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Q&A: Challenges in the Assessment and Diagnosis of Polycystic Ovary Syndrome

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Guests: Dr. Richard Auchus, University of Michigan; Dr. Joely Straseski, University of Utah; and Dr. Alison Woodworth, University of Kentucky.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Polycystic ovary syndrome is a complex endocrine-mediated disorder in women with an estimated prevalence of about 10%. Women with PCOS typically present with heterogeneous clinical signs and symptoms such as excess hair growth, irregular menstrual cycles, infertility and metabolic issues.

Currently, there are no universal criteria for diagnosis of this condition and as a result, women with the disorder often reports significant delays in diagnosis and poor follow-up care.

A Q&A feature in the March 2019 issue of *Clinical Chemistry* asked five experts with different roles in this field to discuss recent advances and ongoing challenges surrounding the current diagnostic criteria, available biomarkers, and the timely diagnosis and management of women with polycystic ovary syndrome.

We're pleased to have several of these experts on this podcast, and our first guest is Dr. Richard Auchus, who is the James A. Shayman and Andrea S. Kevrick Professor of Translational Medicine in the Department of Internal Medicine and Pharmacology and Division of Metabolism, Endocrinology, and Diabetes at the University of Michigan in Ann Arbor.

So, Dr. Auchus, polycystic ovary syndrome is very often a diagnosis of exclusion which can take a considerable amount of time. Now, in your opinion, what's the most effective way to work up a patient you suspect may have this condition?

Dr. Auchus: Right. So, in the NIH Consensus Conference from 1990, there were two criteria for polycystic ovary syndrome: hyperandrogenism, not hyperandrogenemia, but hyperandrogenism, meaning clinical features of androgen excess in a woman, such as facial hair that's in a distribution

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that is typical of the male pattern. So, on the upper lip, on the chin, on the sides of the face, or acne, which again, acne is fairly common in teenagers, so, this is a minimal criteria.

And then, the second thing is a reduced or irregular number of menstrual periods, typically, people say six or fewer a year. So, from that definition, there's absolutely no laboratory testing that's required because it is just two clinical features that are received by the history in physical exam. But the reason we call it a diagnosis of exclusion is that, there are some secondary causes of polycystic ovary syndrome. So, there are some other diseases that cause those same two manifestations. The main ones are non-classic congenital adrenal hyperplasia or non-classic mainly 21-hydroxylase deficiency.

And when we say non-classic, the classic form of those diseases has androgen excess and adrenal insufficiency. The non-classic form, it's just the androgen excess and no adrenal insufficiency. So, that has to be excluded, Cushing's syndrome has to be excluded, and Cushing's syndrome is a neoplastic form of cortisol excess. And when cortisol is made in excess, many times, androgens coming from the adrenal gland are also made in excess.

And then, the third condition is hyperprolactinemia. Prolactin-producing tumors are the most common type of pituitary tumor in women. So, those are the three things that can lead to the same clinical manifestations.

So, the most efficient way we tell people, we always start with history in the physical exam. And so, in the history, you want to find out if the androgen excess started at puberty or if it started before puberty. If it started before puberty, then you have to think about non-classic 21-hydroxylase deficiency because that's something people are born with. You may have heard the term late-onset congenital adrenal hyperplasia as another term for non-classic. We don't like to use that term because late-onset implies that they didn't have it from birth. Well, they did have it from birth. It's just that the clinical manifestations did not appear or nobody recognized them, let's put it that way, nobody recognized them until later.

Now, if they have a history of easy bruising, muscle weakness, osteoporosis, or certain manifestations such as facial plethora, disproportionate fat redistribution around the head and neck compared to the arms and legs, then you would consider Cushing's syndrome. We don't screen everybody for Cushing's syndrome. And then, hyperprolactinemia, that's something we should screen for as well. So, the initial test, we usually would get a

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prolactin, we would get a 17-hydroxyprogesterone, preferably in the morning and in the follicular phase of the menstrual cycle.

And then, if we were concerned about Cushing's syndrome, we would do one of several screening tests for that such as some late-night saliva cortisol collections or an overnight dexamethasone suppression test, most commonly. And that's really about it. And once those are excluded, then by definition, that's what the patient has.

