

**KARA S.**

**HUGHNAH:**

Thank you for the warm introduction and to the organizing committee for inviting me today to talk on the nuts and bolts of polycystic ovaries or polycystic ovarian syndrome, future referred as PCOS. So my outlined objectives today are to identify the diagnostic criteria of polycystic ovary syndrome; identify the risk factors that place these young women at high risk for cardiometabolic disturbances; to help you select the best diagnostic test to document the anovulatory bleeding in females with clinical findings suggesting PCOS; highlight the key investigations of both reproductive and cardiometabolic features of PCOS; and finally, to discuss the management of menstrual, cutaneous, and metabolic abnormalities and PCOS.

As some of you may be aware, polycystic ovary syndrome is the most common endocrine disorder among women of reproductive age. The latest data is estimating now an update of 6 to 15% of adult women being impacted. And this is also growing and being recognized in our adolescent population as well. PCOS is characterized for by oligomenorrhea or irregular menstrual cycles and hyperandrogenism or clinical or biochemical manifestations of elevated male like hormones or androgens.

There are three criteria that exist for PCOS that I've outlined here. The NIH criteria, Rotterdam, as well as the Androgen Access Society. You'll notice a few differences, but they all include clinical or biochemical signs of hyperandrogenism that I will review menstrual irregularity that may or may not include anovulation, and typically excluding other conditions that may mimic PCOS. And a few of the definitions also includes evidence of polycystic ovaries on ultrasound imaging.

PCOS is associated strongly with problems of obesity as well as other cardiometabolic features including glucose dysregulation, dyslipidemia, hypertension, obstructive sleep apnea, and cardiac dysfunction. Hyperinsulinemia, or insulin resistance, with or without obesity is an integral component of PCOS. And this heightens the risk for type 2 diabetes in this population.

There's a lot of debate in the PCOS field right now about whether or not cardiovascular disease is indeed increased in this population and is a strong area of research focus. So the origins of PCOS are thought to stem from a two hit hypothesis. The first being genetic or epigenetic factors that reset the reproductive clock and metabolic trajectories in utero or early in life. While there are later factors that influence the severity of the adult PCOS phenotype including over nutrition or under nutrition, ethnic differences as well as some environmental influences.

So the first hit genetic or epigenetic factors are linked to heritability in that twin studies have shown strong genetic contribution to PCOS. There are several individual gene mutations that are implicated in PCOS that are thought to contribute a moderate effect. And we know that there is an increased prevalence of PCOS in mothers as well as sisters of pro-PCOS probands.

So I've outlined here a few different ethnic populations and the noted prevalence in the medical literature, but I also want to highlight that South Asian as well as Caribbean Hispanic women with PCOS have more insulin resistance than women in other ethnic populations. And this may play into differences in their clinical phenotype and presentation. We know that lifestyle greatly impacts the progression and onset of PCOS in that we know that obesity can unmask or amplify symptoms of both hyperinsulinemia as well as hyperandrogenism.

So you'll see on the top that there is a hormonal abnormality in that there is an increase in luteinizing hormone in comparison to follicle stimulating hormone levels. This drives an increase in ovarian and adrenal androgen enzyme activity that then goes on to lead to increases in both ovarian and adrenal androgen production, as well as a decrease in follicle maturation within the ovary leading to anovulation.

Additionally, the hyperinsulinemia that is fairly consistent in polycystic ovary syndrome drives down the binding protein for testosterone called Sex Hormone Binding Globulin or SHBG, making available more free testosterone to act on skin and hair tissues that drive the signs of androgen excess. This is another overview or way of looking at the pathogenesis of PCOS and are included in your slides.

I'm not going to spend much time but there have been several environmental factors including a widely used industrial plastic that have been associated with PCOS. And I leave this year in your packet, but not going to dwell on that. So coming back to the characteristics of polycystic ovary syndrome.

It's generally thought are kind of divided into two classifications or two sections-- the endocrine disturbances as well as the metabolic disturbances. And I'm going to walk you through each of those. So for the endocrine disturbances, you'll see here-- oh, it's not showing. There we go. You'll see the development of either a decrease in menstrual cycle number or lack of menstrual cycles.

And so I'll oligomenorrhea is defined as menstrual cycle frequency of less than eight cycles per year. In addition, there is hyperandrogenism and this can be seen clinically as excess hair growth in a male like pattern, hair loss in a male like pattern, or acne. When we actually look at the ultrasonographic features of the ovaries, we see the presence of multiple follicles or cysts.

They are small in diameter. And they're peripherally arranged, as you see in both images here, along the edges of the ovary resembling a string of pearls appearance. However, you can also see an increase in ovarian volume. However, you must remember, if you're imaging a female that's on an oral contraceptive, that is going to impact the PCOS morphology on imaging and so these don't necessarily apply.

