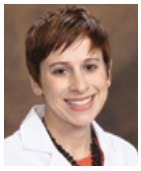
Gender Gap

Sex and Gender Differences in the Treatment of Acute Conditions

LESSON 6



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Reviewed by **Walter L. Green, MD, FACEP**

OBJECTIVES

On completion of this lesson, you should be able to:

1. Name sex- and gender-related differences in the acute management of patients with suspected acute coronary syndrome.
2. Describe the sex-specific risk factors for acute ischemic stroke, and identify gender-related disparities in treatment of the disease.
3. List common emergency department medications that may require sex-dependent dose adjustments.
4. Describe the common differences in injury patterns between women and men.
5. Explain several ways to reduce gender disparities and improve outcomes when managing patients in cardiac arrest.

FROM THE EM MODEL

20.0 Other Core Competencies
20.2 Practice-Based Learning and Improvement
20.2.1.1 Evidence-Based Medicine

CRITICAL DECISIONS

- How should sex and gender differences affect the acute management of ischemic heart disease and other cardiac abnormalities?
- What sex and gender differences should be considered when managing a patient with an ischemic stroke?
- What important sex and gender differences should be considered when prescribing a medication?
- What sex-specific factors influence sports-related injuries?
- How can sex and gender affect the treatment and outcomes of patients in cardiac arrest?

The discipline of emergency medicine continues to evolve as a reflection of science and society. Interestingly, traditional evidence-based medicine assumed without any direct proof that — other than their reproductive organs — women essentially were identical to men. Over the last two decades, however, it has become apparent that disease can manifest quite differently depending on a patient's sex. Unfortunately, much of the current medical science and practice of clinical medicine has failed to account for these significant disparities.

CASE PRESENTATIONS

CASE ONE

A 62-year-old woman presents with fatigue and shortness of breath with exertion; her symptoms began 2 weeks ago and have progressively worsened. She denies chest pain, but complains of occasional "pressure" near her jaw. The patient smokes and has a history of noninsulin-dependent diabetes mellitus. Her electrocardiogram (ECG) demonstrates nonspecific T-wave inversions in the inferolateral leads, and her laboratory results, including troponin tests, are within normal limits. Her chest x-ray likewise is unremarkable.

CASE TWO

A 65-year-old woman with a history of atrial fibrillation, hypertension, and migraines arrives via ambulance after being found collapsed on the floor. She is confused, disoriented, and has a right-sided hemiparesis; her NIH stroke scale score is 22. The patient, who lives alone, was last seen about 5 hours prior to presentation, at which time she appeared normal. Computed tomography(CT)/computed tomography angiography (CTA) tests are positive for a left-sided infarct secondary to a large vessel occlusion of the left middle cerebral artery (MCA). Although her delayed presentation rules out the administration of intravenous tissue plasminogen activator (tPA), the patient is deemed an appropriate candidate for endovascular intervention.

CASE THREE

A 70-year-old woman with a history of hypertension and diabetes presents with a fever of 38.9°C (102°F), altered mental status, and hypotension. She is tachycardic with a heart rate of 115 and blood pressure of 70/40. Her Glasgow coma scale (GCS) is 12. The patient is moaning in pain and intermittently vomiting, but seems to have no focal abdominal tenderness. Her workup is remarkable for an elevated white blood cell count (16.6) and a positive urinalysis; a CT of the abdomen and pelvis reveal stranding around the left kidney, consistent with pyelonephritis.

The patient's ECG shows sinus tachycardia, a corrected QT interval (QTc) of 500, and no evidence of ischemia. Broad-spectrum antibiotics and intravenous fluid are administered; however, her systolic blood pressure remains in the 80s with a progressive decline in mental status. She is intubated and vasopressors are initiated.

CASE FOUR

An 81-year-old man presents with right hip pain, which began 1 week ago after he fell while getting out of bed. X-rays taken by the patient's primary care doctor on the day of the injury reportedly revealed no acute fractures. His symptoms have not been alleviated with pain medications, and is worse when bearing weight. On examination, he is noted to have a pronounced limp.

CASE FIVE

An unconscious elderly woman arrives via ambulance. Cardiopulmonary resuscitation (CPR) is in process, and paramedics report that the patient initially was in asystole, and has not responded to multiple rounds of epinephrine administered in the field. The monitor indicates that she is in ventricular fibrillation. After undergoing two shocks and orotracheal intubation, the patient has a return of spontaneous circulation (ROSC) but remains minimally responsive with a GCS of 3T. A post-ROSC ECG is equivocal for ST-elevation myocardial infarction, and also reveals an old left bundle branch block. Cardiology is consulted.

