Women and Cardiovascular Disease: Sex Differences

Hypertension 2015 Scientific Sessions
September 16, 2015

Martha Gulati, MD, MD, FACC, FAHA
Associate Professor of Medicine in the Division of Cardiology
Associate Professor of Clinical Public Health, Division of Epidemiology
Sarah Ross Soter Chair in Women’s Cardiovascular Health
Section Director for Preventive Cardiology and Women’s Cardiovascular Health
The Ohio State University
Columbus, OH
Hygieia: Goddess of Women’s Health

(With Asclepius, God of Medicine)
The Difference Between Men and Women: The Way We See Ourselves
The Difference Between Men and Women: The Way We Communicate

UNSPoken COMMUNICATION

Girls
- Check Out Hair
- Evaluate Skin
- Inspect Jewelry
- Judge Makeup
- Is That a Real Tan?
- Compare Figures
- Have or Cutie?
- Can We Go Out?
- Long Cellulite?
- Legs Shaved?
- New Jeans or Vintage?
- Shirts and Shoes Are One or Two

Guys
- Cuffs? Oh Please!
- Admire Lone
- Legs Shaved?
The Difference Between Men and Women

"Here's all you have to know about men and women: women are crazy, men are stupid.

And the main reason women are crazy is that men are stupid." - George Carlin
Cardiovascular Disease Death Trends for Males and Females in the United States 1979-2011

Mozaffarian D et al. Circulation. 2015;131:e29-e322
Total Deaths in Women in USA 2011: 1,236,003

Cardiovascular Disease 398,035
Chronic Lung Disease 75,422
Lung Cancer 70,550
Breast Cancer 40,589

Prevalence of CVD in US Women: • 42,900,000

Prevalence of Breast Cancer in US Women: • 2,829,041

Mozaffarian D et al. Circulation. 2015;131:e29-e322
# Remaining Lifetime Risk for CVD vs Breast Cancer in Women

<table>
<thead>
<tr>
<th></th>
<th>Lifetime Risk at Age 40 Years</th>
<th>Lifetime Risk at Age 70 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any CVD</strong></td>
<td>1 in 2</td>
<td>1 in 2</td>
</tr>
<tr>
<td><strong>Coronary Heart Disease</strong></td>
<td>1 in 3</td>
<td>1 in 4</td>
</tr>
<tr>
<td><strong>Congestive Heart Failure</strong></td>
<td>1 in 5</td>
<td>1 in 5</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>1 in 5</td>
<td>1 in 5</td>
</tr>
<tr>
<td><strong>Breast Cancer</strong></td>
<td>1 in 8</td>
<td>1 in 15</td>
</tr>
</tbody>
</table>

Bikini Approach To Women’s Health?

“... The medical community has viewed women’s health almost with a ‘bikini’ approach, looking essentially at the breast and reproductive system, and almost ignoring the rest of the woman as part of women’s health”

Nanette Wenger, MD
Emory University

How do we move #beyondbikini?
WE HAVE STUDIES OF FRUIT FLIES, MICE, HAMSTERS, FROGS, MONKEYS AND MEN WITH THIS CONDITION — BUT MEDICAL RESEARCH USING WOMEN AS SUBJECTS JUST NEVER OCCURRED TO ANYBODY.
Women Have Poorer Outcomes Compared with Men

- Angina: ~2x ↑ morbidity/mortality
- MI: ~1.5x ↑ 1-year mortality
- CAD
- Heart failure: ~2x ↑ incidence
- CABG: ~2x ↑ morbidity/mortality
Do We Follow the Guidelines Equally in Women vs Men?

Sex Differences in Treatment
Sex Differences in Treatment: Euro Heart Survey of Stable Angina

3779 patients, 42% women, initially diagnosed by cardiologist

**Women vs Men**
- ↓ Exercise ECG testing: 73% vs 78%
- ↓ Coronary Angiography,: 31% vs 49%, despite higher angina class
- ↓ Statin, antiplatelet initially, 1 year
- ↓ Revascularization: 13% vs 29%

**Women 2 x ↑ death, nonfatal MI**
- Adjusted for age, DM, LV function, CAD severity, pharmacotherapy, and revascularization

Women ↑ angina at follow up, 57% vs 47%

*Daly, Circulation 113:490, 2006*
### Get With The Guidelines (GWTG): Clinical Performance after MI

