Endocrine Care in Prader-Willi Syndrome

Teens and Adults

2026 FPWR Family Conference • Dr. Diane Stafford, pediatric endocrinologist

This transcript was lightly edited for readability. Brackets mark unclear wording or an omission in the transcript.

Introduction

Kristen White, FPWR board member

Good afternoon everyone. Welcome to Endocrine Recommendations for Teens and Adults with Dr. Diane Stafford. I'm Kristen White. I'm on the board of the foundation and mom to three boys including Raphael who is 10 years old and has Prader-Willi syndrome. We live in Washington DC. And I'm I'm thrilled to be here. In this session, Dr. Stafford is going to provide an overview of care for people with PWS over 10, including medical needs, available medications, supplements, labs, and hormones.

Dr. Stafford is a clinical professor of pediatrics at Stanford University School of Medicine in the division of pediatric endocrinology, our favorite division here at [laughter] at FPWR. She's been caring for patients with PWS for over 20 years, both at Stanford and previously at Boston Children's Hospital, with a particular interest in variations in puberty seen in this group. She is the chair of the newly formed PWS-CLIC, the Clinical Investigation Collaborative, working with FPWR to improve the care of those with PWS through collaborative investigation and research.

So, welcome Dr. Stafford.

Dr. Diane Stafford

Thanks for inviting me to do this talk. My kids always say that if you just like shove me a little I'll talk about puberty. So this is truly my favorite my favorite thing to talk about as teenagers. I will say I'm no longer the chair of the PWS-CLIC. I'm happy to say we have now been around long enough that somebody else has taken over as chair. But we are doing some really exciting work that I'm happy to briefly tell you about if we have time. I do have a couple of conflicts of interests.

I am involved in a lot of the PWS related studies with [company name unclear], Soleno, Aardvark and the foundation. So what I want to talk about today is a variety of things that have to do with the endocrinology of PWS. To talk about the effects of growth hormone therapy both in growing children but also in those who have completed their longitudinal growth to talk about the variations in the timing of puberty in PWS and the need in many cases for hormonal supplementation talk about the risks of decreased bone density with aging in PWS and then really to talk a little bit more about the anti-obesity medications that exist that are either in use or PWS for with good effects or not but in use and the potential new treatments and to emphasize the need for routine monitoring for medical issues in older children and young adults with PWS.

So what do we know about adolescence and young adulthood in PWS? We know that historically before we started using growth hormone, the average adult height was about 155 cm and for females was about 147 centimeters. So well under the average height for typically developing children in and adults in the in the US. That and this has changed with growth hormone and our goal with growth hormone therapy is always to hopefully get people to about where you would expect them to go for their genetics.

Now that's not always where what happens but that's always our goal. The other things that we know are that children with PWS can have actual true growth hormone deficiency in addition to using growth hormone very early on for a variety of non-growth hormone non-growthrelated reasons. We shouldn't lose track that sometimes they actually are not producing enough growth hormone. They can have delayed or absent pub pubertal development. They can have normal or very early adronarchy which is body hair and body odor.

They continue to be at risk for obesity. They have an increased risk of complications from obesity like type two diabetes mellous obstructive sleep apnea and hypertension. They have behavioral issues related to hyperphagia that continue through this period of time and they have ongoing medical needs and issues of transition. I've already talked to a couple people today about transitions of care. And issues with independent living.

Growth hormone and the transition to adulthood

Starting with growth hormone therapy, why do we care about growth hormone therapy? Generally, it growth hormone does a lot of different things. It certainly improves longitudinal growth, but it also improves body composition. So it gives you a higher muscle mass and lower fat mass compared to you know if you are relatively either deficient or relatively deficient. It can increase energy and your ability to engage in physical activity. It improves strength, agility, endurance.

It increases and which is very important in babies. It imp improves respiratory muscle force. So we see quite frequently in young babies that they may have some obstructive sleep apnea that actually gets better with growth hormone because their muscle mass their their respiratory mass muscle force improves and they can and they can breathe better. So all of these things are benefits. They're benefits when children are younger, but they're also benefits as they finish as they finish growing and as they age.

The specific benefits in adulthood are are more difficult to measure. When kids are younger, we're looking at how they grow and we can see what growth hormone is doing for them. In adults, it is, you know, we have nothing that we can that we can objectively not nothing but fewer things that we can objectively measure. What we do know is that discontinuation after completion of growth can result in a deterioration of body composition. So a switch from higher lean mass to higher fat mass and a change in a variety of metabolic markers.

The effects are of transition to adulthood and in adulthood are of growth hormone are reduction in body fat and increased lean body mass, improvements in physical performance. And interestingly psychosocial function and improved physical fitness in general improved cardiovascular risk markers and improved quality of life. And the studies that looked at adult growth hormone deficient patients when growth hormone when prominent human growth hormone first came out were focused on these less

easy to measure but measurable things like quality of life, cardiovascular risk, body composition by DEXA scan and things like that.

And those are the things that we have to think about when children have finished growing. Is what are the what are the potential effects of growth hormone on children with PWS? If they've been on growth hormone and have made all these strides on growth hormone and then that growth hormone is stopped because they've completed their longitudinal growth. The difficulty that we have is that there is no current FDA approval for growth hormone therapy for a diagnosis of PWS.

