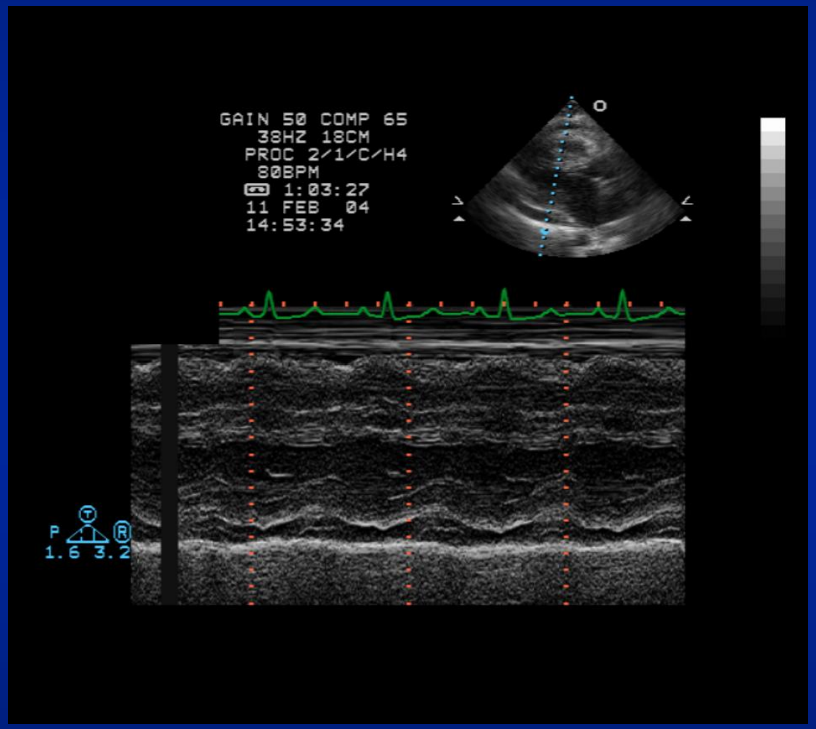
Ueland K. AJOG.1969:8-18.

Cardiac Output



Bonica & McDonald. Principles and Practice of Obstetric Analgesia and Anesthesia

Structural Changes in Pregnancy



5-15% increase chamber dimensions

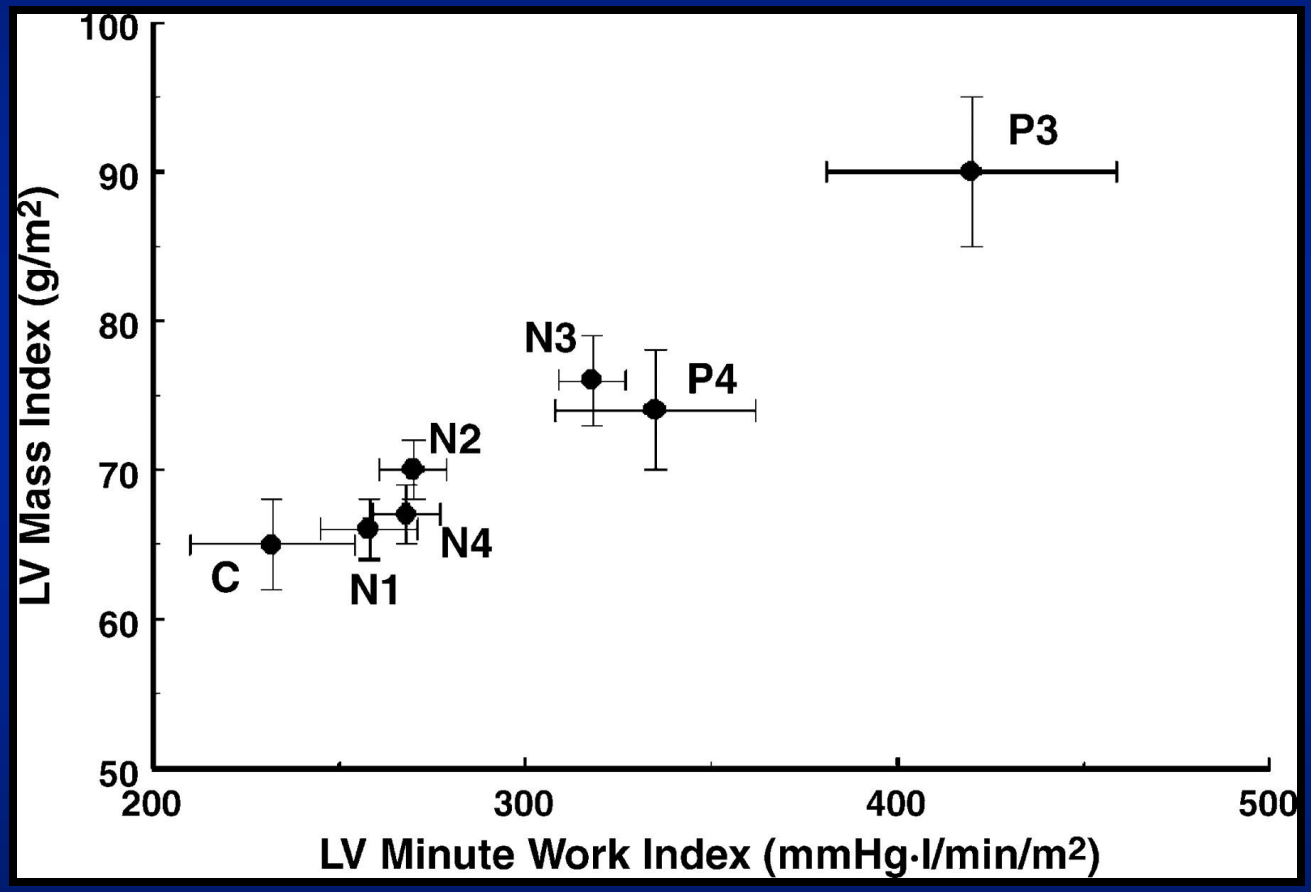
- Atria
  - 10-15% increase
- Ventricle
  - 7-10% increase LVEDD
- Valvular annular diameters
- Return to nml postpartum
  - 6mos
    - Katz Circ ’78
    - Duvekot AJ Ob Gyn ’93
    - Robson Br J Ob Gyn ’87 & AJP ‘89