When we think about hirsutism, or unwanted hair growth in a male like pattern, there's a common classification system that can be used to assess the severity of their hirsutism. It varies on a degree from one to four in each of the individual areas that I've outlined. So this is something that you want to examine in your patients in clinic to see where their pattern is and the severity of their hair growth.

And so if you add up each of the different individual areas, hirsutism is classically defined as having a score greater than or equal to six to eight. And this can be helpful in monitoring them while on therapy. So how might we approach a female who presents with any of the symptoms of PCOS-- irregular periods, unwanted hair growth, excessive acne, troubles with fertility?

Well, we can look at the middle column when we're thinking about polycystic ovarian syndrome and consider measurement of a total in free testosterone, especially when one we're seeing hirsutism or significant acne. But we also need to rule out other conditions that may mimic PCOS. Two conditions that we commonly see in the endocrine field include hypothyroidism as well as hyperprolactinemia, and most commonly, they will present with irregular periods, but not necessarily acne or hirsutism.

And so consideration of a measurement of TSH, or prolactin, may be helpful. If a woman or adolescent presents with a history of primary amenorrhea, never having had a menstrual cycle, whether or not-- or especially, if there's significant clinical hyperandrogenism, then you want to assess their pituitary gonadotropins, luteinizing hormone, and follicle stimulating hormone. Because these would be elevated if there was a case of ovarian failure due to the feedback loop.

If these however are normal and some other labs have already been drawn and are normal for thyroid and prolactin as well as androgens, you may next consider a pelvic ultrasound to define the internal anatomy as well as assessed for any structural abnormalities blocking the flow of blood that occurs with a menstrual cycle. So typically ovarian size will be measured, uterine length to determine is it a uterus that has been exposed to estrogens and is of adult size, as well as presence of or absence of multiple follicles, and then again, an assessment of the thickness of the endometrium as a measure of estrogen exposure.

Additionally, there are several other conditions that may mimic polycystic ovary syndrome. If on physical examination, there are signs of masculinization, acne along with enlargement of the clitoris, you may be thinking about the possibility of a virilizing or masculinizing tumor in the ovaries or the adrenal glands. This tends to present with a more rapid onset of hirsutism that may include irregular menstrual cycle development.

And so, again, you would already be measuring a testosterone level, but in the case that the testosterone levels are more than two times the upper limits of normal, this may heighten your thoughts that this patient could have a virilizing tumor. And so the next step would be to consider imaging of the adrenals or the ovaries to assess for a tumor. Cushing's syndrome can also present similarly.

And so then step to rule that out, especially if you see a central obesity within extremities or other symptoms like dark, wide striae with a buffalo hump and moon-shaped feces, you would want to request a 24 hour urine collection for measurement of cortisol in the urine. And if this is elevated, this may suggest Cushing's syndrome and would warrant further endocrine evaluation through an endocrinologist and further testing.

Finally, another fairly common endocrine condition that may present with irregular menses, especially if you hear or ask about a history in a young female about early pubic hair development during childhood and adolescence, you may be thinking about a condition called non-classical congenital adrenal hyperplasia where there is excess androgens coming from the adrenal glands. And so the test of choice to evaluate for this is something called a 17-Hydroxyprogesterone, and if this were to come back elevated, you would want to consider further endocrine evaluation for an ACTH stimulation test.

So if you've ruled out some of these other conditions that mimic PCOS, and you're left with an individual that may have ultrasound abnormalities that I mentioned or clinical exam findings or biochemical elevations in testosterone, there are a few other steps that you may want to take before you're making therapeutic recommendations. So, as I mentioned, you would have already done your physical exam and ordered some of the hormonal tests to assess whether or not the patient meets criteria for PCOS. And you've already ruled out other conditions.

The next step would be to consider evaluating the patient for anovulatory bleeding. And so, if we think about the typical menstrual cycle with menstrual bleeding occurring here at day 1, you would then expect with ovulation occurring that there would be a rise or a surge in LH followed by a subsequent rise in progesterone in order to support the release of that egg for potential fertilization. So if you follow out where we would expect that normal peak of progesterone occurring approximately three weeks after the last menstrual cycle--

It's helpful to measure around that time, a fasting morning progesterone level. And if it returns lower than 10 nanograms per [INAUDIBLE], ovulation has not likely occurred, and that is commonly seen in the condition polycystic ovary syndrome. We know that PCOS is also associated with the metabolic syndrome. And while there are various definitions or criteria that exist, they generally include a measurement of obesity like waist circumference and elevation in glucose, blood pressure, triglycerides, or low HDL.

