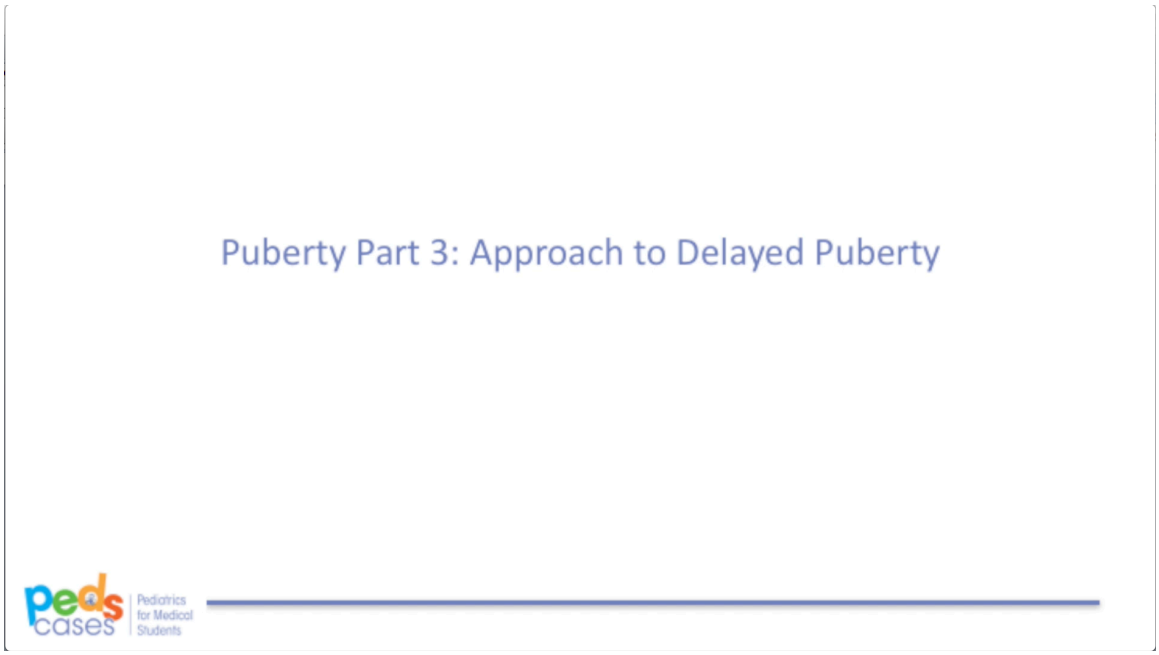
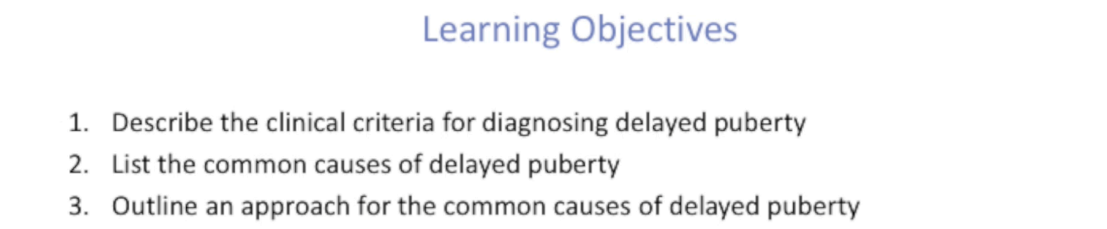


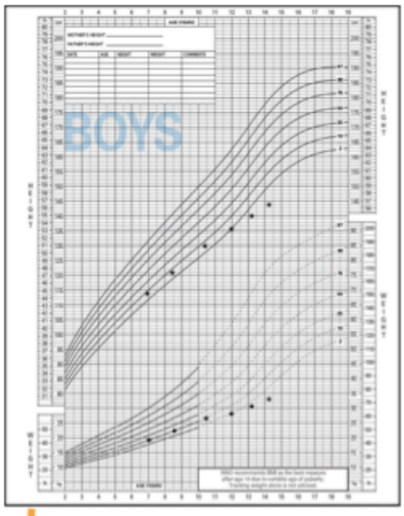
Slide 1:
Hi! My name is Ruojin Bu, and I am a medical student at the University of Alberta. This video is the final instalment of a three-part series on puberty and pubertal disorders. This whole series was made possible with contributions from Dr. Elizabeth Rosolowsky, a pediatric endocrinologist at the University of Alberta.

