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JCL Roundtable: Lipidology and Women's Health

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Abstract: In this JCL Roundtable, we bring together three experts to discuss women's cardiovascular health throughout the lifespan, viewed from the standpoint of clinical lipidology. Overall, heart disease leads to one out of every 3 deaths of American women, but unfortunately patient awareness of cardiovascular risk actually has declined since 2009. Younger women are not exempt, since their risk can be increased by smoking, birth control, adverse lifestyle and diet, and genetic disorders. Age at menarche can influence lifetime risk. Polycystic ovary syndrome, noted in 5-13% of women of reproductive age, has been linked to increased cardiovascular risk, partly through atherogenic dyslipidemia. Oral contraception has improved greatly since its introduction, but remains a risk for venous thromboembolism and stroke, particularly in smokers. Fetal nutritional and metabolic requirements in pregnancy impose high vascular demand on the placenta and lead to escalating maternal triglycerides and cholesterol especially in the 3rd trimester. Triglycerides may require special management. Adverse pregnancy outcomes associated with placental dysfunction signal subsequent increased risk for maternal atherosclerotic disease. Early menopause has long been recognized as a risk enhancing factor for atherosclerosis with pathophysiology remaining unclear. The menopause transition represents a period when cardiovascular risk for women increases rapidly and approaches that of men. Current studies are evaluating hormonal changes and even clonal hematopoiesis as potential causes. At the same time, lifestyle habits and routine chronic conditions such as hypertension and obesity/diabetes/metabolic syndrome play a large role and need attention.

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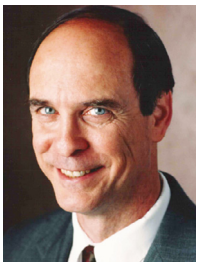

DR. GUYTON: We are privileged today to have a discussion with three experts to discuss the role of lipidology in women's cardiovascular health over the lifespan. We'll cover issues unique to women from menarche to childbearing to menopause. I am joined by Emily Lau, MD, MPH, Samar El Khoudary, PhD, MPH, and Eugenia Gianos, MD. Dr. Lau is director of the Hormones and Cardiovascular Disease clinic in the Corrigan Women's Heart Health Program at Massachusetts General Hospital and an Instructor in Medicine at Harvard Medical School. Dr. El Khoudary is Vice Chair for Education and Professor of Epidemiology at the University of Pittsburgh School of Public Health. Dr. Gianos is Director of Cardiovascular Prevention at Northwell Health and Director of the Women's Heart Program in the Katz Institute for Women's Health (Western region) and Lenox Hill Hospital, as well as Professor of Cardiology at Zucker School of Medicine, Hofstra University.

I'd like to start with a broad question about similarities and differences for cardiovascular disease between women and men, and particularly atherosclerotic cardiovascular disease. Are there more similarities than differences?

DR. GIANOS: Well, we now more commonly recognize distinctive aspects of women's heart disease and unique syndromes such as spontaneous coronary artery dissection, microvascular disease, stress induced cardiomyopathy, as well as the secondary cardiovascular effects of breast cancer treatments. However, we have to keep in mind that the most common thing that women are dealing with is exactly what men face, atherosclerosis. So prevention of atherosclerosis in women is still the first priority of our clinical practices coupled with an additional awareness of all these other unique aspects of women's heart disease.

DR. GUYTON: I read recently an estimate from the World Health Organization that 85% of all the cardiovascular deaths in the world are related to atherosclerosis.

Are there some common misconceptions about cardiovascular, and particularly atherosclerotic cardiovascular, disease in women?

DR. EL KHOUDARY: One critical misconception is that heart disease is for men, and cancer is the real threat for women. This is a very important piece that needs to be clarified. Heart disease is number one killer for women, and it's actually more deadly than all cancer types combined. While one in 31 American women dies from breast cancer, heart disease results in one out of every three deaths, that's literally one death per minute!

Another misconception is that heart disease is a disease for the elderly. However, heart disease affects women of all ages. Epidemiological studies showed that both smoking and birth control combined can increase heart disease risk in younger women by 20%. Sedentary life, bad eating behaviors and family history are all critical risk factors that can increase risk too in younger ages.

DR. LAU: I couldn't agree more, and I think one other thing I would add is the declining awareness that cardiovascular disease is the leading cause of death in women. The American Heart Association conducted a survey that assessed patient awareness of women's cardiovascular disease. The investigators asked women what they thought was the number one cause of death among women. In 2009, about two-thirds of women were able to correctly identify heart disease as the number one cause of death in women. Unfortunately, 10 years later, in 2019, only about 44% of women were able to identify heart disease. We are actually going backwards in terms of awareness, so we clearly have a lot of work to do.

