A Report of the 24th Annual Congress on Women's Health—Workshop on Transforming Women's Health: From Research to Practice

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Abstract

Sex and gender are critical contributors to overall health and disease, and considering both in research informs the development of prevention strategies and treatment interventions for both men and women. The National Institutes of Health (NIH) Office of Research on Women's Health sponsored a preconference workshop on this topic at the 24th Annual Women's Health Congress, which was held in Crystal City, VA, in April 2016. The workshop featured presentations by NIH intramural and extramural scientists who presented data on a variety of topics including polycystic kidney disease, vaccine protection, depression, drug addiction, and cardiovascular disease. In this publication, we discuss the major points of each presentation and demonstrate the importance of considering sex and gender in biomedical research.

Keywords: workshop proceedings, women's health, sex, gender, kidney disease, vaccine, HIV, depression, drug addiction, cardiovascular risk and treatment

Introduction

SEX AND GENDER are critical components of human health, and a greater understanding of sex/gender influences in research studies is needed to fully understand their impact.¹ "Sex" is a biological classification derived from the chromosomal complement. "Gender" is a person's self-representation as male or female.¹ The most thorough research on human subjects would consider the influence of both sex and gender in studies.

In 2015, the National Institutes of Health (NIH) clarified its commitment to Enhancing Reproducibility through Rigor and Transparency in NIH-funded research through a formal policy,² and one component of the policy is a requirement for applicants to consider and report on relevant biological

variables, such as sex, in studies using vertebrate animals or human subjects.³ The NIH expects that sex as a biological variable (SABV) will be factored into research designs, analyses, and reporting in such studies. By engaging with investigators to take sex into account as they develop their research questions, design experiments, analyze data, and report results, the NIH reaffirms its mission to deliver rigorous science that increases generalizability of findings to improve the health of women and men.

The NIH Office of Research on Women's Health (ORWH) sponsored a preconference workshop on this topic at the 24th Annual Women's Health Congress, which was held in Crystal City, VA, in April 2016. The workshop featured presentations by NIH intramural and extramural scientists who presented data on a variety of topics including polycystic kidney disease,

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vaccine protection, depression, drug addiction, and cardiovascular disease (CVD). In this publication, we discuss the major points of each presentation and demonstrate the importance of considering sex and gender in biomedical research.

Dr. Susan Kornstein, Executive Director of the Virginia Commonwealth University Institute for Women's Health, Editor of *Journal of Women's Health*, and President of the Academy of Women's Health, welcomed attendees and introduced the day's first speaker.

Opening Remarks

Dr. Janine Austin Clayton, NIH Associate Director for Research on Women's Health and the Director of ORWH, set the stage for the preconference workshop. Dr. Clayton cited the NIH mission of turning discovery into health, and indicated that sex and gender are critical variables for researchers to consider. A study by neurologist Dr. Louise McCullough showed significant differences between male and female mice that were treated with an inhibitor of nitric oxide synthase after a stroke.⁴ Male mice were protected by the inhibitor while female mice exhibited exacerbated tissue damage. If the data in the publication were not disaggregated by sex, we would have learned less about the biology of both male and female animals.

The NIH has a longstanding policy requiring researchers to include women in clinical studies; however, this requirement has not trickled down into all stages of the research enterprise.⁵ For this reason, as of January 2016, NIH expects that SABV will be factored into research designs, analyses, and reporting in vertebrate animal and human studies,³ and a strong justification is required for researchers proposing to study only one sex. The NIH recognizes that the research community is in the best position to determine how to adequately consider SABV in each field of study. This will be a consideration in peer review, and NIH and the academic community will work together as NIH continues to implement the policy.

The other critical piece of the policy is reporting findings throughout the research process.⁶ Reporting sex-based results in publications and progress reports is crucial, because data disaggregated by sex has little benefit until it is in the public domain.

By ensuring that both sexes are studied and reported across the research spectrum, we can improve our understanding of how sex affects male and female biology, health, and diseases, leading to more precise treatments and better outcomes.

Presentation Summaries

Sexual Dimorphism in Polycystic Kidney Disease

Gregory G. Germino, MD

Dr. Gregory Germino, Deputy Director of the National Institute on Diabetes and Digestive and Kidney Diseases, gave the first research presentation. Autosomal dominant polycystic kidney disease (ADPKD) affects ~1 out of 1000 Americans, and accounts for ~5% of all cases of end-stage kidney failure (ESKF).⁷ Cysts arise at all stages of life and gradually expand to replace normal renal tissue. The disease can be a debilitating systemic disorder that manifests as liver cysts and vascular abnormalities.