So far in our series, we've looked at the physiology and clinical presentations of normal puberty in part 1, as well as an approach to precocious puberty in part 2. In this final episode, we will be covering the topic of delayed puberty.



Slide 2:
At the end of this video, the learner should be able to:

1. Describe the clinical criteria for diagnosing delayed puberty
2. List the common causes of delayed puberty
3. Outline an approach for the common causes of delayed puberty



Case

You meet a 14-year 4-month old boy whose parents are concerned that he is not physically maturing like his peers. He has developed some pubic hair but no armpit hair. His parents do not think he is growing. He has otherwise been very healthy. His growth chart is provided. Physical exam reveals no facial hair and no axillary hair. He has Tanner 2 pubic hair. Testicles are 2 cm in length.

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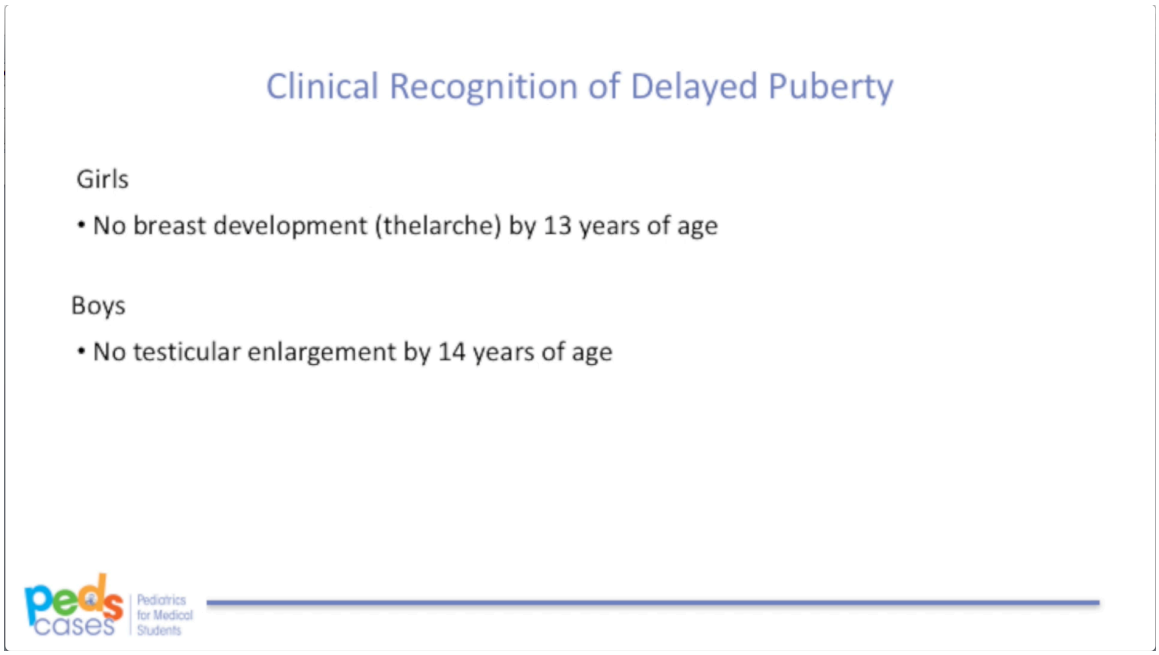
Slide 3:
As a continuation of our case example from part one and two…

The next day at the family medicine clinic, you meet a 14-year 4-month old boy whose parents are concerned that he is not physically maturing like his peers. He has developed some pubic hair but no armpit hair. His parents do not think he is growing. He has otherwise been very healthy. His growth chart is provided. Physical exam reveals no facial hair, no axillary hair, Tanner 2 pubic hair, and his testicles are 2 cm in length.