And why this is important to be thinking about metabolic syndrome is the relation to other conditions that you may be needing to evaluate and treat them for either at the current time or in their future. We know that metabolic syndrome is up to four times more common in women with PCOS, and we also see this in our adolescent PCOS populations as well. And this is after adjusting for obesity.

So individuals that are at high risk for cardiometabolic abnormalities are those that meet metabolic syndrome criteria as well as those with type 2 diabetes, known cardiovascular disease, or kidney disease. But women with PCOS are also at risk if they have underlying obesity, if they have a history of smoking or dyslipidemia, high blood pressure, as well as a history of impairment in their fasting glucoses.

Therefore, the key risk factors to assess when you are following a female that you suspect or that you confirm has polycystic ovarian syndrome is the first, in the office, measure or calculate their body mass index-- are they overweight or not? What is their blood pressure? Can you obtain a baseline fasting lipid profile?

Fasting so that you have an assessment of triglycerides, non-fasting is-- I guess, if you obtained it non-fasting, your total LDL and HDL cholesterol is are not going to be impacted by having eaten. And this is something you definitely want to consider if there's also a family history of hyperlipidemia. Certainly if the patients have a BMI above 27, you also want to consider screening them for pre-diabetes or diabetes with a two hour oral glucose tolerance test.

Additionally, adolescents, as well as adult women with PCOS, are at higher risk for developing mood disturbances including anxiety and depression. And so recognizing these and screening for these are important as well as aberrant eating patterns and recognizing that all of these impact their quality of life and reduce their quality of life. So what are the long term treatment goals for patients with polycystic ovary syndrome?

Well first we want to consider the excess androgens by suppressing them both from production as well as their end-organ action as well as either promoting regular menstrual shedding of the endometrium in women that are not desiring pregnancy. And this is to decrease the risk of developing endometrial hyperplasia. Or promoting for fertility in ovulation in those women at that time that are desiring pregnancy.

So the long term treatment of women with PCOS can vary somewhat. But in those with metabolic syndrome, the first line of therapy should always be lifestyle modification including diet, exercise, and consideration of behavioral therapy. Several larger studies have been conducted that have demonstrated even with three to six months of formal exercise alone, that many of the metabolic factors are improved as well as improvement in menses, ovulation, and even pregnancy rates.

Add-on medication for women with PCOS and metabolic syndrome often includes metformin, or Glucophage, if there's mild to moderate obesity. It is not as effective with severe obesity. And this add-on therapy is helpful for impaired glucose tolerance, for improving signs of insulin resistance that may not be seen on exams such as skin tags and acanthosis nigricans, may help to improve hyperlipidemia, and may be helpful in those in which contraceptive therapy is contraindicated.

So how does metformin act in this condition? Well, it's thought to improve the effectiveness of one's own insulin production, and therefore, can be fairly beneficial for the treatment of the metabolic and glycemic abnormalities that your patients may be experiencing and can help to improve menstrual irregularities. However, you want to caution your patients, especially early in the start of metformin, that they could experience nausea, belly pain, or loose stools, but that this tends to improve after several weeks on therapy and to kind of stick through it.

But also for you and your patient to be aware in the setting of illness, surgery, or IV contrast, that they're at higher risk on metformin for developing lactic acidosis and taking necessary precautions in those situations by withdrawing therapy temporarily until the condition has improved or imaging is completed and contrast is washed out. However, metformin has limited benefit in treating hirsutism, may have some impact on acne, and the literature is still varied on its impact on infertility.

Several longer term studies have been conducted combining lifestyle with metformin showing improvements in androgen levels, but not showing improvements in ovulation rates. However, this was strongly related to the degree of weight loss. Shorter term studies involving exercise, diet, and metformin similarly showed reductions in testosterone, no improvements in ovulation rates but weight was decreased regardless.

So what about women with PCOS who may not have strong features of metabolic syndrome and more struggle with acne or unwanted hair? We like to recommend, and according to guidelines in our field, oral contraceptive therapy, both combined estrogen and progesterone, as the first line of treatment for these women. And at least a six month trial is recommended, especially if hirsutism is their biggest concern as you have to break or a sort of lower the testosterone levels to then allow existing hairs to die off, fall out to then really be impacting or minimizing new hair growth.

The effect of oral contraceptives can also be potentiated when combined with spironolactone, which is a peripheral androgen receptor blocker, and I provided some twice daily dosing guidelines here. But you have to remember to monitor and counsel your patients that with this medication there is a higher risk of hyperkalemia. As well as if they were to become pregnant, there's a risk of feminizing a male fetus and can also be associated with some degree of menstrual dysfunction.