Cardiac Structural Alterations: LV Mass

- Acute, physiological LVH and increased mass
  - Increased volume load and wall stress
  - Eccentric hypertrophy: thickness/dimension unchanged
    - Similar to trained athletes, increase in preload

- Increase in LV mass
  - 10-22% increase, peaks in 3rd trimester
  - Most normalized when adjusted for body mass/wt gain
  - 6mos to return to normal, time for LV remodeling
    - Robson AJP'89, Lee JMFM '92, Poppas '97,
    - Simmons '02, Sadaniantz JASE '92, Mone '97

Change in LVM is proportional to increase in cardiac workload



LVMWI=

SVxMAPxHR

Control, Nml (trimester 1,2,3 & Postpartum(4)

Preeclampsia (trimester 3 and Post(4)

Simmons LA.AJP.2002;238:1627

Structural and Functional Changes

TABLE 3. LV Parameters

	Trimester of Gestation			Postpartum	
	First	Second	Third	8 Weeks	>6 Months
LV structure					
D_{LVOT}, cm	2.0±0.2	2.1±0.2*	2.1±0.2*	2.0±0.2	2.0±0.2
D_{ED}, cm	4.8±0.5	4.9±0.4	4.9±0.5†	4.8±0.4	4.7±0.5
D_{ES}, cm	3.0±0.4	3.1±0.3	3.1±0.4	3.1±0.4	3.1±0.4
h_{ED}, cm	0.8±0.2	0.8±0.1	0.9±0.1	0.9±0.1	0.8±0.1
h_{ES}, cm	1.4±0.2	1.4±0.2	1.4±0.2	1.4±0.1	1.4±0.2
LVM, g	131±36	141±31	147±36†	140±34	132±28
LV function					
SF	0.37±0.04	0.37±0.03	0.37±0.04	0.36±0.03	0.36±0.04
Vcf_C, circ/s	1.07±0.14	1.04±0.13	1.08±0.14	1.12±0.14	1.10±0.15
σ_{ES}, g/cm^2	38±14	37±8	37±11	39±8	41±13

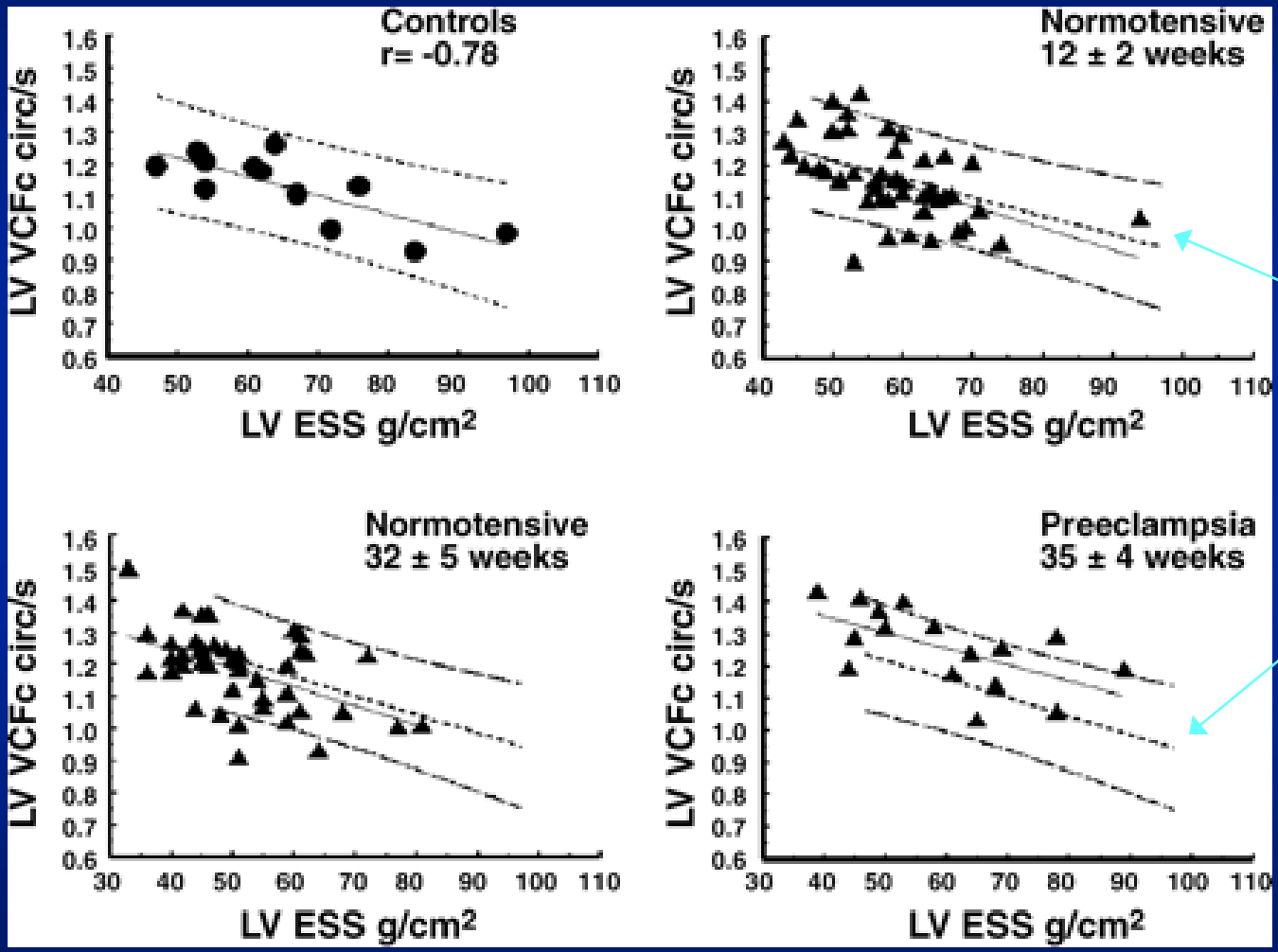
*p<.05 vs 8 week postpartum control

+p<.05 vs >6 month control

Cardiac Function and Contractile Reserve During Normal Pregnancy

- Measures of LV function are load-dependent
  - EF, FS, Vcf
  - Increased in pregnancy
    - Capeless AJObGyn ‘89, Robson AJP ‘89, Mabie AJObGyn ‘94
  - Swan-Ganz, 36wks/12 wks post, No difference PWP/SWI
    - Clark Am J Ob Gyn ‘89
- Myocardial contractility is probably unchanged
  - Vcf_c relative to σ_{es} is an afterload adjusted, preload independent index of contractility
    - Gilson Ab Gyn ‘97
    - Mones Circ ’96

