



Università degli studi
di Modena e Reggio Emilia



CONVEGNO REALIZZATO CON IL CONTRIBUTO DELLA

 **FONDAZIONE**
Cassa di Risparmio di Modena

 **CAPP** Centro di Analisi
delle Politiche Pubbliche

CONVEGNO

LA SALUTE COME DIMENSIONE DI BEN ESSERE: UNA PROSPETTIVA DI GENERE

Riflessioni sui risultati dell'unità operativa istituita presso il Dipartimento di Economia Politica Unimore del progetto ministeriale coordinato dall'Istituto Superiore di Sanità 'La medicina di genere come obiettivo strategico per la sanità pubblica: l'appropriatezza della cura per la tutela della salute della donna'

Modena, 7 dicembre 2011 - Teatro San Carlo - Via S. Carlo, 5

Donne: una questione di cuore

Modena, 7 dicembre 2011

Maria Grazia Modena

La medicina di genere e il Paradosso Femminile

Nel 1998 l'OMS ha pubblicato una "sfida di genere" per le nazioni e le organizzazioni internazionali, un invito a *migliore valutazione dei fattori di rischio che coinvolgono la salute delle donne, allo sviluppo di strategie preventive per ridurre l'impatto delle malattie che affliggono maggiormente le donne* e ad uno sforzo maggiore per comprendere *perché gli uomini muoiono prima delle donne.*

(Organizzazione Mondiale della Sanità 1998, The World Health Report 1998, Ginevra)

Traditional Heart Attack Warning Signs

- Pressure, burning, squeezing in the center of the chest
- Discomfort in one or both arms, shoulders, neck, jaw, stomach or back
- Shortness of breath
- Fatigue, cold sweat, nausea, weakness

Adapted from the Harvard Medical School website – www.harvard.health.edu

Symptoms of Coronary Heart Disease can Differ in Women

- Pain in upper back, jaw or neck
- Shortness of breath
- Flu-like symptoms: nausea or vomiting, cold sweats
- Fatigue or weakness
- Feelings of anxiety, loss of appetite, discomfort

Women's signs are non-specific and more easily overlooked.

Adapted from the Harvard Medical School website – www.harvard.health.edu

Coronary Artery Disease in Women

Macro and microvascular function / dysfunction

The “Two Steps Hypothesis”: WISE Registry

- **1° Phase:** microvascular and/or macrovascular (spasm) dysfunction → symptoms without obstructive CAD
- **2° Phase:** typical atherosclerosis with or without micro / macrovascular dysfunction

In February 1996, the University Hospital of Modena set up the “BenEssere Donna” Center



This Women’s Clinic represents an institution dedicated to the study, prevention and treatment of menopause-related disease.

At Sept.2011, 4500 women have been evaluated.

Prognostic Role of Reversible Endothelial Dysfunction in Hypertensive Postmenopausal Women

Maria G. Modena, MD, FESC, FACC, Lorenzo Bonetti, MD, Francesca Coppi, MD, Francesca Bursi, MD, Rosario Rossi, MD
Modena, Italy

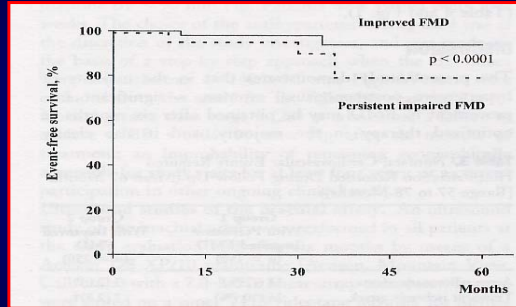
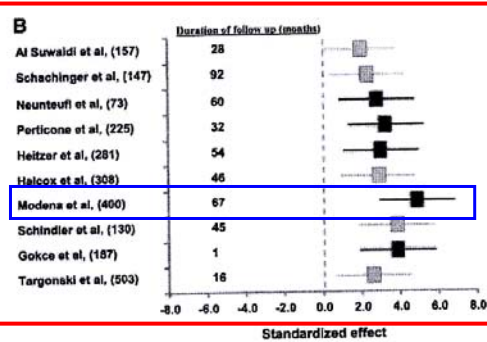
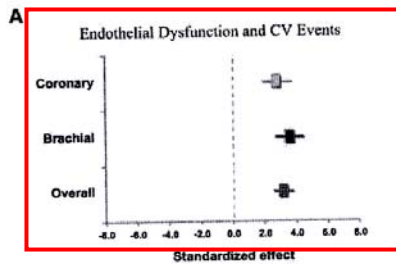


