Chapter 1

Know the Difference: Sex and Gender in Acute Care Medicine

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Defining Sex and Gender

The Institute of Medicine (IOM) has stated that "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). "Sex" refers to biological differences between men and women, such as chromosomes (XX or XY), internal and external sex organs, and hormonal profiles. "Gender" refers to the socially constructed roles, values, and personality traits that vary from society to society and over time. Every cell has a sex. 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 a pharmaceutical in a living human.[1]

The IOM report also listed several barriers to research progress, including "the inconsistent and often confusing use of the terms 'sex' and 'gender' in the scientific literature and popular press."[2] Often, the terms are used interchangeably in scientific writing with both terms referring to whether individuals are biologically male or female.[3] Sex and gender are associated and interactive but are not the same. Each variable has significant health implications, is worthy of dedicated study, and can lead to insights into mechanisms underlying morbidity, mortality, and health behaviors.

In real life, there is a continuous interaction between the two: Health is determined by the biology of being male or female and the social context of gender. Therefore, the significance of sex, gender, and their interaction should be considered in the daily practice of patient care.

Identifying the Problem: Do Sex and Gender Matter?

In its 2001 report entitled "Exploring the Biological Contributions to Human Health," the IOM called on biomedical researchers to increase their investigation of sex and gender as critical variables affecting health.[2] It described the rapidly growing evidence for significant differences between males and females in every aspect of health and disease and urged the scientific community to increase its understanding of the impact of sex and gender to advance the practice of medicine.

The evidence-based research that served as the basis for the practice model used today was primarily conducted on male cell lines and male rats and translated to middle-aged, average-sized Caucasian males. The lack of inclusion of sex differences in health and disease, largely as a result of the greater accessibility and convenience of male subjects, is considered a failure of science.[4]

Cardiovascular disease (CVD) research provides a good case example of how sex and gender differences may have meaningful implications for clinical care and health outcomes. Research regarding therapy and prevention of heart disease had largely been performed on men. For instance, in 1988, the Physicians' Health Study, aimed at examining the benefits and risks of aspirin and beta-carotene in the prevention of CVD and cancer, consisted of 22,000 male participants.[5] The study's finding that a daily aspirin could prevent myocardial infarction (MI) was widely adopted into clinical practice, despite not being studied in women. Today, the US Preventive Services Task Force (USPSTF) recommendations provide gender-

specific recommendations regarding aspirin. Questions still remain about the recognition and treatment of cardiac disease in women, particularly with repeated media reports of undiagnosed chest pain, missed MIs, and negligence on the part of physicians.[6, 7]

Another well-publicized example of the impact of sex and gender is the US Food and Drug Administration's (FDA) process of evaluating new drugs as safe and effective, approving drugs for marketing, and providing post-market surveillance to determine if adverse effects are detected after initial approval.

The US General Accounting Office (GAO) reviewed 10 prescription drugs withdrawn from the market between January 1997 and December 2000 and found that 8 out of the 10 drugs were withdrawn because of adverse events occurring predominantly in women.[8] Women were found to be at a greater risk of Torsades de Points from the antihistamines terfenadine and astemizole; a public health advisory was placed when women were found to make up 70% of reports of Torsades de Pointes thought to be induced by these QTc-prolonging medications.[9] The FDA is also responsible for determining indications and dosing for approved drugs. On May 14, 2013, the FDA issued a safety communication approving label changes to zolpidem for treatment of insomnia and recommended significantly lower doses in women for extended-release products because women are more susceptible than men to the risks posed by "next-day impairment of driving and other activities that require full alertness."[10] Concerns remain as to why these sex-determined adverse events were discovered after the drug was approved and on the market. Because of this lack of participation of women in clinical trials, Congress mandated the formation of the FDA's Office of Women's Health (OWH), which was established in 1994. The OWH supports research that examines biological differences and advocates for inclusion of sex and gender as a critical study variable in research within and outside the National Institutes of Health (NIH).