LV Contractility in Normal c/w Preeclampsia



CTR regression relationship

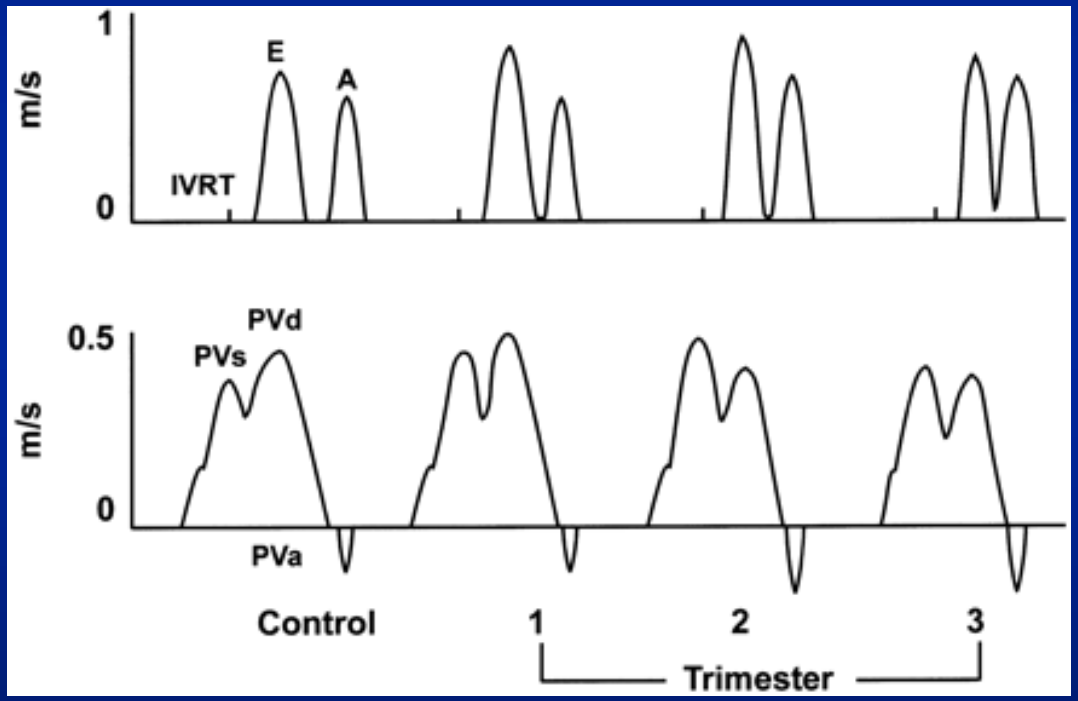
Simmons LA.AJP.2002;238:1627

Diastolic Function in Pregnancy

Reduced LV compliance w/ LVH

- 37 women, echo each trimester
- DT: decreased
- IVRT: no change
- PVdTVI: decreased with increased LV filling
- PVa increases similar to:
  - ***Animal data of increased LAP or volume loading***

E/A: 1.4±.2 1.6±.4 1.4±.3 1.3±.2

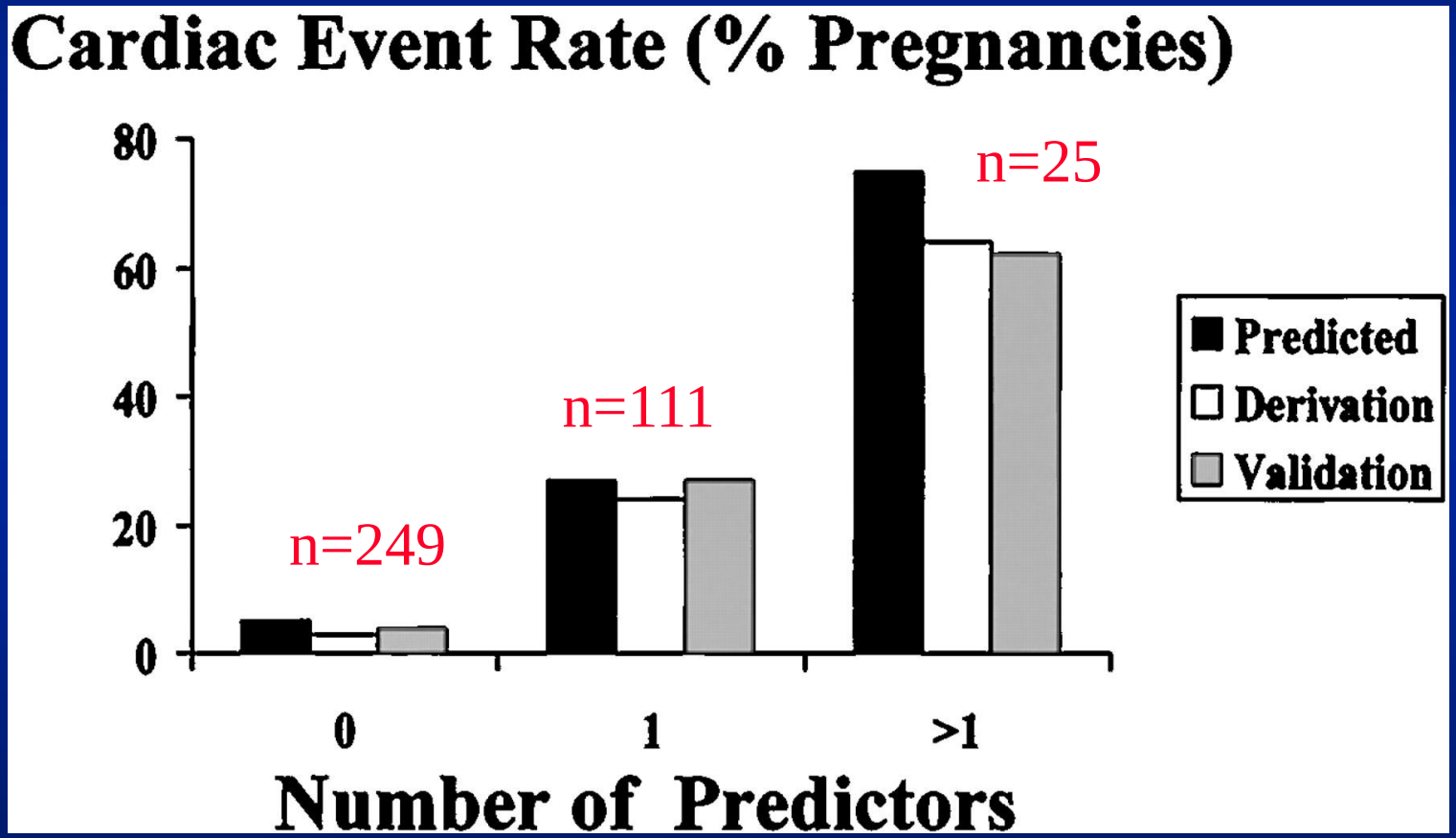


Messa. Circ 1999;99:511.