Sex- and gender-based medicine embraces the influences that sex (a biological construct) and gender (a social construct) have on patient presentations, diagnostic testing, treatment responses, and outcomes (*Figure 1*). A recent US National Institutes of Health requirement [NOT-OD-15-102], which expects research design, analysis, reporting, and generalizability to account for the role of sex as a biological variable in vertebrate and human studies, will unleash an unimaginable quantity of new evidence that can be incorporated into clinical practice.

Additionally, terms *lesbian, gay, bisexual,* and *transgender* (LGBT) attempt to represent a broad group by emphasizing the diversity that exists with respect to gender identity, gender expression, and sexual orientation. Adding to the complexity, no longer can patients simply be categorized as either male or female; instead, gender has evolved into a continuum upon which sexual identity is modified by behavior and subjected to the use of exogenous hormones.

It is incumbent upon emergency physicians to take patient sex and gender into account when interpreting clinical manifestations of disease, potential limitations in diagnostic imaging, sex-specific thresholds for biomarkers and laboratory value references, and medication dosing – not to mention mitigating potential and often-unconscious gender bias.

CRITICAL DECISION

How should sex and gender differences affect the acute management of ischemic heart disease and other cardiac abnormalities?

Ischemic Heart Disease

Coronary artery disease (CAD) remains the most common killer of adults in the United States.[1] While men with CAD present 10 to 15 years earlier than their female counterparts, the incidence of the disease actually has increased among women between 35 and 54 years old, and mortality rates have declined at a slower rate in women.[2]

In addition, women who present with chest pain are treated less aggressively than male patients, and are less likely to undergo stress testing, angiography, coronary revascularization, and other standard medical treatments, including aspirin, statins, heparin, glycoprotein IIb/IIIa inhibitors, and thrombolytics.[3]

The 2012 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines advocate approaching each potential CAD patient with their sex and gender in mind as independent factors. While both men and women with CAD most commonly present with chest pain, women (younger women, in particular) are more likely to present with shortness of breath, profound fatigue, weakness, nausea, and/or referred pain (jaw/shoulder), with or without chest pain (*Table 1*).[4-7]

A sex-related discrepancy in cardiac risk factors also plays an important role when considering risk stratification (*Table 2*). Diabetes, a traditional risk factor for CAD, appears to double the risk of myocardial infarction (MI) in women.[8,9] Similarly, women who smoke are 25% more likely to suffer from CAD than male smokers.[10] On the flip side, hypertension and dyslipidemia disproportionally increase the risk of CAD in men.[11] Nontraditional risk factors associated with MI, including depression, migraines, lupus, vasculitis, and metabolic syndrome, also are more commonly seen in female patients.[12,13] Finally, there is a sex-specific increased risk of CAD in women with pregnancy-related complications.

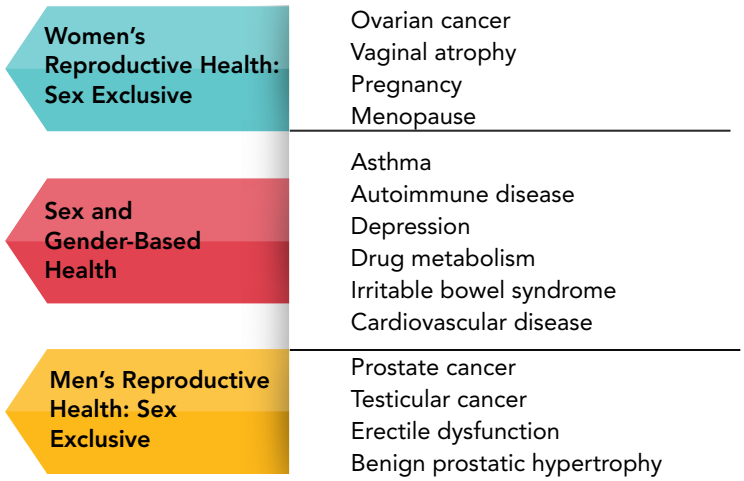
A conventional troponin assay, tested serially, remains the recommended diagnostic test for suspected cases of acute coronary syndrome (ACS).

TABLE 1. CAD Symptoms More Common in Women[6]

Excessive, unusual fatigue
Sleep disturbance
Shortness of breath
Generalized weakness
Nausea
Jaw or shoulder pain

Note: May be prodromal, >1 month prior to presentation.

