

Modern Aspects of Gender Based Medicine

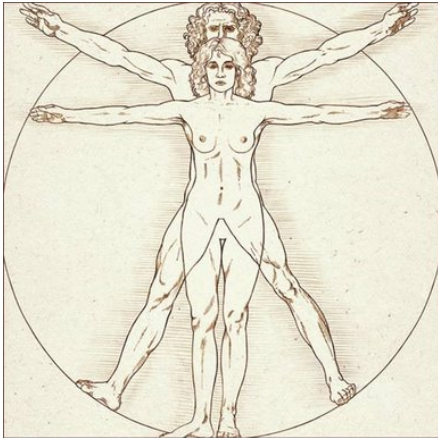
Book Title Page:

Date: May 1, 2019

Course Title: Professions in Medicine: Cultural Competence

Event Title: Modern Aspects of Gender-Based Medicine

Author: Janice Werbinski, MD, FACOG



Cover Page:

Date: May 1, 2019

Course Title: Professions in Medicine: Cultural Competence

Event Title: Modern Aspects of Gender-Based Medicine

Faculty Author: Janice Werbinski, MD, FACOG

Author email: dr.janwerbinski@gmail.com

Summary:

This course is an introduction to viewing medicine through a sex and gender lens. Sex and Gender Based Medicine (SGBM) is a field of medicine which incorporates information about how biological sex and the sociocultural aspects of gender affect health and illness for women and men. It is a broader category, which acknowledges that both biological and sociocultural aspects of women's and men's health need to be incorporated into management of health and disease. It acknowledges that there is an interrelationship between sex and gender on health outcomes. The course starts with the basic biology, physiology, and hormonal aspects of sex and gender development, and expands to a more universal view of health and disease from a sex and gender perspective. Several cases will be presented which emphasize the need to know the sex and gender of the patient in order to properly assess and treat. Students will also be provided tools and other resources to enable them to find timely information in gender based medicine.

Historical Aspect: Traditional textbooks of medicine have approached health and disease from a standard perspective, largely based on research performed on male animals and the 70kg human male. But since 1993, when the U.S. Congress passed laws which established the Office of Women's Health at the NIH, it was mandated that women be included in all NIH-funded research. Since that time, a plethora of research has been published on women. The law did not require that research results be stratified by sex, however, so women are often still invisible in outcomes and recommendations. Men's health, also, is sometimes harmed

or ignored when they are not included in studies (for example: do bisphosphonates help prevent osteoporosis fractures in men?)

Copyright Page: standardized

Chapter 1: Learning Objectives

1. Describe the difference between sex and gender, both of which influence health and disease.
2. Recognize the differential effect of genetics and sex steroids on reproductive and other body systems.
3. Understand the need for specialized gender-based therapies in order to give appropriate healthcare.

Chapter 2: In Preparation

REQUIRED VIDEOS:

1. Canadian Gender and Health Collaborative Curriculum: [“Do You Know the Difference Between Sex and Gender?”](#)
2. TEDx Talk: [“Why Medicine Often has Dangerous Side Effects for Women.”](#) Sept, 2014, McGregor, Alyson, M.D.
3. Colbert Report: [“Co-Ed Lab Rats.”](#)

REQUIRED ARTICLES

[Sexual Differentiation in humans.](#) (Wikipedia)

[Sex Differences in the Brain.](#) McCarthy, Margaret, In: The Scientist, Exploring Life, Inspiring Innovation. Oct. 1, 2015

[Microvascular coronary dysfunction and ischemic heart disease: where are we in 2014?](#) (You only need to read the Abstract)

Chapter 3: Content

Introduction: In this Module of Independent Learning, students will learn the basic genetics, biology and chemistry of males and females, differential effects of sex steroid hormones on body systems, effects of hormones and gender on cardiovascular health (as only one example of an organ with sex differences) and pharmaceuticals, and describe the basic theory of gender-based therapies.