<table>
<thead>
<tr>
<th>Measure/Treatment/Outcome</th>
<th>n</th>
<th>OR (95% CI) (Women vs Men)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early medical therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin within 24 h</td>
<td>70360</td>
<td>0.86 (0.81–0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(\beta)-Blocker within 24 h</td>
<td>64681</td>
<td>0.90 (0.86–0.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Invasive procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>74769</td>
<td>0.91 (0.88–0.94)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCI</td>
<td>67477</td>
<td>0.78 (0.74–0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG</td>
<td>67477</td>
<td>0.60 (0.55–0.65)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Revascularization</td>
<td>67477</td>
<td>0.68 (0.65–0.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Acute reperfusion and timeliness of reperfusion†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTN (\leq) 30 min</td>
<td>2807</td>
<td>0.78 (0.65–0.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>DTB (\leq) 90 min</td>
<td>7673</td>
<td>0.87 (0.79–0.95)</td>
<td>0.004</td>
</tr>
<tr>
<td>Reperfusion therapy</td>
<td>24742</td>
<td>0.75 (0.70–0.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>24742</td>
<td>0.83 (0.78–0.87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinolytic therapy</td>
<td>24742</td>
<td>0.87 (0.81–0.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>In-hospital death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall AMI cohort</td>
<td>70105</td>
<td>1.04 (0.99–1.10)</td>
<td>0.1</td>
</tr>
<tr>
<td>STEMI subpopulation</td>
<td>23015</td>
<td>1.12 (1.02–1.23)</td>
<td>0.015</td>
</tr>
</tbody>
</table>
Get With The Guidelines (GWTG): Age & Gender Differences in Quality of Care and Outcomes in STEMI

Quality of care was significantly lower and mortality was higher in young women vs. young men
(Similar finding in the very young: ≤35 vs 36-45 years)
Younger and Older Women were
• Less likely to receive ACEI/ARB
• Less likely to receive lipid-lowering therapy
• Less likely to have a BP< 140/90 mm Hg at discharge
• More likely to have longer door-to-balloon times (fewer achieving a door-to-balloon time ≤90min & door-to-thrombolytic time ≤30min)
Underutilization of Evidence Based Treatments in Women
Canadian Registry of ACS

<table>
<thead>
<tr>
<th>Medications at Discharge</th>
<th>Male (N=4471)</th>
<th>Female (N=2087)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>93%</td>
<td>93%</td>
<td>0.49</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>79%</td>
<td>76%</td>
<td>0.0015</td>
</tr>
<tr>
<td>Lipid-Lowering</td>
<td>65%</td>
<td>56%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>60%</td>
<td>56%</td>
<td>0.006</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Male (N=4471)</th>
<th>Female (N=2087)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td>50%</td>
<td>42%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCI</td>
<td>23%</td>
<td>18%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CABG</td>
<td>0.08%</td>
<td>0.04%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Male (N=4471)</th>
<th>Female (N=2087)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2%</td>
<td>3%</td>
<td>0.0078</td>
</tr>
<tr>
<td>Death/MI</td>
<td>8%</td>
<td>8%</td>
<td>0.36</td>
</tr>
<tr>
<td>Death 1 year</td>
<td>8%</td>
<td>11%</td>
<td>0.0017</td>
</tr>
<tr>
<td>Death/MI 1 year</td>
<td>16%</td>
<td>17%</td>
<td>0.095</td>
</tr>
</tbody>
</table>

Bugiardini et al. ESC 2011;32:1337-1344
High-Sensitivity Troponin in Acute Coronary Syndrome

- Sex Specific MI threshold of 16 ng/L in women/34 ng/L in men for troponin I based **on defining levels as the 99th percentiles based on sex** vs conventional assay of 50 ng/L

  - High STEAC Trial: Sex-Specific Thresholds: diagnosis of MI in women INCREASED from 13% to 23%; no effect in men (23% to 24%)
    - Sensitivity of the conventional assay: 77% in men and 47% in women
    - Sensitivity of high-sensitivity assay: 86% in men and 95% in women
    - In comparison to men, women are more likely to be misdiagnosed and undertreated for MI

  - 2015 Study: 1126 patients with suspected ACS: 45% women/55% men
    - High sensitivity troponin I increased diagnosis of MI in women (from 11% to 22%; P<0.001) but minimal effect in men (19% to 21%, P=0.002)

*Mills N et al. ESC 2013*
*Mills N et al. JAMA 2011;305:1210-5*
*Shah AS et al. BMJ 2015;350:g7873*
Is the Disease the Same in Women and Men?

