

**SPEAKER:** This is data from several trials aggregated together to just show that the rates of either impaired glucose tolerance or diabetes are about 40% of a cohort of PCOS patients. Now we actually see that a little bit less in our clinic, I think because California in general may be slightly-- at least the San Francisco Bay Area may be slightly healthier than the middle of the country. But there are very high rates of metabolic issues.

It's also not something that is relegated to older population. So we know that even adolescents who have been diagnosed with PCOS have been shown having impaired glucose tolerance 30% of the time, and diabetes can be detected in 7%. We know that it also doesn't necessarily go away. This is an area that we're actively trying to study is what happens to a lot of these features with aging, but most studies seem to show that the prevalence of type 2 diabetes, even in women who are perimenopausal and therefore not really having a lot of the other PCOS symptoms anymore have a fourfold increase risk of type 2 diabetes.

This is a study that just also is showing the increased rates of metabolic syndrome. So these are all risk factors for cardiovascular disease, and in this population in this study it was about 30% of PCOS patients had metabolic syndrome. It's definitely something that's focused in the women with increased weight. So BMI over 30 gives you an increase of 13 fold, basically, for your chances of metabolic syndrome.

And this there is just showing why we think it's really important to do a glucose-tolerance test. So this is one of the things we do before our patients come in. It's obviously easier to just get a fasting glucose, but this study really highlighted that specifically with PCOS there's a fair number of patients that will have a normal fasting glucose but will have increased two-hour glucose tolerance.

So this is the second glucose that you do after drinking the drink, and we find it very important in our workup of patients to fully evaluate them for their glucose management. And our patients where we see abnormalities, either in fasting glucose or in their two-hour glucose, are a focal point for us to focus our treatments.

And we know that this increased rate of abnormalities and glucose tolerance-- so sort of prediabetes does progress to type 2 diabetes. So in this study they showed that there was an annual conversion rate of about 2%-- annual conversion rate from normal glucose tolerance to abnormal or impaired glucose tolerance. And then for those who had an impaired glucose tolerance, about an 8.7% conversion to diabetes.

So because of this, we feel like it's really important to discuss everything we can to help patients modify that risk to whatever degree possible. So long-term health recommendations really focus on lifestyle. There hasn't been large-scale trials done with women with PCOS looking at ways to prevent progression to diabetes, but we use some of the other data that's out there based on patients who are at risk of diabetes.

And for that we really looked at things like the diabetes-prevention trial. This was a large study done in 2002, and it looked at a really large group of people, over 3,000, who had impaired glucose tolerance or elevated BMI. They were from high-risk minority groups, and they compared metformin, lifestyle program, or no intervention and looked at what happened over time.

And so this is over here on the vertical axis, the incidence of diabetes, and on the horizontal axis is time. And you can see that the people actually who did the best, so had the lowest rate of conversion to diabetes were actually those doing lifestyle. Which I always think is so amazing because I think as being compared to a pill, I think we're all in our society biased to think, well, if there's a pill for it it's probably going to be better and certainly easier. But even in this study it was not more effective than taking a drug that's used to treat diabetes. This is a starting point for us to really counsel our patients about what we know is the most effective way to manage this. Our patients who are showing levels of glucose that are in the impaired range, we do also consider using metformin, but we want to try to combine these when possible.

We've been really interested in looking at physical activity in our patients. So we do a pretty in-depth evaluation of their physical activity as a questionnaire before they come in because we want to drill down on this. We've done some studies looking at it to try to better identify which patients are exercising and to also understand what the benefits are, at least in the sort of real-world scenario of our clinic.

This study, we looked at those who were achieving Department of Health and Human Services guidelines for exercise. So the HHS recommends 150 minutes of moderate or 75 minutes of vigorous. And we found that about 60% were meeting the guidelines but 40% were not meeting the guidelines. So we have a high-risk population. We have 40% of them not even doing what is, I think, it's not an aggressive standard to achieve.

We found that active women were more likely to be white, and we also found active women were more likely to not have kids. So once you've had kids, it becomes harder and harder to really achieve the levels of exercise that we should, and I think it's important for us to recognize this and work on strategies to remedy this.

Certainly in this study we were able to find pretty big differences between the active and nonactive group. So our nonactive group had a significantly higher BMI, 33 versus 29, higher or larger waist circumference, which is a marker of insulin resistance. They tended to have larger weight fluctuations. They certainly had higher fasting glucose, and they also had higher rates of depression. So we'll talk a little bit more about this as well.

And of course with some of these things we don't know-- this wasn't a randomized trial. It was cross-sectional. So some of these things could be the result of the lack of exercise, but some of them could be the cause of the lack of exercise. So are people depressed because they're not exercising or if you're depressed do you not exercise? And this is hard to tease out.

The other thing we did as a follow-up study-- and we recently published it-- was to look at physical activity, specifically the type. And we actually have a follow-up study now that's actually a prospective randomized study. So this was looking at moderate versus vigorous, so those who met through moderate exercise versus vigorous. And we found that of those meeting the exercise criteria, most of them were doing it through the vigorous activity, but some were doing it through moderate activity, and we are interested in knowing which one of those was more effective.

We found that both were much better, obviously, than being inactive, but there was this improvement that seemed to be showing up for those who did vigorous. And we did this regression model where we were able to show that even when you were controlling for BMI-- I'll show this one-- BMI, age, and total amount of exercise that those who were doing vigorous had more benefit than those who were doing moderate exercise. So this has been able to help us with our counseling because we want to move patients into that vigorous category in order to achieve the benefits we're looking for.

