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Review Article

ACUTE MYOCARDIAL INFARCTION IN YOUNG WOMEN: A REVIEW

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ABSTRACT

Acute myocardial infarction (AMI) is the leading cause of death in women worldwide. Every year, in the USA alone, more than 30,000 young women, 55 years of age are hospitalized with AMI. In recent decades, the incidence of AMI is increasing in younger women in the context of increasing metabolic syndrome, diabetes mellitus, and non-traditional risk factors such as stress, anxiety, and depression. Although women are classically considered to present with atypical chest pain, several observational data confirm that men and women experience similar rates of chest pain, with some differences in intensity, duration, radiation, and the choice of descriptors. Women also experience more number of symptoms and more prodromal symptoms compared with men. Suboptimal awareness, sociocultural and financial reasons result in pre-hospital delays in women and lower rates of access to care with resulting under treatment with guideline-directed therapies. Causes of AMI in young women include plaque-related MI, microvascular dysfunction or vasospasm, and spontaneous coronary artery dissection. Compared with men, women have greater in-hospital, early and late mortality, as a result of baseline comorbidities. Post-AMI women have lower referral to cardiac rehabilitation with more dropouts, lower levels of physical activity, and poorer improvements in health status compared with men, with higher inflammatory levels at 1-year from index presentation. Future strategies should focus on primary and secondary prevention, adherence, and post-AMI health-related quality of life. This review discusses the current evidence in the epidemiology, diagnosis, and treatment of AMI in young women.

Keywords: acute myocardial infarction, young women, sex differences, women's health.

INTRODUCTION

Acute myocardial infarction has historically been regarded as a man disease and for many years, women have been under diagnosed and untreated. Due to change in life styles and increase prevalence of obesity, incidences of acute myocardial infarction continue to increase, particularly young women, who comprise a special high risk population. It is crucial for both physicians and young individuals to be aware of disease risk factor, as well as cardiovascular signs and symptoms, in order to mitigate the symptom to presentation times, towards optimizing patients care. A few important studies specifically designed to examine female specific risk factors and outcome in ischemic heart disease or AMI are worthy of mention [1-3]. These studies examined the role of female sex, gender and nontraditional risk factors for AMI and CAD. The National Heart Lung and Blood Institute sponsored multicenter Women's Ischemia Evaluation (WISE) Study investigated the mechanisms of non-obstructive disease in women and the influence of reproductive hormones on the evaluation of IHD in women[[1, 4]. The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study was a multicenter international observational study that compared young women between 30 and 55 years of age to young men enrolled at the time of AMI presentation [2].The GENdEr and Sex determinants of cardiovascular disease: from bench to beyond-Premature Acute Coronary Syndrome (GENESIS PRAXY) multicenter study was designed to examine outcomes in men and women between 18 and 55 years of age with premature acute coronary syndrome (ACS) in which gender-related characteristics were measured using a self-administered questionnaire[3, 5].

Incidence of AMI:

The American Heart Association (AHA) Scientific Statement describes cardiovascular death as an equal opportunity killer and while decline in AMI deaths has been noted in both men and women since the year 2000, rates are decreasing more so in men than in women[6]. Talbott et al studied US Centers of Disease Control National Environmental Public Health Tracking Network data from 20 US participating states and showed that between 2000 and 2008, AMI rates decreased by 20% in men and in women[7]. However, using data from the US National Inpatient Sample (NIS) from 1997 to 2006, Towfighi et al noted that MI hospitalization rates decreased over time by 26% in men but only 18% in women between the ages of 35 and 64 years [8]. In fact, MI hospitalization rates increased for women 35–44 years and decreased only slightly for women 45–54 years and men 35–44 years. Recently, Izadnegahdar et al studied 70,628 AMI hospitalizations (17.1% #55 years of age) between 2000 and 2009 in British Columbia, Canada [9]. Age-standardized AMI rates declined in men and women in similar manner; however, interaction was noted by age-sex-year with increasing rates noted only in younger women (+1.7%/year). Younger women also continued to have higher mortality rates than younger men.

