CVD Considerations in Women

Pam R. Taub, MD

Founder and Director of Step Family

Cardiac Rehabilitation and Wellness Center

Professor of Medicine

University of California San Diego Health System

www.taubresearchgroup.ucsd.edu

Module 6 - Taub CVD Women

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PAM R. TAUB, MD.: It is wonderful to be here today as part of the Foundations of Cardiometabolic Health Certification Course. I am going to be talking about a very important topic which is Cardiovascular Disease Considerations in Women. I am Pam Taub. I am a cardiologist and Professor of Medicine as well as Director of our Cardiac Rehabilitation Program at UC San Diego. This is a vast topic, and what I am going to try to do is to distill some of the most important aspects of this topic into this lecture.

These are my disclosures.

I am going to start by giving you an overview of cardiometabolic disease across the lifespan of women, and then highlight some unique aspects of various diseases such as coronary artery disease and diabetes in women. Then, I will delve into pregnancy-associated conditions such as preeclampsia and gestational diabetes, and how these conditions that occur during pregnancy impact future cardiovascular risk.

Then, I will briefly delve into heart failure in women, as well as menopause and valvular heart disease, and within valvular heart disease, I am going to focus on aortic stenosis.

Let us start by talking about cardiometabolic disease generally across the lifespan of women. So, when we look at the infant born to a mother who has gestational diabetes or preeclampsia, this particular infant has a higher risk of obesity and diabetes. This is something that we need to be cognizant of when managing children who are born to mothers with gestational diabetes or preeclampsia, and this is an opportunity to intervene very early in childhood in terms of lifestyle modification. In addition, there is some data to suggest that children that are conceived through assisted-reproductive technologies such as in vitro fertilization may be at increased risk of early hypertension. So these are children that need to be monitored closely, and aggressive lifestyle strategies need to be instituted early.

As we move on to adolescence this is a really important time because it is the time when the first menstrual period occurs. Age at menarche is defined as the age of first occurrence of menstruation and heralds the onset of cyclic ovarian function which includes increased endogenous estradiol secretion and exposure. When you have early menarche which is defined as having your first menstrual cycle before age 12 there has been an association with adiposity metabolic syndrome and increased risk of breast cancer, and it is thought that this may be due to increased lifetime exposure to estrogen.

As we move on to young adulthood, this is the time when we often see an increased prevalence of polycystic ovarian syndrome. And this is associated with insulin resistance and metabolic syndrome, and women with polycystic ovarian syndrome have twice as likely an increased risk of a future cardiovascular event. This is also a time where important decisions regarding contraception are made, and some choices include progesterone- and estrogen-based oral contraceptive and barrier methods, and a woman's intrinsic risk needs to be taken into account in terms of what contraceptive choices are offered. So for instance a woman who is a tobacco user has a higher risk of DVTs or deep venous thromboses with oral contraceptives. Women who have a hypercoagulable state are also at high risk of events such as DVT with oral contraceptive, so all of these lifestyle and genetic factors need to be considered when making the choice of the optimal contraceptive method.

Now we go onto pregnancy, and this is a very exciting time in the lifespan of women, but pregnancy is also a stress test on the body. And during pregnancy, women can develop conditions such as gestational diabetes, preeclampsia, and postpartum or peripartum cardiomyopathy which can increase risk of future cardiovascular events. So this is a very important time and when we see women later on in life, we should still be asking about what occurred during their pregnancy and these conditions impact future cardiovascular risk.

As we transition to middle age, this is the time when fertility issues occur. Many women are deferring childbearing into their 40s and are turning to therapies such as in vitro fertilization, and in vitro fertilization does increase the risk of short-term pregnancy complications such as preeclampsia and hypertension. The good news, based on current data, is in vitro fertilization does not seem to increase future cardiovascular risk. This is the time also where there are cancers of the reproductive system that increase in prevalence such as breast cancer and ovarian cancer, and these cancers emphasize the importance of screening. Women need to be getting their annual Pap smears and during middle age is when we start breast cancer screening with mammograms.