So in children we say you have PWS, you qualify for growth hormone, right? But in adulthood we actually have to diagnose people with growth hormone deficiency in order to be able to continue them on growth hormone. And the diagnosis of growth hormone deficiency is really hard in PWS. It's hard in adults in general, but it's particularly hard in in children with PWS because it requires it usually requires a discontinuation of therapy. So, you have to stop it and then you have to assess them and see whether they meet criteria for a diagnosis of growth hormone deficiency.

And that means looking at IGF-1 levels, looking at other you know looking sometimes at growth hormone stimulation testing and the things that we don't use in PWS but that we do use in other children with growth to show that they have children and young adults and adults to show that they have growth hormone deficiency. And the problem is that most kids with PWS who are finished growing will have normal IGF-1 levels. Although they'll be in the low normal range, they're still normal.

And excuse me, if you do what's called growth hormone stimulation testing, they don't they usually pass. They usually have an appropriate growth hormone stimulation test because a growth hormone stimulation test is basically using medications to hit your pituitary with a biochemical hammer and say, "How much growth hormone can you produce?" And the problem in kids with PWS is not at their pituitary, it's at their hypothalamus. And so their pituitary works just fine and responds to this test in exactly the way somebody who doesn't have growth hormone deficiency would.

So we have to do a lot of a lot of I always call it endocrine handwaving. When you see an endocrinologist start doing this, it means we don't actually know the answer to the question, but we're gonna try anyway. In this case, we do endocrine handwaving with insurance companies, and we have to say they have a low IGF-1. Their their DEXA scan shows that they're we've taken them off therapy and their growth hormone, their DEXA scan shows a change in their body composition even if they haven't gained any weight.

We are you know they their their lipid profile has deteriorated off their you know we basically have to take all of these things that says if it looks like a duck and walks like a duck it's a duck right and prove this to the to the insurance company okay so that's not to say it can't be done and it's not to say people don't try really hard to do it but I'm I want to be a little bit defensive for my fellow endocrinologists and say sometimes no matter how hard you try the answer is still no.

That doesn't mean you can't try again later on or you can't try and find another way around it. But sometimes that can be quite difficult but there is benefit I think and I try to keep my patients on growth hormone if I can. I also try not to do bone ages after people are about 13 or 14, unless somebody forces

me to because if you don't have a bone age, they can't prove that you're not growing anymore. So, I try and I try and play a little fast and loose with the insurance system if I need to.

Adrenarche, puberty, and reproductive development

so turning to the issues of of puberty one of the things that I always like to point out to people which I think is not intuitively obvious to people who watch their children grow up is that there is a difference between the hormones that give you body hair and body odor particularly in girls and it and the hormones that give you breast development and lead down the path toward toward menarchy or in boys give you testicular enlargement and other signs of of puberty.

And that's the distinction between adronarchy, which is a maturation of the adrenal glands production of of androgens, which are male hormones, which is what gives women body hair and axillary hair and body odor. And puberty which is a different which is a an aligned system but a different system of activation of the hypothalamic pituitary gonatal axis and production of either estrogen or testosterone and children with u and so breast development in girls and increase in testicular size and genital changes in boys and it's important to think about this in PWS because there's a very high rate of what we term premature adronarchy in PWS.

So there's a lot of kids with PWS who will develop body hair and body odor at actually fairly young ages. So six, seven, eight. And in a study that we did in in Boston when I was there, it was in our population it was as high as about 65% of kids. So a lot of kids it seems to be benign. It doesn't seem to be a particular problem. It doesn't seem to affect their growth but it obviously causes a lot of you know oh my goodness my my child is in puberty in the minds of families so I want to make a distinction for everybody between adronarchy and puberty in terms of in terms of puberty kids with PWS do almost anything you can see early puberty you can see late puberty you can see kids who start into puberty at an average age but then don't progress and they really are all over the place.

It's actually what got me interested in PWS in the first place in 1998 I think is when I started taking care of kids with PWS. Because at the time I was actually looking into what causes different people at different, you know, to go through puberty at different times. And it seemed like a really interesting model. And what I learned was they're all over the place. It is typically characterized by hypogonadism in both early and later childhood. So the inability for the brain to turn on that switch.

In infants it's actually associated that's what that's what results in the lack of testicular descent. So cryptorism is very common in PWS anywhere from 75 to 95% of children. Small labia majora which is our or minora which is also related to hypogonadism in about 90% that's obviously less less noticeable to people unless you're an endocrinologist and in the newborn period though if you actually look a lot of these children will have normal testosterone or estrogen levels and normal gonadotropins which are the hormones from LH and FSH were the or hormones from the pituitary that actually control production of testosterone one and estrogen.

But then in adolescence, you can get delayed puberty. You can get entrance into puberty but lack of progression. But you can also get early precocious puberty. So, and the studies that have been done show that it's some combination of hypothalamic dysfunction, which we know is sort of one of those

things that's common to a lot of pathways in PWS or central hypogonadism and primary gonatal dysfunction or primary hypogonadism at the level of the ovary and the testice.