DR. GIANOS: Also, cardiovascular mortality is actually on the rise in young women, which is a very sad statistic to note. I think what we're seeing, both in men and women, is the coupling of a strong genetic predisposition with a very poor lifestyle that's becoming more and more common in young patients, and even in children. Our pediatric colleagues are actually seeing a lot of adult diseases in children. So, I think that poor lifestyle, coupled with genetics, is just leading to a lot more atherosclerosis and heart disease earlier in life than ever before.

DR. GUYTON: I agree. As an example, type 1 diabetes used to be considered the typical diabetes of childhood, and type 2 diabetes arising only in adult life. Now at least half of diabetes in children is type 2 because of fast food, lack of physical exercise, obesity, and other risk factors for diabetes, which impacts cardiovascular disease in a major way.

So we're starting here in childhood to project women's cardiovascular health over the lifespan. Let me ask Dr. Lau to comment on clues that might be gained from age at menarche.

DR. LAU: Absolutely. We are recognizing that a women's unique cardiovascular risk really begins very early in life, beginning with menarche. We know that in the United States the average age of menarche is 12 years of age. Menarche before age 10 years or after age 15 years is associated with elevated risk of cardiovascular disease.

DR. GUYTON: It's a U-shaped curve.

DR. LAU: Yes, it's a U-shaped curve. Early menarche is probably a stronger risk factor. It's been associated with about 15-30% higher risk of future cardiovascular disease independent of other sociodemographic factors.

There was a really interesting study that came out of the Women's Ischemic Syndrome Evaluation study that showed an even higher risk estimate for early menarche. The investigators examined 650 women and found that women who underwent menarche at age 10 or younger actually had a fourfold greater risk of major adverse cardiovascular events compared with women who underwent menarche at age 12, the average age of menarche.

They also found that late age of menarche, menarche at age greater than 15 years of age, was also associated with greater risk, but the association was less pronounced.

DR. GUYTON: Polycystic ovary syndrome is something that may appear in adolescence. What are the keys to diagnosing it and the implications for cardiovascular disease later in life?

DR. LAU: Yes, absolutely. Polycystic ovary syndrome (PCOS) is another very important reproductive exposure that occurs early in life. It's a hormonal disorder that affects about 5-13% of women who are of reproductive age, and it often develops shortly after the onset of menarche. The definition of PCOS is based on three criteria, and you have to have two of the three criteria to make the diagnosis. The criteria are (1) either oligo and/or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism and (3) polycystic ovaries by ultrasound.

These women have adverse cardiometabolic profiles, including dyslipidemia, hypertension, and insulin resistance. We have found that women with a history of PCOS are also at elevated risk for future life cardiovascular disease, which highlights the need to be very aggressive with risk factor modification in this population.

DR. GUYTON: Thank you. The dyslipidemia tends to run toward high triglycerides, small LDL particles, and low HDL, I believe.

DR. LAU: That's right. PCOS is accompanied by insulin resistance, and the lipid profile that is seen in women with PCOS is characteristic of insulin resistance.

DR. GIANOS: In terms of recognition of the risk for a PCOS patient, which is not specifically listed as a risk-enhancing factor in our guidelines, the increased risk is captured through the metabolic syndrome. So among women with PCOS, as Dr. Lau is explaining, there is quite a high prevalence of metabolic syndrome, and as you're explaining, Dr. Guyton, the sort of mixed dyslipidemia that you typically see with cardiometabolic disease characterized by small LDL particles, low HDL and high triglycerides.

DR. GUYTON: The term atherogenic dyslipidemia would apply here.

DR. EL KHOUDARY: Totally agree. In fact, there is a missed opportunity to implement prevention strategies in younger women with PCOS. This is because the focus in treatment among those patients is usually on addressing symptoms like infertility and ovulatory dysfunction, rather than addressing the long-term risks of PCOS including cardiometabolic disorders such as diabetes and metabolic syndrome. Embracing healthy lifestyle among these patients can definitely contribute to reducing related risks later in life.

DR. GUYTON: Overweight/obesity would be a big risk factor for polycystic ovary syndrome.

Then the next issue that women face, contraception. Oral contraception has improved quite a lot since I was a young physician. Where do we stand with current oral contraceptive effects on lipoproteins and particularly on venous thrombosis, and is there any risk with regard to arterial thrombosis?