Table 4. Incidence Rates of Cardiovascular Events Among 400 Postmenopausal Women

Group	Events, n/N (%)	Person-Years	Incidence Rates*	Incidence Rates Ratio† (Crude)	p Value	Incidence Rates Ratio† (Adjusted)	p Value
Total cohort	47/400 (11.7%)	3,845.2	1.22	—	—	—	—
Group 1 (persistent impaired FMD)	32/150 (21.3%)	912.7	3.50	6.86‡	<0.0001	7.28§	< 0.0001
Group 2 (improved FMD)	15/250 (6.0%)	2,932.5	0.51	Referent	Referent	Referent	Referent

J Am Coll Cardiol 2002;40:5005-10



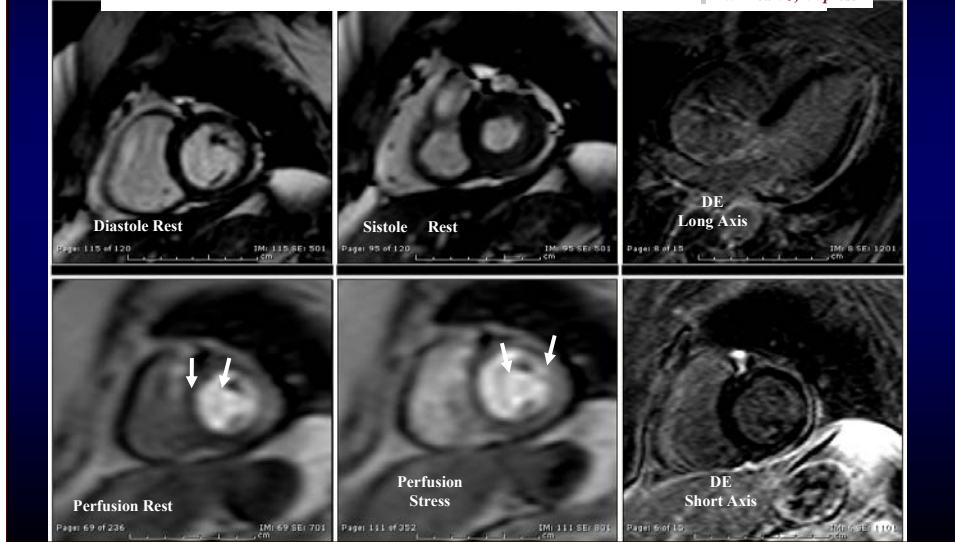
Lerman A and Zetter AM. Circulation 2005

Persistent Chest Pain in Absence of Angiographic Significant Coronary Artery Disease is Associated with Permanent Myocardial Perfusion Defects in Magnetic Resonance Imaging in Post-menopausal Women

Maria Grazia Modena,¹ Annachiara Nuzzo,¹ Rosario Rossi,¹ Anna Lammirato,¹ Federica Flocchi,² Guido Ligabue,² Pietro Torricelli² and Renato Romagnoli¹

¹ Institute of Cardiology; ² Institute of Radiology, University of Modena and Reggio Emilia, Policlinico Hospital, Modena

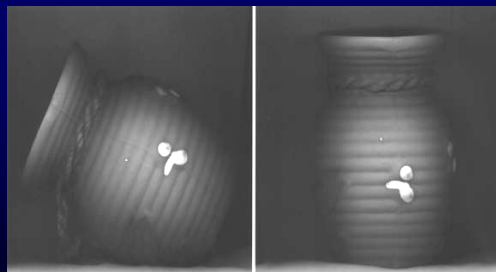
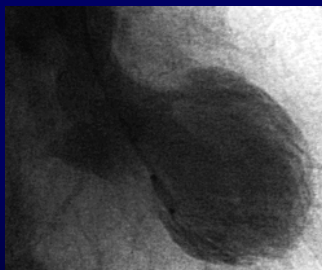
Eur Heart J, in press



Fatal AMI caused by spontaneous dissection of Left Coronary Artery

- Spontaneous coronary artery dissection is a rare but increasingly reported cause of MI.
- It is strikingly more common in young women (80% of cases) and has a high mortality rate.
- The predominance in women and high incidence in the postpartum period suggests an hormonal influence.