Mutations in either of two genes, *PKD1* and *PKD2*, cause most forms of ADPKD.⁸ The protein products of the genes

form a receptor channel complex, and most evidence suggests that disease results from a reduction in *PKD1* or *PKD2* activity. Studies in animal models have shown different rates of cyst growth, depending on when the gene is inactivated.⁹

Sex is a major modifier of the disease; men with ADPKD have worse prognosis, while women are somewhat protected from ESKF.^{10,11} However, women with ADPKD have more severe liver disease.¹² Gene expression profiles of adult mouse kidneys, based on autosomal genotype and sex, indicate that sex influences the gene expression profile as much as the genotype.¹³ Moreover, gene expression profiles differ as much between normal male and female kidneys as they do between normal and cystic male kidneys.¹³

The research from the animal models suggest that sex-based differences in lipid metabolism may offer partial protection from renal cystic disease. Genes differentially expressed in mutant animals are enriched in metabolic and lipid pathways.¹³ Defective fatty acid oxidation is a key part of the expression of kidney disease development.¹³ Males with severe kidney disease show more rapid decline than is seen in females and this correlates with differences in fatty acid metabolism.¹³ Despite the importance of sex-related data, scientists still often fail to record the age and sex of lab mice.

Uncovering a Sex Bias in Simian Immunodeficiency Virus Vaccine Protection

Marjorie Robert-Guroff, PhD

Dr. Marjorie Robert-Guroff, Head of the Section on Immune Biology of Retroviral Infection, Vaccine Branch, NCI, presented recent findings from her lab on the efficacy of simian immunodeficiency virus (SIV) vaccines. Compared with HIV-infected men, HIV-infected women initially exhibit lower viral loads and higher CD4 counts, but eventually progress more rapidly to AIDS.^{14,15} Sex bias is known to be associated with differences in immune responses. Following viral infections, women exhibit elevated antigen recognition by pattern recognition receptors, induction of adaptive immune responses, and production of inflammatory cytokines.^{14,15} However, little information is available on sex differences in response to vaccination.

A recent study was conducted using the rhesus macaque SIV model with the aim of determining the immunogenicity and protective efficacy of a replication-competent adenovirus SIV recombinant vaccine regimen using monomeric SIV envelope glycoprotein 120 (gp120) as a boosting antigen versus an oligomeric SIV envelope glycoprotein 140 (gp140).¹⁶ The study groups included 16 female animals and 8 male animals each, and took advantage of both concurrent and historical controls. Interestingly, the female macaques exhibited delayed acquisition of SIV compared to controls, while the male animals did not.¹⁶

Vaccine-induced rectal envelope specific (Env-specific) IgA antibody levels were found to correlate significantly with delayed acquisition in female but not male macaques. Investigation of Env-specific memory B cells in rectal tissue 2 weeks postinfection showed significant correlation with acquisition delay in gp120-immunized females and approached significance in gp140-immunized females. An investigation of total plasmablasts and plasma cells in rectal tissue showed significant correlation in both gp120- and gp140 immunized females, but not males. These results strongly suggest the

importance of local mucosal immunity for protective efficacy and link these immune responses to the sex bias in SIV acquisition delay.¹⁶

There are many key areas for further investigation, but it is clear that the sex bias in immunity is profound and particularly affects mucosal immunity. The microbiome is important in shaping mucosal immune responses; steroid hormones modulate the microbiome and the microbiome affects HIV acquisition and pathogenesis. More work on this area of study is warranted.

Sex and Gender Differences in Major Depression: Epidemiology, Development, Biology, and Society
Stephen E. Gilman, ScD

Dr. Stephen Gilman, investigator and Acting Branch Chief of the Health Behavior Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, provided an overview of gender differences in the etiology of depression. Per a World Health Organization report, mental and behavioral disorders ranked number 1 among the top 10 causes of years lost to disability.¹⁷ The consequences of depression are significant and include suicide, increased mortality, higher medical comorbidities, and negative impacts on social and economic functioning.¹⁸ Once adolescence occurs, girls exhibit an increased rate for major depressive episodes that persist well into adulthood.^{19,20}

Several factors have been investigated as potential explanations for sex and gender differences in depression. These include genetics, prenatal exposures, differences in brain development, differences in biological maturation, differences in psychological vulnerabilities to depression, social effects of physical differences, differential exposure to risk factors for depression, and differential vulnerability to risk factors for depression.²¹ Enhancing our understanding of sex differences may therefore provide an important window for understanding causality of depression.