Now, when we go into the postmenopausal period, there are some new problems that we need to be thinking about and that includes valvular heart disease, specifically aortic stenosis. This is also again a time where we need to be screening for cancers of the reproductive system. This is also a time when we see an increased prevalence of coronary artery disease. And so, the postmenopausal period is a vulnerable period for women and there are a lot of things we can be doing early on in the lifespan of women to mitigate some of these issues such as aggressive lifestyle therapy and appropriate medications for management of blood pressure and cholesterol.

So, I have summarized some of the cardiometabolic health challenges across the lifespan ranging from the infant to the postmenopausal women.

Now, I am going to really delve into cardiovascular disease and coronary artery disease in women. Cardiovascular disease accounts for 35% of all deaths in women worldwide. It is the number one killer of women, and we sometimes forget this because we are focused on diseases such as breast cancer, but we cannot forget about how cardiovascular disease still remains the number one cause of mortality for women. In 2019, 8.9 million women died from cardiovascular disease, and when we look at myocardial infarction we have seen in multiple studies that women are less likely to receive guideline-based therapies, and younger women in particular are at greatest risk for poor outcomes after acute myocardial infarction. What we have also seen from the clinical trials is that women are understudied, underdiagnosed, and undertreated and not surprisingly, underrepresented in the clinical trial. So, there is a lot more we need to do to get a better understanding of cardiovascular disease, particularly acute coronary syndromes in women.

Now, let us delve into some of the sex differences in coronary artery disease between men and women. Women tend to have a higher prevalence of nonobstructive coronary artery disease, and what I mean by this is when you do an angiogram, you do not see significant luminal stenosis in the coronary artery, whereas in men, they tend to have more obstructive disease, and you clearly see an obstruction when you do an angiogram, and women tend to present younger and they also tend to have more preserved LV systolic function. There are also different mechanisms in terms of plaque characteristics in men versus women.

Now, let us delve into differences in plaque morphology between women and men. Women have a lower prevalence of plaque rupture and thin-cap fibroatheroma and a higher prevalence of plaque erosion when compared to men. Also when you look at coronary flow characteristics, women have a higher fractional-flow reserve for any given stenosis and a higher degree of mismatch between the fractional-flow reserve measurements and luminal size. They also have a higher prevalence of coronary microvascular dysfunction. What we also see is that plaque erosion - which is more common in women - is associated with less-severe narrowing, so you see a larger luminal diameter here in women versus in men, and it is associated with less plaque burden. So, you can see that there is more plaque burden in men versus women, and the thrombus burden is also less when compared with ruptured plaques. So the higher prevalence of plaque erosion in women may, in part, explain the higher frequency of acute coronary syndrome without obstructive coronary artery disease at the time of invasive coronary angiography, and women also tend to have less calcification.

So, what that means is in some of the common screening tests that we use to assess risks such as coronary artery calcium scoring, we are going to see higher calcification in men, and when we see the higher degree of calcification, we tend to be more aggressive. So, it is really important to understand some of these fundamental differences in plaque morphology between women and men. The paradoxical difference where women have lower rates of anatomical CAD but more symptoms of ischemia and adverse outcomes appears to be linked to abnormal coronary artery reactivity including microvascular dysfunction.

Let's talk a little bit more about some of these factors unique to women. When we talk about coronary microvascular dysfunction, we are really referring to pathophysiology impacting smaller coronary arteries, and these tend to be the prearterials and arterials that feed the capillary that regulate the coronary myocardial blood flow. When we look at some of the manifestations of this in women, we see that many women have normal coronary artery lumen and microvascular function is impaired, and a lot of factors contribute to this. That includes autoimmune disease which is more prevalent in women as well as obesity and hypertension, and some of these factors are exacerbated by conditions unique to women such as visceral obesity, low estrogen state that can be seen postmenopausally, and polycystic ovarian syndrome which we talked about earlier.