DR. LAU: Excellent questions. As you say, oral contraception has changed a lot in the past few decades. Certainly, the newer formulations are thought to have safer cardiometabolic profiles. I'll just talk briefly about what we think that exogenous estrogens do to our lipoproteins. In healthy women, estrogen is thought to increase the synthesis of apolipoprotein B100 in the liver, which then increases secretion of very low density lipoproteins (VLDL). Estrogen also increases the expression of the low density lipoprotein (LDL) receptor, which actually reduces LDL levels. Separately, estrogen also inhibits hepatic lipase which increases high density lipoprotein (HDL) levels.

It's interesting, progestins generally have the opposite effects, except the mechanisms are really not understood.

How do we make sense of that? For healthy women, we recognize that oral contraception contributes to changes in lipids. Some of these changes are protective, some are deleterious, but the interplay is not entirely sorted out.

I think the real question we have as women's cardiovascular specialists is: do these changes in lipids actually translate to clinical cardiovascular effects? While the data are very limited, it seems that low-dose combined hormone contraception does not seem to be associated with greater risk of cardiovascular disease in healthy women. But among women with preexisting dyslipidemias, the story may be different.

There was a review of three observational studies, all of limited quality, that showed that combined hormonal contraception was associated with greater odds of myocardial infarction, risk of venous thromboembolism and stroke in women with preexisting dyslipidemias.

I think we all recognize that the estrogen component of combined hormone contraception is thrombogenic, so certainly, we really recommend avoiding combined oral contraception in women who are at greater risk of thrombosis. Of course, we now have other contraceptive methods, like IUDs and dermal implants that are generally safe for all of our patients, including those with existing cardiovascular disease.

DR. GUYTON: Is there an added effect of smoking?

DR. LAU: I really recommend against combined hormonal contraception in women who smoke because of the greater risk of thrombosis. Instead, we recommend IUDs, given their superior safety profile.

DR. GUYTON: So a lot of improvement in oral contraceptives. We stand on pretty good ground, but not with smokers.

DR. LAU: No, certainly not.

DR. GUYTON: What about infertility? Either an inability to achieve pregnancy or not having an interest in childbearing. Please speak to both of those.

DR. LAU: Infertility is something our research group is particularly interested in understanding. It's an underrecognized reproductive risk factor with respect to cardiovascular disease, and the data on the link between infertility and cardiovascular disease are limited. To begin, just to get our definition straight, infertility is defined as the inability to conceive after one year of trying to become pregnant independent of eventual pregnancy outcome. The causes of infertility include hormonal or ovulatory dysfunction (as Dr. El Khoudary pointed out), structural abnormalities, and even partner-related issues. Infertility is actually fairly common. Conservative estimates suggest that infertility affects about 14% of women in the U.S., and I'm certain that that's an underestimate. We have seen that infertility does seem to be associated with a greater risk of atherosclerotic cardiovascular disease.

Our group examined the association of infertility with atherosclerotic cardiovascular disease (ASCVD) in the Women's Health Initiative. We found among 150,000 women there was a moderate overall association between infertility and ASCVD. What was most striking was that among the nulliparous women, infertility was actually associated with 13% higher risk of ASCVD, and among women who were nulliparous and had a history of a prior pregnancy loss, that risk was even higher. They had a 36% higher risk of ASCVD. I think our data suggests that with increasing severity of infertility phenotype, risk of future cardiovascular disease increases.

You bring up this really interesting point about the intersection between parity and infertility, which is a really tricky question to answer. It's very hard to tease out whether a woman did not become pregnant because she didn't want to, or because she tried and was unable to.

DR. GUYTON: Well, thanks for clearing up some of my confusion.

DR. GIANOS: This is a really good discussion, because there are some reports of higher ASCVD risk in nulliparous women and others citing increased cardiovascular risk with increasing number of births. So, as Dr. Lau explains, it really depends on the circumstances. Some risk in multiparous women could be from the effects of the pregnancy itself, related to the weight gain, and other hemodynamic factors that potentially stress the heart and could lead to increased cardiovascular risk. But there's also the socioeconomic and life factors that may be different in a nulliparous woman who chose not to have children compared to the nulliparous woman who faced fertility issues. Perhaps their sociodemographic status, education level or lifestyle factors are different. There are various factors involved, so I think you can't just make gross assumptions about parity and cardiovascular risk. You have to understand the factors contributing to risk in each of these different women.