Maternal immune disruption during pregnancy, such as exposure to influenza, increases risk for offspring mood disorders. A study to investigate the prenatal origins of sex differences in depression began in 1960 when 1258 pregnant women provided serum that was stored for 40 years.^{22,23} Their offspring in adulthood underwent structured diagnostic interviews for major depression. The family's level of social and economic disadvantage influences maternal immune activity during pregnancy. In examining the association between the maternal immune activity mid-gestation and the offspring's risk of major depression by measuring the ratio of pro- to anti-inflammatory cytokines, it was shown that long-term association in offspring was sex dependent, with women at higher risk.

A second factor to be considered is differential vulnerability to risk factors for depression. A 2002 study investigated socioeconomic status in childhood and its relation to the lifetime risk of major depression.²⁴ It found a 10.4% higher risk of depression for women than for men from economically disadvantaged households. The rates of depression risk were similar between the sexes for people from affluent households.

Researchers have also examined differential exposure to interpersonal violence and found that women were signifi-

cantly more likely to report exposure to interpersonal violence,²⁵ explaining about one-fifth of the elevated risk of depression among women. There are also gender differences in vulnerability to adversity throughout the lifetime. In investigating the impact of childhood adversity on the stress-response system, childhood experiences were more highly predisposing factors to depression in women than in men.²⁶ Finally, women have been shown to be more vulnerable to adult exposures to adversity, as exemplified by an increased vulnerability to suicide during military deployment.^{27,28}

Sex and gender influences are crucial to the etiology of major depression and to reducing its population impact. Selected risk factors for depression that vary by gender, influence risk for depression, and have relevance for public policy including sexual abuse and assault, poverty, and equality in employment, earnings, and reproductive rights.

Sex/Gender Differences in Drug Addiction and Why It Matters

Cora Lee Wetherington, PhD

Dr. Cora Lee Wetherington, the Women and Sex/Gender Differences Research Coordinator at the National Institute on Drug Abuse (NIDA) and program officer in the Behavioral and Cognitive Neuroscience Branch at NIDA, provided an overview of several sex/gender differences in the areas of drug abuse and addiction. Highlights from her presentation include the following:

Cannabinoid use disorder (CUD): Data from a large epidemiological survey found that the severity of CUD was higher in men, they were more likely to have longer episodes of CUD, smoke more frequently, were less likely to remit, and were older at remission.²⁹ However, sex differences were striking with respect to CUD and mental health.²⁹ Women with lifetime CUD were more likely than men with CUD to have psychiatric comorbidities, including bipolar disorder, alcohol use disorder, and antisocial personality disorder, while men with CUD did not have an increased risk of any psychiatric disorder.

Cocaine: A study of sex differences in brain neural response to stress cues versus drug cues in cocaine-dependent (CD) individuals showed that women exhibited brain activation to stress cues while men exhibited brain activation to drug cues.³⁰ In another study, brain perfusion changes during cocaine withdrawal were in opposite directions and different brain regions in men and women.^{31,32} Men showed decreased cerebral blood flow in the right precentral gyrus, right superior and medial frontal gyri, and the anterior cortex. Women showed increased cerebral blood flow in the posterior cingulate. Further, in a study that found lower gray matter volume in abstinent CD patients compared to a control group, the affected brain regions were different between CD men and women: the insula and hippocampus (emotion/stress regions) for women and the mid-cingulate cortex (cognitive control region) for men.³³

Smoking/nicotine: Women have more difficulty quitting smoking than men. In a meta-analysis of various nicotine replacement therapies (NRTs), those treatments were more effective in men than women.³⁴ In a meta-analysis limited to the transdermal nicotine patch, women also did not respond as well as men. Nicotine metabolism is faster in women than

men, and faster nicotine metabolizers have poorer smoking cessation outcome with the NRT patch, which may account for the poorer NRT response in women smokers.^{35–37} Sex differences have also been found in the brain's dopamine signature of cigarette smoking showing that, consistent with behavioral studies, men and women appear to smoke for different reasons: the positive reinforcing effects for men versus factors associated with habit and regulation of stress and mood for women.³⁸

Prescription opioids: A large epidemiological study found that among users of prescriptions opioids, women were as likely as men to exhibit abuse or dependence. Men and women had many predictors of prescription opioid abuse or dependence in common, but there were also gender-specific predictors.³⁹ Needle drug use and age were predictors for men but not women, while use of cocaine, marijuana, and hallucinogens were predictors for women but not men. The strongest predictor for both genders was nonmedical use of tranquilizers or sedatives. Those who endorsed nonmedical use of those drugs were 28 times more likely to meet criteria for abuse/dependence of prescription opioids.

