It is an honor to speak here at Grand Rounds. So hopefully you'll enjoy. I have no financial disclosures other than the fact that I spend way too much money at Starbucks. So I think we're in the clear.

I'm sure there's probably at least a few people who are wondering like, what does Kate do with all of her time? Are there really that many pregnant women who need a cardiologist? And I have to say this is really a growing population of patients for a variety of reasons.

Number one, over 90% of our congenital patients are, now, surviving to adulthood, and many of them want to become pregnant. And so that is a rapidly growing group of patients. Also, a lot of women are, now, delaying pregnancy and childbearing because of desires to go to college and pursue careers. And those women, of course, have time to accumulate more cardiovascular risk factors, and they tend to have higher risk of cardiovascular conditions in pregnancy, as well.

There's, actually, a very wide spectrum of pregnancy-related cardiac conditions that I see. Some of those are conditions that are preexisting before pregnancy, including congenital heart disease, cardiomyopathy, such as HOCM or other ischemic cardiomyopathies. We see patients with coronary disease who become pregnant.

Then, there's the group of patients who don't develop their heart disease until they actually become pregnant. So there is a higher risk of myocardial infarction in the pregnancy and peripartum periods, of course, peripartum cardiomyopathy, which we'll be talking about today. And then, also, coronary and aortic dissections occur more frequently in the pregnancy and peripartum periods, as well.

And then, the last group of patients that are kind of interesting, that you may not think of as being pregnancy-related heart disease, but patients with certain cardiac conditions-- or certain conditions in pregnancy, such as preeclampsia or recurrent pregnancy loss.

They're at high-risk of developing future cardiovascular disease, including hypertension, heart failure, ischemia, and stroke. So I think that pregnancy really does play an important role in a woman's spectrum of heart disease.

So peripartum cardiomyopathy is defined as a type of heart failure that occurs within the last month of pregnancy or within five months after delivery. It's really identified with echocardiography. They have to have a reduced ejection fraction. Usually, we say a systolic ejection fraction of less than 45%.

Sometimes, we will use fractional shortening less than 30%, and the patients, usually, have a dilated left ventricle. Although, it's not absolutely required for diagnosis. This has to occur in the absence of preexisting heart disease and other identifiable causes of heart failure.

As you can see, here, from this study, the vast majority of patients really present within the first week or two after delivery. Although, they can present up to a month prior to delivery, and then, rarely, people will present up to several months after delivery.

So it can be difficult, actually, to initially identify peripartum cardiomyopathy because almost all pregnant women have edema. They're all short of breath. I'm pretty certain I was near Heart Association Class III at the end of my pregnancies. They all complain of orthopnea and PND. And so it's difficult to tease out who has normal pregnancy symptoms versus who has something serious going on.

One thing that I do find to be a pretty sensitive marker is cough. They tend to get some pulmonary edema, develop a little bit of a cough. And unless they also have a viral URI, most pregnant women shouldn't be complaining of cough. So it really does require a high index of suspicion.

The incidence of peripartum cardiomyopathy is really variable depending on where you are. In the United States, it occurs in about 1 in 3000 patients, but there are certain hot spots in the world where it occurs much more frequently.

For example, in Africa, it occurs in about 1 in 1,000. And actually, in Haiti, it occurs in about 1 in 300 patients. So we're not entirely sure why there's such variability in the incidence of this. It may be related to genetic or behavioral or environmental factors.

So one of the first questions that women usually ask when they're diagnosed with this is, why did this happen to me? And there's a lot of ongoing research because, I think, we still, often, don't know.

There are certainly some risk factors that are pretty consistently linked to the development of peripartum cardiomyopathy, including twin pregnancies, having had a lot of babies, very old and very young moms. Also, patients with prolonged tocolysis seem to have a higher risk, as well. It probably increases the volume, but beyond that, we're not sure why that's associated with it.

There's some other factors that have been proposed, and several studies have shown some association, including smoking and hypertension. And certainly, African-Americans seem to be at higher risk of developing it, and they have worse outcomes, as well.

In the last several years, there's been some emerging risk factors that we'll talk about a little bit today and I'm particularly interested in the potential link of pre-eclampsia with peripartum cardiomyopathy. And I think it might be an important avenue to continue to investigate.

So one thing that I hear a lot is, well, is this just a preexisting dilated cardiomyopathy that no one knew about until the patient became pregnant and then their heart was stressed and then it came to clinical attention? That is possible.

However, if you think about the hemodynamics of pregnancy, really, patients reach their peak hemodynamic load at the end of the second to the beginning of the third trimester. And when we have patients who have known existing heart problems, that tends to be when they present with their heart failure.

So it doesn't quite fit with the fact that most patients present in the postpartum period. So I really think that that's, probably, not the etiology for, at least, the majority of patients.

