

**DARRYL CHUTKA:** This is *Mayo Clinic Talks*, a curated weekly podcast for physicians and health care providers. I'm your host, Darryl Chutka, a general internist at Mayo Clinic in Rochester, Minnesota. Today we'll be discussing a relatively common health problem seen in women.

The prevalence is between 5% and 10% of childbearing women living in the United States. Complications can include infertility, diabetes, cardiovascular disease, and endometrial cancer. Despite the fact that this problem is common and has potentially serious complications, less than 50% of women with this condition are given a correct diagnosis.

I'm talking about polycystic ovary syndrome. And if you see women of childbearing age, you need to know about this often misdiagnosed health condition. Our guest today is Dr. Alice Chang, an expert in polycystic ovary syndrome and an endocrinologist in the division of endocrinology at the Mayo Clinic in Rochester, Minnesota. Welcome, Alice.

**ALICE CHANG:** Good morning. Thank you for inviting me.

**DARRYL CHUTKA:** Well, let's start by talking about how patients present. What symptoms would make a health care provider suspect polycystic ovary syndrome?

**ALICE CHANG:** Well, that's a great question. It's often the first question I ask patients too is, what led you to come to your provider for the diagnosis? And I get referrals from dermatologists regarding their acne or hair growth or even hair loss. So that's important to look for, that they can get male pattern hair loss as symptoms.

Some are coming in with irregular periods. So that's the first signal that something is off. Others are getting evaluated by gynecology for infertility. And the diagnosis is raised there. So then they often circle back to either their primary care provider or to endocrine to sort of further evaluate whether they have the condition.

**DARRYL CHUTKA:** So it sounds like one of the issues with this condition is the variety of symptoms that patients can develop with it.

**ALICE CHANG:** Exactly, and I think that's part of their frustration is that they might be seen by one type of provider who just focuses on their acne or their hair growth, and then shuttled over to their other provider regarding irregular periods. And then they don't get that unified diagnosis. So I think that's why a lot of them get sort of worried and turn to anybody and anyone, and Google, to try to get more information.

**DARRYL CHUTKA:** So the reading that I did on this-- and since my practice is primarily men, I don't see this. But so many have not been diagnosed. Is it because they don't come in for an evaluation or because health care providers miss it, or maybe a combination?

**ALICE CHANG:** I think it's a combination. And I think that's part of why I'm here to kind of clarify that it is not a one test diagnosis. And that's one of the myths of this condition is that patients, and providers even, think that they need an ultrasound to make this diagnosis. And they think it's about these ovarian cysts.

And I think that's part of the misunderstanding-- is it really is multiple follicles that they see on the ultrasound. And that's the criteria. So if you don't ovulate, you collect these immature follicles that are perfectly healthy and just waiting for the trigger. So that's one thing is demystifying the idea that there's something wrong with the ovary, and that you're going to get these painful cysts that will burst because that's not the condition.

So then the criteria is something that I think providers have a hard time with because, for example, a woman might be on birth control pills. So the criteria for androgen excess it's either/or. It's significant symptoms. And so if you want to get technical, you can use the Ferriman-Gallwey score. But significant hair growth in the body is one thing. And then if a woman's treating the hair growth, then you don't see it.

And I think that's another part of the problem. But I usually go through with women, and I can tell exactly where the terminal hair follicles are because you can actually feel them. So they'll say, oh, it's across the face, on the jaw line, down the chin-- those are kind of ways to sort of clarify how much they're affected because their testosterone levels don't have to be elevated. And then for example, if they're treating their irregular periods with birth control pills, then when they do the blood testing, the testosterone levels will be normal because they're being treated.

So then I can see how it would be confusing for a provider, well, do they have the criteria or not? And then when they don't really know and convey that to the patient, then the patient gets frustrated too because they really want to know, do I have this or not? It sounds scary. And so part of, really, a visit with a patient with PCOS is clarifying where they fit in the scheme and how you're going to treat it anyway, because the symptoms can be treated regardless of whether they have PCOS or not.

**DARRYL** And it sounds like some of the symptoms that these young women will experience are those that many get  
**CHUTKA:** already-- some acne, irregular menses. And I suspect they feel, well, maybe that's just normal for me.