Together, the results of these studies indicate that, in drug addiction research, results are not always the same in men and women—sometimes occurring only in one sex, sometimes more strongly in one sex, and sometimes in opposite directions. It is critical that addiction research is designed to detect such possible outcomes as they can have important implications for differential prevention and treatment interventions in men and women.

Sex Differences in Cardiovascular Disease Risk and Outcomes

Nakela Cook, MD, MPH, FACC

The final presentation of the workshop was from Dr. Nakela Cook, Chief of Staff, National Heart, Lung, and Blood Institute (NHLBI) who discussed sex differences in CVD risk and outcomes.

Several examples demonstrate documented sex differences in risk factors, burden, biology, and pathobiology of CVD. Within the conditions that comprise CVD, the death rate from coronary heart disease is lower for women than for men, while the death rates from stroke and heart failure are higher for women than for men.⁴⁰ Furthermore, heart failure affects women at an older average age than it affects men, and comorbid conditions and risk factors vary.^{40,41} Women are more likely to have hypertension and less likely to have coronary artery disease (CAD) comorbid with heart failure, and diabetes has been shown to be a stronger risk factor for heart failure in women as compared with men.⁴² These trends demonstrate the potency of some risk factors for women over men, particularly diabetes, obesity, and hypertension. There is a greater prevalence of hypertension in women as they increase in age, and the intersection between race and ethnicity demonstrate an increasing rate of hypertension among black women.⁴³ The described relationship between hypertension and heart failure in women contributes to clear differences for black women. In the NHLBI-supported Atherosclerosis Risk in Communities study, black women over 60 years of age have the highest overall incidence of heart failure of any group, again demonstrating this crucial interaction of race and sex.⁴¹

Specific conditions with higher prevalence in women as compared to men exemplify the importance of understanding mechanisms of disease. For example, the data suggest a sex preference in Takotsubo cardiomyopathy, with women accounting for 90% of those affected, and cardiac events in the setting of nonobstructive CAD has a predominance in women.⁴⁴ The NHLBI-supported Women's Ischemia Syndrome Evaluation study pioneered an understanding of differences in etiologies for CVD between the sexes by identifying a different pathophysiology for women, microvascular disease, as the cause of cardiac events without obstructive CAD in women and described its correlation with higher risk of recurrent events.⁴⁵

Beyond differences in burden and pathobiology of disease, it has been recognized for years that women are also less likely than men to receive early medical therapy and invasive cardiac procedures, and they have longer delays to reperfusion and higher mortality rates with ST-segment-elevation myocardial infarction.⁴⁶ A recent statement from the American Heart Association, *Acute Myocardial Infarction in Women*, addressed the challenges of treatment differences between men and women describing the influence of burden of disease, risk factors, pathophysiology, and presentation and treatment on acute myocardial infarction outcomes.⁴⁷ Understanding these sex differences in CVD and documentation of them highlights areas that are ripe for research.

NHLBI's research priorities focus on a multipronged approach to women's health to encourage clinical research on women, sex-specific analyses, preclinical studies of SABV, and raising public health awareness. In a scientific roundtable held in February 2015, the Institute gathered experts in the field to assess the current state of research on the cardiovascular health of women and put forth ideas that would have the greatest impact on women's cardiovascular health over the next 10 years. Overarching themes included the need for a better understanding of sex in all aspects and phases of research, inclusion of both men and women in basic, preclinical research, and clinical research; reporting of clinical research outcomes by sex/gender; awareness of the critical intersection of race and sex/gender for mitigation of disparities; and importance of collaborative approaches to understand the necessity of sex-specific outcomes.

NHLBI subsequently solicited broad input on a research agenda to address compelling questions and critical challenges to inform research priorities for the institute over the next decade. The resulting Strategic Vision represents scientific priorities throughout its objectives relevant to women's health. Key in the Vision is the importance of investigating factors, such as age, sex, pharmacogenetic issues, and race that account for differences in health among populations. Over the next decade, critical factors will be identified that underlie sex differences in heart, lung, blood, and sleep-related health and disease.

Closing Remarks

Terri L. Cornelison, MD, PhD, FACOG

Dr. Terri Cornelison, Associate Director for Clinical Research, NIH ORWH, ended the session by summarizing the afternoon. The workshop focused on transforming women's health from research to practice. In a clinical world, the work that

is done must be based on the science, and the science must be done in a way that reflects human experience. When a scientific story makes it from the bench to humans, it truly is amazing.

Every cell has a sex, with potential implications for clinical research and patient care. Discovering and exploiting this is a new, exciting, and necessary challenge. By ensuring that both sex and gender are studied and reported in research, there will be substantial improvements in understanding male and female biology, resulting in better healthcare.

Author Disclosure Statement

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