People have, also, wondered about maybe this is just a viral myocarditis. It's somewhat plausible. There is a blunted immune response during pregnancy, so, perhaps, they're at higher risk of developing a more severe infection. People have done biopsies in patients with peripartum cardiomyopathy, and one group reported that 62% of them had evidence of myocarditis, where others have reported as low as 9%.

And viral genomes have been identified in about 1/3, or so, of biopsy specimens in another study. So there may be some substance to this, but I don't think it explains, certainly, all of the patients. So I give that a maybe.

Another kind of interesting theory is that maybe this is an autoimmune phenomenon. Perhaps during pregnancy there's sort of an escape of fetal cells into the maternal circulation and those may then migrate into the maternal cardiac tissue. Then, after delivery, the mom's immune system becomes reactivated perhaps there's then an immune response and the development of peripartum cardiomyopathy.

There is some data that can support this, as well. This is a group of 10 patients who had autoantibodies evaluated postpartum. And all of them had, either, anti-myolemmal or anti-sarcolemmal antibodies identified, and many of those were IgM.

And here, you can see this is an immunofluorescent staining for the anti-sarcolemmal antibodies. So I think this, also, gets a maybe. I think that there is some physiologic substance to it.

What I want to spend a little more time talking about, though, is a theory that's really come up over the last several years. And the question is whether or not there is some degree of angiogenic imbalance that, ultimately, leads to the development of the cardiomyopathy.

During pregnancy, there's a physiologic hypertrophy of the ventricles, and that, actually, requires a significant increase in capillary density. And so in a normal pregnant patient, you'll see a great increase in the number of capillaries in the myocardium.

However, late pregnancy is, actually, a very anti-angiogenic state. As you can see here, this is a mouse model, which you probably know, I try to stay away from mice as much as possible. I grew up in rural Illinois, and my backyard was a cornfield. And I've had more unsavory encounters with mice than I'd like to admit.

So in this-- this is a control model, and you can see that during pregnancy in the postpartum period, the density of the capillaries significantly increases. In this knockout mouse, who develops peripartum cardiomyopathy, their capillary density does increase during pregnancy. But then, postpartum, it really drops off, suggesting that, maybe, there is inadequate vasculature postpartum.

So during pregnancy, the placenta excretes a lot of anti-angiogenic factors. One of the biggest ones is sFLT1, which is a soluble VEGF inhibitor. And high levels of this, probably, do contribute to abnormal capillary function.

However, not everyone who-- or I'm sorry. And also, patients who have preeclampsia, excrete these anti-angiogenic factors at much higher levels. However, that can't be enough to completely explain the peripartum cardiomyopathy because, certainly, not all patients with preeclampsia will go on to develop it. So there must be some other factor that's contributing.

And I think, that's what takes us to the myocardium, here. So PGC-1alpha is a transcriptional co-activator that is important in the secretion of, or in, mitochondrial biogenesis. And importantly, it's involved in the activation of mitochondrial superoxide dismutase. And this mitochondrial superoxide dismutase, ultimately, gathers up the reactive oxygen species.

And when you have excessive reactive oxygen species, ultimately, in the postpartum woman, that cleaves the pro-angiogenic 23-kilodalton prolactin protein, into an anti-angiogenic 16-kilodalton protein. And so it's proposed that this may, ultimately, lead to even more excessive anti-angiogenic factors affecting the microcirculation.

So this is a-- back in the mouse model, you can see here, they took mice that they knocked out for PGC-1alpha. And in the control mice and in the male knockout mice, they were unaffected. But with subsequent pregnancies, the females all died after two to three pregnancies. And then, when they looked at those hearts, you can see that compared to the control, there was significant LV dilatation and reduction in fractional shortening.

If you add the sFLT1 to the mice, this is the normal. And then, if you add it to the control mice, you do see some decrease in the systolic function and a little bit of LV dilatation. However, if you add the sFLT1 to the knockout mice, you have marked reduction in systolic function and marked LV dilatation, suggesting that it requires kind of two hits in order to develop the pathology.

As I had mentioned, it appears that prolactin may be involved in the pathology of this. And so they also, then, tried taking these knockout mice who developed the peripartum cardiomyopathy-- if you give them VEGF or if you give them bromocriptine, it will partially rescue the mice.

However, if you give both bromocriptine and the VEGF, it will completely rescue the mice, suggesting that it's, both, the lack of VEGF and the excessive anti-antigenic factors that are needed to, ultimately, develop the disease.

So this does translate to humans, as well. In this study, they evaluated sFLT1 levels in postpartum women and controls in those with peripartum cardiomyopathy. And you can see that the levels, while they were variable, were, ultimately, significantly higher in those with peripartum cardiomyopathy when compared to controls.

They, also, looked at biopsy specimens from patients with peripartum cardiomyopathy and compared that to donor controls and patients with ischemic cardiomyopathy. And these are from heart transplants. And you can see that the PFC-1alpha levels were, also, significantly lower in patients with peripartum cardiomyopathy.