**ALICE CHANG:** Right, or they enjoy it. They don't want to have a period.

**DARRYL** Yeah, yeah.

**CHUTKA:**

**ALICE CHANG:** So they don't really present. I think that's maybe clarifying at this point the classic PCOS diagnosis. So when NIH did their studies or created a diagnosis that everyone could use for this-- research studies about insulin resistance. It's really irregular periods less than nine periods per year. So that gives you a hard number to ask patients.

And then the second criteria was, again, the excess androgen symptoms-- either clinically significant symptoms with normal testosterone. And then the other could be that you actually detected it in the blood, but they don't have any symptoms. So that's the second criteria. And they only use those two back in those days.

So I clarify that the severe PCOS, you have both of those criteria. So I think that's helpful in talking to patients because if they don't have those criteria, they realize they could be more mildly affected. So I think that's helpful for most patients to kind of grasp on to. I also don't recommend pulling patients off of treatment just to make the diagnosis.

I think it's just important to kind of reflect as they go through childbearing, they'll go off oral contraceptives. They might become more symptomatic. And then they might know that they have more of this kind of real PCOS that's severe and has been there since they were adolescents.

**DARRYL CHUTKA:** Well, I was surprised when I did my reading that not all women with PCOS have ovarian cysts. So if you're doing an ultrasound to make a diagnosis, you're going to miss some patients.

**ALICE CHANG:** Right. Well, so that's again-- the criteria actually adds more. So if you go by the prevalence estimates that you gave, that was the classic NIH criteria. But now that they expanded the two out of three, so you add in the ultrasound, you probably are going to catch more women who are less symptomatic, actually, rather than the other way around, erring on the side of missing.

But I guess that's true. If someone thought that they should only get the ultrasound and didn't try to characterize the other two, you're right. They would miss the diagnosis.

**DARRYL CHUTKA:** So what's actually happening hormonal wise? Is this a ovarian hormone problem? Is it a gonadotropin problem? What's actually going on pathophysiologically in these patients?

**ALICE CHANG:** That's a great question. So this is the other challenge, is that this is a very heterogeneous disorder. And I think there is no one cause for any-- for the whole group of living with PCOS. So then it gets into what are the causes for that individual or for certain subgroups of this population. That's the challenge.

So I think you point out an excellent discussion, is really what's the cause? And that's a common question. There's probably multiple different causes. So the way I try to explain it to patients-- because they're all familiar with somebody who has high blood pressure. So I say, there's probably many genetic and environmental reasons why someone might be prone to high blood pressure. But we treat it the same way.

So this group of patients have androgen excess. They have androgens that are interfering, probably, with their ovulation. And then there is this other thing-- that insulin resistance. It's not part of the criteria, so we haven't brought it up yet. But that's clearly a major part of the pathophysiology.

So it might be that for one woman, the high insulin levels are driving the theca cell production of androgens. So that's been seen sort of in cell culture models. So that's possible. So lowering insulin levels does seem to improve, to some degree, androgen excess-- but not to the same degree as ovarian suppression with birth control pills. So it's part of the pathophysiology, the complications that we'll talk about next. But I think for women, I try to point out, it's like a chicken and the egg problem.

**DARRYL CHUTKA:** Yeah

**ALICE CHANG:** So when they do studies, if you lower the androgens, you improve insulin sensitivity. But also, if you improve insulin sensitivity or lower insulin concentrations, you also see an improvement in the androgen excess. And they're more likely to ovulate. So that's where, you know, the cause, it's not one specific thing, but kind of knowing what the major factors are and trying for each individual to see which one is more important in their care. And their pathophysiology is important.

**DARRYL** Well, this is a very technical situation. You've got hormonal changes. You have anatomic changes. How do you  
**CHUTKA:** explain to patients what's going on in words that they really understand?

**ALICE CHANG:** I think just breaking it down to the ovary. First of all, is I realize some women were asking me, well, what if I just take the ovaries out? Won't I be better off? And it doesn't change the fact that they might have insulin resistance as the primary cause and might still have an effect in terms of their medical comorbidities. So trying to discuss the pathophysiology, I explain the major characters or features are the androgen excess, the fact that that can impact how they ovulate and whether they ovulate.

