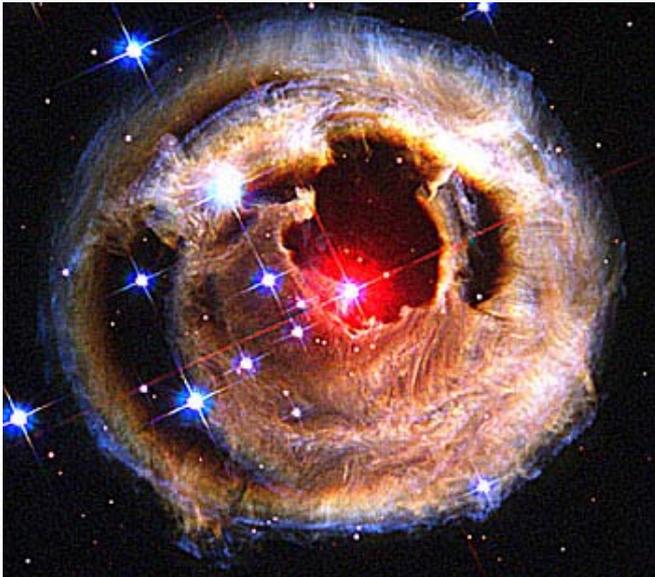


THE IMPACT OF SEX AND GENDER ON MORBIDITY AND MORTALITY TO H1N1 INFECTION



SARALYN MARK, MD

CASE REPORT

CC: The patient was a 42 y.o. caucasian female who presented with SOB, fever, chest pain x 2 weeks and new onset of hemoptysis.

HPI: The pt described an abrupt onset of a sore throat, dry cough and occasional myalgias, denied rhinorrhea, GI sx's or H/A.

Approximately 1 week later while coughing, she heard a "pop" in her chest followed by significant left sided chest pain on inspiration and expiration. Breathing became more labored with wheezes. Pt was unable to lift her arms or lay supine secondary to chest pain. NSAIDS did not alleviate pain. Pt was seen at a CHC and was diagnosed with bronchitis and reactive airways. She was given nebulizers and d/c on albuterol and steroid inhalers, prednisone and azithromycin. There was minimal resolution of sx's with meds. Pt now c/o increased SOB and fever, difficulty with swallowing, and 2 episodes of blood tinged sputum.

PMH: Legionella pneumonia-16 years ago

PSH: None

SHX: Tob neg

MEDS: See above and influenza vaccine 2 weeks before sx's

CASE REPORT

PE: T=102 deg HR=90 BP=105/60 RR=24

HEENT: Ill appearing female in acute respiratory distress,
-adenopathy, + pharyngeal edema and erythema

LUNGS: +Wheezes, +Egophony, +Rhonchi, + Pt tenderness over ribs 4-6
at costochondral junction

LABS: CXR-nl, Chest CT-nl, WBC >11,000, -Blood Cultures x4,
O₂ Sat-94%

DX: 1) Tracheobronchitis
2) Pleuritis
3) Asthma
4) Costochondritis-with possible separation at c-c junction
5) R/O Cytokine Storm*

OVERVIEW: 2009 H1N1 IN UNITED STATES

4/2009-4/2010

- 126 Million Doses of Vaccine Administered
- 57 Million Cases (43M-89M)
- 274,000 Hospitalizations
- 12,000-17,000 Deaths (Voluntary Reporting)
- Age - Impacted Children and Young Adults
- California (4/09-5/09): 553 Cases -21/26 Hospitalized Were Women (5 Pregnant)

OVERVIEW: 2009 H1N1 IN UNITED STATES

- Pregnant Women

- 1% Population

- 9% of Hospitalizations

- 5% of Deaths from H1N1

- 30% of Preterm Births (Usual Rate: 13%)

- NY -7x More Likely to be Admitted Compared to
Non-Pregnant Women

- 7x More Likely to have Severe Disease

DEFINITIONS

Sex: Refers to the classification of living things, generally as male or female, according to their reproductive organs and functions assigned by their chromosomal complement.

Gender: Refers to a person's self-representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation.