Evolution of Women's Health

To understand the evolution of sex and gender within the scientific and medical environment, it is important to recognize the historical transition in the conceptualization of women's health (Figure 1.1).[11]

The female reproductive system was the focus of women's health care in the early nineteenth century. Even mental illness was connected to the female menstrual cycle, such that the word "hysteria" came from the Greek word meaning "uterus."[12] Throughout the twentieth century and with the rise of modern medicine and scientific methods, a number of forces conspired to prevent equal inclusion of men and women in clinical research. One important factor was the federal government's paternalistic approach toward women, particularly pregnant women. This attitude was fueled by the disastrous outcomes that resulted from new medications prescribed to pregnant women: diethylstilbestrol, prescribed in the 1950s for pregnant women to prevent miscarriage, led to gynecologic cancer in the daughters of the women who took it; thalidomide, an antiemetic medication given to pregnant women to alleviate morning sickness, caused severe limb abnormalities in developing fetuses.[13, 14] In the face of these events and pressure from the public, the FDA implemented a policy that would eliminate all women of childbearing potential from clinical trials to do away with any risk to the fetus.[12–14] The FDA's 1977 Guidance of General Considerations for the Clinical Evaluation of Drugs essentially had the effect of excluding women of childbearing potential from participation in industry-sponsored clinical trials.[15] It also led to a reluctance of women themselves to serve as study participants.

Another factor influencing the exclusion of women from research was investigators' concerns that women subjects would make the study population less homogeneous, leading to increased sample size requirements, more complex analyses, and correspondingly higher study expenses.[13] A related concern was that biologic factors, such as hormonal fluctuations resulting from menstruation, pregnancy, oral contraceptive pills, menopause, and hormone replacement therapy, created a web of baseline variables that would be difficult to consider when analyzing research.[13, 14, 16]

The most fundamental obstacle to sex- and gender-specific research, however, was the simple lack of recognition of their impact as independent

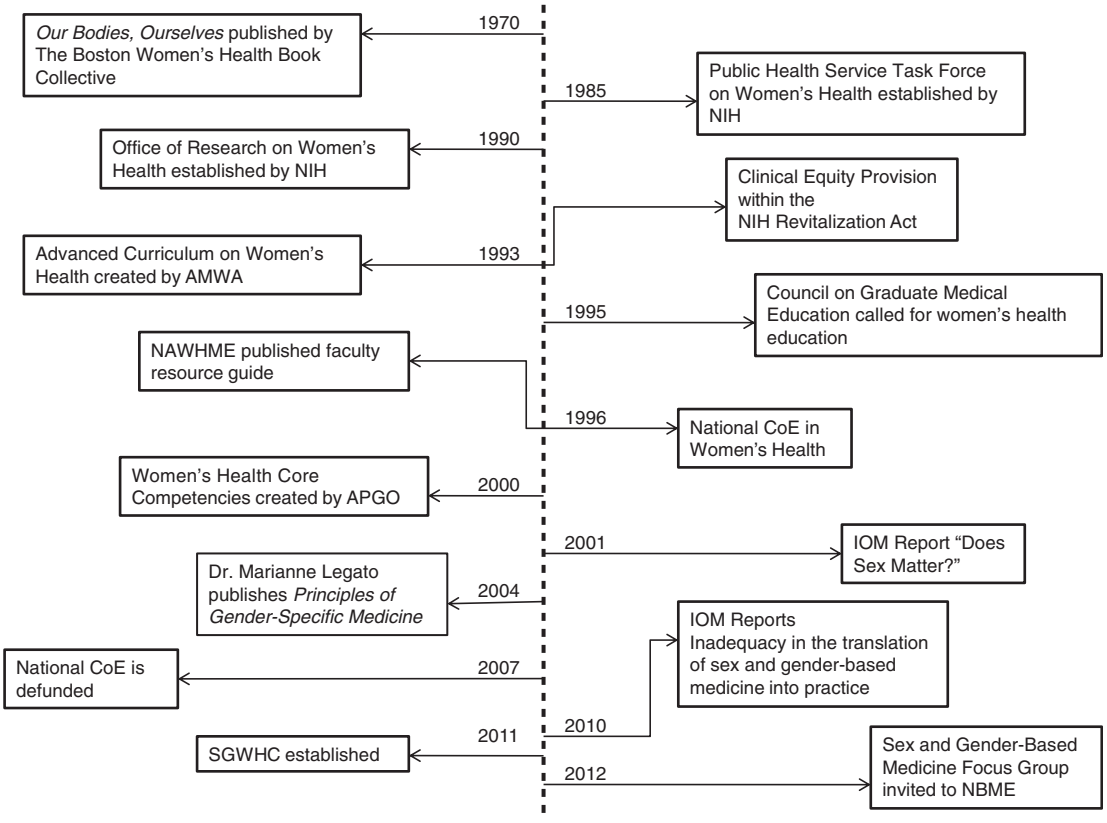

Figure 1.1 Key historical contributions to the evolution of sex and gender in medicine. Reproduced with permission from Biology of Sex Differences

variables in medicine. Ultimately, scientists needed not only to accept the validity of sex-related differences but also to translate this acceptance into how they designed studies and recruited participants into clinical trials.[16, 17]