There's one other protein, STAT3, which seems to be, also, potentially involved in the pathology here. STAT3, also, increases the activity of mitochondrial superoxide dismutase. And when it is missing, you have much lower levels of this, ultimately, leading to high levels of reactive oxygen species.

When there's this-- a lot of reactive oxygen species in the environment, there's a much higher release of cathepsin D from the lysozymes into the cytosol. And ultimately, it seems that cathepsin D is probably, at least, partially responsible for the cleavage of this prolactin into the 16-kilodaltan anti-angiogenic factor.

Also, important to note is that in a normal woman, when this normal 23-kilodalton prolactin protein is released, it actually, also, stimulates STAT3 activity. And so it's sort of a vicious downward spiral.

So this has, also, been evaluated in the mouse model, and you see similar effects to what we saw with the PGC-1alpha knockouts, in that the mice that were homozygous for the knockout of STAT3 had pretty rapid decline in survival following pregnancies, whereas those who were heterozygous, also, ultimately died. But not until later on.

This, also, has been translated to the human. In patients with peripartum cardiomyopathy compared with controls, levels of STAT3 were markedly reduced in their serum, and cathepsin D activity was markedly increased.

This is, also, a little bit interesting, here, if you take peripartum cardiomyopathy patients and compare them with just normal postpartum lactating women. They all have high levels of the normal 23-kilodalton protein, but only those with peripartum cardiomyopathy have high levels of the 16-kilodalton protein. If, then, you treat those patients with bromocriptine, it actually prevents the appearance of the 12-kilodalton protein.

So ultimately, their suggestion, then-- this is sort of a two-hit hypothesis where you have high levels of anti-angiogenic factors, whether that be related to increased release from preeclampsia, from twin pregnancies where you have more placenta, or multiparity, which basically suggests that they've been exposed to these factors multiple times.

And then, you take that in combination with insufficient pro-angiogenic defenses, perhaps related to PCG-1alpha deficiency or STAT3 deficiency. Ultimately, this leads into an angiogenic imbalance, which may cause, then, tissue hypoxia, microvascular dysfunction, low capillary density, and then, ultimately, to peripartum cardiomyopathy.

I think that they're onto something here. I think that it's a very plausible pathway. And it links some of the things such as mutliparity and preeclampsia and twin pregnancy to what we see, in that they are at higher risk of developing peripartum cardiomyopathy.

So how do we manage heart failure? Well, it's basically the standard heart failure regimen. Of course, there are some caveats to that. During pregnancy, ACE inhibitors and ARBs are contraindicated.

So in general, you should use hydralazine or nitrates, instead. In general, it's best to use beta-1 selected drugs, such as metoprolol because there is some concern that the beta-2 2 blockade may promote uterine contraction.

That said, we use a lot of labetalol, here, for hypertension management. And there is good safety data with coreg, as well. The only one that should really be avoided is atenolol because it has, clearly, been linked to fetal growth restriction.

Diuretics are not teratogenic, but if used excessively, it can lead to placental hypoperfusion. So they should just be used when appropriate. And just be cautious with their use. And aldosterone antagonists should be avoided because they can cause feminization of the male fetus.

It's really up for debate how long these women should be treated. I think-- pretty much everyone agrees-- they should be treated for at least a year. But then, if there's complete recovery of the LV, people kind of disagree about whether or not they should stay on their medications or if it would be OK to start to peel them off.

One thing that I do know for a fact is that when cardiologists go to give drugs to breastfeeding women, it creates a state of panic. And I get a frequent phone call that starts off like this, "Hi, we called pharmacy and so--"

The American Academy of Pediatrics-- their most recent update on drug use during breastfeeding was in 2013. And I think this statement is important. They say, "Many mothers are inappropriately advised to discontinue breastfeeding or to avoid taking essential medications because of fears of adverse effects on their infants. This cautious approach may be unnecessary in many cases."

And in fact, they really spend the majority of the time in the document talking about the risks of narcotics, which basically all pregnant women take after they deliver because it's not a very comfortable time.

So there is one resource called LactMed, which is free on the internet, that has a lot of pretty useful information about medications. Unfortunately, a lot of them just haven't been tested in breastfeeding. What we do know, though, is that the vast majority of them are safe to use, and there are only, really, a handful of medicines that have clearly been linked to adverse effects in the baby.

So basically, the way I look at it, the obstetricians look at it, and the American Academy of Pediatrics looks at it, is if mom really needs it, and there's no clear harm to the baby, you should just treat mom because baby needs a mom to be around and to get better. And you're unlikely to harm the baby.

I think that the one drug that people get most concerned about are ACE inhibitors, and that's understandable because we know that they're contraindicated during pregnancy. And there's not a ton of data on these. Although, the most data is probably available for enalapril. Enalapril is actually an inactive drug that's metabolized to an enalaprilat once it's absorbed.