I think what can happen with women is that, they come in just saying, "Well, I have facial hair or I have acne." And they seek treatment for that. And so, they're given treatment for that, like antibiotics or creams or laser therapy or something like that, and the physician is not looking at the big picture, "Is there some underlying unifying diagnosis that is causing this and what else is happening to the patient as well?"

Bob Barrett: And what are some comorbidities you consider when evaluating or treating a patient for polycystic ovary syndrome?

Dr. Auchus: Well, certainly, if they have one of these secondary causes of polycystic ovary syndrome, then there are comorbidities associated with those conditions. So, prolactin-producing tumors can cause galactorrhea, which is milk production from the breast, I should've mentioned that before. It's something one should always ask. But that is only usually seen when people have quite severe hyperprolactinemia. So, the majority of people with high prolactin do not have the galactorrhea.

The Cushing's syndrome can cause a lot of problems with blood clots and bone loss and all sorts of hypertension and diabetes and things like that. So, that's why it's very important when someone comes with menstrual irregularities to ask about the possibility that this is secondary to one of these severe endocrine disorders.

Now, polycystic ovary syndrome itself, the fact that one has androgen excess is unpleasant, that in and of itself is more of a cosmetic issue and that's often dealt with through dermatologists or over-the-counter treatments. And then, sometimes, endocrinologists and gyncologists get involved with those treatments.

The irregular periods can be significant for not only infertility, but if women do not have four to six menses a year, if they have fewer than that, then that puts them at risk of having endometrial hyperplasia in the uterus which is a premalignant lesion that can progress to endometrial

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cancer. So, the irregular menses is not benign or trivial in and of itself because it has those issues associated with it.

Now, it turns out that many women with polycystic ovary syndrome have what we call insulin resistance, and that is that their body doesn't respond as well to a certain amount of insulin as is average in the population. And that is a precursor for developing diabetes.

So, one of the main things that we worry about in women with polycystic ovary syndrome is the progression to diabetes. There are some things one can pick up on physical exam such as acanthosis nigricans. It looks like they have dirty skin around their neck or in their underarms and it's sort of a velvety black area of the skin. And if they have that, that's suggestive of insulin resistance and correlates pretty clearly.

Obesity in itself causes insulin resistance and women with PCOS are often obese, not always, but often are obese and they tend to be more insulin resistant than the non-PCOS women of the same body mass index. And they can have problems with high triglycerides or lipid panel that puts them at risk for cardiovascular disease.

Now, it is controversial though, whether they actually do have an increased risk of cardiovascular disease, because they do feature many of the adverse risk factors. So, being overweight, being hypertensive, although hypertension itself is not necessarily part of the PCOS, it's not required, and the dyslipidemia and the insulin resistance and then it can progress to glucose intolerance.

So, all of those things put people at risk for cardiovascular disease. It's not clear that the woman that meets criteria for polycystic ovary syndrome has any more cardiovascular risk than the woman that does not. So, in a sense, what we do with polycystic ovary syndrome, we deal with those aspects that are important to the patient. So, if the patient is bothered by the unwanted facial hair, we treat that. If they do have irregular menses or infertility, we have to treat that.

But then, the cardiovascular risk, we treat like someone who doesn't have polycystic ovary syndrome. We deal with those cardiovascular risk factors. To some extent, metformin, which is the first-line agent of treating type 2 diabetes, to some extent, it treats all of those things particularly when people have what I would call a mild form of polycystic ovary syndrome. Their androgens are not that high, their menses are irregular but they have sort of just the borderline number to meet criteria. Often times, you

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can treat everything just with metformin, but sometimes not.

And I should've pointed out actually earlier that in terms of the laboratory evaluation, we usually, in women with any form of androgen excess, get a serum testosterone measurement, because there is actually a fourth thing that can cause polycystic ovary syndrome which is tumors that make androgens. Those are quite rare and usually, you have a history that it's a very recent onset and quite severe. And usually, the testosterone in those women is very high.

So, if we see a very high testosterone it sort of moves the diagnosis in another direction, but again, usually from the history, you get this history that there's severe androgen and excess of sudden onset, and then we have to worry about adrenal cancers or ovarian tumors that make these things.