DR. GUYTON: Okay, that's great. Dr. Gianos, what happens to plasma lipids and lipoproteins during a normal pregnancy?

DR. GIANOS: Interestingly, in a normal pregnancy, increases in plasma lipids are a physiologic response in order to provide for the fetus. Plasma cholesterol levels are 50% higher than baseline and triglyceride levels often double, with a peak towards delivery and subsequent reduction back to baseline at approximately six weeks post-delivery. This is something that interestingly enough, has caused people to not want to check lipids during pregnancy, which I understand. You expect them to be high, and you don't know what to do with the results since the norm has been not to treat during pregnancy.

Unfortunately, I think what's happened is that even for women who are at extremely high risk prior to pregnancy, there's just been a feeling that nobody wants to know, either prior to pregnancy or during pregnancy. The important thing to realize is that diet can actually serve to limit the surges that we see in pregnancy and a woman should at least be aware of her ability to impact this during her pregnancy for LDL and triglycerides. All current guidelines suggest lipid screening for the general population in early adulthood, yet many women come to pregnancy with no awareness of what their baseline lipids are.

There are also drugs that are approved for the appropriate patients, and the more recent ACC Expert Consensus Decision Pathway (EDCP) update on the use of non-statins gives options to consider on an individual basis. In someone who has established atherosclerotic heart disease or in severe forms of familial hypercholesterolemia (FH), the clinician can decide through shared decision-making with the patient whether to continue lipid lowering therapies during pregnancy. There's even the option to use apheresis in extreme cases. So, I think with the appreciation of how we could impact a pregnancy with lifestyle and medical therapy, there is a reasonable argument to check lipids, particularly in the high risk patient.

DR. GUYTON: When you're saying continue with the therapy, you're talking about continuing a statin in certain cases of severe FH or clinical ASCVD?

DR. GIANOS: Yes, exactly. In general, it's safe to use bile acid sequestrants. Colesevelam is an approved therapy during pregnancy. But we're also starting to revisit the statin question, particularly around pravastatin (a hydrophilic statin that does not cross the placental barrier) because there have been a number of trials, both observational and small, randomized-control trials, at least showing good safety with no significant increase in congenital anomalies overall.

So I think, again, this is by no means a recommendation by any society to universally use statins in pregnant women, but this more recent guideline in the ACC EDCP is the first to state that it should be considered in select women, specifically those that are at very high risk, with an individual clinician-patient discussion.

DR. GUYTON: It goes as far as a recent U.S. Food and Drug Administration (FDA) modification of the guidance on the use of statins in pregnancy, which now opens the door just a little, especially for women who previously may have had a heart attack or may have had a stent put in, and who are at very high risk. Probably not even the usual FH patient, though, as far as my reading is concerned.

DR. GIANOS: Yes, exactly.

DR. GUYTON: Okay, well, the placenta is a dynamic vascular organ. It grows. It has to rapidly establish a lot of new blood vessels. It has to exchange nutrients from one set of blood vessels to another set of blood vessels. What might the placenta tell us about the risk for vascular problems later in a woman's life?

DR. GIANOS: With respect to the placenta, again, this is a change in our thinking, that essentially the outcomes of a pregnancy and how well that placenta is able to support a fetus really reflects vascular health - a really fascinating concept. Whether it is because of inflammatory processes, oxidative stress or endothelial dysfunction, there are various factors likely tied to cardiometabolic disease and perhaps some degree of vascular abnormalities, that are now reflected in the placenta affecting pregnancy outcomes. Then the same exact processes put that woman at risk later in life for cardiovascular events.

DR. GUYTON: Endothelial dysfunction, inflammation. So adverse pregnancy outcomes (APOs) can be significant risk factors. Do they count as risk-enhancing factors in the 2018 Multisociety Cholesterol Guideline?

DR. GIANOS: They do. And again, some of them seem closely tied to cardiometabolic disease such as hypertensive disorders of pregnancy or gestational diabetes. These are more intuitively linked to cardiovascular disease later in life. But, even APOs such as pre-term labor and a small for gestational age fetus are tied to worse outcomes for the mom, which, again, reflects back upon a disease process of that placenta.

So, yes, these definitely are tied to worse maternal outcomes later in life, and the more of them you have, the risk is actually compounded.