But enalaprilat is poorly absorbed orally. So in the human, the majority of the enalapril is going to be transformed into the enalaprilat. And ultimately, the maximum estimated intake for an exclusively breastfed infant would be about 0.16 of the maternal weight-adjusted dose. And 1/2 of that will be the enalaprilat, which they will not be able to absorb orally.

So ultimately, the amount ingested by the infant are small and are not expected to be cause any adverse effects. So I, literally, don't even blink when I think about starting an ACE inhibitor in these patients because, I think, they clearly need it. And it is extremely unlikely to harm the baby.

This is, probably, generally true for all of the ACE inhibitors. Although, we have the most data for enalapril. So I have kind of changed my practice into mostly giving these patients enalapril because there's some data to support it.

Another kind of unique medical therapy aspect that we need to think about in these patients is antithrombotic therapy. There's actually about a 10% to 20% incidence of LV thrombus in patients with peripartum cardiomyopathy.

And this makes sense. They've got a big dilated heart, and they're 15 times more hypercoagulable than a non-pregnant patient. And it actually takes about 6 to 12 weeks after delivery before that returns to the normal level of hypercoagulability.

And so there's not an exact cut off, but what I tend to do is, for patients who have an EF less than 35%, I will generally go ahead and put them on full dose anticoagulation with coumadin for 6 to 12 weeks. And if it's above 35%, I'll usually hedge bets and just put them on an aspirin.

If they're pregnant, obviously, still, we don't put them on coumadin. They would just be on low-molecular-weight heparin or IV heparin.

There are some novel therapeutic strategies that have been investigated recently. I get a lot of questions about bromocriptine, and I-- personally, I think this jury is still out on it.

This was, probably, the most pronounced study on it. It was done in South Africa, and they gave, either, standard therapy versus bromocriptine to their patients. And you can see there was a marked reduction and a combined endpoint of heart failure, symptomatic heart failure, low EF, or death-- and notably, a significant difference in death.

However, what's concerning about this is that 10% of the patients who receive the bromocriptine still died, which is, certainly, on the upper end of what we would estimate in our normal population in America. And 40% of the people who didn't receive bromocriptine died, which is an appallingly large number of deaths. So I'm not exactly sure how well we can translate this data to our practice because the mortality was just so high.

Going back to the mouse-- so these mice that I'm showing you, here, are the STAT3 knockout mice. And what you can see is-- so as we talked about, there's an increase in capillary density. And if you treat those control mice with bromocriptine, there's basically no difference. They just continue to have the high capillary density.

On the other hand, if you treat the knockout mice with bromocriptine, thus completely preventing the formation of that 16-kilodalton protein, you can see that these patients continue to have normal capillary density. And it's significantly higher than if they didn't receive the bromocriptine. So I think that there is some evidence here that actually treating with a bromocriptine does help with the microvascular homeostasis.

This is another very small study of just 12 patients. They took people who had previously been diagnosed with peripartum cardiomyopathy and, then, treated them-- 1/2 of them-- with bromocriptine following a subsequent pregnancy. And the groups were pretty similar at baseline. If anything, actually, the control group had a little bit higher initial EF and a little bit lower initial New York Heart Association class.

And then, after delivery and treatment with bromocriptine or not, you can see that the patients in the treatment group, actually, had stable or improved LV size, stable or improved LV ejection fraction, and they were, generally, New York Heart Association Class I.

On the other hand, those untreated patients, who had a subsequent pregnancy, had a worsening of their LV dilatation, worsening of their LV injection fraction, worsening of their New York Heart Association class, and, actually, three of those six patients died. So I think there's, also, some support there for some purpose and benefit. So you know, the data isn't robust.

But why don't we just go ahead and treat everyone with bromocriptine? It seems like there is some evidence that it's helpful. Well, unfortunately, there are potential risks of bromocriptine. It used to be routinely used for lactation suppression. And actually, just recently, it's been taken off the market for that indication because of the potential for cardiovascular risks.

So of all adverse drug events with bromocriptine, about 75% of them are cardiovascular events. And importantly, that includes myocardial infarctions and strokes. And we, certainly, don't want to be contributing to strokes in our young patients who already have peripartum cardiomyopathy.

This is another small study that was actually looking at the use of LifeVests in patients with peripartum cardiomyopathy. And all of these patients received bromocriptine in some manner. Some of them just received it for lactation suppression, and some of them received it as a potential therapeutic.

And what's kind of alarming is that, actually, 3 of 12 patients received an ICD shock in that first three months, which is 25% of your patients having sudden cardiac death. That is, also, really, an unprecedented high number.

And ultimately, their final EFs were lower than what we have seen in a lot of other studies. So it does bring up the question about whether or not there is some harm that's being done by the bromocriptine.