FIGURE 1. Defining Sex- and Gender-Specific Medicine



Adapted from Jenkins, MR. Chapter 14: Sex and Gender in Medical Education: The Next Chapter. In: AJ McGregor (Ed.), *Sex and Gender in Acute Care Medicine* (p. 233). 2016. New York, NY: Cambridge University Press

Data suggests, however, that the 99th percentile serum levels for troponin assays (ie, the "MI cutoff") are consistently lower for women than they are for men, who benefit from a lower heart muscle mass. Adjusting this diagnostic threshold to a sex-specific standard likely would increase the precision of the ACS diagnosis in women.

Provocative testing results are affected by pretest probability; since women generally have a lower prevalence of CAD and single vessel disease, their exercise tolerance/treadmill tests are less accurate (roughly 60% sensitivity versus 70% in men). Improvements in nuclear perfusion studies and stress echocardiography have made the accuracy of the tests comparable in all patients. Coronary CT angiography is an alternative in non-obese patients; however, in young women, there is a noteworthy and attributable lifetime risk of cancer that must be considered.[14]

The pathophysiology underlying ACS in men and women also differs frequently. Classic plaque rupture resulting in ST-elevation myocardial infarction is more common in men, whereas 1 in 8 women demonstrate endovascular dysfunction/erosion, coronary artery dissection or spasm, or Takosubo cardiomyopathy — alternatives to the typical thrombo-embolic mechanism.[12,15] This is further evidenced when women undergo coronary angiography; they are more likely than men to have nonobstructive CAD (<50% stenosis of one or more coronary arteries).[16]

Despite these differences, the current ACC/AHA guidelines for treating MI/ACS are similar for both male and female patients. Anticoagulants should be weight-adjusted to reduce the risk of bleeding, a complication more frequently encountered in women. The optimization of cardiac risk factors, given known sex-specific discrepancies, also should be taken into account.

Gender Factors

A recent study that assessed factors affecting outcomes after ACS in young patients (18-55 years old) determined that feminine roles and personality traits (assessed via questionnaire) may be associated with higher rates of recurrent ACS and major adverse cardiac events compared with masculine characteristics, regardless of patient sex.[17]

Other Cardiac Diseases

Heart failure (HF), a complex clinical syndrome that is a major cause of cardiac death in the US and the reason for an ever-increasing number of emergency department visits, also should prompt sex-related adjustments in clinical management. Women are more likely to develop concentric remodeling with pathological cardiac stress (due to myocardial injury or pressure/volume

overload), resulting in left ventricular (LV) diastolic dysfunction and diastolic heart failure with a preserved ejection fraction. Men tend to develop eccentric left ventricular remodeling from similar stresses, resulting in increased LV mass and dilated ventricular cavities.[18,19] These alternative, often sex-specific, models of pathological cardiac muscle remodeling result in distinct acute and chronic presentations with subsequent implications for their acute management.

Atrial fibrillation (AF), the most common arrhythmia encountered in clinical practice, is associated with the same risk factors in both sexes; however, women are more likely to suffer from valvular heart disease, and men more frequently have associated hypertension and myocardial infarction.[20] The treatment for AF is the same for any adult. However, women generally have higher resting heart rates and longer corrected QT intervals, and are at greater risk for torsades de pointes in response to certain antiarrhythmic medications. In addition, female patients appear to be at significantly greater risk for major bleeding events while taking warfarin. These potentially dangerous side effects warrant careful selection and medication monitoring, particularly in women.

TABLE 2. Differentially Weighted Sex-Associated CAD/AMI Risk Factors[8,10]

Confer increased risk to men *(as compared to women)*	Confer increased risk to women *(as compared to men)*
• Hypertension • Dyslipidemia	• Type 2 diabetes • Smoking • Metabolic syndrome • Nontraditional risk factors (eg, depression, autoimmune conditions) more common in women • Pregnancy and pregnancy-related factors (eg, eclampsia, gestational diabetes, and gestational hypertension)

CRITICAL DECISION

What sex and gender differences should be considered when managing a patient with an ischemic stroke?