IOM, Exploring the Biological Contributions to Human Health: Does Sex Matter? 2001

THE IMPACT OF GENDER AND SEX

Gender

Bias: 1) -Access to Care
2) -Aggressive Care

Behavioral: 1) Caregivers
2) Health Care Professionals

Sex

Immunology/Endocrinology

Co-Morbid Conditions (Asthma, Obesity, Pregnancy):

- 55% Hospitalized Pregnant Women
- 63% Women in ICUs
- 78% Patients who Died

ASTHMA

- 23% Hospitalized Patients
- 26% ICU Admissions
- 44% Deaths
- Women have more asthma attacks, hospitalizations and ER visits
- MHT worsens asthma:
 - 58,000 Women in France /12 years
 - 21% More likely to develop asthma
 - 54% Overall risk

Thorax, 2010

- OCPs increase risk for asthma:
 - 4,728 Women/2 years
 - 42% More likely to develop asthma

JAllergy and Clin Immunology, 2009

OBESITY

- 2nd most common underlying condition
- 13% of hospitalized patients
- Women are 50% more likely to be obese compared to men in 138/195 countries (WHO)
 - Women: 25-27% body fat
 - Men: 15% body fat
- Adiposity contributes to increased immunologic and inflammatory responses
 - Active source of macrophages, lymphocytes and pro- and anti-inflammatory factors, cytokines and chemokines
- Proinflammatory molecules linked to insulin resistance and CAD, and responses to infectious agents including cytokine storm

PREGNANCY

OVERVIEW

- Rapid deterioration compared to seasonal influenza
- High risk period continued 2 weeks postpartum (NEJM, 2010)
- Less likely to have underlying conditions
- 95% hospitalized in 2nd or 3rd trimesters (restrictive lung dx)
- inc blood volume, inc hyperemia -> inc pulmonary congestion
- inc progesterone -> inc hyperventilation

PREGNANCY

HORMONES AND IMMUNOLOGY

- Phases of reproductive cycle impact resistance:
 - Diestrus (inc P, dec E) inc Picornavirus infection
 - Estrous (dec P, inc E) dec infection

Schwartz, Virology, 2004
- Sex differences in resistance:
 - Non-pregnant females are more resistant to infection secondary to higher levels of Th1, CD3+, CD4+, CD8+, cytokines
 - Paternal antigen of embryo-fetus stimulates nuclear progesterone receptors on CD8+ T lymphocytes-- the high concentration of progesterone leads to production of progesterone-induced blocking factor (PIBF) which impacts cytokines and immune cells
- Lose resistance during pregnancy by shifting from TH1 (pro-inflammatory) to TH2 (anti-inflammatory) responses to prevent rejection of fetus:
 - Can still mount inflammatory responses to virus once infected (i.e., ARDS, cytokine storm)

CYTOKINE STORM (HYPERCYTOKINEMIA)

"Potentially fatal immune reaction consisting of a positive feedback loop between cytokines and immune cells with highly elevated levels of cytokines."

Osterholm, NEJM, 2005

TREATMENT

- VACCINES

- 1114 adults, ages 18-64 years (18-49, 50-64)
- Randomized to full or half dose TIV
- Women had higher hemagglutination inhibition antibody responses compared to men
- Women's responses to half dose were comparable to men's responses to full dose
- Women had more injection site and systemic reactions (myalgias, H/A, fatigue)

Renata, Arch Int Med, 2008

- ANTI-VIRALS

- Amantadine during pregnancy contra-indicated
- No sex differences clinically seen in safety and efficacy of neuraminidase inhibitors
- Delay in treatment secondary to misdiagnosis and concern about teratogenicity

TREATMENT

- VASOPRESSORS

- Potential sex difference response to stress:

- *Women increase heart rate

- *Men increase vasoconstriction

- Estrogen increases nitric oxide synthase resulting in vasodilation and decrease in BP

- Pregnant women show decrease response to vasopressin
(*Kee, Anesthesiology, 2006*)

TREATMENT

- STATINS

- Decreased HMG-COA Reductase (cholesterol production)

- Decreased cytokines, chemokines, adhesion molecule expression

- 2800 patients hospitalized secondary to seasonal influenza in 10 states:

- *801 Received statins

- *3.2% Died (not on statins)

- *2.1% Died (on statins-47% less likely to die)

- CDC, 2008*

- Potential sex difference response:

- *ASCOT study: randomized trial to examine if women who used a statin had more MIs than the placebo group.

- >Women without CAD or DM may not lower risk of an MI with statin use

RECOMMENDATIONS

- Educate
- Early Awareness and Treatment
- Research Trials - Vaccine Dosage, Novel Therapeutics
- Surveillance





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