We will revisit this case at the end of this video.

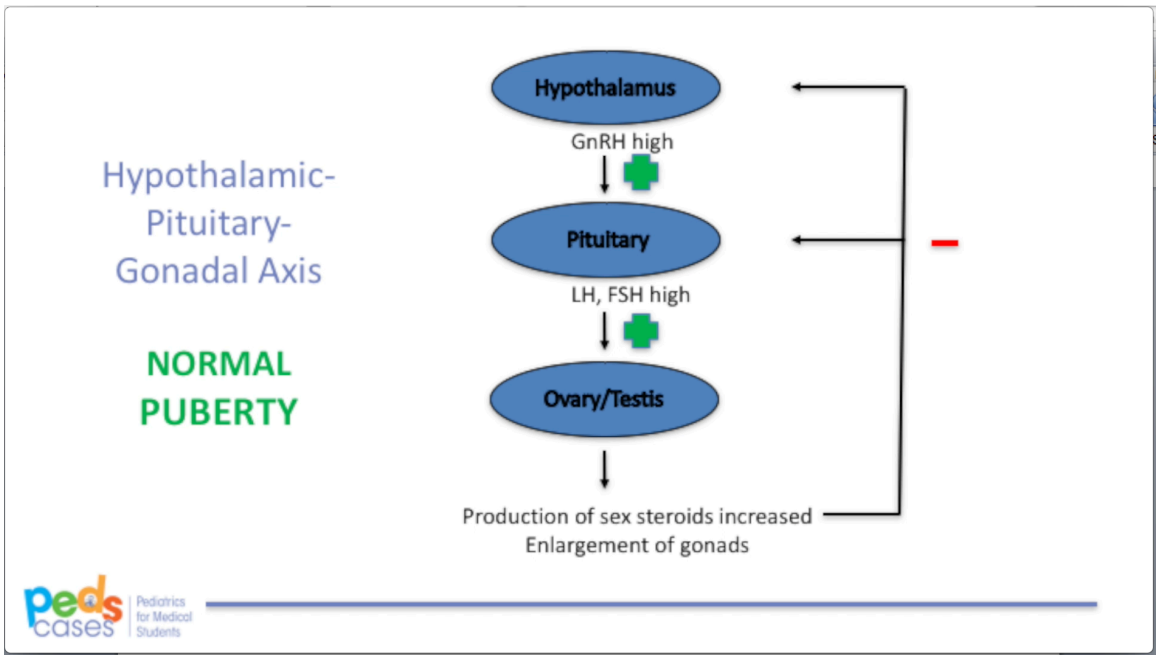


Slide 4:
So let's now talk about the problem of delayed puberty.

Clinically, delayed puberty is classified in girls when there is no breast development or thelarche by 13 years of age. In boys, delayed puberty is classified when there is no testicular enlargement by 14 years of age. In other words, the testicle is less than 4mL in volume or less than 2.5 cm in length.