And then, you know, some women might have normal periods. Some women ovulate with PCOS. So you really can't say for sure. You have to sort of look at the individual case and try to highlight those two major things, I think. And then determine what their symptoms are and what's important to them.

Some women are trying to conceive, so that's their major priority. They don't care about the androgen excess symptoms. Other women are focused on the cosmetic, and sort of how that affects their mood and their sense of self. So I think there's a lot of differences. And I know it can be confusing. We're talking about a lot of different things. But just focus on the individual patient and what their symptoms are, and what it means to them.

**DARRYL** Because it can be different from one patient to the next.  
**CHUTKA:**

**ALICE CHANG:** Exactly, yes.

**DARRYL** So is this a random health condition or is there a genetic component to it?  
**CHUTKA:**

**ALICE CHANG:** Well, there is certainly a genetic component in the sense that it can run in families. And there was even an interesting study looking in the men in the family, that they might have the insulin resistance and metabolic syndrome features. So there's probably a genetic component to it. I also look at drivers for risk factors.

So in terms of diabetes risk, with the insulin resistance, you see a lot more pre-diabetes. And especially it's the impaired glucose tolerance. So I often encourage patients to get an oral glucose tolerance test at baseline, just so they know if they have pre-diabetes. But the rates are-- and when you look at the population or the whole group, it's only about 7% or 8% develop diabetes. It's just that in young women, it's so rare.

**DARRYL** Right.  
**CHUTKA:**

**ALICE CHANG:** But I talked to them about ethnicity and family history of diabetes as being a lot more important in their risk factor assessment than actually PCOS itself. So if you have a family history of diabetes, I think that's a lot more concerning or something that we talk about prevention of diabetes with metformin in those cases. In terms of the ethnicity, I think that's a large driver, especially if you have a Native American ancestry or Hispanic. I think that's a lot more important, again, than being diagnosed with PCOS.

**DARRYL** Well, let's talk about some of the potential complications. You mentioned insulin resistance and diabetes. Is that  
**CHUTKA:** slightly more common in those who already have risk factors for diabetes-- overweight and family history?

**ALICE CHANG:** Exactly, but it is actually even above and beyond obesity. So you raise a good point. There's a lot of obesity in PCOS-- overweight and obesity. And that's often a factor that can confound, whether or not these risks are above and beyond the obesity. But there are thin women with PCOS who have insulin resistance and pre-diabetes.

So they can also respond to metformin in terms of ovulating more frequently. In several cases that I've seen recently, that is the case. So it should always be considered. And I think that's part of the myth, is some patients say they're frustrated because they would like to try metformin, and their provider thinks that they need to have diabetes or pre-diabetes. But they don't have to have those abnormalities. Plenty of studies have shown they respond even if they don't.

**DARRYL** Another potential complication is cardiovascular disease. What's the mechanism there?

**CHUTKA:**

**ALICE CHANG:** So it's interesting because I've seen the shift in my career from saying, there's this several fold risk in developing cardiovascular events, and then stepping back and looking at those studies, they really didn't prospectively follow, like we don't have a prospective population being followed. So there's definitely multiple studies that show increase in risk factors. That's hypertension, the cholesterol, metabolic syndrome, diabetes, pre-diabetes.

However, we don't really see the events. I think that's even a more interesting question, is like why don't we see more heart disease in women with PCOS? So I know it's kind of challenging, the conventional wisdom. But I think there might be something protective, in a way, about having these higher androgen levels and estrogen levels.

But in any case, what I tell patients is that what the data show is there's no increase in events unless you develop diabetes. I know I'm an endocrinologist, but that's clearly an important target, that if they can prevent diabetes, that they won't see necessarily that they're destined to have a cardiovascular event and stroke.

**DARRYL** Obstructive sleep apnea has also been reported. Is that purely due to the increased weight of some of these patients?

**CHUTKA:**

**ALICE CHANG:** From what I can tell, I think that most of the samples that see the sleep apnea, it is from overweight and obesity. But I think it's important to screen because I think we look at young women and we think, well, they can't have sleep apnea. And the studies have shown that if they use CPAP, they can improve their insulin sensitivity as well.