And those multiple causes are really you know when they're when they try to figure this out there are genes on the long arm of chromosome 15 in you know in the same sort of region as the PWS specific region in primates that play a role in spermatogenesis and may and may cause testicular dysfunction if they're not working right. The loss of of nectin which is one of the genes in the PWS specific region can result in impairment in GnRH neurons which are the hypothalamic neurons that control the pituitary that control the ovaries and the testes and can contribute to the central the hypogonatropic hypogonadism aspect.

And there have been if you look in the literature no reports of spontaneous fertility in males with PWS which may be related to this to the role of some of these genes in spermatogenesis. And there are a few spontaneous pregnancies in females with PWS. So never and in both these cases never say never. But they're very unusual. And so the what girls with PWS who have menstrual periods are more likely to be having an ovulatory cycles where they're not really they're not ovulating in the same way that would be expected.

So the next question is why do we care about whether somebody actually goes through puberty and the timing of their puberty? Well, if you don't go through impair through puberty it impairs your growth. What gives you that growth spurt through puberty is actually testosterone and estrogen. And so if you're not making enough of those or if you're making some but not enough to give you a growth spurt, you can actually end up significantly shorter than you would otherwise.

Without the addition of sex steroids, sex steroids also improve bone density. So roughly speaking, you are working off of you pack are packing away bone into your bone bank from the time you're in your early teens until about 25 until your mid20s. And then you're going to take bone out of that bank until you're 90. And so it's really important to pack away as much bone as you can during that period of time. And sex steroids specifically are really part of that process.

So, lack of exposure to sex steroids changes the way your body builds bone density that you're going to live off of later. And when you give back those sex steroids, your bone density improves. There's also a positive association between exposure to sex steries and lipid metabolism. So, your cholesterol level and things like that are affected by affected by estrogen and testosterone. Both of them buil improve your ability to build muscle mass. So the ability to exercise, to be out there and be active and deal with all the issues of of caloric intake and other things, you know, are all affected by by muscle mass and therefore by testosterone and estrogen.

And there is a psychosocial impact to lack of sexual secondary sexual characteristics that some kids will not see it, but other kids will notice that everybody else is having these body changes and they're not. I anecdotally I used to have two patients that I took care of in Boston, two girls almost the same age and they went to school together and I would see them usually not the same day, although sometimes they did manage to do that just to confuse me.

But one would come in and would say, "I need more estrogen." And I would say, "Why?" And they would say, "Because she has more breasts than I bigger breasts than I do." And then the other one would

come in and say, "Why aren't you giving my friend more more estrogen? Her breasts are smaller than mine." And I'm like, "Okay, first of all, I can't have this conversation with either one of you because there's this thing called HIPPA." but second of all, genetics blah blah blah blah blah.

So, I did a lot of endocrine handwaving. But as much as we would like to think that maybe our kids are not aware of the differences in body in body image between or that they don't have a sense of body image they frequently do.

Timing and options for hormone replacement

so then we get to timing of sex steroids and how do we actually think about the about that the decision of the timing of sex steroids or the need for sex steroids should really be made on an individual basis. I think about it as lack of spontaneous progression into puberty. Either at an age that is the definition of delay, right? So that would be no breast development by 13 in girls and no testicular enlargement or other signs of puberty in boys by 14 to 15.

But those are like the outer limits of what we think of as pubertal delay. In PWS, we have to think about it slightly differently because like I was saying, some of these kids will start into puberty and then just like sputter there and stay there for a while. And so I look at patterns of growth to see I look at bone age to see sort of whether the body thinks it should be exposed to sex steroids at a particular time, which is usually in girls a bone age.

A typical girl would start into puberty with a bone age of about 10 and a boy with a bone age of about 12. And so when they get to that point, then I start to watch them a little more closely and say, "Gee, you know, your bone age is going up, but you're not starting into puberty. Or your bone age is going up. You have a little bit of pubertal development, but it's not progressing. And we really need to think about whether we should be supplementing you with sex steroids to get you both the growth that you need as well as the muscle mass that you should see at that particular age.

I use a lot of discussions with families about family history. So, if everybody in the family went through puberty late, the child is probably destined to go through puberty late. So, you have to think about that. Bone density evaluation you can do. I think it's not as useful because the standards are not great, but sometimes I do do what's called the DEXA scan. Because it gives me a sense of bone density, but it also gives me a little bit of a baseline because kids are still on [unclear], so I can use that later potentially.

But I don't do them very often. And then in terms of in terms of treatment, I start at low doses and I mimic I try to mimic the normal increase that you would see. Okay. But I don't start at adult dosing for somebody who's never been exposed to sex steroids before. We are not creating, you know, we're not giving people roid rage by starting them on huge doses of steroids. We start at where the body would normally have started itself if it were doing it on its own.

And then we slowly progress and we watch growth and we watch behavior and we change the timing of the increases in dose to get up to a relatively relatively normal adult dose. Over time in conversation in monitoring growth in monitoring behavioral change. These are a couple of examples of of a couple of my patients. And the first one if you if you notice if you look this a girl if you look at her at her growth she actually started to have an increase in her growth rate right around about 9 years of age.

