VIEWPOINT

Consideration of Sex Differences in Medicine to Improve Health Care and Patient Outcomes

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Viewpoint

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Even though the observation that men and women are different is arguably as old as human life, women have been included in clinical trials for only a few decades. Women have a unique physiology and their experience of illness, and responses to therapeutic interventions are often significantly different from those of men. Recent regulations from the National Institutes of Health requiring grant applicants to consider sex as a variable in biomedical research are a welcome development.[1] However, despite increasing evidence that an individual's sex is one the most important modulators of disease risk and response to treatment, consideration of the patient's sex in clinical decision making (including the choice of diagnostic tests, medications, and other treatments) is often lacking. This is surprising given the increasing interest in precision medicine, which should begin with attention to sex differences in medicine.

In this Viewpoint, we highlight specific examples, focusing on biological sex differences in drug metabolism and cardiovascular risk that appear ready for clinical implementation. Clinicians receive minimal formal instruction about such sex differences, yet incorporation of sex-specific information into clinical practice will improve patient care.

Sexual Dimorphism in Response to Drugs

Many medications are metabolized differently in women than men due to variances in body size and distribution volumes, sex hormone levels, activity of enzymes, and effects of routes of excretion on sex-specific responses to drugs.[2] For example, propranolol levels may be up to 80% higher in women, so dosage has to be adjusted to avoid adverse effects. This is important because survival benefits for women with heart disease who receive the drug are well documented.[3] Zolpidem is more slowly metabolized in women, because of which the US Food and Drug Administration now recommends that the initial dose for women should be half the dose recommended for men.[4] Digoxin, once a primary agent in the armamentarium of drugs used for heart rate control and the treatment of heart failure, has a different and relatively more hazardous effect on women, principally due to reduced distribution volume and the lower glomerular filtration rate in women.[2] Angiotensin-converting enzyme inhibitors reduce cardiovascular events in men but less so in women,[5] and cough is a more frequent adverse effect in women.[6] In contrast, angiotension receptor blockers are equally effective in both sexes.[2] In women, low-dose aspirin reduces the risk of stroke in women but has minimal effect on the risk of myocardial infarction (MI)[2]; whereas, in men the benefits of aspirin appear greater for preventing MI than stroke. Compared with men, women are more likely to experience bleeding after treatment with tissue plasminogen activator or warfarin,[2] suggesting that sex differences should be considered in dose adjustments.

Sex Differences in Cardiovascular Disease

Arrhythmias, particularly atrial fibrillation, have different consequences for women, who have higher mortality, more symptoms, and higher rates of recurrence following ablation procedures.[2] Women have a higher risk of atrial fibrillation–associated stroke than men (25% vs 10%) and experience significantly higher mortality after stroke (25% vs 19% at 6 months).[2,7] Women's unique electrophysiology (which produces a longer cQT interval than that of men) increases the risk of drug-related torsades de pointes (TdP)[8,9]; risk of TdP associated with sotalol is higher among women than men (4.1% vs 1.0%). The observed vs expected prevalence ratio for TdP associated with amiodarone, dofetilide, and azimilide is at least twice as high among women as it is in men.[9]

Coronary Artery Disease

Hypertension, dyslipidemia, smoking, diabetes, and obesity account for 80% of risk of acute MI in both sexes, but presence of diabetes is associated with a 6-fold increase in women's risk of coronary artery disease (CAD), from 107 per 100 000 person-years to 651 per 100 000 person-years vs a 3-fold risk among men with diabetes (**Box**).[2,10] Moreover, women with diabetes and CAD have a 3-fold increased risk of heart failure; men with diabetes have minimal increase in risk.[2] Younger women with CAD have worse outcomes than men of similar age. Timely diagnosis of MI is often delayed in women because of their different symptom complex (shortness of breath, unusual fatigue, sleep disturbances, indigestion, and anxiety; almost one-half may not report chest discomfort). The results of diagnostic testing for CAD can be falsely reassuring in women: the standard stress test has lower specificity and sensitivity in women; stress echocardiography is preferred for women.[2]

Symptomatic women with normal coronary arteries on angiography may have microvascular disease, with metabolic abnormalities evident on magnetic resonance spectroscopy. Statins have a protective effect against CAD in both men and women, but adverse effects of statins (such as myalgias and statin-induced diabetes) may be more common in women than in men.[2] Moreover, women appear more susceptible to catecholamine-related dysregulation of

vascular reactivity and to a reversible cardiomyopathy (takotsubo disease) that occurs in some women in response to profoundly emotional experiences.[2]

Diastolic dysfunction–producing heart failure with preserved ejection fraction is seen principally in women whose only symptom may be dyspnea.[2] Stress echocardiography is the appropriate initial test for diastolic dysfunction and will reveal normal ejection fraction in these patients. Coronary angiography in affected individuals may reveal no obstructive disease. Therapy depends on decreasing the cardiac rate, β-blockers, and nitrates and on reducing blood volume with diuretics and sodium restriction. Blunting the neurohumoral activation with aldosterone antagonists can mitigate fluid retention.[2]

Sex-Specific Medicine in the Genomic Era

Collection of information at the molecular level is rapidly increasing. The nascent ability to edit DNA may create entirely new diagnostic and therapeutic options for patients. Importantly, environmental modification of genomic expression through epigenetic changes clarifies how biological sex and the environment interact to produce the phenotype.[1,2] Biological "sex" and "gender" are no longer separate concepts but components of a unified process that is the consequence of modifications of the genome by individual experiences.

Sex-specific medicine should not be a separate specialty but rather should be integral to all medical educational efforts and clinical programs to support the importance and influence of sexual dimorphism in human physiology and health. This new awareness of the importance of sex differences in patient care is one of the richest features of 21st-century medicine. Research and clinical education in this vital area should be accelerated.

Box. Sex Differences in Metabolism and Cardiovascular Disease

Sex Differences in Medications

Women have higher blood concentrations of propranolol, zolpidem, digoxin, and other medications, when given a standard dose.

Adverse effects of angiotensin-converting enzyme inhibitors (cough) and statins (myalgias and diabetes risk) are more common in women than in men.

Risks of major bleeding with tissue plasminogen activator and warfarin are higher in women than in men.

Aspirin tends to lower risk of stroke in women and myocardial infarction in men.

Sex Differences in Cardiovascular Disease

Women have higher risks for atrial fibrillation–associated stroke, stroke-related mortality, and risk of atrial fibrillation recurrence following ablation.

Women's longer cQT interval increases risk of torsades de pointes with several medications, including sotolol, amiodarone, dofetilide, aximilide, and some antihistamines.

Most coronary artery disease risk factors are similar in men and women but diabetes is a stronger risk factor in women.

Women are more likely to have dyspnea or other atypical symptoms of myocardial infarction (and are less likely than men to report chest discomfort).

Standard stress tests have lower sensitivity and specificity in women: stress echocardiography is preferred for women.

Women may have a higher risk frequency of vascular spasm, microvascular disease, or both.

Takotsubo disease occurs almost exclusively in women.

Heart failure due to diastolic dysfunction (preserved ejection fraction) is more common in women than in men.

ARTICLE INFORMATION

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