Sex Differences in CVD Pathophysiology
Yentl Syndrome

- Term coined by Dr. Bernadine Healy
- Noted discrepancy in inclusion of women in trials, particularly cardiovascular trials
- Most clinical trials at this point excluded women, yet applied the study results to both men AND women
- Assumption that if women (and diseases) present like men, they will be taken seriously
“Typical Angina” definition based on men (exertional)

Women report more angina despite lower rates of obstructive CAD
  - Meta Analysis of 74 reports from 13,311 women 11,511 men
  - Angina prevalence 11%-27% greater for women <65 years

Women have less obstructive CAD regardless of symptoms (typical or atypical)

Symptomatic women without obstructive CAD continue to have signs/symptoms of ischemia, repeat hospitalization and coronary angiography, consumption of health-care resources due to diagnostic & therapeutic uncertainty
Percentage of Patients Who Had IHD But No CAD: GUSTO IIb

GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb) study

ACC NCDR CathPCI Registry: Frequency of Significant CAD* by Race


- Rate of significant CAD was 49% for women and 67% for men ($P<0.0001$)

- OR=0.47 for Significant CAD in women vs. men ($P<0.0001$)

- Black Women: Lowest Rate

*defined as ≥70% stenosis in ≥ 1 coronary arteries
Higher Hospital Mortality for Women of all Races vs. Men: Stable Chest Pain and ACS

Symptomatic (WISE) Non Obstructive CAD vs. Asymptomatic (WTH): Risk Factors

Gulati M et al. Archives Internal Medicine 2009;169:843-50
Cumulative CV death/MI for WISE Women

Estimating Time to Cardiovascular Death (CVD)

Nonobstructive CAD

1 Vessel CAD
RR=3.6 (p=0.004)

2 Vessel CAD
RR=7.3 (p<0.0001)

3 Vessel CAD
RR=6.5 (p<0.0001)

Time to CVD Death (Years)

Model $\chi^2=33$, p<0.0001

Estimating Time to Cardiovascular Death (CVD) or Nonfatal Myocardial Infarction

Nonobstructive CAD

1 Vessel CAD
RR=3.2 (p<0.0001)

2-3 Vessel CAD
RR=6.0 (p<0.0001)

Time to CVD Death or MI (Years)

Model $\chi^2=55$, p<0.0001

Shaw, L. J. et al. Circulation 2006;114:894-904
Cumulative Chest Pain Hospitalizations in WISE

Estimated average lifetime costs: $767,288

Compared with average lifetime costs: $1,001,493 to 1,051,302 for those with 1-3 vessel disease

Model $\chi^2=58$, p<0.0001

Shaw, L. J. et al. Circulation 2006;114:894-904
Overt Focus on Obstructive CAD as pathophysiology for SIHD
Objective of Anti-Anginal Strategies

Reduce Ischemia & Relieve Symptoms

Stable CAD: PCI vs Conservative Medical Management

Meta-analysis of 11 randomized trials (N = 2,950)

<table>
<thead>
<tr>
<th>Event</th>
<th>Favors PCI</th>
<th>Favors Medical Therapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.68</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>CAD Death or MI</td>
<td>0.28</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.12</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>0.82</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>0.34</td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>

Risk ratio (95% CI)

SIHD: Paradigm Shift

- The “SIHD = obstructive CAD” paradigm
- Decades of information from pathological studies have established that CAD underlies SIHD
- Reinforced by coronary angiographic data from large trials/registries assuming SIHD = flow-limiting lesion in a major coronary artery (obstructive CAD)
- Link between symptoms and obstructive stenosis is so ingrained that patients and tests are labeled as “Atypical” or “False Positive” if they have symptoms +/- signs of ischemia, if no obstructive CAD
- Patients without obstructive CAD with symptoms and signs of ischemia have increased adverse event rates, poor QOL, consume health care resources compared with those without evidence of ischemia
Sex and Heart Disease: Female Specific Ischemic Heart Disease

Male-pattern
Obstructive CAD

Female-pattern
Microvascular Coronary Disease
Working Model of Ischemic Heart Disease Pathophysiology in Women

Figure illustration by Rob Flewell.