And so she actually from my point of view started into puberty right she had some breast development. She was increasing her growth velocity. I'm like okay you are going to do this on your own. And then she sort of crossed some percentiles and sort of had a growth rate increase in her growth rate, but not really that much. And she didn't have a huge amount of change in her in her physical exam. And what happened was she actually stopped growing way before I thought she would.

She did not come from a tall family, but she also stopped growing way before I thought she would because she didn't get a normal increase in estrogen and a normal pubertal growth spurt, but she saw enough estrogen to give her that little bit of increase in growth and also age her bones. So, there's So, this gets to that estrogen and testosterone are kind of a double-edged sword in that they make you grow faster, but they also close your growth place eventually.

Right? And that's the effect of it. So, you have to be careful how you do it. You have to think about the timing. Whoops, wrong direction. This is another one of my patients who was who was kind of falling off her growth chart, had been at about the 10th percentile and then fell to below the third percentile. And I said, "You are almost, you know, you are almost 14. You need to be in puberty." and we started her on what's called Viveell, which is a transermal estrogen patch.

And she grew beautifully and actually ended up at her mid-parental target height. So just to say that keeping an eye on children this age and really thinking about where should they be and when do we need to think about so what do we do in terms of therapy for pubertal delay or lack of progression in girls? The most typical thing we use is transcutaneous is transermal estrogen which is a patch that starts at a low dose and increases and you know I say things like put it center of their back where they can't get it at it.

It can go anywhere on the body except around the breast. So you can find a place where if your child tends to pick off the band-aid, you know, skin pick, whatever, you can actually put it somewhere that they can't get at. Usually we will add oral progesterone at the point when people when girls start having menstrual bleeding. That means their uterus their uterine lining has built up enough that they have seen sufficient estrogen. And then there are a whole bunch of methods to use to limit the number of menstrual periods that girls have while continuing to provide estrogen.

So, you can use a standard oral contraceptive pill. You can use an estrogen and progesterone patch. You can use estrogen with transdermal estrogen with oral progesterone, you know, every 3 months. There are a whole bunch of ways to do it. And so again, having a conversation with with your endocrinologist about what your child what you and your child can actually handle. For boys, the most common thing that we do use is either intramuscular or subcutaneous testosterone starting at a low dose with a very slow increase because people worry a lot about about testosterone exposure and the potential for it to affect behavior.

I think if you my experience has been that if you're doing it slowly and carefully, it really doesn't cause a huge amount of behavioral change. The goal is nor is like low normal adult testosterone levels. So, I'm not expecting the normal range is wide. It's 700 plus or minus 300. Okay. So really, really wide. I'm not trying to get people to a,000. I'm trying to get them to, you know, 400 for their bones and their cardiovascular health. So and again you can use there are people who favor using transermal testosterone that you know testosterone gels and things like that.

I always worry a lot about those because you really have to wash your hands really well or you know wear gloves will wash your hands really well after you put it on. The idea that it is actually relatively easy to contact other people and give the testosterone that's on your child's body over to somebody else. So unless I know that you know that a family is really really able to be vigilant about it I tend to use transermal or transcutaneous or subcutaneous I'm sorry intramuscular subcutaneous test

Bone density and monitoring

so the next thing we're going to talk about is bone density and bone density in PWS is there's an underlying risk due to hypotonia, obesity, and hypogonadism. And so all three of those things put those with PWS at risk for having lower bone density. In a metaanalysis of a variety of studies of PWS, the prevalence of osteopenia and osteopherosis is anywhere from 2 to 26% which means we don't really know because it depends on the nature of the study and that is actually likely an underestimate of what the of what the incidence is.

Osteoporosis is more common in males than in females. And the use of psychotropic medication is also related to a decrease in bone density. So all of these things put our put our kids with PWS at risk. How do we prevent it? The first thing we do are e, you know, are are things that are good, normal, healthy habits. We optimize vitamin D. So 800 to,000 international units of vitamin D per day, 30 minutes of exercise daily, preferably with weightbearing exercise if children are able to do that.

That improves that improves in particular bone mass at the hip and the spine. Optimizing sex steroid replacement which we were just talking about and then having an awareness of the risk of fractures and that they have a high pain threshold. So if they may have a fracture, a small fracture that they don't really complain about that much. So looking at, you know, is if their leg is swelling [unclear]. Thinking about this, thinking about the fact that their risk is higher.

In adulthood, you can use so you can do DEXA scans in kids. And sometimes, like I said, I do do them so I have a baseline for them. The but you have to compare them to other children their age or with their bone age. So you need to be careful about the comparisons you're making because the z these are presented as what is referred to as zcores or standard deviation of the mean and so you have to be comparing them to the right people. In adulthood usually, the idea would be to get one sort of as people reach adult age and then every 5 years if they're normal.

If they're abnormal and you're going to put somebody on sex steroid replacement, I'll sometimes repeat them a year later and see whether we're actually making positive strides with respect to bone mass and then measuring vitamin D yearly.