DR. LAU: I'd like to add one additional point to Dr. Gianos' excellent discussion. There have been several causal mediation studies that have looked at how a history of adverse pregnancy outcome, like hypertensive disorders of pregnancy, translates to later-life cardiovascular disease risk. It seems to be mediated in part by traditional risk factors. About 50% of the elevated risk of cardiovascular disease in a woman with a history of hypertensive disorder of pregnancy is mediated by traditional hypertension. There's another 50% that we're not entirely clear about.

What this highlights to me is that we need to be very aggressive about managing cardiovascular risk factors in patients with a history of adverse pregnancy outcomes. We need to make sure that their hypertension, dyslipidemias, and glucose are well controlled. We also really need to be asking our women patients what happened during their pregnancies. Did they have preeclampsia? Did they have gestational diabetes? We don't ask our patients these questions at all.

DR. GIANOS: That's a good point. I think every single aspect that Dr. Lau and Dr. El Khoudary are explaining should really be in the questionnaires that we offer our women - what was the age of your menarche, did you have PCOS, did you have pregnancy complications, when was your menopause age? Those should all be in a questionnaire.

Then, I think another key concept is post-delivery, we really need to work on more strategies that connect women who had APOs or cardiovascular risk factors to clinical care for long-term risk stratification and risk reduction.

DR. GUYTON: I think at the National Lipid Association meeting, one of you showed an intake form. That was yours?

DR. GIANOS: That was mine. Although I'm going to revise it. As I was looking at it today, I realized that I don't ask about age of menarche which is also important.

DR. GUYTON: That's great. Well, with increasing prevalence of obesity and aberrant nutrition, severe hypertriglyceridemia is becoming more common. Hypertriglyceridemia can actually be a risk factor for adverse pregnancy outcomes. And severe hypertriglyceridemia is a different story, because it leads to a very dangerous risk for pancreatitis. Have you had the experience of guiding a woman through pregnancy who has had pancreatitis in the past from high triglycerides?

DR. GIANOS: I have actually had the circumstance of providing guidance for a woman with severe hypertriglyceridemia who was pregnant and admitted with very high risk for pancreatitis. It was definitely a scary circumstance as there's tremendous risk involved, both for the fetus and for the mother related to potential development of pancreatitis. In these cases, I think there's room for prevention well in advance to avoid getting to these markedly elevated levels. Hypertriglyceridemia, as we talked about, is also a risk factor for adverse pregnancy outcomes.

On average, there's about a 1.5 hazard ratio for adverse pregnancy outcomes in women who have hypertriglyceridemia. So I think recognizing that and targeting it early is key. The 2015 NLA Dyslipidemia Recommendations and the 2018 Multisociety Cholesterol Guidelines both recommend that women at high risk see a lipid specialist for guidance, and the 2015 NLA recommendations also recommend testing each trimester for those with elevated triglycerides. These are people who you want to keep track of, so you avoid extreme situations. Most importantly, I think it's just important to screen more moms prior to pregnancy to appreciate their full cardiometabolic risk.

DR. GUYTON: Yes. I would say there's some confusion and debate about the level of high triglyceride that can cause pancreatitis. My own view is that a triglyceride level of 500 mg/dL is a risk factor for pancreatitis, but a triglyceride level of 500 will not cause pancreatitis. It's really got to be above 1000 and even close to 2000 before risk really escalates. It's just that a triglyceride level of 500 will predict a certain likelihood of encountering a level of 2000 or higher at some point in the future.

This is an area that needs further research. You can't just do an epidemiologic study that finds increased risk for pancreatitis in people with triglycerides of 500 mg/dL and conclude that 500 mg/dL is sufficient to cause pancreatitis, because triglyceride levels are so variable.

Another unanswered question is the tipping point at which lipoprotein lipase activity saturates, and then dietary fat intake gains the potential to cause explosive plasma triglyceride elevation. I recall discussing this long ago in a phone

call with John Brunzell. My clinical rule of thumb is that at levels of triglyceride below 1000 mg/dL, it's simple carbohydrates that drive plasma triglycerides upward. After plasma triglyceride levels reach 1000, the patient usually won't clear one day's intake of dietary fat from the blood in 24 hours. At that point you get stacking from day to day, and the plasma triglyceride level can go sky-high very fast. When triglycerides are 1000 or higher, I advise the patient to follow a "zero fat" diet. It's really a minimal fat diet, because you get a little fat from phospholipids present in almost every food.

DR. GIANOS: That's interesting. There do seem to be dietary factors that cause an acute surge linked to these mechanisms.

DR. GUYTON: Dr. El Khoudary, we learned more than 40 years ago that early menopause is a strong risk factor for atherosclerosis. Do we know why that's the case?