GENERAL Predictors of Maternal Complications Based on Cardiac Risks

1. NYHA functional class >II, or cyanosis
2. Myocardial dysfunction:
   - LVEF<40%
   - Complex CHD
3. Left heart obstruction
   - MS, MVA<2 cm2
   - AS, AVA<1.5cm2, LVOT P>30mmHg
4. Prior Cardiac events:
   - CHF
   - TIA/CVA
   - Arrhythmias requiring therapy

Multicenter Prospective Study : 599 pregnancies



23 DCM, 7 NYHA class III, 6 new dx

12/23 AE (7 CHF, 1 CVA, 1 SCD)

Siu S. Circ.2001;104:515.

PPCM and DCM

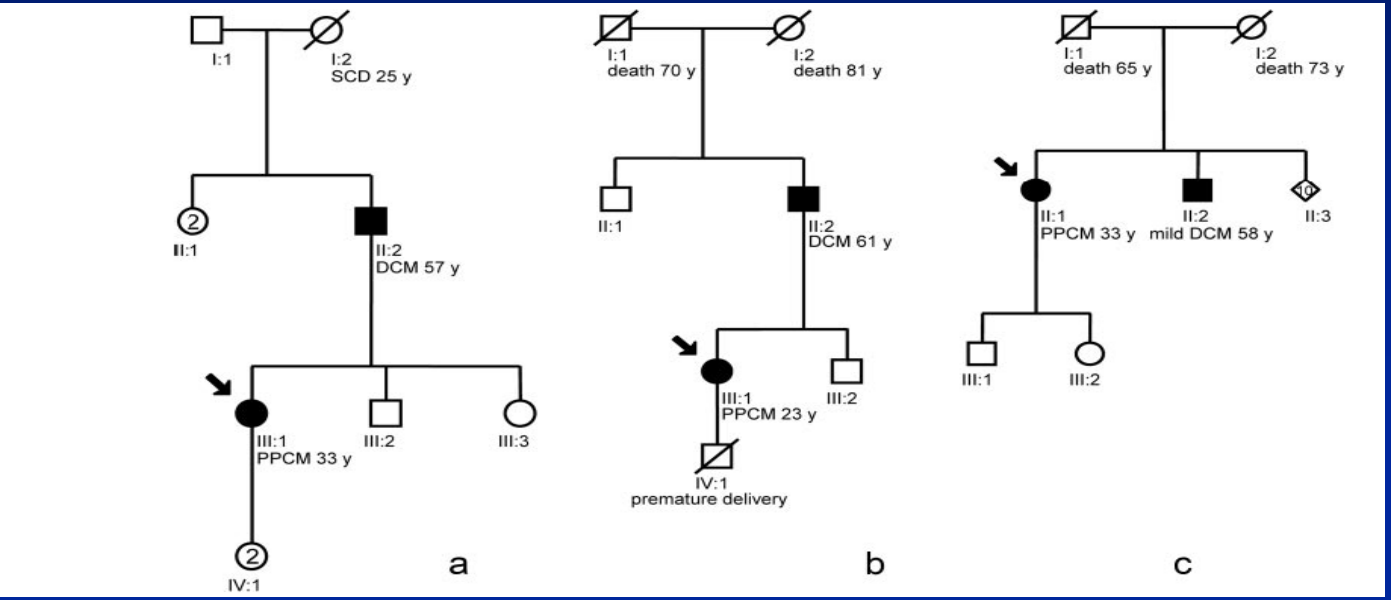
- Brazil: 18 PPCM (7 recovered) and 8 DCM
  - Cardiac complications greatest DCM compared with PPCM with persistent LV dysfunction
    - Avila WS. Arq Bras Cardiol 2002;79:484.
- NYC: 23 PPCM and 8 DCM, 1990-2000
  - 3 deaths and 4 transplants in PPCM
  - 1 TAB then transplant in DCM
    - Bernstein PS. Am J Perinatol. 2001;18:163.

PPCM and Genetics

Background: Familial clustering

- 20-50% of idiopathic DCM likely familial
- Two recent studies:
  - 110 women in 520 families with DCM
  - 45 PPCM cases, 23 with familial clustering, 6/19 sequenced +DCM genes
    - Morales A. Circ 2010;121:2176.
  - 90 DCM families with 5 PPCM cases
  - 3/10 PPCM w/o recovery, ALL w/ DCM in family
    - Van Spaendonck K. Circ 2010;121:2169