Sindrome di Tako-Tsubo: un esempio peculiare di infarto della Donna che subisce uno shock fisico o psichico



LAVBS

- *Limited myocardial enzyme release relative to the extent of ventricular akinesia.*
- *The clinical presentation mimics AMI: angiographically normal CA.*
- Phenotype: postmenopausal, hypertensive, emotionally stressed women.

S Novo, MG Modena et al. La cardiomiopatia Tako-Tsubo: Documento di Consenso.
GIC Ital Card 2008 (9): 785-797

Coronary Artery Disease in Women

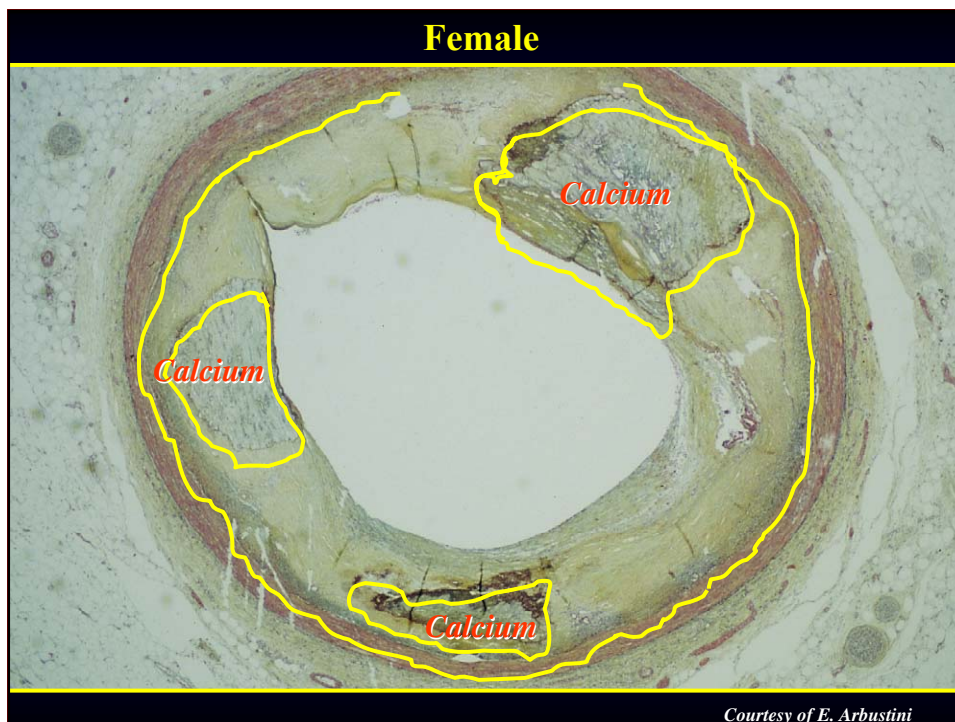
Macro and microvascular function / dysfunction

The “Two Steps Hypothesis”:

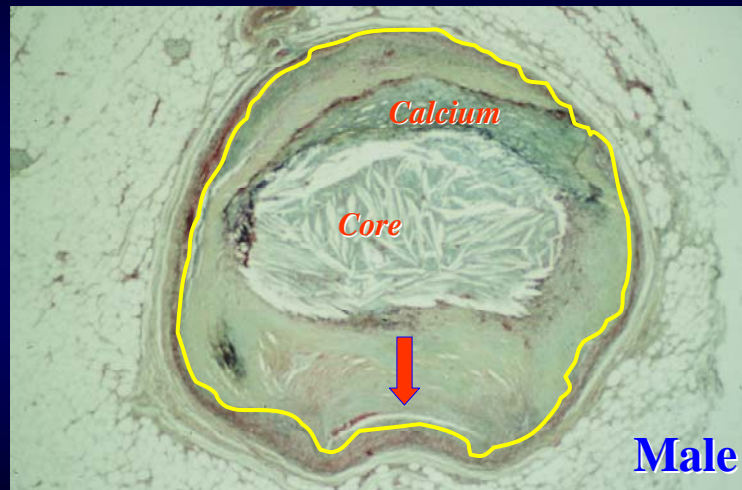
- **1° Phase:** microvascular and/or macrovascular (spasm) dysfunction → symptoms without obstructive CAD
- **2° Phase:** typical atherosclerosis with or without micro / macrovascular dysfunction