Prevalence of risk factors:

Studies have consistently shown than young women presenting with ACS have significantly greater comorbidities than young men, including smoking, diabetes, metabolic syndrome, hypertension, and chronic kidney disease [10-12]. In general, the prevalence of obesity and diabetes is increasing in US adults in both men

and women [13]. Even though the age-adjusted prevalence of metabolic syndrome has been reported to fall in women between 1999 and 2010, there has been an increase in the prevalence of hypertriglyceridemia and increasing waist circumference attributed to decreasing physical activity, intake of fast food and sugar-sweetened beverages, and shorter sleep duration [14]. While diabetes is considered a risk equalizer for overriding the benefits of estrogen in women, non-diabetic women have similar outcomes to diabetic men; thus, female sex itself lends risk equivalence to diabetes mellitus in men. Women with AMI also have greater prevalence of other comorbidities including congestive heart failure, chronic obstructive lung disease, and poor baseline mental health, with higher inflammatory markers than men [15].

Young women also have greater prevalence of depression, anxiety, and stress, with higher depression and stress scores at the time of AMI presentation compared with men, as a function of greater comorbidities, familial conflict, financial concerns, and care giving demands [6, 10, 16, 17]. Certainly, untreated depression in AMI patients is correlated with greater risk of 1-year mortality than patients with treated depression or patients without history of depression [18]. Women had greater traditional risk factors than young men, but also greater non-traditional risk factors such as anxiety, low household income, and depression. Female gender encompassing social and cultural factors, namely, stress level and responsibility at home, stress management, femininity score, primary earner status, number of hours worked per week, and social support, were observed to be more important than sex for health-related quality of life outcomes after ACS [19].

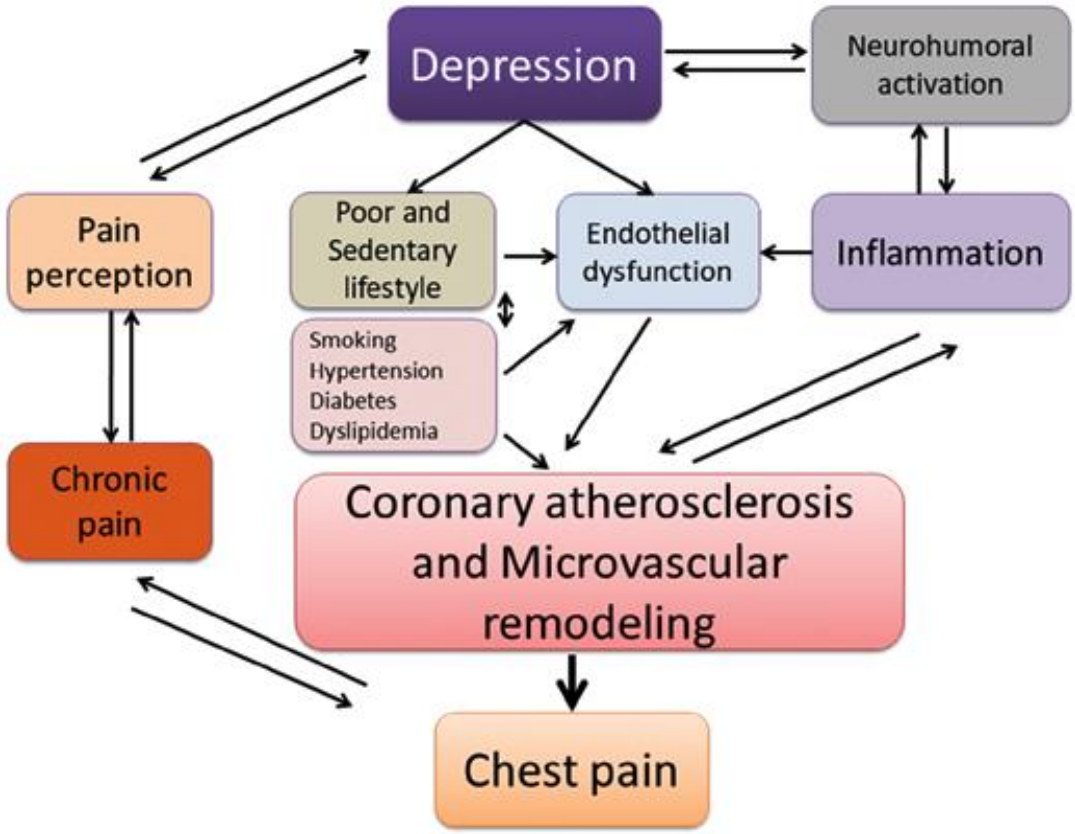

Figure 1: Flow chart showing the pathophysiology of myocardial infarction in depression patients.