DR. EL KHOUDARY: That has been the $1 million question for so long time.

DR. GUYTON: I know you're working very hard at it.

DR. EL KHOUDARY: Let us go back to the 1970s. The Framingham study provided some of the strongest evidence linking menopause with cardiovascular disease risk among almost 5200 premenopausal women, postmenopausal women, and men matched on age, and followed over 20 years to determine coronary heart disease mortality. This seminal work showed that the risk of coronary heart disease doubled among women who reached menopause early. Losing estrogen at younger ages has been proposed as the main driving risk factor for increasing the risk. However, clinical trials testing whether estrogen is cardioprotective could not prove this hypothesis, which strongly suggests that factors other than estrogen likely contribute to the increased risk in those women.

In fact, novel research suggests that clonal hematopoiesis of indeterminate potential (CHIP), which is an age-related expansion of hematopoietic cells with leukemogenic mutation without detectable malignancy as a possible pathway through which early menopause could be related to a greater risk of cardiovascular disease. CHIP has been linked to both atherosclerosis and premature menopause. Ongoing research also suggests that the relationship between age at menopause and cardiovascular risk may be bidirectional.

DR. GUYTON: Okay. A new theory suggesting that this interesting cardiovascular risk factor of clonal hematopoiesis could lead to early menopause.

I recall that experts once talked about iron. After menopause, the lack of menstrual bleeding leads to higher iron levels, which have an oxidizing effect. But I'm not sure that's a cogent theory today. Even so, menopause before age 40 is a clear risk-enhancing factor.

DR. EL KHOUDARY: Yes, absolutely. It has been acknowledged in recent guidelines, which is great. However, there are characteristics of menopause, other than the age at which it occurs, that have been linked to increased risk for cardiovascular disease. These should also be acknowledged with additional efforts directed to make women and their health care providers aware of them.

DR. GUYTON: Recently I saw a graph on rates of cardiovascular death. At a certain age, there are more women living than men. But also, at a certain age there are more annual cardiovascular deaths from women than from men, which means that after menopause, women catch up quickly.

You spoke at the NLA meeting about the AHA Life's Simple Seven Metrics for Cardiovascular Health. Where, in particular, do we need better Simple Seven Metrics? Which of the Simple Seven would it be?

DR. EL KHOUDARY: That's an important question, because that's how we have been measuring cardiovascular health since 2010. Interestingly, the latest statistics show that only 21% of adult females have at least five healthy lifestyle metrics at the ideal level. Additionally, the prevalence of sticking with healthy lifestyle measures at ideal level declines when we go from reproductive to middle age to elderly. The current data suggests that compared to men, women are less likely to keep their physical activity at ideal levels. The prevalence of severe obesity is also higher in women than men.

If we focus on midlife, data from the Study of Women's Health Across the Nation (SWAN) looked at the prevalence of the Life's Simple Seven in midlife women, and interestingly, only 7.2% of women meet the guideline for physical activity at their midlife. And less than 20% consistently maintain a healthy eating dietary pattern. So definitely this points to where we should focus our efforts.

DR. GUYTON: Let me ask a question about that. One of Life's Simple Seven is healthy eating, but another one is BMI. Is that correct?

DR. EL KHOUDARY: Yeah.

DR. GUYTON: So healthy eating is not just about controlling your weight.

DR. EL KHOUDARY: Absolutely, it's about eating better by getting the balanced nutrients that your heart needs to stay healthy while avoiding foods known to harm heart health.

DR. GUYTON: Right. What are some relevant things that occur in the menopause transition? I think it's a period of about 4-10 years - would that be a reasonable estimate of what the menopause transition would be? It extends for some time after the last menstrual period as well. What are some things that happen during the menopause transition that might be responsible for closing that risk gap between women and men?

DR. EL KHOUDARY: Let us first define the menopause transition. Technically, once a woman starts to have irregular menstrual cycles, she enters into the menopause transition. The term perimenopause is used to describe this stage of women's life which ends a year after the last menstrual period. Perimenopause means "around menopause". The average duration is 3-4 years, although perimenopause can last for just few months or extend for as long as a decade! It splits into early transition and late transition based on bleeding patterns and hormone levels. The length of each of these stages varies across women.

Let us now address the question about what women experience during this stage resulting in risk acceleration. Studies

that followed women over the menopause transition enabled us to better understand this.