**DARRYL** Do we need to be alert for mood disorders?

**CHUTKA:**

**ALICE CHANG:** So patients often ask me that question. I also get referrals from psychiatrists because they're wondering if that maybe treating their hormone imbalance and kind of stabilizing their androgen levels will help to improve their mood disorder. So I think that it's kind of interrelated with the fact that there is this self-image. And if androgen excess or if you're having fertility issues, that it increases their risk for having depression and anxiety. So it's good to pay attention to it, and then even offer treatment to see if controlling the androgens will help. So that's important to consider.

**DARRYL** And finally, endometrial cancer-- I assume that's related to the hormonal imbalance?

**CHUTKA:**

**ALICE CHANG:** Right. So I think the data is basically for a meta analysis looking at case control studies. And so that it would support the possibility of a two-fold, two to three-fold greater risk. But where I try to sort of temper that in discussing with patients is that it's not clear if all women with PCOS have that increased risk. Or it might be the ones who don't have a period for many months and then the lining can be thickened and over grow, and tend to hyperplasia.

So as long as they're aware that they need to have a period every three months, or need to have some strategy to prevent the excess development of the lining, then I don't think that they necessarily have an increased risk. So I'm a little bit skeptical of the data and just want the patients to understand that as long as they control the disease or control the condition, that they are not destined again to have cancer.

**DARRYL CHUTKA:** All right, let's talk about treatment. This is a very diverse disease. And I suspect the treatment varies depending on the symptoms of the patient. But in general, what's the treatment?

**ALICE CHANG:** So then it always turns back to the patient. I say, what are your goals? What are your symptoms and what are your goals? And I think that's important for providers to realize because sometimes patients feel like they got the message that if they don't take a treatment, if they don't take birth control pills, even if they're not symptomatic, that they're going to somehow make their disease worse or that things will progress.

But we have to realize that many women don't want to be on birth control pills. So I think it's not an automatic treatment. It's the best treatment if you have androgen excess symptoms. So it will slow down hair growth. That's the other thing that's important, is setting expectations.

So the patients don't think that I take the treatment and all the hair is just going to fall off my body. It's that hair is slower. It's thinner. And that's enough for them. It's often enough for them to feel like things aren't getting worse or getting better. And it's controllable.

So birth control pills for androgen excess is first line. If you can't take birth control pills, spironolactone is actually an excellent drug, especially for acne. And it may help to slow down-- it certainly helps slow down hair growth. And androgen levels will fall with it as well. So that's considered second line.

The only downside is that you need to have another strategy because it can promote irregular bleeding of the lining if you don't have birth control pills or something like a Mirena IUD is ideal with a combination of spironolactone. So that's a good option. Androgenetic hair loss is very challenging for patients because it may not respond to either of those treatments as well. So I've been using an off label finasteride sometimes in those cases because certainly there was the indication for men, for male pattern hair loss.

So I think some women, if they don't respond to spironolactone-- I should also mention that the dosings for spironolactone, I see a lot of patients come in and they're only on 25 milligrams of spironolactone. But guidelines would actually suggest you go right to 100 milligrams at the start. You check a potassium in a couple of weeks, just to make sure. And very rarely do I see that their potassium is affected.

And then I tell them in three months, let me know if your symptoms are not optimally controlled because we can then just go right up to 200. So I think that's the one other kind of pearl I would convey is that you can be a little more aggressive in the treatment, and that they will respond very well. So that's androgen excess.

Then if a patient says that they just really don't like the irregularity they're bleeding or they're not having a period every three months, then we talk about a couple of different strategies. So birth control pills, again, would be ideal. And it certainly can be used for contraception.

But then for the patients I was telling you about that don't want to be on birth control pills, strategy of Prometrium-- 100 milligrams for 10 days every three months is enough to just make sure the lining doesn't over grow. So that's the woman who really doesn't have any androgen excess symptoms, maybe their testosterone levels were elevated. But they would just like a strategy to prevent complications.

**DARRYL CHUTKA:** Sure. What about the woman whose treatment goal is fertility and wants a successful pregnancy?

**ALICE CHANG:** Right. So then I vary it depending on their age and kind of discuss the data with them. For some women, if they're obese and they know about lifestyle strategies being important, but I often encourage them to try metformin, especially if they're under the age of 30 because if they ovulate more frequently, that would be a better strategy in the long run, might also help them with their weight loss goals and the prevention of diabetes that we talked about. So that's one option.