Young women with history of adverse pregnancy outcomes are at higher risk of accelerated atherosclerosis and premature CAD [20]. While premenopausal women are thought to be of low risk from a cardiovascular perspective due to the protective effects of estrogen, the higher rates of traditional cardiovascular risk factors outweigh these benefits. Premenopausal women may also be at higher risk of MI when estrogen level is low such as during the menstrual and follicular phases of the menstrual cycle [21]. Nevertheless, postmenopausal hormone replacement therapy, although shown to be beneficial.

Symptoms and signs:

Women commonly present with atypical right-sided chest pain, neck or shoulder pain compared with men who experience typical left-sided chest pain radiating to the left shoulder and jaw [14]. In a retrospective survey study conducted in 1,270 women, 96% of women documented prodromal symptoms at the time of ACS presentation, and unusual fatigue (73%) and sleep disturbance (50%) were the most common symptoms [9].

However, from the Advantageous Predictors of Acute Coronary Syndrome Evaluation multinational registry (n=2,475, 32.2% women), investigators noted that out of 34 chest pain characteristics, 29 were similar in men and women [22]. Differences were observed only in chest pain radiation, intensity, and duration. Women more commonly reported radiation to the back and pain lasting for more than 30 minutes.

Other studies have also shown that men and women experience a majority of similar symptoms [23]. Kreatsoulas et al showed that both sexes experienced chest pain equally, although women twice as often used the terms “discomfort”, “crushing”, “pressing”, and “bad ache” compared to men [24]. Men and women equally reported pain in the arms, back, and shoulders, and there were no sex differences in non-chest pain symptoms such as shortness of breath, fatigue, sweating, and weakness, but women more often experienced a dry mouth than men.

Further, compared with younger women, older women were more likely to present without chest pain. Even though women have had low symptom severity, the number of symptoms was high compared with men.

While women have delays in presentation and higher clinical risk scores, men have more classic electrocardiography findings, allowing faster access to care. Female gender is strongly correlated with delayed hospital arrival and symptom to balloon time in STEMI due to low awareness, sociocultural and financial reasons [25, 26]. In a qualitative study of women between 30 and 55 years, authors noted that women were not accurately aware of their cardiovascular risks, reported poor preventative behaviors, and delayed seeking care for their symptoms [27]. Despite significant risk factors, only one-half of men and women correctly perceived their risk of heart disease [28].

Pathophysiology:

Majority of AMI occur in the context of plaque rupture, however, in a third of cases, thrombus occurs with an intact fibrous capsule [29]. The plaque erosions in the context of AMI, [[30] observing that premeno-pausal women had more plaque erosion compared with plaque rupture noted in postmenopausal women. On the other hand, coronary thrombosis in the setting of calcific nodules is more common in elderly women. Plaque

erosion, associated with a thick-cap fibroatheroma, smooth muscle cells, greater proteoglycans, few macrophages, and inflammatory cells, is the cause of 25%–30% of STEMI cases, and younger smokers are more often affected [29]. Different biomarkers may be implicated in plaque erosion and rupture, serving as useful targets for disease modulation [31]. Recent studies have examined whether use of intravascular imaging with optical coherence tomography is useful in AMI patients to detect plaque erosion, which may allow a different treatment strategy avoiding Stenting [32, 33].

Angiographic characteristics and diagnostic dilemmas:

Women tend to have less adverse anatomical characteristics than men with lower plaque burden and less calcification, particularly among younger women [34, 35]. In the PROSPECT trial, there were no differences in culprit lesion number, location, or complexity by sex. Women tended to have more plaque erosion whereas men had plaque rupture [36].

However, invasive angiography may be inaccurate, and intravascular imaging is often required to confirm the presence and extent of plaque. From the WISE trial, 80% of patients with normal coronaries on angiography were observed to have plaque in the coronaries on intravascular ultrasound [37].

In a VIRGO sub-study, patients were grouped according to the type of MI using the third universal definition [38]. while most patients had plaque-related MI (82.5% women, 94.9% men), other types included obstructive disease with (1.4% women; 0.9% men) and without (2.4% women; 1.1% men) supply demand mismatch, non-obstructive disease with (4.3% women; 0.8% men) and without supply demand mismatch (7.0% women; 1.9% men), other mechanisms for MI (1.5% women, 0.2% men), and unexplained MI (0.8% women, 0.2% men).