So, a lot of different conditions that are unique to women can predispose them to microvascular dysfunction and when you have microvascular dysfunction and endothelial dysfunction this does lead to decreased perfusion. In addition, women have what we call positive coronary artery remodeling in which there can be luminal preservations and no narrowing but plaque that is still present and causes what we call eccentric remodeling, which is that the artery expands, and the reason that this is important is because when we do an angiogram we do not detect luminal stenosis. Eventually, this can evolve into obstructive CAD where there is luminal stenosis but in early phases of the disease in women we are going to see more microvascular dysfunction, and we are not necessarily going to see luminal stenosis which is what is classically seen in men on angiogram.

So, coronary microvascular dysfunction is an important condition to recognize in women and before decades of research on this topic, when women used to present to the emergency room with chest pain and had normal coronary artery diameters on angiogram, it was thought that this condition was because of anxiety and stress. Now, we see that this is actually a physiological condition that stems from abnormal pathology in the coronary microvasculature. So when we look at the prevalence of normal and

nonobstructive coronary artery disease, we see in multiple clinical trials that nonobstructive coronary artery disease is much more prevalent in women, and so what this means clinically is when you see women present with chest pain and even if they have a normal coronary angiogram do not dismiss their symptoms as being psychosomatic. There is probably underlying microvascular disease which you can assess for through modalities such as cardiac MRI or in the cath lab, but women with chest pain and normal coronary arteries should not be dismissed.

There are many factors that contribute to microvascular disease in women that I highlighted earlier, but we need to be aware of some of the hormonal alterations that occur in women such as decreased estrogen in menopause, some of the insulin resistance that is associated with conditions such as metabolic syndrome and polycystic ovarian syndrome and how this microvascular dysfunction can lead to atypical symptoms that women often present with such as shortness of breath, fatigue, decreased exercise capacity, and this is because there is subendocardial and epicardial ischemia, and there is a decrease in coronary vascular perfusion. So, it is really important to recognize atypical symptoms are more prevalent in women.

When we talk about patients who present with ischemia and nonobstructive coronary artery disease, we are talking about the term INOCA. The patients who have INOCA have coronary microvascular dysfunction, and we still need to be treating these patients aggressively with the conventional therapies that we use for coronary atherosclerosis such as aspirin and statin. We also need to be thinking about deploying anti-ischemic and anginal therapies such as nitrates, calcium channel blockers, and there are some clinical studies that suggest ranolazine and ivabradine are also impactful in treating angina in these patients. Sometimes these patients are undertreated because this term of ischemia and nonobstructive coronary artery disease is not well recognized.

Now, let us shift to briefly talking about diabetes in women and unique aspects of diabetes in women. So, the prevalence of diabetes in women has been rising, and over 199 million women have diabetes and this is projected to increase to an alarming 313 million by 2040. It is the ninth leading direct cause of death in women, causing 2.1 million deaths every year. Women who have type 2 diabetes are 10 times more likely to have coronary artery disease than women who do not have type 2 diabetes. So, when we look at how diabetes uniquely impacts women, we see that elderly women with type 2 diabetes and end-stage renal disease have significantly higher incidence of death compared to men. Women with diabetes are four times as likely to have a stroke than women without diabetes, and there are a lot of hormonal changes that occur in women that can make diabetes more difficult to control. There is also a higher prevalence of diabetic ketoacidosis in women compared to men. Unfortunately, women tend to receive less-intensive care in treatment for diabetes such as evidence-based therapies like SGLT2 inhibitors and GLP receptor agonists that also have an impact on cardiovascular disease compared to men.