Compounding considerations of risk, complexity, and cost was the implicit assumption that outcomes in men would be adequate proxies for outcomes in women, despite the fact that physiologic, anatomic, and metabolic differences between men and women argued against this assumption.[11] In the latter half of the twentieth century, with women's individualism brought to the nation's consciousness by the feminist movement, the concept of "sex" in human biology began to shift. In the 1980s, the NIH established a Public Health Service Task Force on Women's Health. Recommendations for increased attention to women's health issues led to the development of specific guidelines and processes regarding the inclusion of women as subjects in NIH-funded extramural research.[18]

Identifying a Difference

In 1986, the NIH set up an advisory committee that recommended but did not mandate that grants include women as subjects in clinical studies.[19] Nevertheless, the Congressional Women's Caucus commissioned the GAO to evaluate the implementation of this policy advising the inclusion of minorities and women in clinical studies.[19] In the 50 NIH grant applications reviewed during this audit, 20% did not mention gender, more than 30% did not provide breakdown percentages, and some all-male studies gave no reason for women's exclusion.[20] This led to the creation of the NIH Office of Research on Women's Health (ORWH) in 1991.[13] In 1992, the GAO reported that more than 60% of trials submitted by the

pharmaceutical companies to the FDA lacked female representation.

As the recognition of the research gap for women became more apparent, the FDA policy was reevaluated; modifications issued in 1993 encouraged drug companies to include minorities and women and provide subgroup analyses.[13, 21] In addition to inclusion of women, this Revitalization Act, signed into law by President Clinton, required that the NIH ensure that cost would not be an acceptable reason for exclusion.[22]

Yet, even after 1993, there were more reports of unexpected adverse events in women than men during post-market surveillance.[23] In 1994, the IOM established a Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies.[22] In November 1999, the IOM formed a Committee on Understanding the Biology of Gender Differences. This was the first major step taken by the IOM in the area of sex-based science and policy. The 2001 report "Exploring the Biological Contributions to Human Health: Does Sex Matter?" presented scientific evidence in support of the biologic basis of sex differences, promoted sex- and gender-related research questions, identified barriers, and clearly solidified sex as an important variable of health.[24]

Calls to action have not been adequate to radically change researchers' behaviors. In 1997, the FDA implemented the Modernization Act, stating that further guidance was necessary in the inclusion of minorities and women in research trials.[17, 25] More than 15 years later, the NIH acknowledged that basic science studies still lack equal consideration of males and females: A recent joint statement by NIH Director Francis Collins and ORWH Director Janine Collins addressed ongoing neglect of sex inclusion in basic science studies.[26] Multifaceted strategies, coupled with funding, need to be in place to address the gaps in women's health and ensure that sex is taken into account when addressing health and disease.

Why Focus on Emergency Care?

The emergency care setting provides access to a vast array of disease conditions at critical periods in their management. The concept of a treatment "window," during which definitive action within minutes to several hours is critical to improve clinical outcomes, is almost exclusive to the field of emergency medicine. The Emergency Department (ED), therefore, is an ideal place to observe where and how men and women diverge in their presentations and responses to treatment. Furthermore, with its access to a large proportion of the population, any sex- or gender-specific clinical practice within emergency care has the potential to have a large impact.

As with every area of medicine, the study of sex and gender in emergency care is in its infancy; the lack of attention to sex and gender within the emergency medicine literature has been documented.[27] However, the specialty has begun to mobilize its research efforts around sex and gender in a coordinated manner, notably through a 2014 national consensus conference aimed at defining a research agenda for sex- and gender-specific research regarding emergency and acute care.[28] Hand in hand with these early research efforts, we must review the existing multidisciplinary literature and make informed decisions about how to apply the available scientific knowledge around sex and gender to clinical practice. The future holds promise for a better understanding of sex-based differences in acute care, leading to new, personalized approaches to prevention, diagnosis, and therapy.