Non-obstructive disease:

Women have a high prevalence of non-obstructive disease on angiography [39, 40]. Chest pain and AMI in the absence of atherosclerotic or obstructive coronary disease may be due to several reasons including coronary vasospasm, microvascular ischemia, spontaneous coronary artery dissection and stress cardiomyopathy. Myocardial infarction with normal coronary arteries tends to affect young women and includes both endothelial dysfunction and vasospasm in the epicardial vessels and endothelial dysfunction in the microvasculature [40]. Various descriptors have been used for this scenario including, syndrome X, vasotonic angina, sensitive heart, angina with normal coronary arteries, microvascular angina, non-obstructive CAD, or the overlapping term INOCA (ischemia and no-obstructive coronary artery disease)[40, 41].

Although prevalence varies from 6% to 30% in women with ACS and outcomes are generally better than with obstructive disease, it is not a benign condition, and therefore, deserves careful evaluation. In the WISE study, the incidence of non-obstructive disease with core laboratory-assessed angiographic stenosis between 20% and 50% was quite common, occurring in 25% of women, no disease occurred in 37% and obstructive disease was present in 38% [39]. Ten-year cardiovascular death or MI occurred in 6.7%, 12.8%, and 25.9% of patients with no disease, non-obstructive disease, and obstructive CAD.

Microvascular dysfunction and coronary vasospasm:

Nearly two-thirds of women with non-obstructive disease may have evidence of microvascular dysfunction [42]. The cause for coronary microvascular dysfunction (CMD) may be epicardial abnormal vasomotion or endothelial microvascular dysfunction, atherosclerotic emboli or inflammation [41, 43]. CMD has been noted both in the presence and in the absence of traditional cardiovascular risk factors [43]. Microvascular ischemia can be objectively tested using echo Doppler, positron emission tomography, cardiac MRI, or invasive assessment of coronary flow reserve [41, 43].

Treatment for suspected microvascular ischemia includes calcium channel blockers and nitrates [41], Statin, Angiotensin-converting enzyme inhibitors, and Amitripyline may be beneficial via a vasodilator action.

Coronary vasospasm, variant or Prinzmetal's angina, is caused by vagal withdrawal or increase in sympathetic drive, albeit other mechanisms may play a role such as decrease in nitric oxide, increase in phospholipase C or magnesium deficiency [40, 44]. It is common in young patients and smokers and frequently associated with ST-segment elevation or ventricular arrhythmias, but may also be caused by ingestion of recreational drugs (cocaine, cannabis, and amphetamines) or chemotherapy, antibiotics, and anti-migraine medications [44]. Treatment includes calcium channel blockers and nitrates. Stains are anti-inflammatory and may be beneficial through inhibition of rho-associated kinase [44].

Spontaneous coronary artery dissection:

Spontaneous coronary artery dissection (SCAD) is defined as a tear or separation in the layers of the coronary artery wall between the intima and the media, which is spontaneous and may be associated with intramural hemorrhage [45]. Majority of patients tend to be young women in the peripartum period, although an association has also been observed with fibromuscular dysplasia, with a SCAD prevalence of 25%–86% in this subset [46]. Presentation is commonly with STEMI and may be associated with ventricular arrhythmias or sudden cardiac death [47, 48]. Although different angiographic types have been recognized, currently, the term SCAD is used to refer only to non-atherosclerotic variants of the disease [45]. Diagnosis may be facilitated by the use of intravascular imaging [48]. Treatment tends to be conservative rather than coronary Stenting for risk of extending the dissection flap, but is dependent on the individual clinical setting. However, recurrence has been noted in up to 13%–17% of patients [46, 48] hence, follow-up is crucial. SCAD is also associated with a high prevalence of anxiety and depression, particularly among young women and those with peripartum SCAD [[46, 49]. Thus, dedicated follow-up and rehabilitation can assist in early recognition for channeling appropriate specialist care [50, 51]. After the initial diagnosis of SCAD, computed tomography angiography may be useful in patients with recurrent chest pain or to monitor for lesion healing.

Stress cardiomyopathy:

Takotsubo (stress) cardiomyopathy is a left ventricular apical ballooning syndrome, triggered by emotional or physical stress and noted more often in older postmenopausal women, commonly presenting as ACS or STEMI in the absence of obstructive coronary disease [52]. In a large international registry, the mean age of women presenting with Takotsubo syndrome was 66.8±13 years, but men compared with women

experienced worse short- and long-term mortality [52]. Some reports indicate that this condition may also be noted in younger patients suggesting that physicians should remain vigilant when other causes for MI have been excluded [53].