Symptoms/Presentation

Because emergency physicians are responsible for the initial evaluation and diagnosis of patients with acute ischemic stroke (AIS), it is important to be aware of sex and gender differences in the way the disease presents. Women tend to be 6 years older at the time of their incident stroke and are more likely to be living alone, a factor that may affect whether or not symptoms are witnessed. While most research has not shown a significant difference in the time between symptom onset and emergency department arrival, the presence of a witness often is key to obtaining an accurate time history and may affect the applicability of acute treatments such as IV tPA and endovascular intervention.[22]

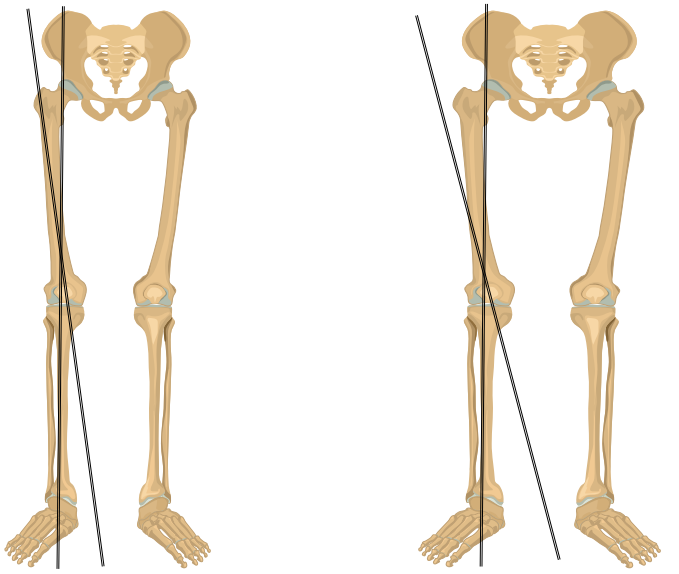
Some data indicate that women are more likely than men to call 911 when experiencing stroke symptoms, but this propensity varies by race; white women are most likely to use EMS.[23] Women are more likely than men to report nontraditional symptoms such as pain, altered mental status, and non-neurological symptoms.[24,25] Women also are more likely to present with stroke mimics, including atypical migraines and conversion disorder; these mimics make diagnostic and therapeutic decisions more difficult, including the determination to administer IV tPA. Emergency physicians should be cognizant, however, that symptomatic intracranial hemorrhage following the administration of IV tPA for the treatment of stroke mimics is rare and occurs even less frequently than spontaneous intracranial hemorrhage among those with an ultimate diagnosis of AIS.[26]

Pathophysiology/Risk Factors

Reported sex-related disparities in the pathophysiology of AIS have been based on data from animal models; in human patients, however, these differences are thought to involve variances in coagulation, fibrinolysis, inflammation, and cell death.[27] AIS resulting from acute embolism is more common among women, and may be related to higher rates of AF with ischemic stroke coupled with lower rates of anticoagulation.[28,29]

Risk factors also differ between men and women and should be considered when risk stratifying patients with

FIGURE 2. Q-Angle Differences



Small Q-Angle (typical male) Large Q-Angle (typical female)

Adapted from McGregor AJ, Choo EK, Becker BM. Sex and gender in acute care medicine. New York, NY: Cambridge University Press; 2016.

stroke symptoms. Female patients are more likely to present with classic stroke symptoms such as hypertension and AF, while men are more likely to suffer from CAD and atherosclerotic disease.[30] Interestingly, there also are differences in the strength of the associations between certain risk factors and AIS. For example, the risk of a first-ever stroke is higher in diabetic women than in diabetic men.[31]

There also are several risk factors that are more prevalent in or unique to women. For example, migraine with aura, which has been established as a risk factor for stroke, is three times more common and has a stronger association with stroke in female patients.[32] Oral contraceptives, especially those containing estrogen, are a sex-specific AIS risk factor for women. Women taking oral contraceptives who smoke and have a history of migraine with aura have a stroke risk that is nine times greater than women without these risk factors.[33]

Finally, in addition to asking about pregnancy, emergency physicians should ask about a history of preeclampsia and gestational diabetes. These pathologies confer a greater stroke risk, even decades after the associated pregnancy.[33]

Treatment Disparities

There are critical contrasts in the way in which men and women with AIS are managed. These disparities must be addressed, as women with the disease suffer from consistently worse functional outcomes. Some data indicate that female patients are less likely to receive timely brain imaging, and women in a large national stroke registry were less likely to have defect-free care as defined by AHA quality measures.[29,34] Specifically, women in the study were less likely to receive anticoagulation for AF and IV tPA within 1 hour of arrival. Several other studies echo this finding, and show that women are less likely to receive IV tPA for acute ischemic stroke.[35]

Although we lack data on sex and gender differences regarding the effectiveness of mechanical thrombectomy for large vessel occlusions, some evidence indicates that women with AIS are less likely to receive intra-arterial therapy, including intra-arterial tPA.[36] While women with stroke are, on average, older than men with stroke, emergency physicians should be aware of possible treatment disparities and should ensure that eligible patients of either sex receive acute interventions.