Blood sugar, cardiovascular health, sleep, and ongoing care

so what about other comorbidities, other things that we see? There was a study actually Shawn McCandless and I worked with [company name unclear] who was a company that was in this space about 10 years ago now to pull billing data billing encoding data. So to go to into a database and say what are physicians when people go see physicians and they're billing and they check a box that says you know these different diagnoses what are they seeing? So this is not perfect data, but it does give you an idea of what we see as people age.

And the rates of type 2 diabetes in the PWS population, the red is PWS and the gray is a nonPWS population. The rates of type 2 diabetes become really significantly higher starting between 9 and 17 years of age. And hang out somewhere about about 30% over time. Some of this is affected by obesity. Some of it is also affected by just family history, right? If you have a strong family history of type 2 diabetes, you're more likely to develop type 2 diabetes.

And then you add in PWS on top of that and obesity on PWS related obesity on top of that and it increases the rates. In terms of cardiovascular disease, you also see a difference and particularly looking out at the 18 to 26 and beyond a pretty significant difference between the cardiovascular disease prevalence in patients with PWS compared to nonPWS patients in the younger patients is almost certainly you know related to congenital disorders rather than rather than other issues.

But the it primarily takes the form of in young people of hypertension, hyper lipidmia or in older patients of hyper lipidmia and hypertension.

It would go into here it would go into cardiovascular disease. Yeah. Hyperlipidemia for sure. Hypertension and hyper liyademia generally manifest at younger ages in PWS patients compared to non-PWS patients. And the relative difference between PWS and nonPWS is greatest in sort of young to middle adulthood when you look when you start to break it out. Obstructive sleep apnea also prevalence increases compar is higher in the PWS population compared to the nonPWS population.

It looks like it's really high in the very young kids probably because people are coding for sleep apnea in order to be able to do sleep studies on children with PWS. Right? So, we don't know whether that's an actual prevalence or whether that's an artificial prevalence because of the way we as silly doctors code things when we put them into into billing. But the prevalence of obstructive sleep apnea later on seems to be somewhere in the 15 to 20% range you know throughout the lifespan.

So what all of those things mean are that care for late childhood and adolescent and early adult children with people with PWS really requires multiddisciplinary management that there are you need a cardiovascular evaluation. So in terms of like just medical evaluation, physical exam findings for pubertal development, scoliosis, you know, feeding problems, exercise, exercise rates, psychosis, cardiovascular things, anticipatory guidance about about weight management, about access to food, about socialization, talking about guardianship when kids get into their, you know, into their later teens.

And yearly labs looking at thyroid function, growth factors, on or off, growth hormone, insulin, glucose, hemoglobin A1C as looking for evidence of type 2 diabetes, CBC electrolytes, just sort of a routine, some of these are very routine yearly things, but some of them are more PWS related and need to have a little bit more attention paid. And then they may need DEXA, polynography, MSLT to look for daytime sleepiness, so multiple sleep latency test.

I can talk the pulmonary talk sometimes. Scoliosis screening, etc. And really just having, you know, thinking about drugs that they may need, including including sex steroids and growth hormone over time.

Weight management medications

so I want to take a few minutes and talk about anti-obesity medications in PWS. The literature would say and certainly those of us who spend a lot of time in the PWS world would say that there's a really high degree of variability of response to standard anti-obesity medications in PWS. What we really need is more investigation including some large-scale multicenter trials to try to better understand these AOM whether that whether these anti-obesity meds actually work in PWS either for hyperphagia or for weight loss.

There is limited literature on their use in pediatric patients in general and many of these medications are not approved u FDA approved for weight management. So some of the things that people are doing in weight programs in different places are not actually approved for weight management, but they think they probably work and so sometimes they go to and not all drugs are are FDA approved for this indication or in those less than about 10 or 12 years of age.

So we really find ourselves in a difficult position with not enough understanding of how these medications affect pediatric patients generally but more specifically patients with PDWS and also not enough you know not enough safety data for a lot of them. So to talk about a few that are that are used including off label use for some of them. There are there are some things like topyramate and fenturamine that are sometimes used together. Topyramate is actually a migraine medication or seizure medication with an off label use for binge eating disorders, mood stabilization and weight loss.

There have been a bunch of clinical trials de that demonstrate associations between topyramate and weight loss in the general population with with side effects of fatigue, dizziness, mood change. There was a 2019 study that showed a trend to decreased BMI without any statistical significance when they and some dose dependent improvement in hyperphagia in a small trial over about 8 weeks. But there's not a huge amount of data in PWS about it. And there was another open label study that showed some weight loss and improved mood in seven patients.

So in J, you know, we're talking about 70 patients that they've treated with this drug. And the results were really kind of meh. So not a great drug. Metformin is a drug that's classically used for type 2 diabetes. And is quite good at glycemic control at controlling type two diabetes. And it decreases glucose production in the liver and glucose absorption in the tension in at the in the intestine and increases insulin s sensitivity. That's how it works.

But it has really bad abdominal side effects like diarrhea, you know, nausea and vomiting. There was a study in 2014 of 21 kids with PWS that showed an improvement in food related distress and anxiety u but no significant weight loss. So again as a weight loss medication not particularly useful might have some other things but the side effect profile for metformin we use it a lot in pediatric type 2 diabetes and the side effect profile is definitely a problem.