A. Sex and gender-specific medicine (From: McGregor, AJ , Templeton, K, et. al. [Advancing Sex and Gender Competencies in Medicine: The SGWHC](#))

Every cell has a sex and all bodies are influenced by gender. From the embryo to the grave, sex and gender have undeniable effects on a person’s health and life. Diseases differ between men and women in terms of prevention, clinical signs, therapeutic approach, prognosis, psychological and social impact. Traditional textbooks of medicine approach health and disease from a standard perspective, largely based on research performed on male animals and the 70 kg human male. But since 1993, when Congress passed laws which established the Office of Women’s Health at NIH, it was mandated that women be included in all NIH-funded research, where appropriate. Since that time, a plethora of research has been published on women. The law did not require, however, that research outcomes be stratified by sex, so women are sometimes still invisible in outcomes and recommendations. Women (and men) are sometimes actually harmed when their unique presentation, metabolism, size, and reactions are not taken into consideration. This will hopefully change with the October 2015 GAO report, [Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research at NIH.](#) (Page 1-5 are the most informative)

“Sex” refers to biological differences between women and men, including chromosomes, sex organs, and hormonal profiles. “Gender” refers to socially constructed and enacted roles and behaviors which occur in a historical and cultural context and vary across societies and over time. And gender identity can vary along a continuum between “woman” and “man”, depending on perception of the individual, thought to be influenced in utero by various factors, including hormonal exposure. Every cell has a sex. All individuals act in

many ways that fulfill the gender expectations of their society. With continuous interaction between sex and gender, health is determined by both biology and the expression of gender.

The Institute of Medicine (IOM) reports, “Sex, that is being male or female, is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health related research” (IOM 2001, p.3). Whether a cell contains an XX or XY chromosome may have an impact on everything from regulation of gene expression in a cell line to efficacy or toxicity of pharmaceuticals in humans. It is now evident that gender also has a significant role in disease and response to treatment. Therefore, the significance of sex, gender, and their interaction should be considered in the daily practice of patient care.

Important examples of sex and gender differences and their interaction include:

- Aspirin has different preventive effects in men and women. It prevents stroke but not myocardial infarction (MI) in women, while preventing MI but not stroke in men.
- Musculoskeletal disease has differing incidence and manifestations between sexes. For example, women have a higher incidence of osteoarthritis, osteoporosis, and non-contact sports injuries, such as anterior cruciate ligament tears.
- For the same number of cigarettes smoked, women are more likely than men to develop chronic obstructive pulmonary disease. It is theorized that for a given increase in the thickness of airway mucosa, women suffer a greater degree of airflow limitation given their typically smaller stature and smaller airway caliber.
- Gender differences in morbidity and self-reported health status by women are thought to contribute to the increased use of medical services and higher outpatient expenditures compared to men, even when controlling for health status and other variables.
- Men and women experience stress differently based on gender roles, which has an impact on their neurobiology. For example, in men, there is a significant positive correlation in perceived stress and physiological responses at work. However, in women, physiological stress levels at work seem to spill over into non-work situations. This interaction between stress from paid employment and unpaid work at home is important to consider in the study of women’s stress. For example, cortisol levels generally decrease in the evening among men, but not for women.

As sex and gender factors are considered in research and results are published, the transfer of scientific findings to practice is only possible if they are incorporated into medical education and training.

B. Population Health and Responsibility of the Healthcare System From: [HealthyPeople.gov](https://www.healthypeople.gov/):

It is the responsibility of the healthcare system to provide care to all populations equally, and it is the responsibility of doctors and doctors in training to be exposed to healthcare needs of all populations. Unfortunately, a limiting factor to identifying and addressing these needs is that most research in the past was performed on males, either excluding special populations, or not identifying those populations, so the science behind the care can be limited.

