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# Coronary Atherosclerosis in Women

*Abhishek Ojha and Nishtha Sareen*

## Abstract

Despite numerous studies focused on women's cardiac health, deaths from cardiovascular disease continue to rise in women. Cardiovascular disease (CVD) continues to be the leading cause of death even in women in many areas of the world. It has been noted that despite higher frequency of chest pain/angina in women compared to men, the incidence of obstructive coronary artery disease (CAD) remains lower in the female population compared with men presenting with similar symptoms. It is critical to have a deep understanding of these topics to ensure a meaningful communication between public, patients, and healthcare professionals. One reason to which this discrepancy has been attributed to is that chest pain in women is less likely to be secondary to obstructive coronary stenosis in comparison to men presenting with similar symptoms. The other issue is that the gold standard for coronary atherosclerosis continues to be coronary angiography. This is a key limitation in cardiovascular atherosclerosis management since endothelial dysfunction in addition to a higher risk of atherosclerosis is prevalent in women with hypertension, diabetes, and dyslipidemia. In this chapter, we will focus on the aspects of coronary atherosclerosis that deserve attention with respect to gender-specific considerations, particularly with respect to clinical practice.

**Keywords:** atherosclerosis, coronary, myocardial infarction, females, gender

## 1. Introduction

Despite numerous studies focused on women's cardiac health, deaths from cardiovascular disease continue to rise in women. Cardiovascular disease (CVD) continues to be the leading cause of death even in women in many areas of the world. It has been noted that despite higher frequency of chest pain/angina in women compared to men, the incidence of obstructive coronary artery disease (CAD) remains lower in the female population compared with men presenting with similar symptoms [1]. It is critical to have a deep understanding of these topics to ensure a meaningful communication between public, patients, and healthcare professionals.

It is important to note that despite all the literature diagnoses, cardiovascular illness in women remains underdeveloped. One of the reasons which it has been attributed to is that chest pain in women is less likely to be secondary to obstructive or flow-limiting coronary stenosis in comparison to men presenting with similar symptoms [1]. The other issue is that the gold standard for coronary atherosclerosis continues to be coronary angiography [1]. This is a key limitation in cardiovascular

atherosclerosis management since endothelial dysfunction, in addition to a higher risk of atherosclerosis is prevalent in women with hypertension, diabetes, and dyslipidemia [2].

Gianturco et al. [3] have also explained the role of systemic inflammation as a potential under-recognized player in endothelial dysfunction. Both inflammation and immunity seem to be the critical players [3]. The authors have emphasized on the need for preventive strategies after detailed understanding of the possible underlying pathogenesis [3].

In this chapter, we will focus on the aspects of coronary atherosclerosis that deserve attention with respect to gender specific considerations, particularly with respect to clinical practice.

## **2. Pathogenesis**

Endothelial dysfunction, inflammation, and atheromatous plaque in women, as well as men, is primarily caused as a result of aging, dyslipidemia, hypertension, cigarette smoking, and diabetes. These five risk factors mentioned are all well-known traditional risk factors with well-documented correlation to pathophysiology of CAD [4].

### **2.1 Oral contraceptives and heart disease**

Oral contraceptives (OC) have been associated with a higher risk of atherosclerosis and venous thrombosis since their introduction in clinical practice [5]. The risk for acute heart attack was increased by a factor of 2.5 in those who used second-generation contraceptives when compared to third-generation OC (OR1.3) on comparison of the different generations of these medications. This suggests a lower risk in newer generation OC but the overall findings remain inconclusive. The authors, hence, concluded that the recommendation to health care providers should include a dedicated screen for traditional cardiovascular risk factors and events before prescribing OC [6].

### **2.2 Pregnancy and heart disease**

Pregnancy is associated with elevated atherogenic responses, including insulin resistance and dyslipidemia, with consequent manifestation as preeclampsia and gestational diabetes. These complications can contribute to higher postpartum risk of CVD, with a two-fold increase in CAD and cerebrovascular disease [7]. Preeclampsia has been associated with insulin resistance, hypertension, lower high-density lipoprotein concentrations, higher plasma levels of triglycerides, high uric acid, and high levels of insulin. This is in addition to its recognition as a state of sympathetic overactivity and proinflammatory changes [7]. Thus, preeclampsia should be carefully evaluated as a potential index manifestation of the metabolic syndrome.

### **2.3 Parity and heart disease**

There is a well-established relationship between number of children, CAD risk factors and prevalent CAD in both women and men in the age range of 60–79 years [8].

The comparison of gender indexes helps delineate whether the association is secondary to biological processes or due to lifestyle factors. The results have consistently shown an association of increasing number of children with increasing

obesity in both sexes. In women alone, there was suggestion of association between number of children and CAD, even after adjustment for obesity and metabolic factors [8].