There's also fenturamine which is thought to release norepinephrine in the hypothalamus and thereby reduce hunger. The side effects of it are dizziness, dry mouth, GI symptoms, whole pestle of things. It is currently FDA approved for as an obesity medication in patients over 16 and older, but there have been absolutely no studies of phentermine in PWS. GLP-1, everybody wants to talk about GLP1s these days.

Spend a lot of time talking about GLP ones. GLP-1 receptor agonist and GLP-1 GIP combination drugs are are quite ubiquitous these days in in the world.

GLP-1 stimulates insulin release and inhibits glucagon secretion slowing gas slows gastric emptying and increases satiety after eating. The brand names for this are pink and we go. There's also GLP-1 mixed with GIP. GIP receptor expressing hypothalamic neurons contribute to appetite suppression. And so activating those would would seem to be a good way to decrease decrease hunger. And Monaro and Zepbound are the are the two brand names for that. The side effects are predominantly gastrointestinal with some with obviously if you slow gastric motility you can get reflux you can get you can get some some u generalized distension they can also cause diarrhea as well it's given as a weekly injection and it is approved as an obesity medication specifically ally WGO and Zeppbound as an obesity medication in patients over 12 years of age.

The only multic-center placebo control trial was in 55 subjects in PWS was in 55 subjects over 16 weeks of placebo control and the hyperphagia total and drive scores were lower in adolescence treated with liraglutide which was an earlier version of a GLP-1 versus no treatment but there was no significant change in BMI versus no treatment. So, and I think those of us who use these drugs fairly regularly in talking with our own patients, they are really, really good for type 2 diabetes.

They are excellent at maintaining good glucose metabolism and normal glucose control. They do not seem to have a huge effect on hypophasia and they do not generally relate you know result in the kind of weight loss in PWS that we see in the more sort of the term we use is an iatrogenic obesity the typical obese population. So most of us are using them in our patients if they have type 2 diabetes but we're not seeing a huge effect in PWS.

VYKAT XR and safety considerations

so it definitely you know nothing would be complete without taking a little bit of time to talk about VYKAT XR (DCCR) which is the first FDA approved medication for the treatment of hyperphagia and PWS. And I know there's been a lot of conversation about this over the last few days was approved in in March of 2025 for use in children four years of age and older. And the benefits that the stated benefits are improved behavior around food, fewer outbursts related to food, improved metabolism and less worry or talk about food.

And I think you know for a lot of people they definitely feel that there have been advantages to being on VYKAT XR that but it's important to remember that the benefits here are not weight that you don't see weight loss as one of these benefits that the presumption is if you treat the hyperphagia and you improve the hyperphagia that the weight loss will follow from that but it's not a weight loss medication. And so I think making sure that as you start to decide whether whether VYKAT XR is something you want to try that you're focused more on the behaviors than you are on the weight.

What I do hear from people is that their child may not be losing weight but they're no longer gaining. And that's a win right for a lot of people. But it also takes a long time. It can take you know 6 to 12 months before you really see any significant changes with vicet and there are side effects and risks to vicat. Those of us in endocrinology have been using a related drug dioxide not dioxide choline but well dioxide

choline but not extended release for a long time to for babies with low blood sugar because it decreases your insulin secretion and therefore raises their blood sugar.

And we know that those children are at risk for fluid overload, for elevated blood sugar. That's the point in those patients in those children. And an increase in hair growth or what's called hypertriosis. And being aware that swelling or edema can be significant and monitoring blood glucose, it should really always be done when when using this drug. So there was a study or not a study but a statement that came out from a group of us in specialists in PWS along with FPWR, IPWSO, PWSA talking about the groups that we think are of specific concern with or you know with respect to increased risk for the use of VCAD and that is patients with obesity particularly with significant obesity with known own histories of either cardiac problems or breathing problems.

So people who've had multiple multiple episodes of pneumonia or have bad reactive airways disease, asthma, things like that. People with histories of swelling or fluid buildup. So if you have a history of pulmonary edema, or a history of peripheral edema, your risk is probably higher. Patients with sleep sleep apnea that's either not treated or not well controlled and other breathing issues hypoventilation other things that may that may that where any compromise of your lungs from fluid may actually tip you over the edge and severe history a history of severe respiratory infections and pneumonia.

So, these decisions need to be made carefully and, you know, in conjunction with conversations with your physician to make sure that everybody is comfortable with the idea that your child is not at increased risk or if they are at increased risk, how are you going to mitigate that? What investigations do you want to do before you start? If you have a cardiac history or or a significant pulmonary history, maybe you actually need or or you know, sleep apnea that isn't being treated, you may need an echo cardiogram.

You may need, you know, actually look at the function of your heart before you go on this drug to make sure that your risk is no higher. And then there are a couple other clinical trials. Just earlier today, there was like a recap of what's going on.

Clinical trials and future treatments

there are currently trials of a triple monoamine re-uptake inhibitor called [study drug name unclear]. There's another one [study drug name unclear]. There is actually a study looking at tirzepatide (Mounjaro and Zepbound) which I'm very happy to see. And then there are future trials with Aardvark and [company name unclear] with ARD-101 and [study drug name unclear]. And I'm sure there are ones that I don't have on here that are related that are endocrine related.