Pregnancy-related complications and premature atherosclerosis:

Pregnancy-related complications such as gestational diabetes, gestational hypertension, preeclampsia, low birth weight, and preterm labor are associated with endothelial dysfunction, metabolic derangements, and premature atherosclerosis contributing to future risk of cardiovascular events[20]. Similarly, infertility and high parity are associated with greater risks, although precise mechanisms are unclear [53].

Clinical outcomes:

Based on pooled data for the period 1995–2010 from the Framingham Heart Study, Multi-Ethnic Study of Atherosclerosis, Atherosclerosis Risk In Communities, and Coronary Artery Risk Development in Young Adults, the 2016 Heart and Stroke Statistics update reported that for patients between 45 and 64 years of age, within 1 year of first MI, 3% White men, 5% White women, 9% Black men, and 10% Black women will die [14]. Several data have shown that young women have worse long-term outcomes than men after ACS presentation, correlated with worse baseline risk factors [54]. Interestingly, investigators of the GENESIS PRAXY study noted that female gender but not female sex was associated with greater risks and 1-year adverse outcomes [55].

The recent PLATINUM DIVERSITY multicenter US study was specifically designed to analyze outcomes in women and minorities undergoing PCI who are underrepresented in PCI trials compared with White men [56]. The authors noted that women and minorities had higher incidence of 1-year death or MI compared with White men. Women with ACS have also been shown to have greater rehospitalization rates than men [57].

Treatment:

A treatment bias has long been described for women presenting with AMI. Despite significantly higher risk of adverse events, women are less likely to be referred for cardiac catheterizations or PCI, due to underdiagnosis and perceived risk of complications [57, 58]. In the Canadian ACS study, 66.1% men and 51.8% women received cardiac catheterization in the same admission [57].

Women are also less likely to receive evidence-based therapies than men [59]. In the WISE study, during 1-year follow-up, women with non-obstructive disease were less likely to receive statin (12% in women with no disease vs 33% in non-obstructive disease vs 53% in obstructive disease) and other medications compared with patients with obstructive disease.

Rehabilitation and health quality post-ACS:

Prior research has shown that women are less likely to be referred for cardiac rehabilitation than men, despite guideline recommendations. Some factors limiting attendance at rehabilitation might be depression, arthritis, and distance from the hospital, and poor social support, which can be overcome by home and community-based approaches. Cardiac rehabilitation dropout rates are highest in young women, with high depression and anxiety scores, even though rehabilitation and physical activity have been shown to alleviate depression [60]. In a small randomized trial, dedicated rehabilitation with motivational interviewing was

superior to traditional cardiac rehabilitation in women for reducing depressive symptoms [61]. Contemporary approaches using digital health technology may be successfully used to encourage young patients to complete cardiac rehabilitation. Being married, engaged in a professional or clerical job, better physical health, and no previous CAD or hypertension were associated with higher likelihood of returning to work. Low perceived social support had a significant impact on health outcomes in young men and women after AMI.

CONCLUSION

The incidence of AMI in young women is increasing in conjunction with increasing lifestyle risk factors and greater prevalence of diabetes, obesity, and metabolic syndrome. Risk factors are evolving and non-traditional risk factors such as depression, anxiety, and stress warrant careful consideration in clinical assessment. Non-atherosclerotic mechanisms of ACS should be evaluated in patients without obstructive disease, since non-diagnosis can result in high morbidity and healthcare costs. Along with improvements in symptom awareness of young women for early presentation, focus on secondary prevention with guideline-directed therapies is necessary to improve outcomes. Dedicated post-ACS care and rehabilitation may be tailored to patient needs to optimize long-term health-related quality of life.

Abbreviations:

CAD: Coronary artery disease.

MI: Myocardial infarction.

STEMI: ST-segment elevation myocardial infarction.

ACS: Acute coronary syndrome.

AMI: Acute myocardial infarction.

SCAD: Spontaneous coronary artery dissection.

CMD: Coronary microvascular dysfunction.

INOCA: ischemia and no-obstructive coronary artery disease.

Conflicts of Interest:

There authors have no Conflicts of interest to declare.

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