So there's, actually, currently a randomized control trial going on in Europe looking at this. They're randomizing 60 patients with peripartum cardiomyopathy, reduced EF, to either receive or not receive bromocriptine. There are some interesting things they're doing this.

The control group is, actually, receiving one week of bromocriptine for lactation suppression, which is certainly not standard of care here. And they're only following up the patients for six months, which I wonder if that may be too short of a period to reach their endpoint. So I'll be interested to see how that goes. We, certainly, need a randomized controlled trial to further evaluate this.

So in addition to asking why did this happen to me, the next question that people want to know is, will my heart get better? And just recently the IPAC study was published in JACC. And actually, Washington contributed some patients to this, and Greg Ewald was an author on this paper. And I think that the results are, ultimately, pretty encouraging.

There, certainly, does seem to be an effect of-- a prognostic effect of how sick the patients were when they were first diagnosed. You can see that patients who initially had an ejection fraction less than 30%, did have about a 15% incidence of some sort of event, which was either death, transplant, or requirement for LVAD over the course of the first year.

But on the other hand, those who had a only mild and moderately reduced EF, greater than 30%, had a very low incidence of death or need for additional support.

Then, if you look at how likely they were to recover, this group with the low EF kind of fits what we have traditionally told patients, which is that about 1/3 will get better, 1/3 will get partially better, and about 1/3 will not have any significant improvement. On the other hand, those who had an initial EF greater than 30%, 86% of them had complete recovery.

Now, I don't know that I would use 50% to call complete recovery. But that is the cutoff that was used, so they, at least, have marked recovery. And then, only 3% of those patients, ultimately, died or required mechanical support or transplant. So I think that is encouraging that those with less severe disease, have a good chance of getting better.

Now, I want to talk just a few minutes about some using advanced therapies in peripartum cardiomyopathy. Traditionally, we say, if you don't get better after three months of medical therapy for your heart failure, then you need an ICD. I think that it can be a little bit more challenging in this group because, as you can see here, while patients often have some initial recovery in the first couple months, they do tend to continue to have recovery in their function over the course of 6 to 12 months.

And you can't-- while we know that LV dilatation and severely depressed ejection fraction is associated with poor prognosis, you can't just say everyone who starts out really sick is going to stay really sick, or those who aren't as sick at the beginning, are going to do well.

As you can see here, those who started out with an EF less than 20%, many of them stayed that low. But there is one person who had complete recovery. And on the other hand, people who started out with mild dysfunction, some of them, ultimately, had decline in their function.

So I don't think you can use that as a trigger to just immediately put ICDs in people who started off very sick. Of course, we try to avoid using mechanical supporter transplants as much as possible. Sometimes people just can't be supported with medical therapy, and they, ultimately, require those advanced therapies.

This is some data from INTERMACS that was published last year looking at their survival of women who undergo device placement. And ultimately, it looks like patients with peripartum cardiomyopathy have better survival than those who have other causes of cardiomyopathy. Although, ultimately, when the risk factors were evaluated, it looks like a lot of that is related to the fact that they are younger, and they have fewer comorbidities.

One particular concern that has been raised in these patients is that if they require mechanical support shortly after diagnosis, as we discussed earlier, they're very hypercoagulable. And this does raise concern for increased potential for pump thrombosis.

So what happens to these women who get mechanical support? Well, unfortunately, if patients are sick enough to require mechanical support, it's very unlikely that they're going to be able to just be bridged to recovery. As you can see here, only about 2% of patients, ultimately, recovered and were able to be explanted. While the rest of them either continued on with their LVAD or got transplanted or died.

And what about women who, ultimately, require a heart transplant? Up to about 10% of patients with peripartum cardiomyopathy, it's been reported, may, ultimately, require a transplant. It appears that they're at higher risk for developing graft rejection. As you can see here, within the first year, and particularly prior to discharge, they seem to be much more likely to develop graft rejection.

And I think that does lend some support to the autoimmune theory that, perhaps, they have developed more autoantibodies against their own heart. And this may lead to ultimate rejection. They, also, tend to have a little bit lower graft survival, as well. In this study here, patients with peripartum cardiomyopathy had a half life of about 8 years versus about 10 years in other patients.

So one, I think, important question that's not answered is, should we be bridging these people with LifeVests? And really, how likely is it that they're going to have a sudden cardiac death event? I mean, it's just a LifeVest. They can put it on, take it off. But I mean, they're very expensive, they're not well covered by insurance, and they are irritating for the patients to wear.

As I mentioned before, this is a very small study of only 12 patients who wore LifeVests. And three of them, ultimately, received a total of four, reportedly appropriate, shocks in the first three months, which, as I said, is not consistent, really, with what we think to be true about the risk of sudden cardiac death. I mean, that is markedly elevated.

On the other hand, there was a larger retrospective study that looked at this. And they took 107 women with peripartum cardiomyopathy versus 159 nonischemics, and, actually, the peripartums wore the LifeVests, on average, longer than the nonischemics. And there were no appropriate shocks in that group versus only one in the nonischemic cardiomyopathies.