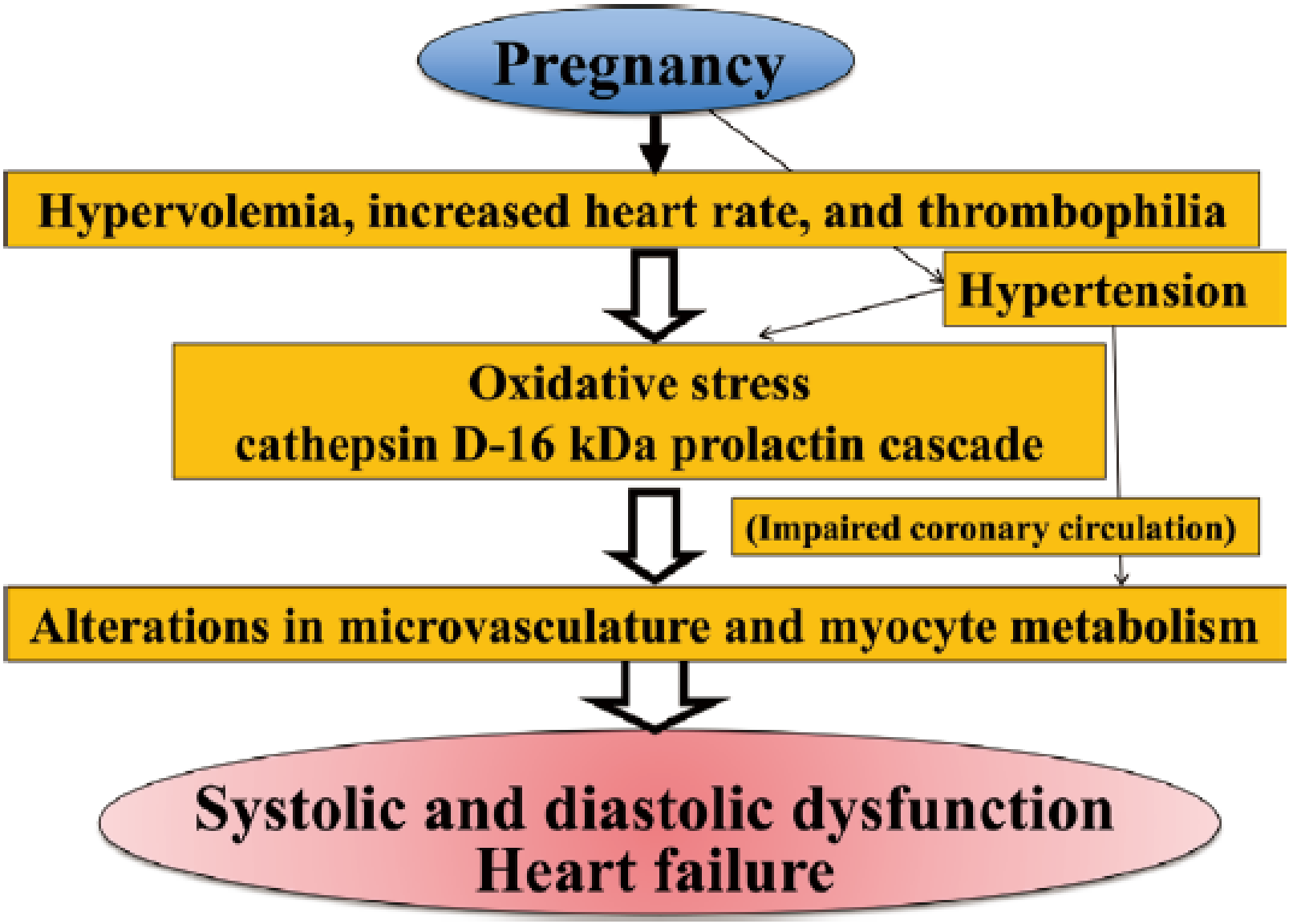
Genetics



- All three PPCM patients in whom screening was done had at least mild DCM in 1st degree relatives
- Suggestive that there may be some genetic predisposition to PPCM, which is unmasked by environmental agents (viral, nutritional, hormonal, etc)

PPCM and Genetics

- Single nucleotide polymorphisms association
  - Chromosome 12p11.11
    - Closest gene: parathyroid hormone
    - Calcium transfer in uterus/placenta, prevents contractions, assoc PEC, inotropic CV
  - Compared 40 women with PPCM to controls
    - Pre and postmenapausal and pregnant
    - OR6-8
    - No difference with preeclampsia
      - Horne BD. Circ Cariovasc Genet 2011. 44:359



Okamoto H. Circ J. 2011;75:1827

PPCM: : Proposed mechanisms

- Inflammatory Cytokines:
  - TNFa, IL6, Fas/Apo1
    - Sliwa K. JACC 2000 35(3):701, EHJ 2006;27:441.
- Viral-associated inflammation
  - Bx: viral genomes & interstitial inflammation
    - PV B19, HSV6, EBV, CMV
- Angiogenic imbalance
  - Increased VEGF inhibitors (soluable FLT1)
- Prolactin subunit
  - 16kDa fragment induces damage

Angiogenic Imbalance

- Mouse knockout model:
  - cardiac PGC-1a (regulator of angiogenesis/energy)
  - Develop PPCM, reversed with proganiogenic
- Humans: late gestation placenta secretes
  - VEGF inhibitors (sFLT1)
  - Anti-angiogenic environment
  - Increased in multips and PEC
  - PPCM serum with high sFLT1
    - Patten IS. Nature 2012;9:485:333-8.