## **2.4 ACS in women**

A detailed review of the Rapid Early Action for Coronary Treatment (REACT) study designed by the NHLBI was performed, which tested multistrategy campaigns to reduce patient delay to seek care for ACS symptoms [9]. It was clearly shown that reducing the time to treatment was associated with significantly lower rates of death and disability caused by AMI [9]. This is critical information for education not only of the healthcare providers, but also of patients, individual women and the general public. Timely recognition of symptoms of ACS with prompt medical response to early symptoms can be lifesaving.

The study has, hence, made some direct recommendations. One is patient awareness of symptoms in addition to chest pain, pressure, or discomfort. In addition, the fact is that the symptoms may not be dramatic or sudden. The recognition of symptoms by women in the community and the healthcare providers in female patients requires further research. This research should focus on the prodromal syndromes with dedicated dissemination of public messages and information aimed at healthcare providers. Lastly, the NHLBI document diligently encourages better understanding of all pathophysiological basis of ACS in women with the intention to optimize treatment recommendations.

## **2.5 Endothelial dysfunction**

Endothelium interacts with nearly each and every system of the human body, with definite implication in end organ diseases of systems including neurologic, renal, hepatic, vascular, dermatologic, immunologic, and cardiac [10]. Additionally, the endothelium regulates vascular tone, maintaining careful balance between vasoconstriction and vasodilation with the intention to provide adequate perfusion pressure to target organs. Additional functions include regulation of angiogenesis, wound healing, smooth muscle cell proliferation, fibrosis, and inflammation [10]. Interestingly, the factors that adversely affect the endothelium are also the common cardiovascular risk factors such as tobacco use, obesity, age, hypertension, hyperlipidemia, physical inactivity, and poor dietary habits [10].

## **3. Management strategies of atherosclerosis in women**

It has been shown in studies that in female patients with coronary artery disease, persistent impairment of endothelial vasomotor function despite optimized therapy to reduce risk factors can adversely affect clinical outcomes [11].

The following, however, should be aggressively managed to combat atherosclerotic disease in female patients:

### **1. Life style modifications (diet, exercise, smoking, weight reduction)**

Adherence with healthy eating habits, regular exercising and weight reduction are all important determinants of atherosclerosis and should be recommended in both genders [12]. Smoking cessation is critical and dedicated time should be spent with patients to generate that awareness [12].

## 2. Receptor and enzyme pathways (beta-blockers, ET, ACE-I, ARB)

Just as the traditional risk factors play a critical role in the pathogenesis of atherosclerotic CAD in females, the routine therapies should be considered in this patient population [13].

Most studies have found the benefit of statins in ameliorating and even eliminating endothelial dysfunction [13]. These medications are well known mainstay in decreasing CVD risk in most patients secondary to their lipid-lowering and anti-inflammatory mechanism [13]. Addition of ACE-inhibition to statin therapy has been shown to improve endothelial-dependent relaxation in the coronary vasculature through NO-dependent mechanism [14, 15].

## 3. NO pathway (L-arginine, PDE-I)

Both intravenous and intracoronary administration of L-arginine, the physiologic precursor for NO, has been shown to acutely improve endothelium-dependent, but not endothelium-independent, vasodilation in participants with hypercholesterolemia or CAD [16]. The longer-term effects of oral L-arginine have additionally been evaluated. Among patients who have underlying heart failure, oral L-arginine improved endothelial function, arterial compliance, and functional status [17].

The other agent is Nicorandil, which is a potent antianginal, however, unavailable in the US. It has dual nitrate and potassium-ATP channel agonist properties and increases the formation of cyclic GMP. This agent has been shown to improve endothelial function in patients without prior CAD at 1 year follow up with concomitant documented reductions in inflammatory markers [18].

## 4. Channel pathways (Ca, K)

Nifedipine has been shown to have antioxidant effects with additional effect on endothelial nitric oxide synthase expression. In a study including 454 patients undergoing percutaneous coronary intervention, endothelium dependent vasodilatation was evaluated with intracoronary acetylcholine following 6 months of therapy with nifedipine. There was well documented improvement in endothelial function, however, no plaque regression [19].

Ranolazine is a sodium channel inhibitor used in patients who have refractory angina. It has been shown to improve symptoms of microvascular angina, however there was no clear change seen in microvascular function with the use of ranolazine [20].

## 4. Conclusion

In summary, atherosclerosis in females is a complex process. There is an integral role of endothelial dysfunction. In order to close the gaps in care of cardiac disease in women, the steps must include timely recognition of the symptoms of cardiac disease with the effective management. Treatment strategies are diverse with decent evidence base. Larger studies dedicated to address atherosclerosis in women are urgently required.

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