So because of the latter two side effects, it is often recommended that the spironolactone be used in combination with an oral contraceptive pill. I know most of you are going to be familiar with the actions of oral contraceptives, but I bolded with progestin and estrogen how an oral contraceptive is helpful specifically with PCOS in terms of its suppression of luteinizing hormone. As well as estrogen's impact on increasing sex hormone binding globulin so that will kind of tie up more of the testosterone and make less free testosterone available or circulating in the bloodstream to act on skin and hair follicles.

As I'm sure you're all aware, there are some side effects if you are prescribing an oral contraceptive to your females that you want to guide them on. But I do want to point out that a recent Cochrane review has demonstrated that there is no association of weight gain with oral contraceptive pills. I think this is a common myth that many adolescents and adult women are concerned about. But I think you can put them at ease with the large amount of data that has been accumulated over the last several decades.

But keeping in mind that there are several absolute contraindications to prescribing oral contraceptive pills that I've outlined here. There are some other considerations that you might want to think about when prescribing an oral contraceptive pill to your female with PCOS. To date, the jury is still out there on whether oral contraceptives really have much impact on glucose metabolism.

But we do have pretty strong evidence that oral contraceptive pills do, in a beneficial way, help to increase good cholesterol, but also is associated would rise in triglycerides. And so, having a baseline fasting lipid profile in your patients may also help guide you on whether or not you may want to consider an OCP for their treatment. In addition, we know about the link between oral contraceptive use and risk for thromboembolism.

There is no conclusive data specifically in the PCOS population, but we do know in general users of OCP's that they do have a higher risk of venous thromboembolism. It tends to be estrogen dose dependent, and the risk decreases after one year of OCP use. Because progestin components of combined oral contraceptives are linked to have some androgen promoting potential in the early oral contraceptive generation pills, we tend to recommend prescribing oral contraceptives that fall in the third or fourth generation OCP's.

So these are OCP's that contain as they're progestin component desogestrel, norgestimate, drospirenone, or-- drospirenone, but with that knowing that there has been some emerging data over the last decade or so with the fourth generation OCP's reporting a higher risk of venous thromboembolism when compared with the more androgenic class progestins levonorgestrel.

So what about specific acne treatments in polycystic ovary syndrome? In general, OCP's are still the most widely effective treatment in addition to lifestyle management. There's been some studies on comparing OCP to placebo as well as OCPU to metformin that has demonstrated improvements in inflammatory as well as total acne with OCP. And that said, there has been a few studies that has actually shown improvements even when compared to metformin.

If hirsutism is a particular concern or problem for your patient, in addition to lifestyle, OCP, and consideration for spironolactone, patients may also want to consider other alternate therapies. There is a newer topical cream on the market over the last several years that can inhibit hair follicle growth by inhibiting that particular enzyme. And this therapy is generally applied twice a day for a therapy of eight weeks.

However, it is associated with some side effects that may not be very desirable including scarring as well as stinging, redness, and rash. There are also as you know temporary measures that can be taken, such as waxing or bleaching. And then some more permanent treatments, including laser therapy and electrolysis. These tend to be more expensive, but a bit more longer lasting, but are also associated with scarring or depigmentation.

So I'm going to end today just reminding you as you're evaluating and treating your women with PCOS that there are the underpinnings of greater metabolic abnormalities and mood co-morbidities and to not forget these in your evaluation and your treatment. I've highlighted here dyslipidemia and included some additional slides for the audience that I'm not going to go into today but are generally treated with lifestyle and statin therapy.

But because this population is specific to women, I do want to bring up that with statin therapy as a reminder that there is a risk of OCP use should the female become pregnant in that there is a growing body of data that demonstrates not only structural abnormalities to the CNS system of the unborn baby as well as cardiac and limb abnormalities, intrauterine growth restriction, as well as fetal demise with statin use. So again, something that you want to counsel women on in this reproductive age and to discontinue their statin should they discover that they are pregnant.

Additionally, I've some slides specific to hypertriglyceridemia-- the higher the triglycerides, the greater the risk for pancreatitis. In which that category, you really want to be limiting fat intake. Whereas, kind of mild to moderate triglyceride elevations, you want to consider counseling them on reducing simple sugar intake from beverages, sweets, and cereals.

So in close today, as PCOS management goals in your office, you want to provide to these women the expectations of the various therapies that are available, discuss the risks and benefits with each, as well as the potential side effects. See them back frequently every four to six months to reassess how are they doing with their lifestyle modification, how are their symptoms progressing and improving, assessing for side effects, and certainly advising them on further management decisions. And really for them, setting realistic goals and individualizing their therapy as they progress with you throughout their lifetime.