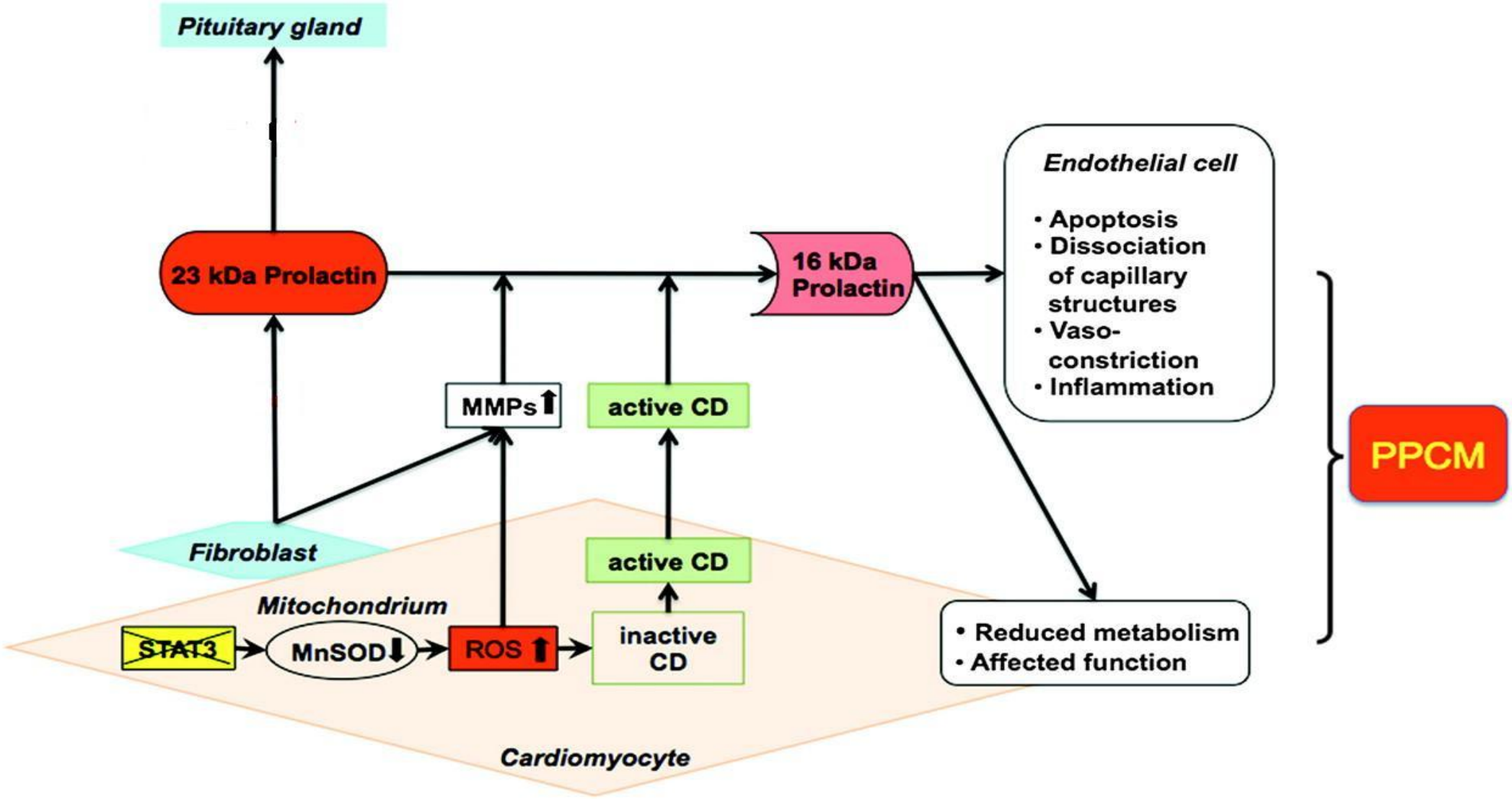
PPCM: prolactin

Prolactin: is upregulated peripartum

- 2 biologically active forms with opposing effects
  - Physiologic full-length 23kDa: promotes angiogenesis and protects endothelial cells
  - Cleaved 16kDa induces endothelial apoptosis and disrupts capillary structures.
- Oxidative stress promotes postpartum generation of 16kDa
  - Related to PPCM
  - Blockade with bromocriptine prevents PPCM in mice, high risk women and in 2pts sped recovery.

- Hilfiker-Kleiner D. Cell 2007;128:589.

Prolactin


Pituitary gland
23 kDa Prolactin
16 kDa Prolactin
Endothelial cell
• Apoptosis
• Dissociation of capillary structures
• Vaso-constriction
• Inflammation
PPCM
MMPs
active CD
Fibroblast
active CD
Mitochondrium
STAT3
MnSOD
ROS
inactive CD
• Reduced metabolism
• Affected function
Cardiomyocyte