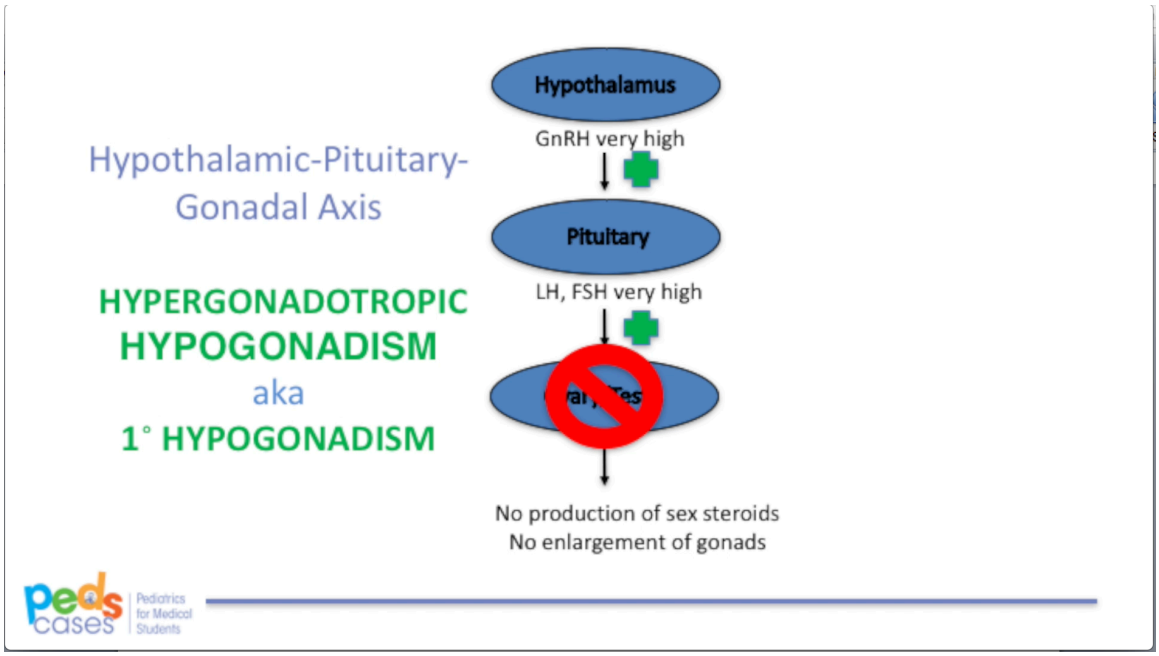
Both of these age cut-offs reflect more than 2 standard deviations above the population mean.

Please take note that the criteria for delayed puberty only concerns the gonadotropin-dependent process, or true puberty. Breast development in a girl or testicular enlargement in a boy is the key to true puberty.

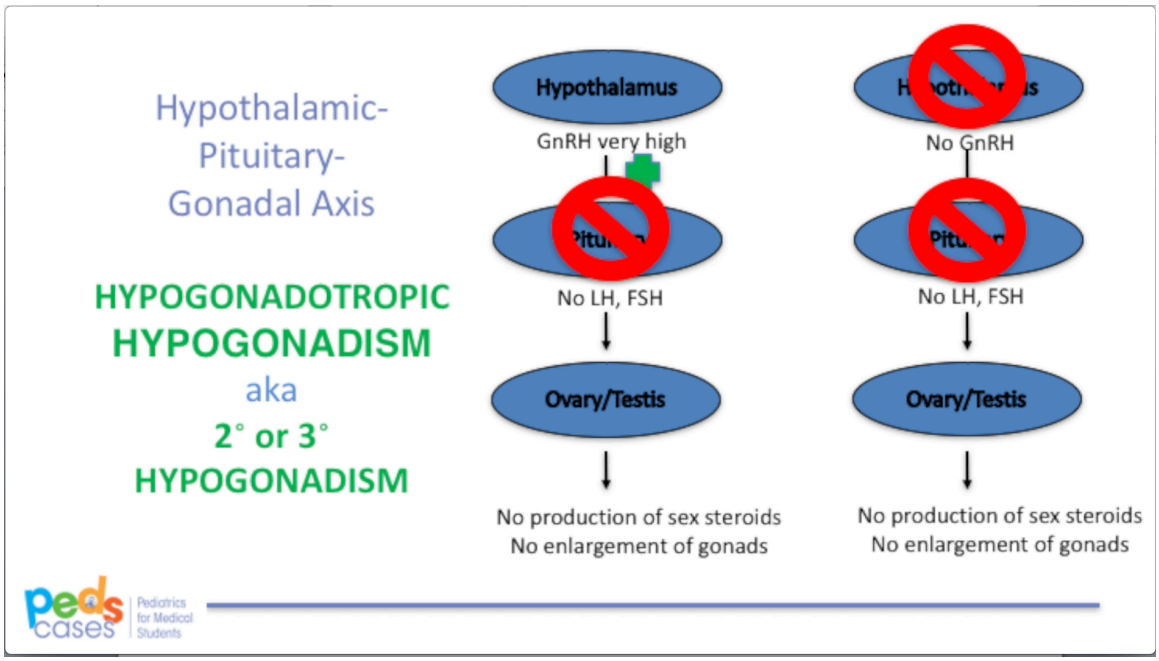


Slide 5:
To help us understand different causes of delayed puberty, let's revisit the HPG axis.