First, we know now that total cholesterol and low-density lipoprotein significantly increase during perimenopause independent of aging. These increases were previously thought to be benign. However, studies showed that the increase happening during this time indeed is associated with a greater risk of carotid plaque later in life in women.

Second, we know that women experience an increase in their body weight during this time, although this seems to be more driven by the aging process. Simultaneously, women experience changes in the location of where they store fat, which is now believed to be a menopause-related phenomenon. Midlife women start to accumulate fat in the visceral abdomen approximately 2 years before their final menstrual period, which is really dangerous and could put women at higher risk for cardiometabolic comorbidities.

Third, we now know that during perimenopause women experience deleterious changes in their vascular health. Significant increases in the intima-media thickness, as well as arterial stiffness, are happening during this time. Such changes may contribute to changes recently observed in blood pressure. Using data from the SWAN study, we were able to show that not all women who transition through menopause experience the same kind of increase in their blood pressure. There are a group of women who experience a sharp rise in the blood pressure around menopause, supporting a contribution of menopause beyond aging in this process.

Fourth, prevalence of metabolic syndrome also rises at the time of final menstrual period independent of age. Inflammation seems to be also impacted by the menopause transition. We just published a paper where we saw that complement proteins, C3 and C4, rise around the time when women reach menopause.

So, when you think of all these changes together happening during a specific period, and women are not aware of these changes, definitely it's a big impactful thing that can put women at higher risk as they get older.

DR. GUYTON: Yes. So it's a multiplicity of factors that range from lipids, fat distribution, blood pressure, and inflammation all the way to specific changes in the arterial wall.

DR. EL KHOUDARY: Yes, and each of those shown to be really impacted by the menopause transition.

DR. GUYTON: Where do we stand with hormone-replacement therapy? A big question over the last 20 or 30 years, right?

DR. EL KHOUDARY: Yes, it's a big question. Mainly because of the conflicting data coming from observational studies versus clinical trials. Interestingly, observational studies and animal models consistently suggested a 40-50% reduction in cardiovascular disease in women using hormone therapy. However, similar conclusions could not be made based on clinical trials. In particular, the Women's Health Initiative (WHI), which was a primary prevention trial, and the Heart and Estrogen/Progestin Replacement Study (HERS), which was a secondary prevention trial, both concluded that there was no benefit of hormone therapy for cardiovascular disease. In fact, WHI reported increases in cardiovascular disease events in older women randomized to hormone therapy, while HERS showed risk increase during the first year of using hormone therapy.

Subsequent analysis from WHI trying to explain the unexpected findings concluded that it is all about the timing when women start using hormone therapy. This is what we now call the timing hypothesis. The additional analysis from WHI suggests that women using hormone therapy within the first 10 years after menopause, or at the age of 50-59, are not at increased risk of cardiovascular disease. On the other hand, starting hormone therapy after the age of 60 actually increased the risk for cardiovascular disease. Interestingly, a Cochrane review of randomized control trials data showed less coronary heart disease risk in women who started hormone therapy <10 years after menopause. There are also some beneficial effects on subclinical measures of atherosclerosis. In a WHI ancillary study, women who were within 5 years of their last menstrual cycle had lower coronary artery calcium scores when randomized to hormone therapy versus placebo after 7 years of follow up.

Two clinical trials were conducted to test the timing hypothesis - the KEEPS trial (Kronos Early Estrogen Prevention Study), as well as the ELITE trial (Early versus Late Intervention Trial with Estradiol). Both of them focused on younger postmenopausal women. The KEEPS trial included midlife women within three years of menopause randomized to oral conjugated equine estrogen or transdermal estradiol combined with cyclic oral progesterone, or to placebo, and the ELITE trial included midlife women within six years of menopause or women older than 10 years after menopause randomized to oral estradiol with vaginal progesterone versus placebo. The main outcomes in both trials were subclinical measures of atherosclerosis, carotid intima-media thickness (CIMT), and coronary artery calcium score (CAC). KEEPS did not show any differences in CIMT or CAC among the trial arms, while ELITE was able to show a lower progression of CIMT among women who used hormone therapy, oral estradiol, within six years since menopause.

In light of the accumulated results from initial as well as more recent clinical trials and relevant sub-analysis, the position statement from the North American Menopause Society does not recommend hormone therapy for prevention of cardiovascular disease. It endorses hormone therapy as the gold standard treatment for vasomotor symptoms and genitourinary syndrome in healthy women within 10 years of menopause and under age 60. If women want to use it, history of cardiovascular disease needs to be discussed through a shared decision model between physicians and patients.