If they're over the age of 30 or pushing 35 especially, then I talk to them about the data that really show head to head, clomiphene or Clomid does better than metformin. And then now the aromatase inhibitors letrozole are being encouraged because they did better than clomiphene in trials. So the data would support that they should really go directly to a reproductive endocrinologist for those strategies.

But I like the idea, if you have some time or the ability to even discuss with patient and preplan. So when you go off your oral contraceptives, this is another thing to kind of time is that they don't realize that in the first three to six months, they're more likely to ovulate because the androgens haven't started to rise yet. So I talk to them about really getting ready to go instead of waiting a year. And then the second thing would be you could start the metformin before they stop the birth control pills.

So those are the kind of things that we as providers in internal medicine or family primary care providers could offer. But then just realizing that the better strategies for someone who's really approaching their middle 30s would be to really go right to reproductive endocrinology. And they should know, though, that they're more likely to have better outcomes than someone without PCOS because they have those multiple follicles just waiting for the trigger. It's just that they have a higher risk for multiple pregnancy. And they can have hyperstimulation syndrome as well. So that's important for them to realize.

**DARRYL CHUTKA:** So what happens at menopause?

**ALICE CHANG:** Great question. I get that a lot too because technically you only have PCOS before menopause. But what I discuss with them, is it's possible-- first of all, they'll actually get a relief from their androgen excess symptoms. That's probably more likely to happen because the ovary was producing 80% of their androgens before menopause.

And that will change. So that should improve. The second thing, though, is understanding the genetics, that if you have insulin resistance, especially if it's strong in the family, that that's not necessarily going to go away just because the androgens are now normal.

**DARRYL CHUTKA:** Well, you've covered a lot of ground. Let's finish up by asking you to summarize what you think are the most important points our listeners should know about polycystic ovary syndrome.

**ALICE CHANG:** I think if they focus on first of all knowing the criteria, that androgen excess evidence of not ovulating regularly. So instead of less than nine periods per year, it could be more frequent periods. You can check a day 21 progesterone to see if they're ovulating. So there's a lot of little subtle tricks to try to figure that out.

And then the third thing is that you don't really need an ultrasound to make the diagnosis, kind of focusing on the other criteria. So knowing about those criteria are important. And then knowing when you don't necessarily need to just make that diagnosis and focus in on the symptoms-- a lot of patients are happy to know where they fall in sort of the higher severe category, maybe mild, maybe you don't even have this. And they like to know that. So I think just telling them upfront and being honest about it is important.

I think also emphasizing sometimes patients are told, you just need to lose weight. But they don't really focus in on all those strategies we discussed. You want to find out what is of greatest concern to the patient. And then focus in on different treatment strategies. And then feel comfortable to refer.

Now, I think this is the other part that I find a lot of patients are frustrated with, is that I know even among my colleagues who are focused more on thyroid or diabetes, for example, that they might get referred to an endocrinologist who doesn't necessarily have the answers or all the discussion that we just talked about. I can say that there's a great reference for patients now-- if you Google PCOS Monash, M-O-N-A-S-H.

They did a comprehensive review, included patients in their guidelines. And they have a lot of tools for patients to read up more and kind of understand the condition. So I think that's a nice thing to offer now. Also be flexible. Be flexible about understanding what their concerns are and trying to offer advice and some reassurance, more than anything else.

And then finally, there's a lot of what I call metformin resistance in the community. I think you should be open to trying it. It's a good drug. It's been around for a long time. And it's safe. So I think for patients who would like to try that, either because they're trying to ovulate more frequently or as a strategy to make their periods more regular, that's another thing. And then again, for the prevention of diabetes, it certainly can be used off label for that without PCOS. So that's why it's not specific to PCOS. But it's a great indication as well.

**DARRYL CHUTKA:** We've been discussing the diagnosis, potential complications, and management of polycystic ovary syndrome with Dr. Alice Chang from the division of endocrinology at the Mayo Clinic. Alice, thank you so much for sharing your knowledge with us. I've learned a lot.

**ALICE CHANG:** Thank you.

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