We mentioned earlier polycystic ovarian syndrome, and we need to keep in mind that this is a condition that increases the risk of diabetes in women, so lots of unique aspects of the reproductive cycle in women that can predispose to insulin resistance such as polycystic ovarian syndrome into heart failure in women. I briefly talked about how preeclampsia with severe features can be considered a type of heart failure with preserved ejection fraction that occurs earlier in the lifespan of women. What we know is that heart failure with preserved ejection fraction disproportionately impacts women later in life and it is

intricately linked to type 2 diabetes and other risk factors that are prevalent in women that are associated with type 2 diabetes.

So, for instance obesity, autoimmune disease, and preeclampsia are all associated with increased risk of heart failure with preserved ejection fraction. Interestingly, female sex is independently associated with the present diastolic dysfunction and worse clinical outcomes. What we see is when women have heart failure with preserved ejection fraction, they have worse outcomes when compared to men. So, they have a higher incidence of all-cause death and higher heart failure readmission when compared to men. So it is an important condition to recognize and to also know that it impacts women at a higher rate than men.

Now let's talk about a really important topic which is pregnancy-associated conditions and how they impact future cardiovascular risk. Women have conditions during their pregnancy - which is a stress test on the body - such as gestational diabetes and preeclampsia that can continue to impact maternal health long after the pregnancy is over. Pregnancy can unmask some of these conditions that are really important in determining future cardiovascular risk, and so we really need to be incorporating these conditions into our risk assessment later in life. So, for instance when we are assessing if someone needs to be on a statin or aspirin, or how aggressive we need to have certain targets such as LDL or A1c. These pregnancy-associated complications should be incorporated into our decision-making.

In fact, the guidelines ask us to think about conditions specific to women such as preeclampsia and premature menopause when we are making a decision on whether someone should be on a statin. For instance, there may be a patient who is considered borderline risk that we would not typically consider starting on a statin, but if they have pregnancy-associated conditions such as preeclampsia and gestational diabetes, this is the patient where you would consider starting a statin. So these are really important things that we need to be asking routinely with our patients. And here again the guidelines highlight some of these conditions that are unique to women such as a history of premature menopause that occurs before age 40 and pregnancy-associated conditions.

So, when we look at some of these outcomes in detail such as future risk of hypertension, diabetes, and atherosclerotic cardiovascular disease, we see these conditions such as gestational hypertension and preeclampsia can impact these outcomes. So for instance, gestational diabetes is not only associated with future risk of diabetes and ASCVD, preterm delivery is also associated with future risk of atherosclerotic cardiovascular disease and conditions that are unique to the fetus, such as fetal growth restriction is also associated with future risk of atherosclerotic cardiovascular disease. And so, when we think about conditions in pregnancy and post-pregnancy outcomes, we also need to be thinking about pre-pregnancy states such as patients who are obese, who have metabolic syndrome, and who have decreased physical activity, because these all have a very intricate interaction.

So, women who have risk factors pre-pregnancy tend to have more pregnancy-related adverse outcomes such as preeclampsia and gestational diabetes, and this continues into later life where there is a risk of metabolic syndrome and cardiovascular disease. So, what does this tell us? This tells us that in the pre-pregnancy state when we are counseling women who are trying to get pregnant, these are all factors that we need to be looking at: Does the patient have obesity? Do they have glucose intolerance? Do they have mild hypertension? Because these conditions are associated with endothelial dysfunction and inflammation so in the pre-pregnancy state there is a lot of counseling that we should be doing to really optimize some of these risk factors so that when a patient does become pregnant, we can try to

decrease the incidence of these pregnancy-associated conditions such as gestational diabetes. If a woman does have these conditions during pregnancy, after pregnancy we need to be instituting aggressive lifestyle modification and pharmacotherapy as needed to decrease cardiovascular risk.

So, gestational diabetes can impact 1 in 7 births, and 50% of women with gestational diabetes will develop diabetes in 10 years after delivery. Even if a woman does not have overt gestational diabetes, about 20.9 million women have some form of hyperglycemia in pregnancy. So, even if a woman is not labeled as having gestational diabetes but there is evidence of insulin resistance during some of the testing that we do during pregnancy such as the oral glucose tolerance test, this woman also needs to have aggressive monitoring and lifestyle modification and pharmacotherapy if needed. So, pregnancy is an important time where we can detect insulin resistance early in the lifespan of women and institute early therapies.