We're also doing now a randomized control trial to try to look at this. So we've been able to enroll patients from our clinic in an exercise intervention, which patients really like because it gives them a lot of support. Yes?

**AUDIENCE:** How [INAUDIBLE]?

**SPEAKER:** It's a good question. So in our questionnaire, it's a standardized questionnaire called the International Physical Activity Questionnaire, and it has sort of instructions for the patient when they're filling it out how to consider what's vigorous or moderate. So the vigorous says things like you should be breathing hard while you're doing it. It represents running, walking uphill fast, but I think it really tells them you've got to be breathing hard and kind of getting sweaty. Moderate is more like you're walking, you're riding a bike casually, things like that. On that questionnaire they have to fill out number of days per week, minutes per day, and then from there that's how we did all these calculations.

Before I talk about the formal recommendations just in terms of some of the research work that comes out of this, we also have a diet study ongoing in collaboration with the endocrine unit over at Parnassus where we're randomizing our patients to two different types of diet, a Mediterranean versus a paleo diet, to look for improvement in menstrual cyclicality. So there's some thought that just manipulating the insulin levels through diet could really modify some of the features that patients are experiencing.

So I think for patients who are interested in doing that kind of thing, it's one of the other benefits of the clinic because it can kind of get hooked into a program essentially for free, or they even paid for it a little bit. That then gives them some accountability towards making some of these lifestyle changes.

So recommendations for management-- we base this on sort of consensus recommendations. Lifestyle modifications are 5% to 10% of weight loss with moderate physical activity if you have impaired fasting glucose or impaired glucose tolerance. But if you have some of these other features, then we recommend lifestyle and metformin, and many women in our clinic would have one of these additional features. So lifestyle and metformin is not uncommon for us as a strategy once we're in this impaired range.

All right, so we've talked about menstrual-cycle control, hyperandrogenism, fertility, and long-term health, and then I've overlaid psychology on here. And you may have noticed that we have a psychologist as part of our PCOS clinic, and that is to help us with understanding and evaluating and managing potential depression and anxiety that may exist within PCOS. I think all of us could understand that if I were to draw arrows here, you could see how, for some of these factors, the arrows could go both ways.

So in particular, depression and anxiety may lead to more trouble with long-term health because it may lead to not being able to make the lifestyle changes that are required.

So depression and PCOS is really common. It's been found to be four times more common in PCOS than in normal populations. A recent meta-analysis demonstrated that this is really independent of BMI. So BMI certainly increases the risk of it and we see more depression in the heavier women, but it is not just being caused by the BMI. There's something particular about PCOS that leads to more depression, and the mechanism right now is unknown.

We are really interested in understanding this better. This is just some of our data. So we, as I said with our extensive questionnaires, one of the other questionnaires we do is depression screening. And I feel strongly that this is really important for all women with PCOS.

We find that if you use a Beck depression index score of greater than four-- which has been universally accepted as at least mild depression-- that 56% of our patients will meet that standard. So not all women with PCOS, clearly, and with PCOS it's also heterogeneous and we don't want to assume anything, but it is important to screen and look for this.

We did a study recently where we looked at our depressed patients versus our not depressed patients to just see how they might be different, and we did see higher BMIs and higher waist circumferences in this group. We did not see differences in hirsutism, and I think that's really interesting. We didn't see differences in MFG4, which is a way of measuring hirsutism, and we didn't see differences in our elevated testosterone scores.

So I think this is really interesting because, as I said, it's commonly said, even amongst practitioners that I've worked with in the past, it goes like, oh, it must be the testosterone that's leading to this mood disorder, but we're really not seeing that in our data. The other thing I've heard people say is, well, they're probably depressed because they're hairy and they don't like that. We're not seeing that. This doesn't appear to be something related to their appearance or something that's related to how they feel about that. It seems to be deeper than that.

What we've actually seen to be a really strong indicator of depression is the degree of insulin resistance. So in this study, we showed that the HOMA-IR, which is a measure of insulin resistance, is essentially twice that than the nondepressed counterparts. We also see more glucose intolerance in this group.

Now you might be wondering, well, you already said that the women are also heavier, so maybe is it just linked to that? So we looked at it and we showed that even in-- sorry, why does that keep happening-- even if you stratified by level of obesity we saw more depression-- I'm sorry, we saw a higher HOMA-IR so more insulin resistance in our depressed patients versus nondepressed. So just in this box you can see in all women who are overweight-- so BMI between, say, 25 and 30, if you look at the depressed patients, their insulin resistance was more than twice that of the nondepressed patients.

So we're really interested in further understanding whether the insulin resistance is really part of what's causing the depression through mechanisms in the brain. And this is an area that's actually not that novel if you talk to people who study diabetes where this is also potentially a factor.

So to summarize-- and I'll take a few questions-- PCOS is clearly a multisystem disorder. It has effects that range through a variety of systems. And it ranges across the lifespan, starting in adolescence and moving really through and past menopause. We find certainly as a reproductive endocrinologist that there is a lot of features of PCOS that we can address, but we really feel like the care of the PCOS patient is greatly improved by combining our work in a multidisciplinary approach with a dermatologist, genetic counselor to understand family history, for sure the psychologists who really can help us with the mood issues, and then a nutritionist who's able to help us with the lifestyle management.