Is ATS pathologically identical in M and F?

- Effects of the disease on the vessel wall: remodeling
- Plaque composition
- Types/prevalence of complications in acute coronary syndromes



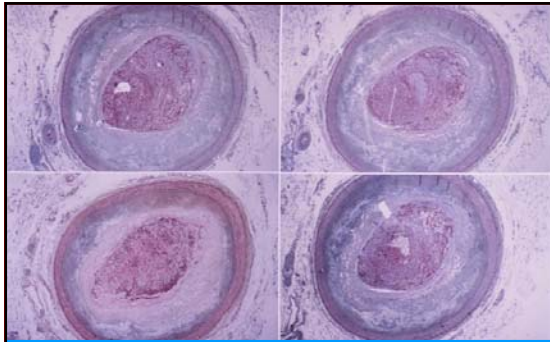
Coronary artery wall: remodeling



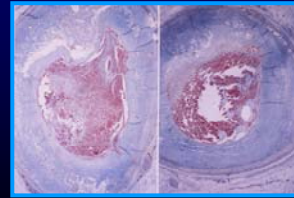
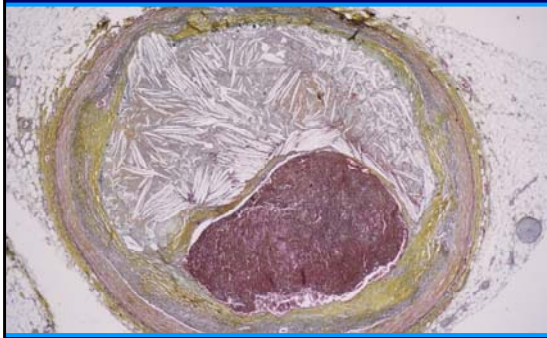
Courtesy of E. Arbustini

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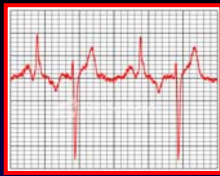
Plaque erosion:
Substrate of acute thrombosis in 40% of SCD and 25% of AMI



Courtesy of E. Arbustini

Epicardial CAD

- *Critical plaques: 10 years later than in men*
- *Less negative remodeling: < growth toward lumen*
- *More loose fibrosis: “young plaques”*
- *Smaller cores*
- *Complications: erosion 25% (MI) → 40% SD*
- *< 50 years: < core than > 50*



Arrhythmias *La teoria ormonale*

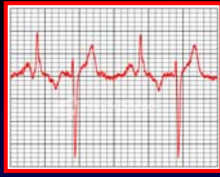
It was shown that women **have higher heart rates at rest** and **longer corrected QT intervals** than man, probably due to differences in exercise tolerance, autonomic modulation and intrinsic properties of the sinus node.

Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1999;7:353-370.

Effetti del ritmo circadiano del ciclo mestruale



Jochmann N et Al. *Eur Heart J*. 2005



Arrhythmias

La teoria ormonale

Also the incidence of arrhythmias is **increased during pregnancy and postpartum period**. The mechanisms of these gender differences are unclear but may be related to hormonal effects, increased intravascular volume and autonomic tone.

Wolbrette D, Naccarelli G, Curtis A, et al. Gender differences in arrhythmias. Clin Cardiol. 2002 Feb;25(2):49-56



HF: the female's paradox

As with ischemic heart disease, female patients with heart failure are older than males and more likely to be hypertensive and diabetic, but they tend to have **better preserved systolic function**, a lower prevalence of ischemic etiology and are less likely to have a history of prior AMI.