So I think there's quite a bit of disparity between these studies. And the jury's still out in terms of how high is the sudden death risk.

And then, ultimately, who should get an ICD and when? As I mentioned before, these patients tend to recover over the course of 6 to 12 months. And so putting an intravascular device into a 22-year-old woman after three months, may be a little bit aggressive because she may, ultimately, recover her heart function and not require it.

On the other hand, sudden death is, obviously, not an acceptable alternative. So I think there are some questions that still need to be answered in terms of, should we wait till at least six months before deciding on ICD therapy? Should we be bridging them with LifeVest? And I think, another potential question is, maybe, would these patients be a good candidate for the total subcutaneous ICD? That's going to be a little bit less risk of infection, et cetera.

So after those two questions, the third question that I frequently get is, can I have another baby? And I think, the initial gut response of most people is, no-- absolutely not. But I think if you look at the data, it only partially supports that initial reaction. And I think a lot of it depends on how much the patients are able to recover their LV function.

In those who have completely recovered LV function in the red, about 20% of them are at risk of developing heart failure symptoms or decline in their EF with a subsequent pregnancy. Importantly, though those patients don't die. So, obviously, getting recurrent heart failure is not a good thing, but their mortality does not seem to be particularly elevated.

On the other hand, in patients with any persistence of LV dysfunction, nearly 1/2 of them will develop heart failure symptoms in a subsequent pregnancy, 1/4 will develop decline in their LV function, and 20% of them will die, which is, clearly, unacceptable.

So when patients are initially diagnosed what I tell them is, maybe. The jury's still out. We need to give you at least a year, and then we can rediscuss. Now, certainly, they're still at elevated risk of having potentially significant complications with a subsequent pregnancy with recurrent heart failure, but they're not likely to die.

And so I counsel them very seriously about those risks, but if they have complete recovery, I think a cautious approach is not unreasonable. Whereas, if they have any residual LV dysfunction, I tell them, absolutely not. You already have a baby that you need to be alive and take care of.

So I have boiled down my huge soapbox of contraception into a single slide, here. So what we do know is that they need at least a one year interpregnancy interval. And so it is very important that these patients are on highly effective methods of contraception.

And they really should not be placed on combined hormonal methods because the estrogen is associated with increased risk of thrombus formation. And they're already hypercoagulable, and they already are at risk of LV thrombus, and they have LV dysfunction. So it's not recommended. What I really encourage these patients to get, if they decide not to get a permanent method, is a long acting reversible option.

There are three options out there right now. There's the levonorgestrel implanted IUD, the copper IUD, and the etonogestrel impregnated rod, which is called the Nexplanon. There, actually, have, recently, been two new IUDs come out on the market.

So there's now Mirena, Skyla, and Liletta. Mirena is the one that's been out for a while now. It lasts for five years. The Skyla is a little bit smaller frame, and it only lasts for three years. So it sort of was developed for nulliparous women or adolescent women because it might be easier to insert.

And there's, actually, no difference between Liletta and Mirena, other than the company that makes this has some great programs to help make it affordable for patients who might have difficulty affording it. So I think that's a good option for people who are financially having trouble.

The copper IUD has no hormones in it all, and it lasts for 10 years. And then, this Nexplanon rod, also, only has progesterone components, and it lasts for three years. It's a little like plastic toothpick that goes subcutaneously in the arm.

The important thing about these methods is that they're, actually, more effective than tubal ligation. And they're totally estrogen-free, and they're completely reversible. You can take it out and get pregnant the next month. And they're FDA approved for 3 to 10 years.

So these are safe for all of our cardiovascular patients, including those with peripartum cardiomyopathy. And preventing pregnancy, or at least helping them plan for pregnancies, is just of utmost importance. So I have a conversation with all of the patients about this.

I'd like to spend just a few minutes talking about something that I have a particular interest in, which is kind of the overlap between peripartum cardiomyopathy and preeclampsia. Preeclampsia is, really, a disease of the placenta, which the placenta-- I think myself and Mike Nelson are the only people in this institution who get so excited about it.

But it's a very interesting temporary vascular endocrine organ and, clearly, plays an important role in the development of preeclampsia, which is really new-onset hypertension. Classically, it's associated with proteinuria, and it causes widespread endothelial dysfunction. We know that it's more common in women who have cardiovascular risk factors.

And so a lot of people have said, oh well, the fact that women with preeclampsia, ultimately, are more likely to develop heart disease is just by association. They were already at higher risk to develop it. On the other hand, we know that the preeclampsia does cause widespread endothelial dysfunction. And so it may be that it's, actually, accelerating vascular disease in women who develop it.

There's recently been more interest in the overlay between preeclampsia and peripartum cardiomyopathy with some of the data that's come out looking at the high sFLT levels. And this was a meta-analysis that was done a couple years ago.