It is important to note that pregnancy is a known risk factor for both ischemic and hemorrhagic stroke; the incidence is highest in the third trimester and peripartum period.[33] Although pregnant patients have not been included in randomized controlled trials on the use of IV tPA, reported outcomes (including the incidence of spontaneous intracranial hemorrhage) appear to be similar in both pregnant and non-pregnant women who receive the therapy.[37]

When managing a transgender patient with suspected ICH, it is important to know if the patient is taking exogenous sex steroids, which can affect the risk of stroke.

Other Stroke Types

There are important sex and gender differences in other stroke types, including subarachnoid hemorrhage (SAH). The incidence of SAH in premenopausal women is similar to that in men; however, women older than 50 years have a greater prevalence of unruptured aneurysms and about twice the risk of SAH. Emergency physicians should consider these epidemiological factors when assessing any patient with a headache potentially consistent with SAH. Although there is no data suggesting that a diagnostic evaluation with imaging and lumbar puncture should differ between women and men, further research is needed.

TABLE 3. QTc-Prolonging Medications[77]

Class of Medications	Commonly Used Drugs
Antibiotics	Ciprofloxacin, azithromycin, sulfamethoxazole/trimethoprim
Antiemetics	Ondansetron, prochlorperazine
Antipsychotics	Haloperidol, quetiapine
Other	Amiodarone, procainamide

*QTc prolongation associated with these medications should be considered in both women and men; however, women are at higher risk of QTc prolongation and torsades de pointes.

CRITICAL DECISION

What important sex and gender differences should be considered when prescribing a medication?

Due to variances in body size and composition, drug metabolism and clearance, and hormonal effects, drug pharmacokinetics and pharmacodynamics vary between the sexes.[38] Such factors lead to differences in circulating drug concentrations, therapeutic effects, and complications that must be considered when choosing and dosing medications. Some animal studies suggest that even measured drug concentrations must be interpreted differently in females and males due to distinctions in plasma-binding proteins that affect drug activity.[38]

Although this principle cannot be applied to all classes of medications, women often have higher drug concentrations and greater rates of adverse effects than men.[39] Causes likely include higher weight-based dosing in women or the use of inaccurate weights, differences in volumes of distribution or renal clearance, or incongruities in the action of cytochrome P450-related proteins.[39] For example, renal clearance (as measured by the glomerular filtration rate) is lower in women and may lead to adverse reactions in renally-cleared drugs such as digoxin, vancomycin, and cefepime.[39]

Women, who generally have a higher percentage of body fat than their male counterparts, should receive higher doses of lipophilic drugs; these agents have larger volumes of distribution and lower plasma concentrations.[40] The opposite often is true for hydrophilic medications. Unfortunately, women have been historically underrepresented in drug trials, and data on sex-specific efficacy and adverse reactions frequently go unreported.[38,40]

TABLE 4. Musculoskeletal Injury Patterns More Common in Women

ACL strains and tears
Patellofemoral subluxation and anterior knee pain syndromes
Type 1 ankle sprains
Hallux valgus syndrome
Stress fractures (tibia, femoral neck, metatarsals, and pubic rami)
Osteoporotic fragility fractures

Opioids

While responses vary based on factors such as the etiology of pain and the specific drug used, it generally is believed that female patients experience both more analgesia and more adverse effects than men.[41,42] The increased effectiveness of morphine in women seems to be especially true in studies of patient-controlled analgesia.[42] Women also appear to experience more complications from opioids, including respiratory depression.[38] Whether opioid consumption is higher in women or men is a complex question that depends on the context and setting, the provider, and the side effects experienced.[43] There are no current recommendations to support a different female-specific protocol for the administration of opioids, but more research is warranted.

QT-Prolonging Agents

QT interval prolongation as an unintended side effect of some of the most commonly used medications in the emergency department (*Table 3*). Torsades de pointes, the feared complication from QT prolongation, is about twice as common in women, who have longer corrected QT (QTc) intervals at baseline.[39,44] Men appear to benefit from the protective effects of testosterone, while women become more susceptible to the disease over the course of their menstrual cycles due to fluctuations in estrogen and progesterone levels.[45] Medications that can prolong the QTc interval include antiemetics, antibiotics, and antipsychotics, among others. Prior to administering these drugs, it is critical to evaluate the patient's ECG, taking into account sex-specific guidelines for the normal range of QTc intervals.[46]

Neuromuscular-Blocking Agents

Despite routine weight adjustments in the dosing of nondepolarizing induction agents such as rocuronium and vecuronium, there are sex-related differences in the clinical effects of these medications that are rarely considered in acute care. Because of the drugs' hydrophilic properties, women experience higher plasma concentrations, a more rapid onset, and longer duration of effect.[38,40] As a result, most women can be treated with doses at the low end of the recommended range; conversely, men should receive doses at the higher end. No significant sex-related differences have been found or studied with respect to succinylcholine.