Now, let's talk about preeclampsia. This is really a multisystem disorder that is characterized by hypertension, and that is usually of new onset and proteinuria in the second half of the pregnancy. Two to 8% of pregnancies can have preeclampsia, and we need to be thinking about preeclampsia as a systemic disorder with impaired endothelial dysfunction and systemic inflammation. And women with preeclampsia are at increased risk of future cardiovascular events. When we look at the impact of preeclampsia on future cardiovascular risk, we see that it is associated with increased risk of hypertension, diabetes, hyperlipidemia, heart failure, and overall death from cardiovascular disease as well as stroke.

There is also an increased risk of preeclampsia in patients who have peripartum cardiomyopathy, and so when we see women with preeclampsia we see that they have some shared features with women that have heart failure with preserved ejection fraction. So I view preeclampsia as the HFPEF of pregnancy because when you look at these women echocardiographically, they have diastolic dysfunction, they have left atrial enlargement, they have pulmonary edema, all of these features which we see in conventional heart failure with preserved ejection fraction. So when you hear of a woman having preeclampsia during pregnancy, this is a woman that you want to be thinking about in terms of modifying risk factors to prevent future heart failure with preserved ejection fraction. And what we have seen is that women who have preeclampsia with a preterm delivery have the highest risk of future cardiovascular disease. You can see an eightfold increase in risk in these women compared to women who have no preeclampsia and who had a term delivery.

Now let us talk about peripartum cardiomyopathy which is much more rare but it is an important condition to diagnose because these women have a very high risk of developing peripartum cardiomyopathy in future pregnancies, and it is also associated with maternal mortality. So in women who have peripartum cardiomyopathy detected in one pregnancy, we counsel them to really not have a future pregnancy because of the risk of maternal mortality. What we see is in women who have peripartum cardiomyopathy, we see that 50% of them have deterioration in their LV dysfunction and some of them do have recovery of their LV function, and this is associated with better prognosis, and they can have a normal pregnancy, but there is still a risk of subsequent peripartum cardiomyopathy even when there is complete recovery of LV dysfunction.

And another condition we need to be thinking about that can occur with pregnancy is spontaneous coronary artery dissection. This usually occurs in the first month peripartum, so typically these women present to the emergency room after delivery with chest pain. So these are patients that we need to

have high on our differential spontaneous coronary artery dissection. This is an area that we need a lot more research on to understand the relationship between spontaneous coronary artery dissection and conditions that can occur in pregnancy such as preeclampsia and peripartum cardiomyopathy.

Now, let us start to transition to condition later in the lifecycle of women. That is menopause and how it impacts cardiovascular disease risk. Menopause is a difficult time for women. It is associated with estrogen withdrawal and androgen excess, and this translates into changes in body composition. This is when women can have abdominal fat deposition. There is increased total fat mass. There is increased subcutaneous abdominal fat. There is also decreased peripheral fat and a decreased and reduced total and peripheral lean body mass, and so menopause is causing changes in body composition, and there are many different effects of menopause on women. Women have the classic hot flashes which are the vasomotor systems.

There is often evolution in metabolic syndrome and insulin resistance is sometimes more evident during the perimenopausal and menopausal period, and this is also a time where there is an increased prevalence of atherosclerosis and stroke. With some of these body composition changes, we also see sarcopenia, which is a decrease in skeletal muscle mass, and this is also a time we see progression of osteoarthritis and changes in bone mineral density, some of which are mediated by these hormonal changes.