In this simplified diagram of the HPG axis, all three components, the hypothalamus, pituitary and the gonads are functioning normally. We see that the hypothalamus is cranking out GnRH, the pituitary is cranking out LH and FSH, driving an increased production of sex steroids in the gonads and an enlargement of the gonads. The sex steroids, in turn, keep the hypothalamus and pituitary under an appropriate control through feedback inhibition.

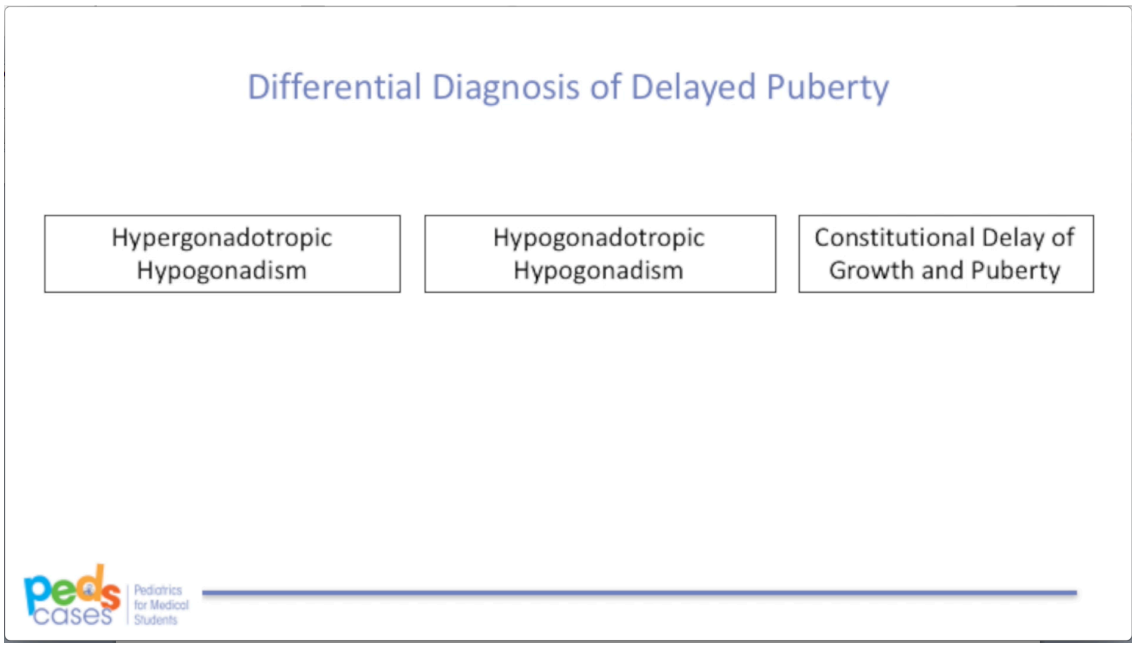


Slide 6:
Now what happens when the gonads no longer follow the commands of the hypothalamus and pituitary? The gonads do not produce sex steroids and do not increase in size. In other words, they become hypogonadal. Because we are also losing the negative feedback from the gonads to the hypothalamus and pituitary, more GnRH, LH and FSH are being made to drive the system but to no avail. We will see very high levels of LH and FSH that can even exceed pubertal levels, thus “hypergonadotropic”, “hyper” means “over.” This is a condition called hypergonadotropic hypogonadism. We have an over-production of gonadotropins. Another term for this condition is Primary Hypogonadism, because the hypogonadism occurs at the level of the gonads.