Sedatives/Anesthetics

In addition, there are some notable contrasts in the pharmacodynamics of sedatives and anesthetics, likely due to a sex-related differences in the volume of distribution. One important example is propofol, a lipophilic substance and widely used sedative agent in acute interventions. Women have lower plasma concentrations and more rapid declines in plasma propofol levels.[47] As a result, they may require higher infusion rates and tend to emerge more quickly when the drug is discontinued.[47] In order to achieve the same clinical effects, female patients may necessitate higher weight-adjusted doses of propofol.[40]

Vasopressors

Men and women metabolize vasoactive medications differently, resulting in distinct clinical effects. The protein that metabolizes these drugs is 25% more active in men, a process that necessitates potentially higher dose requirements when prescribing vasopressors, including epinephrine, norepinephrine, and dopamine.[40]

Other Agents

There are many other medications whose effects differ by sex. While an exhaustive review of these agents is beyond the scope of this article, the hallmark example is zolpidem (Ambien). The recommended dose for women is now *half* of the original dose approved by the FDA 20 years ago. This important adjustment was made after it was determined that women metabolize the drug at a slower rate than men, a delay that can lead to adverse effects such as increased and prolonged sedation and impaired driving.

CRITICAL DECISION

What sex-specific factors influence sports-related injuries?

Joint Injuries

The number of female athletes has grown tenfold since the passage of Title IX in 1972, a development that has led to increasingly apparent sports injury patterns (*Table 4*). For example, notable sex discrepancies have been displayed in anterior cruciate ligament (ACL) injuries of the knee. Women are two to eight times more likely to sustain an ACL tear than men.[49] Due to multiple factors, including sex-specific biomechanical differences, leg muscle strength incongruity, and the influence of sex hormones such as estrogen, women (particularly female athletes involved in basketball, soccer, skiing, and other sports that involve turning and jumping or pivoting) are more likely to sustain an ACL tear from a noncontact injury.[50,51]

An ACL injury should be considered in any patient with knee pain from an acute contact or noncontact trauma. Risk factors such as the mechanism of injury and patient sex should be taken into account when considering acute stabilization and follow-up instructions. In addition, the implementation of preventative measures such as core strengthening, appropriate and safe landing position training (landing with both hips and knees flexed, on the balls of the feet), and leg muscle stretching and balance exercises, should be routinely considered by trainers and/or sports medicine physicians for female athletes.

Contrasts in the sex-specific anatomical alignment of the pelvis and femur are evidenced by an increased Q angle in women (*Figure 2*). This variance, which can be illustrated by drawing a line from the anterior superior iliac spine to the center of the patella and another from the central patella to the tibial tubercle, contributes to an increased risk of ACL injury

and predisposes female patients to patellofemoral subluxation and anterior knee pain syndromes.[52] Patellar and knee dislocations, however, do not appear to differ by sex.[51]

Conversely, dissimilarities in the neuromuscular control of jumping and landing, which also affect the loading stress on the foot and ankle (as well as the knee), appear to be responsible for an increased incidence of fifth metatarsal fractures and Achilles tendon ruptures in male patients.[53] Upper-extremity evaluation and injury patterns also reveal sex-specific differences. While traumatic injuries generally are more common in men, women have greater glenohumeral instability and increased ligamentous laxity in the elbow. These physiological distinctions, due in part to hormonal influences on collagen elasticity, result in atraumatic shoulder dislocations and elbow dislocations from less forceful injuries.[54,55]

Female athletes are at greater risk of stress fractures, which are caused by repetitive subthreshold stress on abnormally weak bones (due to demineralization and inadequate healing and remodeling time).[56]

Osteoporosis and Low-Impact Fractures

Osteoporosis and osteopenia are major health threats for older men and women, affecting more than half of Americans 50 years and older. These bone disorders disproportionately affect female patients, who live longer than men, on average. While osteoporosis was once considered a women's disease, men have a 20% lifetime risk of sustaining an osteoporotic fracture (most commonly in the spine, hip, proximal humerus, or distal radius).[57,58]