And there are other studies that are non-endocrine related that I did not try to cover here. But I actually having been doing this for a long time and I'm am really excited by the amount of excitement that there is from from pharmaceutical companies and you know people who are really whatever gets them into this space is fine with me. I want more drugs. Because I think that we need to we need to understand that nothing's going to work for everybody.

And everybody's going to have different risks and we really need to need to start to figure out how to how to utilize more tools and do so safely. So with that, I will finish. We've got about 10 minutes or so for questions and then I'm afraid that I have to bolt out of here or I'll miss a plane. But my email is up there.

Please, if you have questions that we don't cover. Please send me an email. I'm I'm usually pretty good, although I'll be off campus for about the next 3 weeks.

So give me some time.

Audience questions and answers

Hi, I'm going to take the first question, please. You talked about in in what we see in infancy and then what we see in puberty. Is there a correlation between what you see in terms of like testicles dropping in newborns and then like how they present in puberty? And then second unrelated question is on in terms of medications, do you see adults who are taking stimulants or ADHD medication and that having any impact on weight or hyperphagia? Both really great questions.

The question about the association between sort of neonatally diagnosed hypogonadism and progression into puberty later is that there doesn't seem to be a great relationship. That we know that kids with PWS really frequently have delays in pubertal development or don't enter puberty but having cryptorchidism for instance which is the easiest thing to which is what usually people are focusing on not having not having your testes descend and having to have surgery to have them pulled down is not strictly speaking related right If your testes are sitting up in your abdomen, they are never going to work very well.

So, that's related, right? But if you bring them down and put them where they're supposed to be, it's really hard to know whether their whether their function is going to be sometimes their function is actually relatively normal. What I see really typically are boys in particular in boys is that they start into puberty and they get to testosterone levels of like 150 and then they just sit there and they don't grow well because they don't have enough testosterone for a good gross bird.

But they age their bones and they end up shorter because they sort of miss out and they're not getting what they need in terms of bone density and you know all the other effects because they're never getting to those low normal adult levels. In terms of ADHD meds, I have a lot of kids on ADHD meds, with PWS. And I haven't really noticed that they that it has the same effect on them that it does on on typically developing kids where all of a sudden they decide they're not going to eat lunch because their ADHD meds are working.

It doesn't seem to have the same effect. Other questions? Yeah. Oh, sorry. You already have the microphone, please. [laughter] I also have two questions, but I'll make them quick. One is my daughter is 24. She had a sort of baseline EKG at a physical and they diagnosed Wolf Parkinson white. Does that make take by off the table for me? I can see your cardiovascular back. I would not think so. I think it's a great question for her cardiologist, right, to say, you know, does this would this put her any more at risk for fluid overload for pulmonary hypertension based on her WPW?

But, WPW is a is an electrical system problem as opposed to a cardiac function problem. And so I would think that it would not be exclusionary. Great. Thank And then my other question is when her pediatric entage they're on birth control pills. Yep. Which to be a while to understand why. When she was about 15 and now she's on a three-month cycle. She has the period every 3 months. Yep. Yep. Yep. Can can she stay on them for life? Yes. And should and she probably should.

You can change you can change. So the question was can can you stay on birth control pills forever? Don't think of them as birth control pills. First of all, think of them as hormonal supplements, right? It's just a really convenient way to give estrogen and progesterone nicely packaged. Also, it's really normalizing for girls with PWS to be, you know, it to something that seems like, oh, there are lots of girls my age who are taking this. It's the qu there is some question about whether birth control pills are as effective at improving bone density as transermal estradile which has to do with how it gets processed in the liver.

I'm very big on whatever you're going to be able to use and take is what I want you to be able to use and take. So if trans dder dermal isn't going to work, you know, if if if it's working for her, I would leave her on it. Yeah. Hi. I know Don, I used to take care of her daughter. [laughter] So, my daughter was on growth hormone till got about 16 or so, went off it. And is now back on it as a low dose. Is I don't know. I guess it's two-part. Is what is the detriment that she went off it and then like should we be seeing differences now that she's back on it?

How long would that take? Like what kind of changes might we see? Yeah. You know the detriment, you know, it pro possibly, right? It's hard to know. It probably depends a little bit on just how relatively growth hormone deficient she is and there's a lot of variability in that. You know, if you're off for a few years, it'll change your probably change your muscle mass and fat mass, but you can regain that. There's no there's no data to say, you know, it's going to change in 6 months or it's going to change in a year, but it should change over time.

And what I would be looking out for are things like exercise tolerance. You know, are you is she noticing or are you noticing that things that used to really make her tired are now not making her quite so tired? That's a that's a really good like off-the-cuff measure of muscle mass, right? And you know, so I think there are things you can see and then there are things you can measure like DEXA, like B, which does both bone density and body composition.

And you know, looking at if she's had a DEXA before, looking at it again in another year or maybe getting one now that she's just gone on so you can see sort of where she is and track that a little bit and know whether she's actually gaining, you know, gaining muscle mass, losing, you know, decreasing fat mass over time. I think if you're going to give your child or somebody, you know, she someday is going to give herself growth hormone all the time, you probably need to prove to her that it's good for her.