DR. GUYTON: Yes. I'd like to make just one comment. Sometimes we see patients with high triglycerides who are postmenopausal, and the question is estrogen replacement therapy driving those triglycerides higher? If it's oral estrogen, the liver is getting a very heavy dose of estrogen, which might raise triglycerides through hepatic effects. This might also apply to women who've had venous thrombosis in the past, since estrogen can augment hepatic production

of clotting factors. But for estradiol delivered transdermally, there's very little effect on the triglyceride level, except for the younger women who are using the contraceptive patch, where the estrogen dose is much higher. Sometimes switching to patch therapy can lower triglycerides.

Now, estradiol delivered by transdermal patch is actually more physiologic. The average person wouldn't think that. But the ovaries deliver estrogen to the vena cava, which means the systemic circulation rather than the portal circulation. Estrogen delivered to the portal circulation by oral ingestion will provide a heavy load of estrogen to the liver. You think about 0.625 mg, or 625 micrograms, of estrogen with oral Premarin versus 50-100 micrograms of estradiol delivered transdermally, as the average dose. So you can see the difference in the amount right there.

DR. EL KHOUDARY: Yes, I would say there's an agreement that using the transdermal format of the hormone therapy would reduce the risk of stroke and venous thromboembolism. But we have to acknowledge that we don't have a clinical trial that compares transdermal with the oral estradiol. That's the best we can do with the data we currently have.

DR. GUYTON: We don't have a clinical trial with clinical endpoints. But we do have trials with lipoprotein endpoints.

DR. EL KHOUDARY: Yes, totally agree.

DR. GUYTON: All right. Well, this has been wonderful, and I'll just ask for any closing remarks that you might have. I'll start with Dr. Lau, who started us off this evening.

DR. LAU: Thank you again for the opportunity to participate in this really important Roundtable. I think it's so uplifting to see an acknowledgement of the importance of women's cardiovascular health. I would just end by emphasizing the need to consider the entire life course when thinking about a women's cardiovascular risk and the importance of incorporating the reproductive history into our standard history and physical for every one of our women patients.

DR. GUYTON: Great. Dr. Gianos.

DR. GIANOS: I echo what Dr. Lau said, that one of the key aspects of this is recognizing risk and then changing our systems in order to more appropriately target that risk. This is an extremely important component. I've also learned a lot from Dr. Nanette Wenger that, when it comes to pregnancy, we will have to accept the fact that we're just not going to have the randomized controlled trials that we have in non-pregnant patients, yet we still need to use all the data available to figure out better ways to treat women.

My hope is that with real world data and large registries, we can tailor care more appropriately.

DR. GUYTON: Thank you. And Dr. El Khoudary.

DR. EL KHOUDARY: Yes. I would echo what Drs. Lau and Gianos said, and I would definitely emphasize that despite the considerable advances in our understanding of sex-specific risk factors for cardiovascular disease, many unanswered questions remain. To achieve that, more women of all reproductive life stages should be included in clinical research. Studying reproductive history and the menopause transition in clinical trials is critical for us to generate evidence-based recommendations. Additionally, we need to incorporate reproductive history and the menopause transition characteristics to better refine cardiovascular risk assessment in women. Current risk equations should be modified to include sex-specific factors. With the great advancements made in women's health research, I believe we are in the right track to make this happen.

DR. GUYTON: A modified risk equation. Great idea.

Finally, with a nudge from Dr. Gianos, I want to mention a resource available at the National Lipid Association website - patient tear sheets on Women's Health, including lipid treatment through childbearing, high triglycerides in pregnancy, polycystic ovary syndrome, and statin use in women (https://www.lipid.org/patient-tear-sheets).

Suggested Reading

1 Lau ES, Binek A, Parker SJ, Shah SH, Zanni MV, Van Eyk JE, Ho JE. Sexual Dimorphism in Cardiovascular Biomarkers: Clinical and Research Implications. Circ Res. 2022;130:578-592. doi: 10.1161/CIRCRESAHA.121.319916. PMID: 35175850

2 El Khoudary SR, Greendale G, Crawford SL, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). Menopause. 2019;26:1213-1227. doi: 10.1097/GME.0000000000001424. PMID: 31568098

3 Gianos E, Karalis DG, Gaballa D, et al. Managing cardiometabolic risk factors across a woman's lifespan: A lipidologist's perspective. J Clin Lipidol. 2021;15:423-430. doi: 10.1016/j.jacl.2021.03.005. PMID: 33836983

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