This book is designed to bridge the gap between our traditional clinical practice of considering the differences between men and women within the confines of reproductive health to our growing certainty about the profound significance of sex and gender in every aspect of disease.

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Chapter 2

It's not all Chest Pain: Sex and Gender in Acute Care Cardiology

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An Introduction to Gender in Acute Care Cardiology

This chapter focuses on the gender differences in epidemiology, pathophysiology management pearls, and prognosis of cardiovascular disease with a clinical focus on acute coronary syndrome (ACS), non-ischemic cardiac syndromes, structural heart disease, and arrhythmias. We also discuss cardiac diseases with increased prevalence in women, such as Takotsubo's cardiomyopathy and Syndrome X.

Section 1 Acute Coronary Syndromes

Patient A A Case of Acute Coronary Syndrome

A 54-year-old woman with history of diabetes and high blood pressure presents to the Emergency Department (ED) with a sensation of burning in her chest for the past week each time she walked upstairs. She thought the burning would subside as it had previously; however, on the day of presentation, the burning worsened and was associated with shortness of breath and fatigue. She attributed her symptoms to anxiety resulting from increased financial stress but came in at the urging of her son. She has a history of diabetes for which she takes metformin 1000 mg twice daily but otherwise reports no other significant medical issues and takes no other medications. She smokes about 10 cigarettes per day. She has no significant family history of coronary artery disease (CAD), stroke, or sudden death. On initial exam, she is afebrile with a blood of pressure 145/85, a heart rate of 98 beats/min, with normal respirations and oxygen saturation of 96% on RA. In general, she is in mild distress without jugular venous distention and has clear lung fields. Her cardiac exam demonstrated a regular rhythm, without murmurs, rubs, or gallops. PMI was non-displaced. Her abdominal exam was benign and extremities were without edema with 2+ pedal pulses. Work-up revealed an EKG with sinus rhythm and T-wave inversions in leads I and AVL. Initial troponin was negative. Chest X-ray was normal.

Clinical Questions

- How would you approach a cardiac work-up in this patient?
- What are the gender-specific elements in diagnosis and management that you should consider?

The following section summarizes the most recent literature on key gender-specific differences in epidemiology, presentation, physiology, diagnostics, treatment, and prognosis for ACS.

Prevalence of Acute Coronary Syndrome in Women

ACS should be the first diagnostic consideration for this patient with chest pain, as CAD is the most common cause of death for women and men in the United States.[1] The onset of CAD in men occurs 10 to 15 years earlier than in women. Nevertheless, heart disease remains a leading cause of death in women. Over the two decades, the mortality rate from CAD has been declining at a slower rate in women than in men and, in fact, has increased for women in mid-life (35–54 yrs).[2]

Gender-Specific Diagnostic Approach to ACS

In accordance with 2012 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, the initial approach for evaluating this patient should include risk stratification through a gender-specific lens. Early detection relies on three basic pillars for identifying critical CAD based on risk estimation. These are history of presentation (including cardiac risk profile), serial ECG, and biomarkers, which should be determined before conducting an anatomical or functional stress test.[3]

Elements of the History of Presenting Illness

Warning Signs Only about one-third of women with ischemic heart disease experience warning chest pain prior to presentation. Compared with men, women are more likely to complain of shortness of breath, profound fatigue, and weakness in the month preceding their myocardial infarction.[4]

Presentation Earlier reports suggest that women with CAD present more often with atypical symptoms. However, a recent prospective study of 2,475 ED patients showed that chest pain or discomfort was the most common presenting complaint in both men and women and accounted for almost 90% of acute myocardial infarction (AMI) ases regardless of age.[5] The difference in presenting complaints between men and women with CAD can be found in their description of chest discomfort as well as an increase in reporting associated atypical symptoms (excessive fatigue, nausea, jaw/shoulder pain, etc.) by women.[4] Gender-specific variation also appears in symptoms based on whether the primary event is a ST-elevation myocardial infarction (STEMI) or a non-STEMI. In general, women under-recognize their symptoms and delay seeking care (on average by 2–3 hours).[6] Women are also overrepresented in a third of AMI group that presents without chest pain (42% women vs. 21% men),[7] further delaying the initiation of definitive care.