So this is a very complicated time where many different hormonal changes are happening, and they are impacting multiple different systems. So menopause is the time when we also see some vasomotor symptoms such as hot flashes, and there are associations with hot flashes and things that we traditionally think about as more cardiovascular such as carotid intima-media thickness and endothelial dysfunction. So what we have seen in some studies is that patients who have hot flashes have higher carotid intima-medial thickness which can be associated with decreased endothelial function, and hot flashes are also associated with a lower HDL-cholesterol which is often seen in patients with metabolic syndrome and also higher levels of intracellular adhesion molecules which suggest higher vascular risk. Interestingly, hot flashes are also associated with a higher risk of depression.

So we need to be thinking about hot flashes as a marker of endothelial dysfunction because there are some studies that show that flow-mediated dilation with lower and early menopause compared to women that did not have menopause, and the severity of hot flashes did correlate with endothelial dysfunction suggesting that endothelial dysfunction occurs early in this transition to menopause. So what does this mean clinically? This means that we need to be addressing endothelial dysfunction before a women enters hot flashes, and if we address endothelial dysfunction earlier, women may have less severe hot flashes when they enter menopause, and addressing endothelial dysfunction includes addressing high blood pressure, improving exercise levels, and improving diet because endothelial dysfunction is impacted by many of these lifestyle factors.

So what I tell my patients is we want to get them in their fighting form when they enter menopause. We want to optimize all aspects of their cardiovascular health including endothelial function before they enter menopause, and we want to have their endothelial dysfunction basically gone as much as possible through lifestyle and pharmacologic therapy before they enter menopause so that they can deal with some of the quality-of-life aspects of menopause such as hot flashes. One of the things that I highlighted earlier, is the change in body composition, and what we have seen in many studies is the waist

circumference in women increases during menopause and this is associated with this abdominal obesity and abdominal fat deposition that we see during menopause.

Now that we talked about some of the symptoms of menopause such as hot flashes, let us talk about hormone replacement therapy which can be used to alleviate some of the symptoms of menopause. Women typically have an average age of menopause around 51 with 95% of women entering menopause between age 45 and 55. Although initial observational studies suggested benefit from menopausal hormone replacement therapy for primary and secondary prevention of coronary disease, this has not been confirmed in subsequent large trials; however, the use of hormone replacement therapy in the early menopausal years does not appear to be associated with excess risk of coronary heart disease when compared to older postmenopausal women. This is then referred to as the timing hypothesis, and what the timing hypothesis suggests is that in early menopause there seems to be some beneficial effects of hormone replacement therapy on endothelial function including increase in nitric oxide, but when hormone replacement therapy is initiated later in menopause when there is more established atherosclerosis there can be more detrimental impacts in terms of plaque instability.

When we talk about initiation of hormone replacement therapy with women, we need to be thinking about the timing hypothesis, and trying to initiate hormone replacement therapy earlier in the course of menopause and the reason being that studies have shown when hormone replacement therapy is initiated earlier, there is a lower risk of coronary heart disease. We also need to be incorporating other risk factors such as history of breast or endometrial cancer if they had prior cardiovascular disease, if there is a hypercoagulable state such as history of DVT, and this needs to be juxtaposed with the current symptoms that adversely impacting their quality of life. In many women this is a very difficult discussion because they are impaired by hot sweats but yet they may have risk factors that make hormone replacement therapy not the ideal choice.

So in these women, you may want to consider doing it for a very short period of time and these are women that we need to really optimize their cardiovascular risk factors such as LDL or high blood pressure before starting hormone replacement therapy. So for many of these patients I will put them on a moderate-intensity statin, aspirin, and optimize blood pressure medications and diabetes and if hormone replacement therapy is initiated, watch them very carefully.

So diabetes is also another condition that we need to be thinking about in the context of menopause because when estrogen and progesterone levels decrease, this is a time when insulin resistance occurs. So many women start to develop or manifest overt diabetes during menopause, and so this is also an important time to be looking at fasting glucose and hemoglobin A1c. In addition, there may be some weight gain during menopause. We talked about changes in body composition and this could further exacerbate insulin resistance. So menopause is an important time where we need to be looking at insulin resistance and diabetes.