And they, actually, found that there was an incidence of about 22% of preeclampsia in women who had peripartum cardiomyopathy, and that's compared with about a 5% background incidence worldwide. So it's, certainly, much higher in those with peripartum cardiomyopathy.

Unfortunately, this hasn't really been well studied because, in a lot of the initial studies, patients with preeclampsia were excluded because they wanted to make sure that they sort of had a peer cohort of patients.

So we have started doing a little bit of work here looking at this. And one question that I was interested in is whether or not the preeclampsia effects or likelihood of peripartum cardiomyopathy-- I would often hear people say, oh, it's just preeclampsia associated cardiomyopathy. They're going to do fine. It's not the same as peripartum cardiomyopathy.

And I really couldn't find data to support that. So we've identified a retrospective cohort of people who delivered at Barnes between 2004 and 2014. And we identified 39 women who had their initial echo data available, here. And a few interesting things.

Number one, if you look at their baseline characteristics, there's really no difference between those who did and did not have preeclampsia-- similar age, they all had about two to three babies, a majority were African-American, most of them were overweight, which is Barnes I think, and similar other cardiovascular risk factors.

If you look at their initial echo, the patients with preeclampsia seemed to have higher initial filling pressures and less dilated left ventricles and a little bit higher pulmonary pressures, which I suspect may be related to backup from the higher left-sided filling pressures.

But if you look at some other parameters of systolic function, their strain was pretty similar, their stroke volume was similar, and their initial EF was pretty similar. So just looking at their initial systolic function, I don't think you could clearly differentiate the two.

However, we, then, took the patients who we had echo data on, at least for one year, and what you can see is that, while they started out with similar initial EFs, those who had preeclampsia had a much higher final EF. So it suggests that, maybe, they're more likely to have recovery than those who did not have concomitant preeclampsia.

Importantly though, while only about 1/2 or 60% of the non-preeclampsia had a complete recovery of their LV, still about 1/4 of those with preeclampsia continued to have some persistent LV systolic dysfunction. So I don't think we can say, well, just because it was associated with preeclampsia, you're definitely going to have full recovery.

And also, very importantly, I think, is the vast majority of them continued to have some diastolic dysfunction. So even though they've had complete recovery of their systolic function, I'm not sure that their myocardium is truly normal.

You see the same thing when we look at their global strain. They started out with markedly reduced average global strain, but on average, they did not ever reach back up to normal levels even after they had recovery of their LVs. So I think that there does continue to be some subtle myocardial dysfunction there, and we're interested in looking a little bit more at that patient group in the future.

So I think that this data kind of brings up a few unanswered questions. Are these two different diseases with a similar presentation, given the apparent difference in recovery? Are there different genetics? Is it sort of a dose-dependent effect, whereas, maybe, the preeclampsia have the really high anti-angiogenic levels, but they don't have as much of the lack of pro-angiogenic factors?

And then, what are the risks for future pregnancies? Are those with preeclampsia-associated cardiomyopathy at the same risk of recurrence as those who didn't have it? And then, lastly, an important question is, does the myocardium truly recover? And I think that this really merits further investigation so we can help determine, I think, who is likely to have problems with future pregnancies.

So I used to watch David Letterman, and he did this thing periodically called, "Is This Anything?" And so--

[VIDEO PLAYBACK]

--time now for a little something we call--

Can you hear that?

-Take a look.

Where's the thing?

[MUSIC PLAYING]

-Wow. You see the illuminated hoops? Anna Jack has the illuminated hoops. I think that's new.

-That was something. The illuminated hoops were something.

-What did you think about the guy?

-I did. What did he do exactly?

-It kind of reminded me of my honeymoon-- part of it. I mean, the equipment reminded me of my honeymoon.

-You used equipment on your honeymoon?

-I had to. I had to. It was part of the deal.

-Other than that though, I didn't think--

-I didn't think that was anything.

-Pretty much nothing.

-No that was--

-Nothing.

So that one was nothing.

--Kat Von D, ladies and gentlemen.

[END PLAYBACK]

Sometimes they determined it was something.

So I have a similar question about this patient, here. So is this anything? So this is a normal patient postpartum, and you can see that, normally, postpartum women are very hyperdynamic-- normal to hyperdynamic LV function. Now, this patient here, they don't have an EF, probably less than 45%, but it's, certainly, not as robust as this ventricle. And you know maybe that's a little more dilated.

So here you are on the short axis, and you can see this normal patient has really hyperdynamic, robust function, whereas this patient, over here, you know it's low, normal maybe mildly reduced. And then, you look in the apcial four chamber, and again, you can see this LV is a little bit more dilated, a little more left atrial enlargement. And you know this LV function just is not robust as this normal person, and this person's in clinical heart failure right now.