O'Meara E, Clayton T, McEntegart MB et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation. 2007 Jun 19;115(24):3111-20.

Woman's peculiar risk factors for HF

- **Chemotherapy** for breast cancer
- **Peripartum cardiomyopathy**: multiparity, advanced maternal age, multifetal pregnancy, pre-eclampsia, gestational hypertension and Afro-American race
- More **depression**, less recovery, more GP's care, who are less aggressive in treatment.
- Women have **unique comorbidities** which may influence HF as well as CAD.

MG Modena : Peculiar CV risk in Women. Chapter in Book Elsevier,2010

Pts with established diagnosis of CHF, referred to Heart Failure Clinic of our Institutions for prognostic stratification and evaluation for HT

M.G. Modena, J Heart Lung Transplant 2006 Jun; 25(6): 648-52

CLINICAL HEART TRANSPLANTATION

Prognostic Stratification of Women With Chronic Heart Failure Referred for Heart Transplantation: Relevance of Gender as Compared With Gender-related Characteristics

Francesco Grigioni, MD, PhD,* Andrea Barbieri, MD,* Antonio Russo, MD,* Letizia Reggiani, MD,* Silvia Bonatti, MD,* Luciano Potena, MD, PhD,* Francesca Fabbri, MD,* Fabio Coccolo, MD,* Gaia Magagnoli, MD, PhD,* Francesca Bursi, MD,* Carlo Magelli, MD,* Maria G. Modena, MD,* and Angelo Branch, MD*

Background: Few studies are available regarding prognostic stratification of women with severe chronic heart failure (CHF). Although women seem to have a better outcome than men, this may be due to favorable baseline characteristics.

Methods: We analyzed a cohort of CHF patients referred for heart transplantation (HT) who underwent clinical-functional evaluation. Women and men were frequency matched for baseline age (53 ± 14 vs 53 ± 9 years, $p = 0.92$), left ventricular ejection fraction (35 ± 10 vs 31 ± 8%, $p = 0.90$) and ischemic etiology (17 vs 22%, $p = 0.50$).

Results: A total of 198 patients were analyzed (109 women matched to 89 men). In addition to matching parameters, prevalence of severe symptoms, diabetes and hypertension were also comparable ($p \geq 0.25$). After 3 years, cardiovascular death or need for HT (CD/HT) event-free survival was 78 ± 4% in women and 52 ± 6% in men ($p = 0.005$). On multivariate analysis, female gender was associated with a lower risk of CD/HT (relative risk [RR] 0.52; 95% confidence interval [CI] 0.30 to 0.89; $p = 0.017$), independently of symptoms, blood pressure (BP), left ventricular end-diastolic diameter (LVEDD) and mitral regurgitation (MR). Nevertheless, CD/HT event-free survival at 3 years was 49 ± 9% for women with New York Heart Association (NYHA) Class III or IV status, who presented with either severe MR, mean BP ≥60 mm Hg or LVEDD ≥35 mm/m².

Conclusions: In advanced CHF, women patients seem to have a better prognosis irrespective of baseline characteristics, supporting the hypothesis that female gender is protective against myocardial injury. However, women with severe symptoms accompanied by either hypotension, severe left ventricular enlargement or MR are at high risk and deserve cautious follow-up and consideration for HT. J Heart Lung Transplant 2006;25:648-52. Copyright © 2006 by the International Society for Heart and Lung Transplantation.

Reliable risk stratification in chronic heart failure (CHF) is mandatory to deliver the most appropriate therapeutic strategies, including heart transplantation (HT). Few studies are available to help stratify the prognosis of women with severe CHF,¹ largely because female patients have been consistently under-represented both in

clinical trials and in studies on prognostic stratification.^{1,2} Most studies^{1,3-6} but not all⁷ indicate that women seem to have a better outcome than men. However, these results may have been influenced by profound gender-related differences in baseline characteristics.⁸ Indeed, women were almost invariably older at baseline,^{7,9} and had (when assessed) better preserved left ventricular ejection fraction (LVEF),³ lower prevalence of ischemic etiology¹⁰ and higher prevalence of diabetes.^{6,7} Furthermore, because the original data included only select clinical/instrumental parameters,^{1,3-7} it was not possible to adjust for the confounding influence of several important predictors of outcome.^{2,9}