Role of Cardiac Risk Factors

There is gender-specific moderation of traditional and nontraditional cardiac risk factors. Traditional factors such as diabetes and smoking differentially increase the risk of MI in women as compared to men. The Copenhagen City Heart Study demonstrated this by prospectively following 13,000 patients with type-2 diabetes for 20 years and found a twofold higher risk of MI in women as compared to men.[8,9] Similarly, smoking increases the risk of CAD in women by 25% compared to men.[10] Even small amounts of tobacco use, as little as 1.4 cigarettes per day, have been shown to increase cardiovascular risk in women.[10] On the other hand, hypertension and dyslipidemia increase the risk in men to a greater extent than in women.[11]

Nontraditional risk factors, such as depression and autoimmune conditions, present with greater frequency in women as compared to men.[12,13,14] Depression has been associated with a fourfold increase in mortality post AMI.[15] Similarly, metabolic syndrome (impaired glucose tolerance and any two of the following: [1] BP ≥ 130/85 mmHg, [2] TRG ≥ 150 mg/dL, [3] HDL < 40 for men and < 50 for women, [4] central obesity or BMI > 30 kg/m^2, and [5] microalbuminuria [30–300 mg/24 hours]) may result in a differential higher risk of mortality and CAD in women.[16,17]

Knowledge of the gender-specific risk attribution by these conditions is important in overall risk stratification of symptomatic patients. While some authors debate the role of cardiac risk factors in ED chest pain patients, evidence suggests that these factors have a predictive role, especially in patients <55 years.[18,19]

Investigative Studies

Serial ECGs are recommended for ruling out ACS regardless of gender. The frequency of ST-segment abnormalities in women with ACS is similar to that for men, but women more often have T-wave inversions.[3] The prognosis of these T-wave inversions in the absence of positive stress tests needs further investigation.

Biomarkers While several cardiac and inflammatory biomarkers are elevated in ACS, the 2012 ACC/AHA guidelines recommend serial testing of troponin in suspected cases. New data indicate that the 99th percentile for troponin assays are consistently lower for women as compared to men; changing the diagnostic threshold would increase the precision of diagnosis in women as

compared to men if high-sensitivity troponin assays are obtained. The upcoming results of the High STEACS (High-Sensitivity Troponin in Evaluation of Patients with Acute Coronary Syndrome) study would likely change our current practice. Additional prognostic value has been attributed to elevated beta-natriuretic protein and C-reactive protein (CRP), especially in women, but larger trials are needed before these tests become standard of care in acute ACS.

Risk-Stratification Scores

Several risk-stratification tools divide patients with chest pain into low-, intermediate-, and high-risk groups to guide outpatient management. Traditional scores such as the Framingham Score (FRS) or the ATP-III score have been shown to underestimate the 10-year risk of CAD in asymptomatic women as compared to the Reynolds Risk score.[20,21] The latter score is derived from 24,000 women and is unique in considering sex-differential factors such as metabolic syndrome and CRP in its algorithm. Age also affects the accuracy of traditional scoring instruments by gender. Whereas young women have a low pretest probability of developing CAD, a recent study of young women (<55 yrs) reported a high burden of cardiac risk factors in these patients when compared to the general population. Nevertheless, traditional scores underestimate their risk. Choi et al.'s paper called for 30-year risk scores to better accommodate the age- and gender-specific nuances of risk stratification.[19] Also, none of these scores is predictive of acute events.

In patients with acute chest pain, measures such as the Thrombolysis in Myocardial Infarction (TIMI) risk score, the Global Registry of Acute Coronary Events (GRACE) risk score, the HEART (History, ECG, Age, Risk factors, Troponin) score, the Vancouver Chest Pain rule, the Quantitative Pretest Probability (QPTP) ACS instrument, and the Emergency Department Assessment of Chest Pain Score (EDACS) provide a more immediate assessment for risk of AMI or death. Of these contemporary risk scores, however, only the EDACS score includes patient gender as a variable in the final model and has been validated in at least one study thus far.[22] As high-sensitivity troponins become more widely used over time, it is likely that risk scores for ED chest pain patients will require additional refinement and validation.