So is this anything? If you look at their strain, it does tend to be reduced in these patients. So, here, the average global strain is about 10.8%, compared to 21.5% in the normal patient. And if you look at markers of stroke volume, their LVOT TVI is reduced at 14.4, compared to 25.7 in the normal patient.

So this is something I call peripartum HFPEF, and I'm quite interested in learning more about it. I think there are two risks that we run when we see patients like this. One is we come to the same conclusion as David Letterman and say, this is nothing. They don't get any treatment. They don't get any follow up. But do we really know it's nothing? Is their myocardium truly normal?

On the other hand, people may say, you have peripartum cardiomyopathy. You should never get pregnant again. Well, that might also be overly aggressive counseling because their LV, certainly, doesn't look as bad as the people who had true peripartum cardiomyopathy.

So I see patients who are given both sides of this counseling. I think the answer is probably somewhere in-between. So we don't know what is the risk of recurrence of this in future pregnancies.

How likely is this to progress? Maybe with subsequent pregnancies, they'll get progressively low EF? We don't know. And then, is this just a mild form of peripartum cardiomyopathy or is this something completely different? And will this, ultimately, benefit from medical therapy? Will putting them on a beta blocker or ACE inhibitor give them any benefit?

So we started doing some work and looking at this. We found about 53 patients who delivered between 2003 and 2014, and we identified them by having imaging evidence of pulmonary edema, elevated BNP, and an echo with preserved ejection fraction more than 45%. So right now, we're still just doing some phenotyping.

You can see these patients, also, tended to have about three babies, the majority were black, reasonable amount of tobacco use, pretty low incidence of hypertension. Many of them, but not all, had preeclampsia. Many of them had cesarean delivery, and quite a few of them have had prior miscarriages.

So I think this data that we have thus far is kind of hypothesis generating. I'm still going through and reading the echoes, and I'm very interested in looking at the echocardiographic parameters.

But this group of patients did have a relatively high gravidity. They all had, on average, three or more pregnancies. So maybe this is another one of those repeated anti-angiogenic insults that, ultimately, leads to some mild myocardial dysfunction. They are predominantly black, so maybe there's a genetic contribution. There was a somewhat high incidence of tobacco use in preeclampsia, so maybe this supports that there are some underlying microvascular disease.

And there's also a high rate of c-section. 66% of them had had c-sections, as compared to about 35%, is our average rate, here. So that brings into question, maybe it's just related to the volume that they get with pregnant-- or with a c-section.

So to conclude here, I wanted to put in just one quick shameless plug for the Maternal Cardiovascular Management team that I've kind of headed up over the past year and a half. And what it is is really a multi-disciplinary management approach to these women, involving cardiologists of specialties, maternal fetal medicine, and when appropriate, those from imaging, pulmonary, genetics.

And I think that the value of multi-disiplinary input into these, often complex, pregnant patients just should not be underestimated. Each person brings kind of a different perspective and different type of expertise to their care. In the last year, we've actually managed over 100 women with pregnancy-related complications. And I am happy to say that we have had quite good outcomes.

And we meet the fourth Friday of each month in Cain at 7:30. Everyone is welcome. If you have a patient that you would like to be discussed, we will not steal them from you. You will still be managing the patient, but we're happy to give our input into their management. And I think the multi-disciplinary approach is really of benefit for the patients.

And lastly, I just want to thank a few people who have really been instrumental in my development of this program and my career thus far. First of all, Doug Mann-- I came to him with this like totally harebrained idea about three to four years ago, and I said, is this even a feasible, viable clinical career opportunity? And he was like, I don't know, but we'll just make it happen. And so far we're making it happen.

Joe Billadello, Phil Barger, and Phil Ludbrook, our congenital crew, have just been endlessly supportive of me and taught me almost everything I know. And they're incredibly involved in the Maternal Cardiovascular Management team, as well. And I would say, it's probably like, at least, once a week that one of us is calling one or the other, running a pregnant woman by them, getting their input. And I really appreciate the collegiality there.

Victor Davila, also, has really no reason to care anything about pregnant women, but despite that, he has been, really, a tireless advocate for me in terms of research. He has given me a lot of-- he's provided resources and time and great mentoring. So I really appreciate that.

And then, the maternal fetal medicine department and obstetrics department have, also, been absolutely essential for this. They have really been great collaborators, and I think that's the only reason we're able to be successful. Alison Cahill heads up maternal fetal medicine, and we've done a lot of collaboration. George Macones is the head of OB, and he's been incredibly receptive to my interest.

Shayna Conner, Method Tuuli, and Jen Durst have all-- I collaborate with them quite a bit on research and clinical patient management. And then, Tessa Madden is, actually, one of our family planning attendings who has been very involved in both helping us get patients appropriate contraception in a timely manner and, also, in some research, as well.

And then, lastly Kelly Carlson helped out with a lot of the data extraction for the HFPEF database that we've been working on. And so I appreciate her time with that.

And that said, I will take time for questions.