Things are changing in this arena, and that is especially evident in the U.S. Healthy People 2020 Goals and newer policies established at the NIH. Until more research is available which more accurately identifies

outcomes in these special populations, the student must at least be aware of these disparities, and continuously ask pertinent questions:

“Does this disease, treatment, presentation have data which applies to disparate populations?”

“Do hormones (endogenous or exogenous) affect the metabolism, absorption, excretion, distribution, or interaction with this medication or treatment?”

“Was this medical device tested and found to be safe/similar on diverse populations, especially women?”

C. Fetal Development and Hormones: A Review of Human Embryology:

Sexual differentiation in humans: is the process of development of [sex differences in humans](#). It is defined as the development of [phenotypic](#) structures consequent to the action of hormones produced following gonadal determination.^[1] [Sexual differentiation](#) includes development of different genitalia and the internal genital tracts, breasts, body hair, and plays a role in gender identification.^[2]

The development of sexual differences begins with the [XY sex-determination system](#) that is present in humans, and complex mechanisms are responsible for the development of the phenotypic differences between [male](#) and [female humans](#) from an undifferentiated [zygote](#).^[3] Females have two [X chromosomes](#), and males have a [Y chromosome](#) and an X chromosome. At an early stage in [embryonic](#) development, both sexes possess equivalent internal structures. These are the [mesonephric ducts](#) and [paramesonephric ducts](#). The presence of the [SRY gene](#) on the Y chromosome causes the development of the testes in males, and the subsequent release of hormones which cause the [paramesonephric ducts](#) to regress. In females, the mesonephric ducts regress.

D. Sex Determination:

A [baby's](#) sex is determined at the time of [conception](#). When the baby is conceived, a [chromosome](#) from the [sperm](#) cell, either X or Y, fuses with the X chromosome in the egg cell, determining whether the baby will be genetically female (XX) or male (XY).^[5] To be genetically female, one needs to be (XX), whereas to be a genetic male, (XY) is needed. It is the Y chromosome that is essential for the development of the male reproductive organs, and with no Y chromosome, an embryo will develop into a female. This is because of the presence of the sex determining region of the Y chromosome, also known as the SRY gene.^[6]

A [fetus](#) doesn't develop its external sexual organs until -the fourth month of [pregnancy](#) —seven weeks after conception. The fetus appears to be sexually indifferent, looking neither like a male or a female. Over the next five weeks, the fetus begins producing [hormones](#) that cause its sex organs to grow into either male or female organs. This process is called sexual differentiation. The precursor of the internal female sex organs is called the Müllerian system.

Chapter 4: Case Presentations. Sex Steroids, Chromosomes and their effects on Various Organ Systems

A. Brain:

From: [Sex Differences in the Brain](#). McCarthy, Margaret, In: The Scientist, Exploring Life, Inspiring Innovation. Oct 1, 2015.

There is now increasing evidence that differences in brain function are prevalent across the sex divide, and that these differences manifest in surprising ways in animal models of both health and disease. (See [Gender bias in neuropsychiatric disorders](#) for discussion of gender differences in anorexia, autism, ADD, schizophrenia and bipolar disorder) Many sex differences in adult brain structure and behaviors are the result of in utero organizational effects of gonadal steroid hormones, in particular androgens and their aromatized derivatives,

estrogens, both of which are present in substantially higher concentrations in male fetuses due to testicular steroidogenesis. Brain differences between the sexes can also arise from diverse factors, including the expression of genes carried on the sex chromosomes and discrepancies in maternal treatment of male and female progeny. Together, these factors mediate differences in neurogenesis, myelination, synaptic pruning, dendritic branching, axonal growth, apoptosis, and other neuronal parameters.