Osteoporotic fractures often present after a low-impact injury such as rolling over in bed; bending over; or, most commonly, a fall from standing (a traumatic event that happens to one-third of adults ≥65 years every year). While women sustain more nonfatal injuries from these low-impact falls, the fall-related death rate is higher for men.[59] Likewise, men who sustain fragility fractures have a higher mortality, often because they are older and suffer from more comorbidities than their female counterparts.[60]

Concussions

Concussion, the most common type of traumatic brain injury, has been seen with increasing frequency in the emergency department over the last decade, according the Centers for Disease Control and Prevention. Defined as a complex pathophysiological mechanism manifesting after a direct or indirect blow to the head or face, a concussion can result in a host of neurological, cognitive, and psychological symptoms that can be cumulative and debilitating.[61]

Women are at higher risk of concussion than men in comparable sports (eg, soccer, hockey).[62] Biomechanical factors, including lower neck-muscle mass and neck muscle strength in women, may result in the decreased mitigation and absorption of rotational acceleration forces.[63] Other evidence suggests that women may have a lower biomechanical threshold for concussion, sustaining injuries at lower linear and rotational acceleration forces than their male counterparts.[64]

Female high school and college athletes are more likely to report concussive symptoms, specifically headache, dizziness, fatigue, and difficulty with concentration.[65] Likewise, objective neuropsychological testing of athletes after concussion found women to be twice as likely to be cognitively impaired than men.[66] Women also take longer to recover from concussions and are more likely to manifest postconcussive syndrome, a constellation of persistent neurocognitive, somatic, emotional, and sleep-related symptoms related to the initial head injury.[67]

Concussions, which can affect both athletes and trauma patients, result in distinct sex-related differences in presentation and long-term recovery. While we are perhaps just beginning to understand the etiology of these discrepancies, the potential implications are important for emergency department management, patient counseling, and future research. In addition, preventative measures such as neck strengthening, early sidelining following injury, and early recognition of concussion are key for all athletes, regardless of sex or gender.

CRITICAL DECISION

How can sex and gender affect the treatment and outcomes of patients in cardiac arrest?

Epidemiology

Cardiac arrest, a condition associated with extremely high rates of mortality and morbidity, differs by sex and gender in several notable ways, including epidemiology, management, and outcomes. Women are more likely to present with nonshockable rhythms, including asystole and pulseless electrical activity (PEA), and are more likely to have causes of arrest other than cardiac ischemia, including pulmonary embolus.[68] On average, women are 3 to 4 years older at the time of the event than their male counterparts, and are more likely to suffer cardiac arrest at

Pearls

- Consider the possibility of nonobstructive disease in women with symptoms of ACS and negative traditional testing, including catheterization and stress tests.
- Women who smoke, have migraine with aura, and are on oral contraceptives are at 10 times the risk of stroke than women without these risk factors.
- Women may require higher doses of lipophilic medications such as propofol.
- Sex differences in hormones and biomechanics lead to different orthopedic injury patterns in women and men.
- Both women and men who present with cardiac arrest and VF/VT may benefit from aggressive and timely interventions, including PCI and TTM.

home.[68] They also are less likely to have witnesses present at the time of the arrest, a social factor that can delay the administration of CPR and other prehospital interventions.[68]

Outcomes

There is ongoing debate about the effect of sex and gender on the rate of survival to hospital discharge. Some studies indicate that women fare better than men, while others assert the opposite is true.[68-70] Survival to hospital discharge can be influenced by factors such as age, comorbidities, and the context of cardiac arrest; adjusting for these variables may reduce any disparities in survivabilty.[71] Survival also may be affected by the early withdrawal of care secondary to a presumed poor neurological prognosis, one of the most common causes of death among patients with out-of-hospital cardiac arrest.

A secondary analysis of a large, randomized control trial of out-of-hospital cardiac arrest patients showed that women are more likely to have an early withdrawal of care (within 72 hours of arrest).[72] The likelihood of a good neurological outcome appears to be the same across gender lines, but there is little data on longer term outcomes after cardiac arrest.[69] While there is some evidence that elderly women (>65 years old) who are alive at hospital discharge are more likely to survive to 1 year than elderly men, they are more likely to be readmitted to the hospital.[73]

Treatment Disparities

Timely and aggressive interventions, including bystander CPR, defibrillation for shockable rhythms, targeted temperature management (TTM), and timely percutaneous coronary intervention (PCI) can help improve the poor outcomes typically observed following cardiac arrest. Although these interventions are being used more frequently than ever before, they are employed significantly more often in men than in women.[74]

A woman is less likely to undergo PCI or coronary angiography, regardless of her initial rhythm and relevant confounders. Furthermore, female patients with VF/VT are less likely to receive TTM than male patients.[74] Some speculate that this gender-related polarity in the management of cardiac arrest may be related to code status limitations or the early withdrawal of care in female patients.[72] When managing any patient with ROSC, it is imperative for clinicians to consider therapies such as angiography, PCI, and TTM.