We analyzed and compared the outcome of women and men within a cohort of CHF patients receiving optimized medical treatment who were referred to the outpatient clinic of our institution, which offers an HT program. Frequency matching was performed accord-

From the *Cardiology Institute, University of Bologna, Bologna, and *Cardiology Institute, Modena, Italy. Submitted August 4, 2005; revised October 10, 2005; accepted February 11, 2006. Supported by a grant from the University of Bologna donated from the Fondazione Sestini. Reprint requests: Francesco Grigioni, MD, Istituto di Malattie dell'Apparato Cardiovascolare, Ospedale S. Onofrio Maggiore, Via Marsilio 4, 41126 Bologna, Italy. Telephone: 0521/656174; Fax: 0521/65114480; Email: francesco.grigioni@unibo.it Copyright © 2006 by the International Society for Heart and Lung Transplantation. 1053-2498/06/25-648-52. DOI:10.1016/j.hlt.2006.02.004

Conclusions

Women CHF patients experienced a lower incidence of adverse cardiac events irrespective of baseline characteristics, supporting the hypothesis that **female gender per se** exerts a protective effect against myocardial injury.

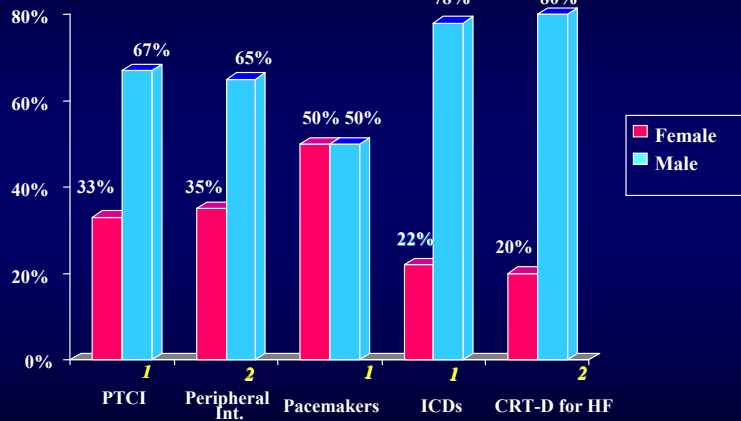
M.G. Modena. J Heart Lung Transplant 2006 Jun; 25(6): 648-52

Differences between women and men with HF in relation to HT

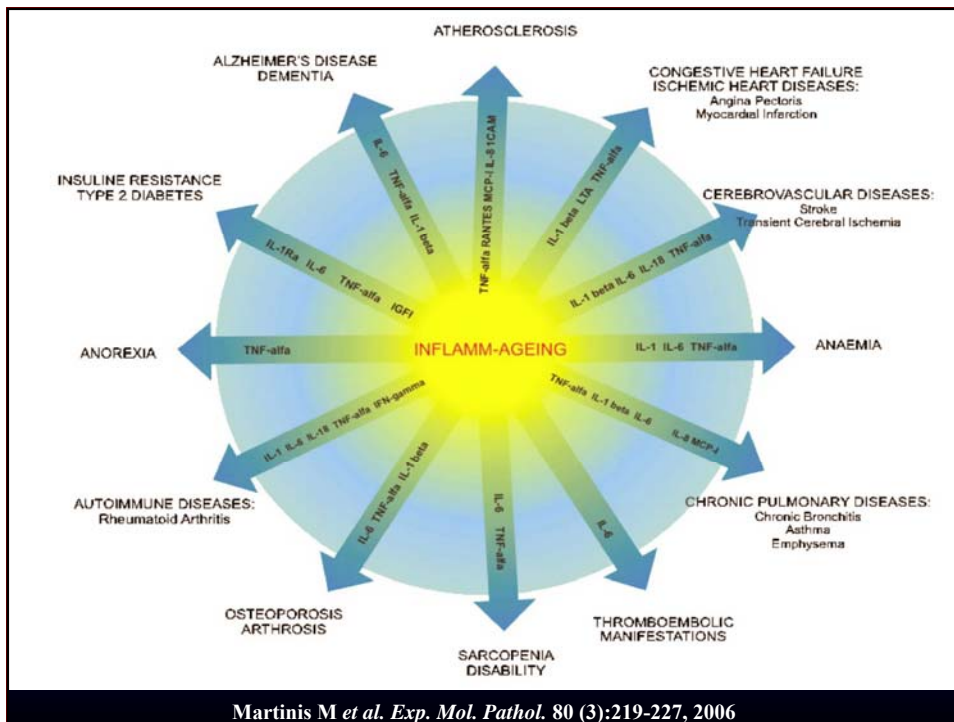
- 20% of the HT recipients are women
 - because HF develops earlier in men
 - women more often than men refuse transplant as a option
- Men have a lower risk of rejection and a > 1-year survival
- Women experience a > level of symptoms frequency related to immunosuppressive therapy (corticosteroid)