B. Heart: Heart Disease in Women is more often due to Coronary Microvascular Disease

Discussion: *Coronary Microvascular Disease*

1. More common in women, especially <50 yo
2. Associated with hypertension, diabetes, obesity, FH coronary disease
3. Fatigue, chest, jaw, neck, or back pain, insomnia, SOB. (only 30% experience chest pain)
4. "Unwell feeling"
5. Abnormal cardiac stress test, yet no blockage of coronary arteries on angiogram

Discussion: *Cardiac Testing In Women*

New insights into ischemic heart disease in women. Bellasi, A, Raggi, P, Bairey-Merz, N, et.al. CCJM 2007 Aug;74(8):585-594.

1. Risk Factors and Presentation Differ
 - a. Depression and autoimmune disorders are more common in women
 - b. Only 1/3 of women describe chest pain as a symptom of MI
2. Older tests may be more appropriate for men, but not women
 - a. Stress EKG less useful because women can't exercise to maximum as well as men
 - b. Angiograms are useful, but if no blockage seen, ischemia can still be present
 - c. Up to 50% of women with MI will have no blockage of a major coronary vessel
3. Newer tests might be more appropriate in women
 - a. Coronary calcium screening
 - b. Assessment of endothelial function
 - i. Vascular Ultrasound of coronary arteries
 - ii. Instillation of acetylcholine into arteries to assess spasm component to ischemia
 - c. Stress echocardiography
 - d. Exercise single-photon emission computed tomography (SPECT)
4. Troponin levels are not elevated as drastically as in men
 - a. A [high sensitivity troponin assay](#) with sex specific thresholds can double the chance of diagnosis of MI in women.

C. Pharmaceuticals

Case #2. Pharmaceuticals and Women (MVA 8 Hours after 10 mg dose of Zolpidem)

History: 42 y.o. single woman working full time and caring for two children, with insomnia and anxiety.

Medications: Prescribed Zolpidem, 10 mg @ hs with good response

Case Presentation: Two weeks later, while driving to work at 8:00 AM, she noted she was very sleepy, and drove off the road, driving into the ditch.

She had bruising in seat belt area with pain

Taken to local Emergency Room

Labs: Her blood level of Zolpidem was 197 ng/ml (normal at 2 hrs is 69-197 ng/ml)

Treatment: She was hydrated and observed and allowed to sleep, and blood levels returned to normal after 3 hours.

Discussion: [Drugs Can Affect Sexes Differently.](#)

1. 80% of drugs removed from the market in a 10-year period were due to side effects in women
2. 20 years after release on the US Market, Zolpidem was found to be more slowly metabolized in women than men, so women more often have a therapeutic blood level 8 hours after administration.
3. Only in April of 2015 did the FDA release a correction that the recommended effective dose in women should be 5 mg.

Chapter 5:

Summary: Special Gender Based Therapies (for extra reading/information).

1. Most research before 1993 was done on male animals and male humans
2. Virtually all animal research before 2015 was done on male animals
[Colbert: Co-Ed Lab Rats.](#)
3. 2015 [Blue Cross Study](#) shows women receive less aggressive treatment after a heart attack than men, particularly for angioplasties, angiography, and coronary bypass surgery. Future research implications
4. [Gender Medicine: A Task for the Third Millennium](#)

Summary: "In this review we point out some major issues in five enormous fields of medicine: cardiovascular diseases (CVDs), pharmacology, oncology, liver diseases and osteoporosis." Attention to these areas will improve men's, as well as women's health

5. [Twenty years and still counting: including women as participants and studying sex and gender in biomedical research.](#)

Summary: "Awaiting a cultural shift to allow the study of sex and gender to be embraced is not seen as an effective strategy for change. Specific instrumental recommendations are offered for how to include the study of sex and gender in research to increase our understanding and promotion of health for the benefit of all."

6. [Healthy People 2010: Companion Document for LGBT Health](#)
7. IOM Report: [The Health of LGBT People: Building a Foundation for Better Understanding](#)
8. [AMSA "White Coat Cards" of Gay, Lesbian, Transgender, and Postpartum Health Care.](#)

THEREFORE: Knowledge of sex differences must be included in curriculum of all health professionals. If we don't ask the right questions, the answer doesn't matter.