So, again, the comorbidities are those features related to diabetes in the metabolic syndrome that come along with it. But the fact that you have polycystic ovary syndrome may not add anything to those risks above just having those metabolic syndrome properties without the polycystic ovary syndrome.

Bob Barrett: Thanks so much, Dr. Auchus. And we're now joined by Dr. Joely Straseski. She's an associate professor in the Department of Pathology at the University of Utah, and the Medical Director of endocrine testing at ARUP Laboratories in Salt Lake City.

Doctor, I'm amazed at the complexity of the diagnostic workup for women with suspected polycystic ovary syndrome. Are there any new diagnostic tools or strategies on the horizon to improve the diagnosis of this disease?

Dr. Straseski: So, it's a great question because, of course, the diagnosis is so complex. Having better biomarkers would be extremely useful. And, of course, the holy grail is having one single diagnostic test that tells you a patient does or does not have PCOS, but obviously, we're not there yet. The measurement of testosterone can help define hyperandrogenism in these patients, but beyond that, there really aren't very many biomarkers in the arsenal.

So, AMH ,or Anti-Mullerian Hormone, is talked about quite a bit in this particular area, and that's because of its possible use as a surrogate marker of polycystic morphology. However, AMH use isn't currently recommended in any of the guidelines for PCOS diagnosis. One of the main reasons is the lack of a reference material for AMH, so different assays just aren't standardized at this point.

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There are also considerable differences in AMH concentrations as women age and there's also overlap in AMH concentrations from women with and without PCOS. So, all of this makes determining an AMH cutoff that actually defines PCOS very difficult.

So, larger studies in diverse populations are obviously what are needed, but if those issues can be overcome, AMH could one day be a very useful biomarker of this disease. There have also been recent studies using proteomic profiling to identify proteins that are either up regulated or down regulated in women that do have PCOS. And microRNAs that are associated with insulin, testosterone, and cell cycling have all been identified in women with PCOS.

These types of studies may eventually reveal new biomarkers of this disease that will support its biochemical diagnosis.

Bob Barrett: Okay. Thank you, Dr. Straseski. We're also joined by Dr. Alison Woodworth. She's Associate Professor of Pathology in Laboratory Medicine at the University of Kentucky Medical Center and also serves as Medical Director of the Core Clinical Laboratory and Point of Care Testing. Dr. Woodworth, what's your take on new markers for this condition?

Dr. Woodworth: The diagnosis of PCOS is really complex as you mentioned. Mostly because it isn't really one disease, it's a group of disorders with overlapping clinical signs and symptoms. And one strategy that was recommended by the NIH is to separate the different clinical syndromes of PCOS in order to more accurately characterize the disease into sort of subsets, if you will, in order to better identify diagnostic strategies that can more accurately identify our patients.

And so, segregating these patients with suspected PCOS into clinical subsets actually will allow better interpretation of the diagnostic workup of the test as well. However, I think that the real key to a quicker and more accurate diagnosis with our current available tools involves a team approach. The Institute of Medicine Committee on Diagnostic Error and Healthcare concluded that the proper diagnosis of many disorders actually requires a team of clinical experts across specialties.

This is often been referred to as a diagnostic management team, a team that might be composed of experts in endocrinology, obstetrics and gynecology, radiology, and clinical pathology could work together to synthesize the results to the clinical, radiological, and laboratory tests.

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And they could work together to provide specific interpretations for our patients with suspected PCOS. Not only could this type of team provide patient-specific reports, but it could also work together to develop evidence-based diagnostic algorithms that are specific for these clinical subsyndromes that I described earlier for PCOS.

So, I really think in general, a PCOS diagnostic management team would add significant value to our healthcare process and it would improve patient care by improving diagnostic efficiency, diagnostic accuracy, and a likely overall patient outcome.

Bob Barrett: That was Dr. Alison Woodworth from the University of Kentucky. She was joined by Dr. Joely Straseski from the University of Utah and Dr. Richard Auchus from the University of Michigan. They are three of the experts that participated in the Q&A feature in the March 2019 issue of *Clinical Chemistry* on polycystic ovary syndrome and they have been our guests in this podcast. I'm Bob Barrett. Thanks for listening!

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