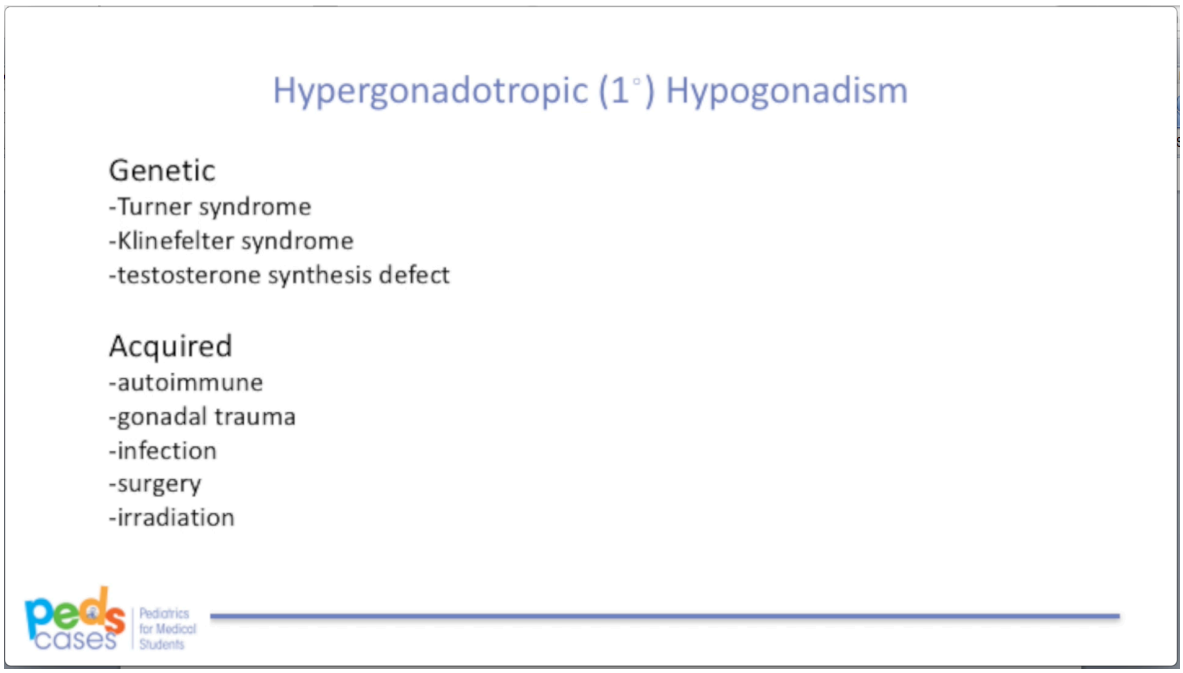
Slide 7:

Alternatively, there may be a pathology in the hypothalamus and/or pituitary. The central command of the HPG axis is destroyed or not functioning properly. Because we cannot generate gonadotropins -- LH and FSH -- there is no production of sex steroids and no enlargement of gonads downstream, a state of hypogonadism. We expect to see low levels of gonadotropins in the blood, so we call this condition “hypogonadotropic hypogonadism.” “Hypo” means “under.” Hypogonadotropic hypogonadism is also known as secondary (as seen on the left) or tertiary (on the right) hypogonadism because the deficiency occurs at the level of the pituitary or the hypothalamus, respectively.



Slide 8:
Now that we've introduced you to the possible mechanisms behind delayed puberty, let's look at the different causes.

Conveniently, these causes can be organized based on their mechanisms. In general, we can talk about them in terms of hypergonadotropic hypogonadism or hypogonadotropic hypogonadism. There is also a condition that stands on its own because it is a normal variant and also the most common cause of delayed puberty -- Constitutional Delay of Growth and Puberty. We encourage you to listen to a PedsCases podcast on the Approach to Short Stature for more detailed information on Constitutional Delay of Growth and Puberty.