And you know, and in that way, having that having something like a DEXA to look at at lean body mass actually gives you something quantitative that you can that you can say, "Yep, we definitely should stick with this." Yeah, sorry. So, you're fine. Please go. [laughter] So, my daughter is 17 years old. She didn't start her menstrual cycle yet. And the So there's two questions. Would you suggest sex hormone therapy? I think you were saying earlier for her.

And then the second question is we have Brocka Gene and our family. Would that affect her? This a really really good question. I think I think one of the things to think about is if she's you know if she's never had a period what do hormonal levels actually look like, right? If her body is making estrogen on its own, which some girls do, she may not need estrogen supplementation to have a period. She may be just fine if we give her just that progesterone part.

Like she's not cycling normally, right? But you can you run you know LHFSH testosterone you know run a whole endocrine what I would refer to as an amenorhea panel right somebody who's not having their periods and I want to look at all of these various hormones if her estrogen level is actually reasonable you can do what's called a provera challenge where you actually give somebody progesterone for 5 to 10 day 5 milligrams to 10 milligrams for 5 to 10 days, ask five endocrinologists, get five different opinions about how to do that.

But you give them progesterone in the short term. When you stop the progesterone, what the progesterone does is stabilize the uterine lining. And then when you stop it, if that lining has been built up, if you've been if you've been exposed to enough estrogen to build up that uterine lining, you'll have a menstrual period. Okay? If that happens, her body's making enough estrogen and we don't need to give it back to her. We just may need to every 3 months give her a little progesterone to, you know, to actually shed that lining.

If she doesn't withdraw to pro if she doesn't have a period with the provera, that would imply that her body's not seeing enough estrogen and then starting to think about starting to think about replacement is, you know, is reasonable. The broa question is harder to answer. I think most people would say that lowd dose estrogen is probably of benefit to her in a lot of different ways and probably doesn't increase her risk because all we're trying to do is mimic what her body would normally be making.

I wouldn't use an oral contraceptive pill which have sort of generally a little bit higher levels of of estrogen, but using using a transdermal estradiol patch at a relatively low dose or what's called a combination patch which has estrogen and progesterone in it may be a reasonable way to think about it. Okay, I think I can probably do one more question.

Yeah.

I'm excited because people are actually in this space, right? Like I said I started seeing patients with PWS in in 1998 and it wasn't until about when 200 15 I think you know it was like you know almost 20 years I was doing this before anybody was interested in looking at hyperphagia in PWS and trying to find a drug that worked in hyperphagia. And you know, since 2015, we've had four or five different trials specifically focused on hypopasia and PWS.

People are looking at at daytime sleepiness and P in PWS. People, you know, all of a sudden there's excitement about a rare disease and in specifically the rare disease that I actually care about, right? And that's what I mean by we're excited by that. I think I also think that the basic science work that's being done is really exciting. Like I spent Wednesday and Thursday going that's so cool. If we could just find out the answer to that question, right?

And there are people looking into those questions and that's what I mean by we're excited.

I think that you know I don't think GLPs are the answer. But I think I think having and I won't get them all right but having Real Mada having Arvar having Seleno having OT OT4B having having industry in you know pharmaceutical companies interested in PWS is a huge change right because people used to say a rare disease you know what's the point? Well there's a huge point and they may be in it for a different reason than I am right they may be eventually saying well if we can show that it works in PWS and that people in PWS have less hyperphagia and more weight loss we can use it in people with exogenous

obesity right I don't care where they take it I just want them to go through the rare disease process because it'll be of benefit to this community I hope that makes sense Okay, I thank everybody very much.

I'm going to turn it over to Lisa to talk about the registry. I'm going to put my own plug in for please be part of the registry. Our PWS-CLIC, the group that we were talking about earlier, is trying to collect a whole bunch of information to be able to look at the natural history of PWS. And that is significantly easier if we have good registry data that we can correlate with the clinician reported data that we're collecting and really answer a whole lot of questions.

So, thanks everybody.

Closing remarks and the Global PWS Registry

Thank you, Diane. I appreciate all of your time and answering everyone's questions. And as always, I think we always learn so much when we hear from you. So I appreciate it and I hope you have safe travels. So for those who may not know me, I am Lisa [last name unclear]. I am a study coordinator for the Foundation for Prader-Willi Research and mom to a 20-year-old with PWS. I'm one of the administrators for the Global PWS Registry. So you probably see some materials on the table that talk to you about some of our findings from the registry.

But as Diane mentioned, you know, this is a way that caregivers can actively participate in research by contributing your experiences with your loved one. The registry, if you've not been in there before, has a lot of surveys and that should not overwhelm you. It should excite you because there are a lot of things that we are collecting data on. There are some active projects in there right now with different researchers and we encourage you to go in and explore it.

If you haven't been in there in a while and you have an account and you need to get reestablished, you can contact me. There's the email address on the slide up here. Anything that you can contribute has tremendous value and we would be so grateful if you could take a moment and reinitiate your access to the account or start one today if you haven’t already.