Diagnosis of Ischemic Heart Disease Without Obstructive CAD

Control

Peak Myocardial Enhancement during the First Pass of Gadolinium in a Control Subject at Rest (Panel A) and during Stress (Panel B): Uniform Myocardial Signal Enhancement.

Female Specific Ischemic Heart Disease

Peak Myocardial Enhancement during the First Pass of Gadolinium in a Patient with Ischemia/No CAD at Rest (Panel A) and during Stress (Panel B): Ring of Delayed Subendocardial Enhancement (Arrows in Panel B).

IHD/No CAD may have subendocardial ischemia as demonstrated using cardiac MR perfusion
Understanding the Yentl Syndrome: Sex Differences in Ischemic Heart Disease

- “Normal” coronary angiograms (luminal irregularities <50% stenosis) are seen far more frequently in women with SIHD & ACS vs. men.
- For women presenting with ACS, 10-25% women vs 6-10% of men have no obstructive CAD: 1.4 million patients discharged after an ACS/year, 600,000 are women- translates into 60,000-150,000 US women with ACS having nonobstructive CAD.
- Specific investigation is needed to understand the paradox whereby women have less obstructive CAD and less severe MIs yet worse clinical outcomes compared to men.
WOMEN ≠ SMALL MEN
Sex Differences in CVD

• Sex Differences in Treatment: Risk for women with obstructive CAD is increased compared with men, yet *women are less likely to receive guideline-indicated therapies*

• Sex Differences in Risk Factors: Sex Specific CVD Risk Factors & Sex differences in traditional risk factors

• Sex Differences in Ischemic Heart Disease: Pathophysiology needs to be further understood, as does treatment and impact on symptoms and outcomes
Women are Just More Complicated
SAVING WOMEN’S HEARTS

How You Can Prevent and Reverse Heart Disease With Natural and Conventional Strategies

MARTHA GULATI  MD, MS, FACC, FAHA
SHERRY TORKOS  BSc  PHM

@drmarthagulati

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
Do CVD Risk Factors affect Women in the same way as Men?

Sex Differences in Cardiac Risk Factors
The Current Guidelines

- Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update
- 2013 ACC/AHA Guidelines on the Assessment of Cardiovascular Risk
- 2014 AHA Stroke Prevention Guidelines in Women
# CVD Risk Factors in Women

<table>
<thead>
<tr>
<th></th>
<th>Prevalence vs Men</th>
<th>Relative Risk vs Men</th>
<th>Sex Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>↓</td>
<td>↑↑</td>
<td></td>
</tr>
<tr>
<td>Diabetes/Metabolic Syndrome</td>
<td>↑</td>
<td>↑↑↑</td>
<td>Gestational DM PCOS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>↑</td>
<td>↑</td>
<td>Preeclampsia Gestational HTN</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Physical Inactivity/ Poor Fitness</td>
<td>↑↑↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>↑</td>
<td>-/↑</td>
<td>Postpartum Weight Gain</td>
</tr>
<tr>
<td>Depression</td>
<td>↑↑↑</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>SLE/RA</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td></td>
</tr>
</tbody>
</table>
Sex Differences in Type I Diabetes and Risk of Death

- 26 studies: 214,114 individuals and 15,273 events
- Women with Type 1 DM have ~40% greater excess risk of all-cause mortality, 2X excess risk of fatal and nonfatal vascular events compared with men with Type 1 DM

Huxley RR et al. Lancet Diabetes Endocrinol. 2015; doi:10.1016/s2213-8587(14)70248-
“Baby Weight” and Risk of Heart Disease and Diabetes

• Followed 305 Patients for 1 year post partum
• Women who maintained excess pounds between 3-12 months postpartum had elevated risk factors for diabetes and cardiovascular disease
• Women who didn't lose weight had higher blood pressure, higher levels of LDL, apo B and greater resistance to insulin (25% of cohort)
• Indirect Evidence that women who don’t lose their “baby weight” are at greater risk for heart disease

Kew S et al. Diabetes Care 2014
Cohort (N=47,908): women who delivered preterm (<37 weeks' gestation) [N=5992 (12.5%)] vs. Normal term birth at the same period

During a follow-up period of >10 years, patients with PTD had higher rates of simple and complex cardiovascular events and higher rates of total cardiovascular-related hospitalizations.