MG Modena J Heart Lung Transplant 1994;13:561 –70.
Circulation 1995;91:2753 –61.
Heart Lung 1998;27:315 –25.

Gender Distribution Estimates for Interventions



Sources:
 1-AHA: Heart Diseases and Stroke Statistics - 2009 Update
 2-Guidant Internal Estimates



Martinis M et al. *Exp. Mol. Pathol.* 80 (3):219-227, 2006

Documento del Gruppo di Lavoro SIPREC



Presidente: Massimo Volpe

Prevenzione dell'Infarto del Miocardio nella Donna

Coordinamento Scientifico
Maria Grazia Modena
Massimo Volpe

Comitato di Esperti componenti la Task Force
Fabio Bellotto, Massimo Chiariello, Lauro Cortigiani, Francesco Cosentino,
Stefano Del Prato, Claudio Ferri, Enzo Manzato, Carlo Maria Rotella,
Antonio Tierigo, Bruno Trimarco, Diego Vanuzzo,
Paolo Verdecchia, Annibale Volpe,
Roberto Volpe, Augusto Zaninelli



Malattie Autoimmuni

- L'autoimmunità è causa di diverse malattie croniche è tre volte superiore nella donna rispetto all'uomo.
- Le malattie autoimmuni si associano ad un incrementato rischio di morbilità e mortalità CV, per lo stato infiammatorio sottostante e la non rara trombofilia concomitante
- Tra i meccanismi aterogenetici nelle patologie autoimmuni gioca un ruolo determinante l'uso di farmaci capaci di favorire eventi cardio- e cerebrovascolari (steroidi, FANS, etc.) e la scarsa attenzione del medico e del pz nei confronti di patologie diverse da quella "principale".

Artrite Reumatoide: definizione

Malattia infiammatoria cronica
che colpisce la membrana sinoviale
delle articolazioni diartrodiali
generando distruzione del tessuto cartilagineo ed osseo



Sclerosi Sistemica (SSc)

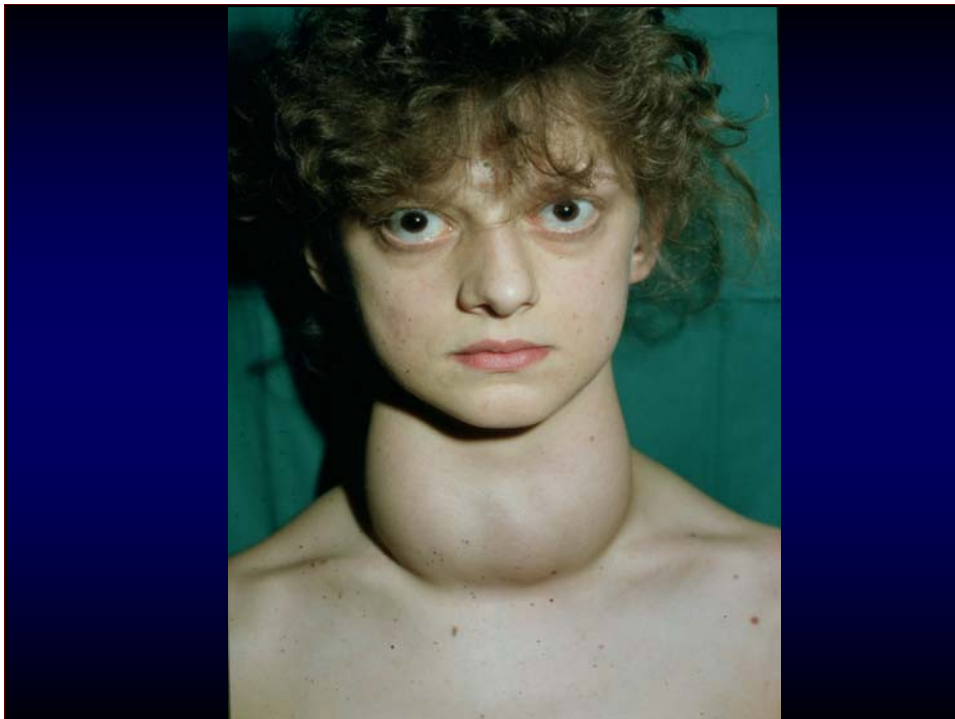
Malattia del tessuto connettivo
caratterizzata da fibrosi della cute
e dei visceri e da alterazioni diffuse
del microcircolo