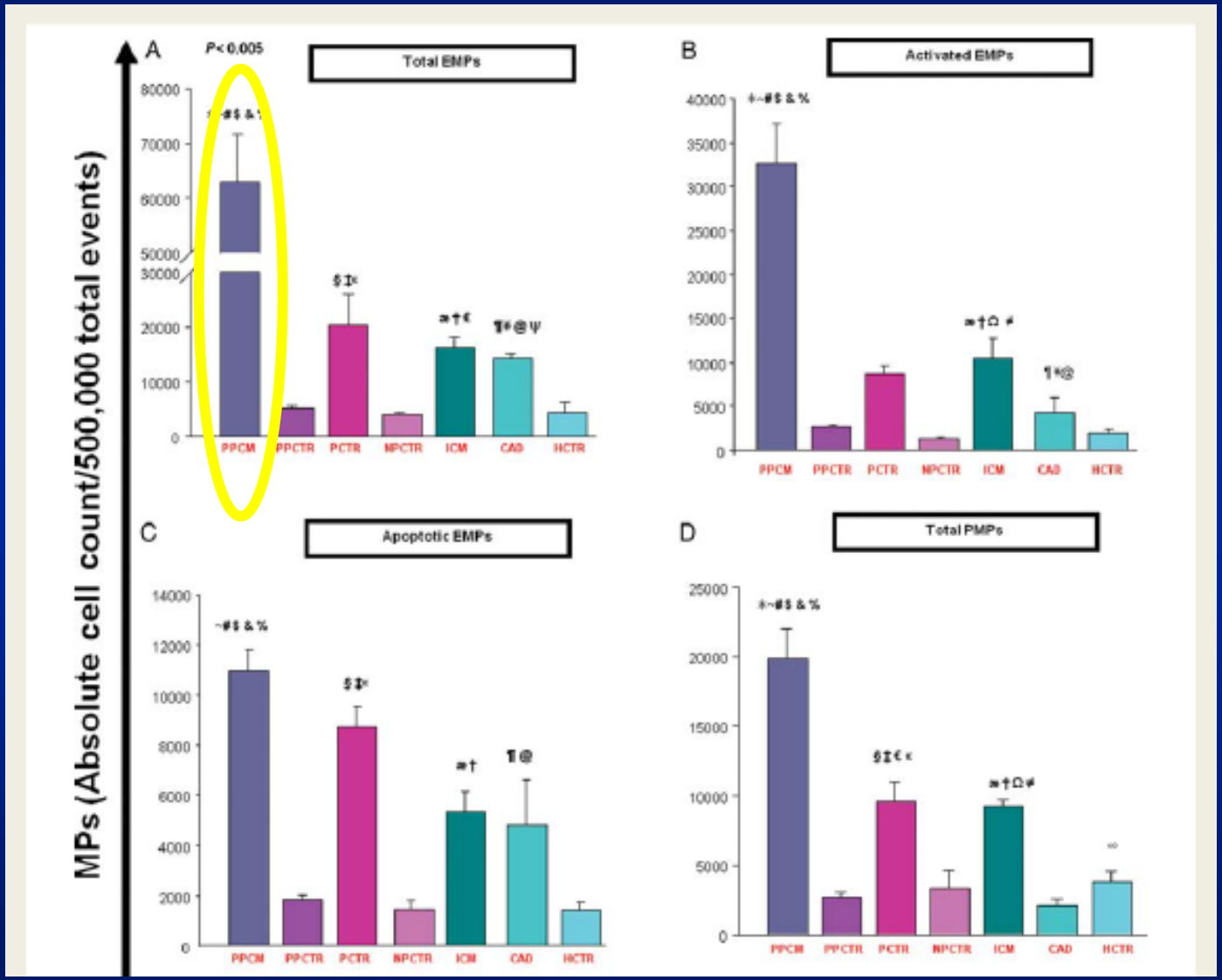
PPCM: prolactin

- STAT3, transcription factor activated by IL-6
  - Angoigenesis and cardiac hypertrophy
    - Deletion in cardiac tissue results in loss of capillary density with age.
  - Reduces reactive oxygen species (and cathepsin D)
  - Cathepsin D increases cleavage product (16kDa) prolactin
  - Prolactin activates STAT3
- Mice cardiomyocyte-specific knock out of STAT3
  - Develop nml pregnancy induced hypertrophy and increase in angiogenises but develop PPCM due to inability to maintain increased density (decreased VEGF & vWf).
- PPCM pts: 3/5 16kDa in serum
  - Decreased STAT3 & increased cathepsin D in EMbx

Potential diagnostic serum markers

- Endothelial damage from cathespin D/prolactin 16kDa
- PPCM c/w healthy postpartum, pregnant and nonpregnant women and ICM, CAD and normal
- Circulating microparticles were significantly increased
  - Activated endothelial particles
  - Platelet-derived particles
- Microparticles were reduced in PPCM treated with bromocriptine
    - Walenta K. Eur Heart J. 2012;33(12):1469

Microparticles marker of endothelial integrity



Walenta K. Eur Heart J. 2012;33(12):1469

Possible Treatment Options

Bromocriptine

- Compelling animal data
- Small randomized pilot study
  - LVEF improvement 58% vs 36%
  - Mortality 1/10 vs 4/10
    - Silwa Circ 2010;121:1465

PPCM: Treatment

- General CHF treatment per guidelines postpartum
- DURING pregnancy:
  - Angiotensin inhibition contraindicated
  - Metoprolol preferred over atenolol
  - Hydralazine IF afterload reduction needed
  - Digoxin is safe
  - No data on aldosterone antagonists
- Anticoagulation postpartum for LVEF<30%
- Arrhythmias: ICD for primary prevention

32 yo G2P1 DOE at 36 weeks

Diagnosis:

- Peripartum cardiomyopathy
- Pregnancy-induced hypertension

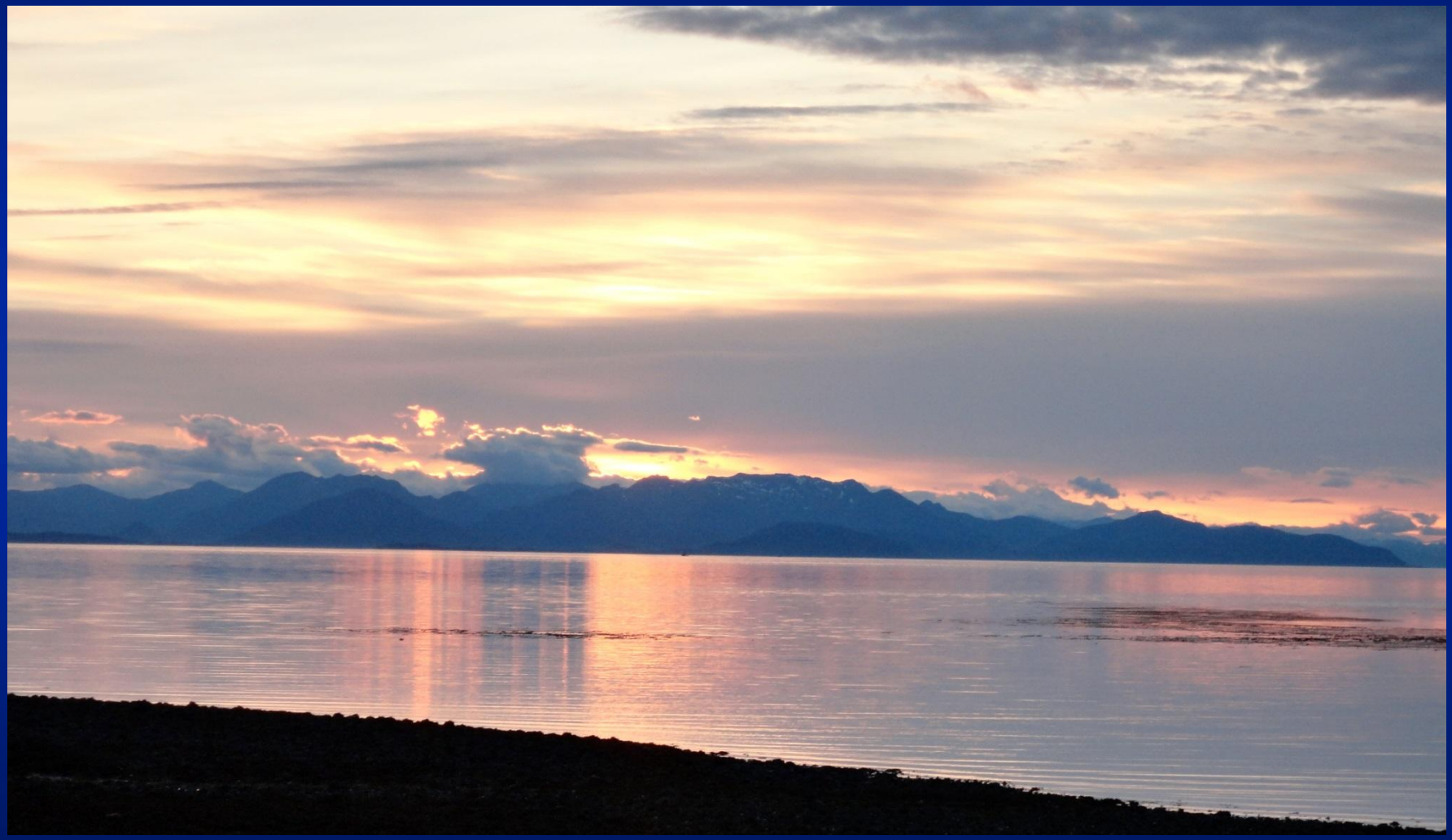
Course:

- Admitted, treated with labetolol and hydralazine, induced and delivered
- One week in ICCU: iv diuresis, ACEI, betablocker
- NSVT at 6 week f/u, LVEF 20%, ICD implanted
- IUD at 6 weeks, counseled against future pregnancy
- Improved LVEF to 40% after 8 mos , 60% after 4 years

SUMMARY

Definition	1 mo pre*, 5 mos post LVEF<45
Prognosis	50-60% recover, 6mos 0-15% mortality
Risk Factors	African descent Age, HTN
Treatment	Avoid ACEI during Coumadin post ?bromocriptine

Thank you for you attention!