Treatment disparities also have been found in the prehospital management of cardiac arrest patients; women receive less aggressive care, including basic life support and bystander defibrillation.[70,71] Specifically, the time to initial rhythm capture and CPR by EMS providers is longer in women, and female patients are less likely to receive successful intravenous access and code medications, including epinephrine.[75] Data on sex disparities in bystander CPR are conflicting.[68,69]

Pregnancy

Pregnancy presents very specific challenges with respect to women in cardiac arrest. The American Heart Association recommendations for treating cardiac arrest in pregnant patients (with a uterine fundus palpable at or above the mother's umbilicus) are focused on performing an emergency perimortem cesarean delivery within 4 minutes of cardiac arrest if ROSC is not achieved.[76]

The Future

Historically, women have been underrepresented in randomized control trials of patients with out-of-hospital cardiac arrest. In the ROC PRIMED trial, for example, women comprised only 36% of the research sample.[72] In order to gain a better understanding of sex and gender differences in the pathophysiology, treatment, and outcomes of cardiac arrest patients, future studies must include samples balanced between women and men, and should report sex-specific outcomes.

Summary

As clinical research continues to evolve and embrace the parameters of sex and gender in design and analysis, so will the appreciation of when and how these two defining characteristics matter. Although the topic areas and cases presented here represent a small portion of the existing multidisciplinary research on sex- and gender-specific health, they demonstrate the vast array of acute conditions in which important differences exist between men and women. Emergency clinicians have the opportunity to transform these advances in knowledge into a more precise, informed, and safer delivery approach for treating any patient.

Pitfalls

- Failing to recognize that exercise stress tests are 10% less sensitive in women.
- Undertreating a female patient with AIS. Women are at risk for receiving less aggressive treatment, including IV tPA, than men.
- Administering medications that prolong the QTc without first evaluating the patient with an ECG and obtaining a list of home medications.
- Failing to recognize that that the early withdrawal of care in cardiac arrest patients is more common in women, and may be a contributor to sex-related differences in mortality.

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CASE RESOLUTIONS

CASE ONE

The fatigued woman was admitted for further risk stratification, and the clinician initiated an exercise stress test. Unfortunately, the test provoked her symptoms (primarily exertional dyspnea) and was deemed nondiagnostic. A subsequent coronary arteriogram revealed a significant occlusion (>95%) in her right coronary artery. A drug-eluting stent was successfully placed. Six weeks later, the patient had successfully implemented a tobacco cessation program, remained compliant with her medications, and reported resolution of her fatigue and exertional dyspnea.

CASE TWO

The neurointerventional team successfully retrieved a clot and restored flow to the confused patient's left MCA territory. Four days later, her NIH stroke scale score had improved to 4 and she was discharged to a skilled nursing facility for further rehabilitation and help with the activities of daily living.

CASE THREE

Aware of the literature on sex-related differences for the administration of rocuronium, the emergency physician elected to treat the critically ill woman with a dose at the low end of the approved range (0.8 mg/kg). Infusions of propofol and norepinephrine also were administered and titrated frequently to ensure adequate sedation. Once stabilized, the patient was transported to the medical intensive care unit.

CASE FOUR

Concerned about the elderly man's markedly limited mobility, the clinician initiated magnetic resonance imaging of his right hip, which revealed a minimally displaced intertrochanteric femur fracture. He was admitted for orthopedic management, and discharged to a rehabilitation facility following an uncomplicated surgical repair. He returned home 6 weeks later, but required in-home assistance for the activities of daily living. His primary care provider formally diagnosed him with osteoporosis during a follow-up visit.

CASE FIVE

The critically ill woman was admitted to the intensive care unit following consultations with the cardiologist and critical care team. After 72 hours without improvement, a discussion was held with the patient's family regarding her poor neurological prognosis, and her code status was changed to comfort measures only. Care was withdrawn, and she ultimately was terminally extubated.

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