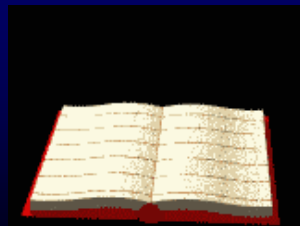
Endocrinopatie e Cardiopatia Ischemica nella donna

- Un eccesso o un difetto ormonale possono favorire la comparsa di cardiopatia ischemica e di IMA nella donna.
- Come le “fisiologiche” modificazioni ormonali che si instaurano in menopausa riducono la “protezione” presente in età fertile nei confronti della CI, specifiche disendocrinopatie, pongono la donna che ne è affetta a maggior rischio di IMA.
- Il corretto trattamento dell'ipercortisolismo, dei distiroidismi e dei deficit di ormoni gonadici ed ipofisari, **oltre che dei fattori di rischio metabolici**, frequentemente associati a queste disendocrinopatie, costituisce pertanto un'importante azione preventiva dell'IMA nella donna.





*Open questions regarding
ischemic heart disease in women*





Are pink or more pink

- Coronary artery and heart: smaller
- Plaque phenotype younger: minimal or absent in fibrous plaques with large amount of loose fibrous component
- Later onset of disease
- Positive remodeling
- Plaque erosion
- Endothelial dysfunction and microvascular disease
- Heart rupture
- Coronary dissection
- LV ballooning
- Important role of comorbidities different aspects in HF etiology / treatment, and of arrhythmias



Are azure or more azure

- All bigger
- Phenotype documenting a longer history of disease
- Early
- Negative remodeling
- Plaque explosion
- Lower or absent
- Rare
- Rare
- Rare
- Old data to be revisited in a Gender prospective

Sex and Gender medicine

**WOMEN ARE NOT
SMALL MEN ...**



Evaluation of endotheliAl Function in wOmen undeRgoing fErtility drugs treatment for in-Vitro fERtilization

EVA for EVER

*MG Modena, C. Giulini, R. Marzullo,
A. Volpe, work in progress*

Study Objectives And Hypotesis

The objective of this study is to evaluate endothelium function with Flow mediated dilatation (FMD) of brachial artery in women undergoing fertility drug therapy during In-Vitro Fertilization (IVF). We hypothesize that endothelium dysfunction induced by high hormonal stimulation may predispose to an increased risk of cardiovascular disease in these patients.

Effects of Pregnancy on Endothelial Function and Cardiovascular Disease Risk in HIV-Infected Women.

Guaraldi G, Luzi K, Ross A, Mancini M, Zona S, Neri I, Bruno R, Petrella E, Facchinetti F, Modena MG.

Antiviral Therapy 2011, in press

Conclusions:

No differences were observed in FMD or brachial artery diameter between HIV-infected and healthy pregnant women, and neither measure changed significantly during pregnancy. HIV status did not affect endothelial function or brachial artery diameter.

Pregnancy does not appear to further increase the CVD risk associated with HIV infection.

Sex and Gender medicine

Il paradosso femminile:

- **Memoria ormonale?**
- **Protezione telomerica?**
- **Prospettive future : autodistruzione di una protezione atavica?**