Robbins et al. AJOG 2014; 210: 285-297
Heida et al. Eur J Prevent Cardiol 2015
Gestational Diabetes Mellitus and Relative Risk of Maternal CVD

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Relative Risk (95% CI)</th>
<th>Mean or Median Years of Follow-up</th>
<th>Caption Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr, 2006 (56)</td>
<td>1.58 (1.00, 2.49)</td>
<td>30</td>
<td>a</td>
</tr>
<tr>
<td>Shah, 2008 (55)</td>
<td>1.71 (1.08, 2.69)</td>
<td>12</td>
<td>b</td>
</tr>
</tbody>
</table>
Hypertensive Disorders of Pregnancy (HDP) and Risk of Maternal CVD

Northern Finland Birth Cohort 1966: Risk For CVD, MI and MI Deaths in Women with Hypertension during Pregnancy.

Northern Finland Birth Cohort in 1966 (12,055)

Elevated BP during pregnancy, regardless of type, signals high risk of CVD, CKD and DM

Women’s Perception of Future CVD Risk Following Pregnancies With Preeclampsia

Interviews with 12 women with a recent history of preeclampsia who had attended a postnatal follow-up clinic.

- The interviews were held a median of 47 weeks postpartum (24-62 weeks).
- Family history of CVD was associated with a greater awareness of future CVD risk.
- Women without traditional risk factors found it hard to envisage themselves as being at risk (saw less relevance of such information)
- May take several months after delivery for a woman to be able to fully consider her own health as well as the baby’s
- Situational factors of being a new mother need to be taken into account to successfully engage with this patient group

Brown MC et al. HTN in Pregnancy 2013, Vol. 32, No. 1, Pages 60-73
Theoretical Timelines of Impairment of Endothelial Function and Development of CVD following Preeclampsia

- In women there is a gradual age-related reduction in endothelial function (exacerbated by the presence of CV risk factors).
- Women who experience preeclampsia have impaired endothelial function during pregnancy and up to 3 years following an affected pregnancy.
  - Theory 1: Begin with normal endothelial function, which is acutely impaired during preeclampsia, followed by ongoing age-related decreases.
  - Theory 2: Women who develop preeclampsia may have primary endothelial dysfunction which both puts them at risk of preeclampsia. May be exacerbated by preeclampsia (solid line), or simply persist (dotted line).
Pregnancy Related Disorders and CVD Risk Association

The Evidence to Date:

- GDM: 1a evidence as a risk factor for DM (>7X)
- HDP: 1a evidence as a risk factor for DM (1.8X)
- HDP: 1a evidence as a risk factor for HTN (3.7X)
- Preeclampsia: 1a evidence as a risk factor for CVD/Mortality (2X)
- GDM: 1b evidence as a risk factor for CVD/Mortality (1.7X)

<table>
<thead>
<tr>
<th>Type 2 DM</th>
<th>HTN</th>
<th>CVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDM</td>
<td>1a</td>
<td>ND</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1a</td>
<td>1a</td>
</tr>
<tr>
<td>G-HTN</td>
<td>1a</td>
<td>1b</td>
</tr>
</tbody>
</table>

Level of Evidence based on Oxford Classification

Nerenberg N et al. Canadian Journal of Cardiology 2014;1-14
Risk of IHD after Radiation for Breast Cancer

Rates of Coronary events increased by 7.4% per Gy (P<0.001)
Avg radiation 1-2 Gy to Right Breast, usually higher in Left Breast
Risk of major coronary events began within the first 5 years after exposure

Darby et al. NEJM 2013;368:987-998
Classification of CVD Risk in Women

At risk

1 major risk factors for CVD, including:

- Cigarette smoking
- Poor diet
- Physical inactivity
- Obesity, especially central adiposity
- Family history of premature CVD (CVD at <55 years of age in male relative and <65 years of age in female relative)
- Hypertension
- Dyslipidemia
- Evidence of subclinical vascular disease (eg, coronary calcification)
- Metabolic syndrome
- Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise

History of Gestational DM, Pregnancy induced HTN, preeclampsia
Lupus, Rheumatoid Arthritis