Neonatal Risks in Women with Heart Disease

- 13 centers: 302 women with heart disease (HD)
  572 healthy controls (NML)
- Neonatal events: HD 18% vs NML 7%
  - age 20-35; no smoking, anticoagulants, OB risks:
    - 5% HD vs 4% NML
  - **age <20 >35 & smoking, multi gestations or OB risks**:
    - 27% HD vs 11% NML

– Siu SC. Circ. 2002;105:2179.

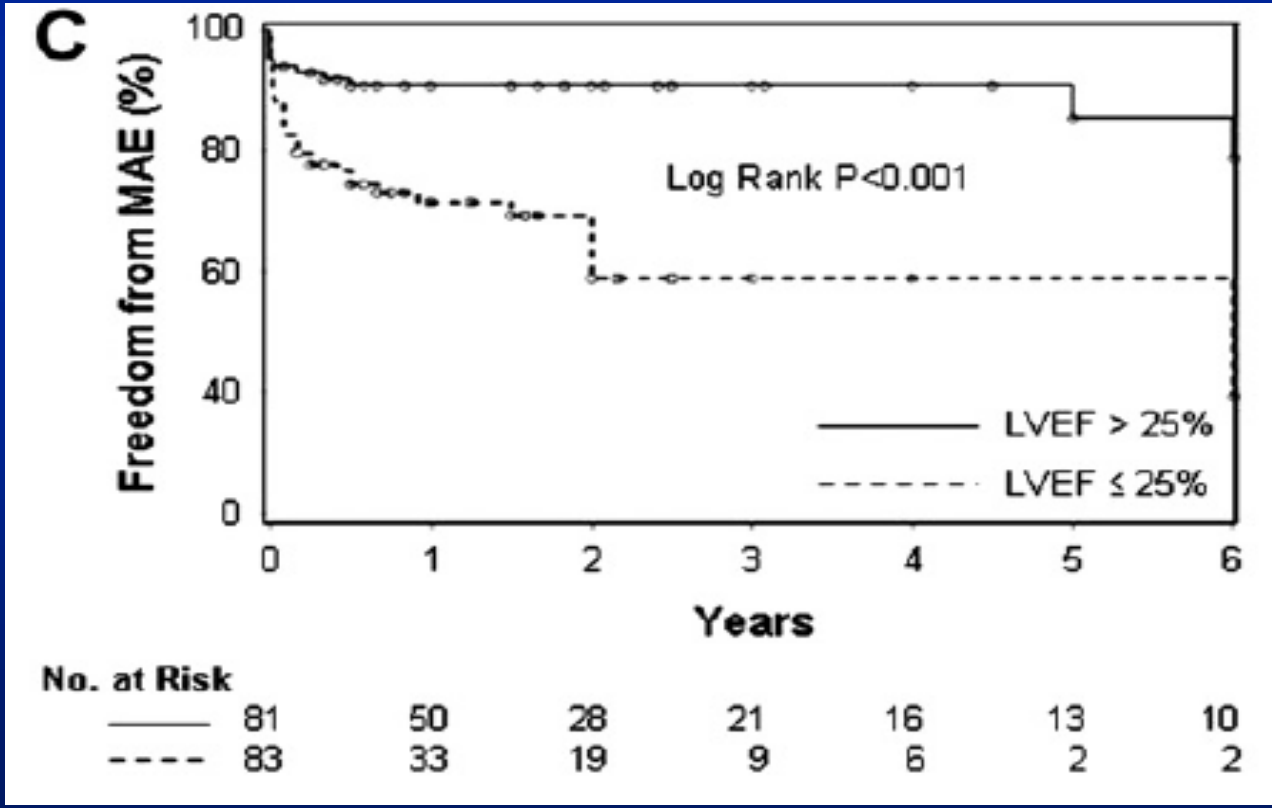
Prognosis - Complications

Table 1. Comparison between clinical characteristics of PPCM patients with and without major adverse events

	No MAE n=136	MAE n=46	p-value
Age (years)	30±6	27±8	0.03
Age > 30 years	53%	42%	0.3
Non-Caucasian	37%	61%	0.005
Parity	2.0±1.6	2.0±2.1	0.3
Multipara	53%	41%	0.3
Twin or triplet pregnancy	19%	4%	0.02
Gestation hypertension	46%	32%	0.2
Tocolytic therapy	18%	17%	1.0
Index pregnancy			0.3
1st	43%	56%	
2nd	16%	14%	
3rd and more	41%	30%	
Caesarian delivery	21%	15%	0.7
Occurrence of symptoms antepartum	30%	41%	0.2
Occurrence of symptoms postpartum	64%	54%	0.3
Diagnosis delay (weeks)	1.7±3.0	3.8±6.1	0.02
Diagnosis delay (≥ 1 week)	48%	60%	0.3
LVEF (%) baseline	31±11	24±10	<0.001
LVEF ≤ 25%	31%	63%	0.001
LVEF (%) at ≥ 6month	47±13	32±14	<0.0001
LV Recovery (LVEF ≥ 50%)	45%	18%	<0.001

Prognosis - Complications

- Retrospective review of 182 patients, analyzing MAE (transplant, death, ICU stay, CPR, device implant)



PPCM: Risks of Recurrent Pregnancy

- 15/99 pts with PPCM, Haiti/5years
  - 15/16 pregnancies with ***persistent LV dysfunction***
  - 53% worsened CHF: 1/8 recovered LVF, 1/8 died
  - 47% no change, all recovered LVF
    - Fett JD. Ann. 2006;145:30.

- Survey of 15,000 doctors, 409 response, 92 pts:

  44 women, 60 pregnancies
  - 16 abn LVF: EF=36 to 32%, CHF 44%, mortality 19%
  - 28 nml LVF: EF=56 to 49%, CHF 21%, mortality 0
    - Elkyam. NEJM.2001;344:1567.

  **? Bromocriptine