Stress Testing and Other Diagnostic Modalities

Symptomatic patients who have not sustained a myocardial infarction should undergo provocative imaging to rule out critical CAD. In 2005, a consensus group reviewed the sensitivity and specificity of commonly available tests and recommended stress testing for intermediate- to high-risk women.[23] The 2013 ACC and AHA guidelines recommend no differences in testing recommendations for men and women. The sensitivity and specificity of diagnostic tests are influenced by the lower prevalence of CAD in premenopausal women and the fact that single-vessel disease is less common in women. This is why the exercise treadmill test has diminished accuracy (61%–70%) in women as compared to men (70%–80%).[23] Nuclear perfusion studies have comparable accuracy in women and men (near 80% specificity) and are comparable to stress echo (85% specificity). In non-obese patients with a low and stable HR, coronary CT angiogram (cCTA) provides excellent image quality.[24] There is, however, a non-negligible lifetime attributable risk of cancer associated with cCTA. This risk appears to be largest in women who are younger and have combined cardiac and aortic scans; rates are as high as 1/715 women and 1/1,911 men age 60.[25] The risk of contrast-induced nephropathy must also be taken into consideration.

In summary, both men and women with ACS present often with chest pain, but their descriptions of pain and associated symptoms may differ. Variable risk of cardiac risk factors, nonspecific ECG changes, and lower cutoff levels of troponin should be incorporated in gender-specific risk stratification. Risk scores should be validated in gender-specific clinical models. Decisions for optimal imaging strategy should incorporate risk stratification, weight, functional capacity, sensitivity and specificity, institutional expertise, and the radiation risk associated with each modality.

Clinical Pearls

CAD is the leading cause of death for both women and men in the United States.

Women with myocardial infarction present most frequently with chest discomfort. However, they are more likely than men to have atypical symptoms and absent warning chest pain that can lead to a delay in diagnosis and treatment.

Diabetes and smoking differentially increase the risk of MI in women as compared to men.

Nontraditional risk factors such as depression and autoimmune conditions present with greater frequency in women as compared to men and contribute to cardiovascular disease incidence.

No ideal risk stratification score exists. The Reynolds Risk Score allows more sex-specific risk assessment than conventional scores.

Exercise stress testing is best utilized in women with an intermediate pretest probability.

Gender-Specific Pathophysiology for Ischemic Chest Pain

Varying gender-specific mechanisms of pathophysiology influence the clinical course of ACS in men and women. Observations that support pathophysiologic differences include the following: (1) Women have less obstructive disease than men; (2) among women, chest pain symptoms and disability do not correlate with the severity of coronary artery stenosis; (3) women show higher rates of adverse outcomes after acute MI than men of similar age despite having less severe stenosis, smaller infarcts, and more preserved systolic function; and (4) women have higher rates of other disorders suggestive of vascular dysfunction such as Raynaud's phenomenon and migraine headache.[26] The gender-specific causes of cardiac chest pain are varied; they are summarized in Figure 2.1 and outlined next.

Obstruction of the coronary artery (>50%) is the most common cause of ischemic chest pain regardless of gender. However, clinicians now