Chapter 6:

To Learn More

ARTICLES FOR MORE IN DEPTH KNOWLEDGE:

[Advancing Sex and Gender Competencies in Medicine: The SGWHC.](#) McGregor AJ, Templeton K, et.al.

[Embedding Concepts of Sex and Gender Health Differences into Medical Curricula.](#) Miller V, Rice M, et.al.

[Consideration of Sex as a Biological Variable in NIH-funded Research.](#) NIH Notice #NOT-OD-15-102, June 9, 2015.

[Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research at NIH.](#) US GAO Office Report, October, 2015.

[Genetic factors and hormones that determine gender.](#) Module 21: Human Embryology and Organogenesis.

[Sex Differences in the Brain: A Whole Body Perspective.](#) DeVries, GJ, Forger, NG. Aug. 15, 2015.

[How to Study the Impact of Sex and Gender in Research: A Review of Resources.](#) McGregor, AJ, Hasnain, M, et.al. October, 2016.

[Sex and Gender Based Medicine: The Need for Precise Terminology.](#) Madsen T, Werbinski J, et.al. Gender and the Genome. Volume 1, Number 3, 2017. DOI:10.1089/gg.2017.0005.

[The Need to Integrate Sex and Gender Differences into Pediatric Pedagogy.](#) Werbinski J, Rojek M, Demma-Cabral M, Advances in Pediatrics. April 30, 2019. <https://doi-org.ezproxy.med.wmich.edu/10.1016/j.yapd.2019.03.001>

WEBSITES WHICH ADDRESS GENDER BASED MEDICINE:

Sex and Gender Health Collaborative www.sgwhc.org

Jeannette Wolfe's Website (contains Jeopardy Game) www.sexandwhy.com

NIH Office of Women's Health www.orwh.od.nih.gov

OWH at US Department of Health and Human Services www.womenshealth.gov

The Laura W. Bush Institute for Women's Health www.laurabushinstitute.org

Texas Tech Sex and Gender Specific Health Project <http://www.sexandgenderhealth.org/>

The Society for Women's Health Research www.swhr.org

Canadian Women's Health Curriculum www.genderandhealth.ca

GenderMed Database www.gendermeddb.charite.de

Gendered Reactions www.genderedreactions.com

BOOKS FOR MORE IN DEPTH, REFERENCES, AND COMPREHENSIVE READING:

Legato, Marianne J. MD. *Principles of Gender Specific Medicine, Third Edition*. Elsevier Academic Press. Calif. 2017

Oertelt-Prigione, S, Regitz-Zagrosek, V, eds. *Sex and Gender Aspects in Clinical Medicine*, Springer.2012

Schenck-Gustaffson, et. Al. *Handbook of Clinical Gender Medicine*, 2012 Karger (www.karger.com)

McGregor, Choo, et.al. *Sex and Gender in Acute Care Medicine*. [2016 Cambridge](http://2016.Cambridge) www.cambridge.org

PRACTICE QUESTIONS:

1. What is the difference between sex and gender?*
2. In embryonic development, what is the default "sex" of the developing fetus? *
3. Describe the changes from "default sex" which occur under the influence of the SRY Gene.
4. Name three organs or organ systems that manifest disease differently depending on the sex of the host?*
5. In humans, why do genetic mutations occur more often in female eggs than in male sperm?
6. How do symptoms of myocardial infarction differ between women and men?*
7. Why do women sometimes still have narcosis 8 hours after ingesting a "normal" dose of Zolpidem?
8. Name three risk factors for Cardiac Syndrome X?
9. What does the term MINOCA mean?
10. Why do women manifest symptoms attributable to alcohol at much lower doses of alcohol than men?

*Recommended Test Questions

JUST FOR FUN! PLAY JEOPARDY <http://www.sexandwhy.com/body-pod/#saemjeopardy>