To summarize, when we are considering hormone replacement therapy, we need to be taking into account the timing hypothesis in initiating hormone replacement therapy earlier in the course of menopause. We also need to be thinking about concomitant diseases such as hypercoagulable state or history of prior cardiac events because these women are more predisposed to events with hormone replacement therapy such as MI and DVT. We typically do not think of hormone replacement therapy as primary or secondary prevention for cardiovascular disease. It is really for symptom relief. It should also

not be used for osteoporosis prevention, and the general guiding principle is, use minimal doses for the shortest period of time and also consider nonhormonal alternatives such as antidepressants like SSRIs.

Now, let us focus on valvular heart disease in women. Valvular heart disease is one of my favorite conditions to manage. The way I describe it to my patients is it is a well-defined problem with a well-defined solution. And valvular heart disease impacts women across their lifespan and pregnancy is particularly an important time when valvular heart disease can manifest and can have adverse hemodynamic consequences. This is sometimes the first time that women are aware that they have valvular heart disease as I mentioned earlier because pregnancy is a stress test for the body in many ways. When you juxtapose the history of valvular heart disease and some of the hormonal changes occurring in women around age 50 at the time of menopause, this is an important time when valvular heart disease can manifest. This is also when we start to see an increase in the prevalence of coronary artery disease in women. So we need to have on our radar, "Valvular heart disease is something we need to be screening for in our women."

Let us talk about aortic stenosis. Aortic stenosis is a lethal disease. The natural history of severe aortic stenosis has not changed much. Data from contemporary trials such as the PARTNER trial show that the one year mortality of severe symptomatic aortic stenosis is 50%. So this is a very important disease that we need to diagnose and treat because there are some great treatment options for patients with aortic stenosis. Unfortunately women with aortic stenosis are underdiagnosed and undertreated. Women tend to be older at the time of diagnosis, and they tend to be more symptomatic, and they are often referred later in their disease course and thus have higher operative risk and worse surgical outcomes.

Now, let us focus on some unique aspects of aortic stenosis which is the most common valvular heart disease. Women can have the same degree of hemodynamic stenosis as men but less calcification of aortic valve. Women also have a higher prevalence of the paradoxical low-flow low-gradient aortic stenosis which can be hard to detect on physical exam, and this is a more malignant phenotype. They also have a smaller body surface area and a smaller annulus and this needs to be taken into consideration with intervention such as TAVR

Women also need smaller prosthetic aortic valves, and from a procedural perspective, may need aortic annular enlargement. So a lot of different valve-specific features in women compared to men that need to be considered and just some of the other differences that we need to be thinking about is they also have different left ventricular remodeling. So women tend to have more concentric remodeling of the left ventricle, and this probably also results in a higher prevalence of heart failure with preserved ejection fraction and a low-flow, low-gradient state. They also tend to have a higher degree of diffuse myocardial fibrosis on cardiac MRI compared to men.

Now let us shift to mitral regurgitation, and this is a condition in which women are less likely to be treated and to receive procedures that are associated with improved outcomes. Tricuspid regurgitation predominantly affects women and occurs secondary as a consequence of increased pressure and or volume overload followed by annular dilation and one of the interesting hypothesis that had been raised is could some of the hemodynamic changes in pregnancy, predispose women to more annular dilation and tricuspid regurgitation. So we need to also be thinking about screening for tricuspid disease in women, and there is a big association with tricuspid regurgitation and heart failure with preserved ejection fraction that occurs more commonly in women.

So we have a done a whirlwind tour of some of the unique manifestations of cardiovascular disease in women ranging from coronary artery disease to pregnancy-associated complications to menopause-related conditions. Well, I hope this is giving you an appreciation of how complicated women are and some of the sex-specific characteristics that need to be taken to account in clinical decision-making.

Thank you for your time.

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