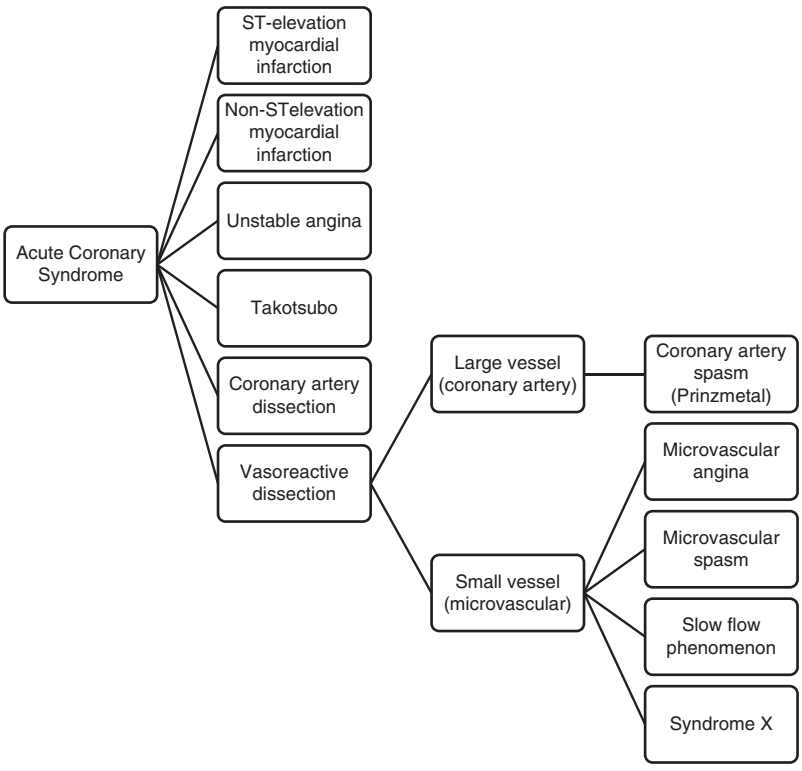

Figure 2.1 Gender-specific causes of acute coronary syndrome

understand that there can be multiple alternate mechanisms of cardiac chest pain, which are more prevalent in women than in men. Syndrome X represents vasoreactive dysfunction and can be categorized as (1) large vessel (coronary) dysfunction commonly seen as coronary artery spasm[27] and (2) small vessel (microvessel) dysfunction. Small vessel dysfunction represents a heterogeneous group of disorders including slow flow phenomenon,[28] microvascular angina,[29] microvascular spasm,[30] and cardiac Syndrome X.[31] Two theoretical explanations of sex-specific differences in coronary pathophysiology may be found in microvascular and endothelial dysfunction as illustrated in Figure 2.1. Microvascular dysfunction can be further differentiated on the basis of exertional/rest angina, timing of pain, presence or absence of typical cardiac risk factors, changes in coronary flow reserve, lactate measurements in the coronary sinus, and microvascular resistance.[32] Higher vasoreactive dysfunction occurs in women for several reasons: Women have a higher proportion of vascular conditions including hypertensive disorders of pregnancy, peri-partum dissection, migraine, vasculitis, and Raynauds. Women also have smaller coronary vessels and more diffuse disease patterns.[33] They have stiffer aortas and more dysfunctional microvessels than men.

In addition to ischemia, two other sex-specific mechanisms of chest pain include coronary artery dissection and Takosubo cardiomyopathy, both of which are discussed in more depth in the section titled "Transient Left Ventricular Apical Ballooning."

Non-obstructive Coronary Artery Disease

The Women's Ischemia Syndrome Evaluation (WISE) Study showed that up to 47% of women undergoing elective angiography have <50% obstruction of one or more coronary arteries as opposed to 17% of men as reported in historical cohorts. Vasoreactive dysfunction often coexists with non-obstructive CAD causing angina despite so-called negative angiography. At least 20% of women with normal or non-obstructive angiography have myocardial ischemia as assessed by perfusion imaging.[34] These patients are often labeled as having Syndrome X, even though the original description of Syndrome X was different.[35]

Testing for Microvascular Angina

Even though endothelial dysfunction of large and small vessels has been described for more than three decades, there is no consensus on uniform definitions for each of these two types of dysfunction.[28] The lack of consensus and definition has made diagnosis a challenge. Classically, administration of intravenous ergonavine, acetylcholine, or adenosine during angiography was considered the gold standard for measurement of endothelial reactivity, but it is no longer performed routinely. More noninvasive forms of testing, such as hemodynamic measurements of coronary flow reserve by cardiac PET scan or MRI have shown some promise. Their widespread use, however, has been limited by cost and availability. At present, the diagnosis of Syndrome X is often made clinically based on classic symptoms, presence of risk factors, and non-obstructive CAD demonstrated by an anatomical study with or without a positive functional test.

Clinical Pearls

Obstructive CAD is the most common cause of ischemic chest pain in both men and women. Other causes of ischemic chest pain such as Syndrome X and microvascular disease are more prevalent in women than men.

Women with chest pain who undergo coronary angiography are more likely than men to have non-obstructive CAD (<50% stenosis of one or more coronary arteries).

Microvascular angina is a clinical diagnosis based on symptoms, risk factors, and often a finding of non-obstructive coronary artery disease. However it can also exist with and without CAD.

Treatment of ACS in Women

For patients with STEMI, immediate reperfusion is recommended for both men and women. Percutaneous coronary intervention (PCI) is shown to be superior to fibrinolysis in women with STEMI, reducing the incidence of subsequent cardiovascular sequelae more effectively than in men.[36] However, the timing of treatment is considered more important than the choice of strategy.[3] For NSTEMI patients, the treatments do not demonstrate gender-specific advantages. However, the recommended dose of anticoagulant