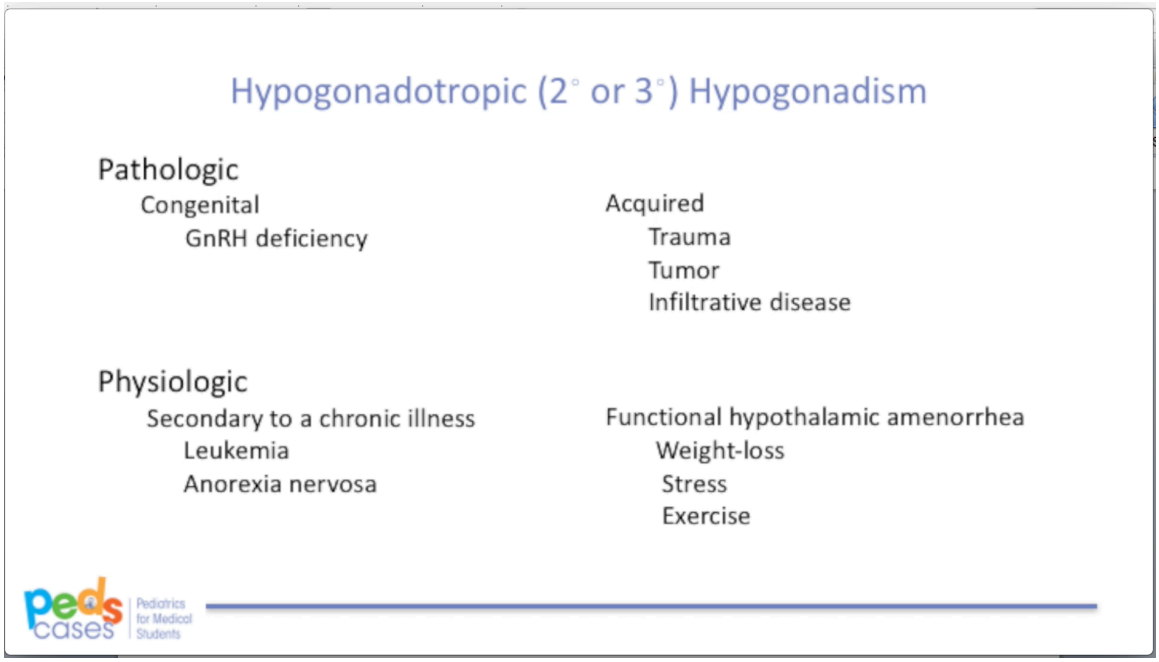


Slide 9:
All causes of hypergonadotropic or primary hypogonadism are, unfortunately, pathologic.

Hypergonadotropic hypogonadism is marked by very high concentrations of gonadotropins, due to bilateral gonadal insufficiency. Some people are born with gonadal insufficiency because of their sex chromosome complement. Rather than a 46,XX complement, for example, girls with Turner syndrome have only one normal X chromosome. These girls do not form ovaries properly and are not able to achieve a full pubertal development. Turner syndrome in girls is the most common cause of gonadal insufficiency. For more information on Turner syndrome, please have a listen to a PedsCases podcast on An Approach to Turner syndrome.

In boys, the most common genetic cause is Klinefelter Syndrome, due to the inheritance of an extra X chromosome, in other words, 47,XXY. Their testicles do not form properly. These patients often present with smaller testes and an abnormally low production of testosterone. They can usually initiate puberty, but most do not fully progress through puberty. There are other more rare genetic causes like certain inborn errors of metabolism or testosterone synthetic defects that can result in hypergonadotropic hypogonadism.

The acquired causes are less common. Gonadal insufficiency can result from an autoimmune process, trauma, infection, surgery and irradiation.



Slide 10:

On the other hand, hypogonadotropic hypogonadism is characterized by low, pre-pubertal levels of gonadotropins.

The causes can be pathologic and permanent, meaning that there is an abnormality in the HPG axis.

Some children may be born with an abnormal hypothalamus and/or pituitary gland. There may be a dysfunction in the production, release, or the ability of GnRH to stimulate the pulsatile secretion of LH and FSH from the anterior pituitary. The GnRH deficiency can be isolated or in combination with other pituitary hormone deficiencies.

Many acquired insults to the hypothalamus can lead to hypogonadism, including trauma, tumor, and infiltrative disease.

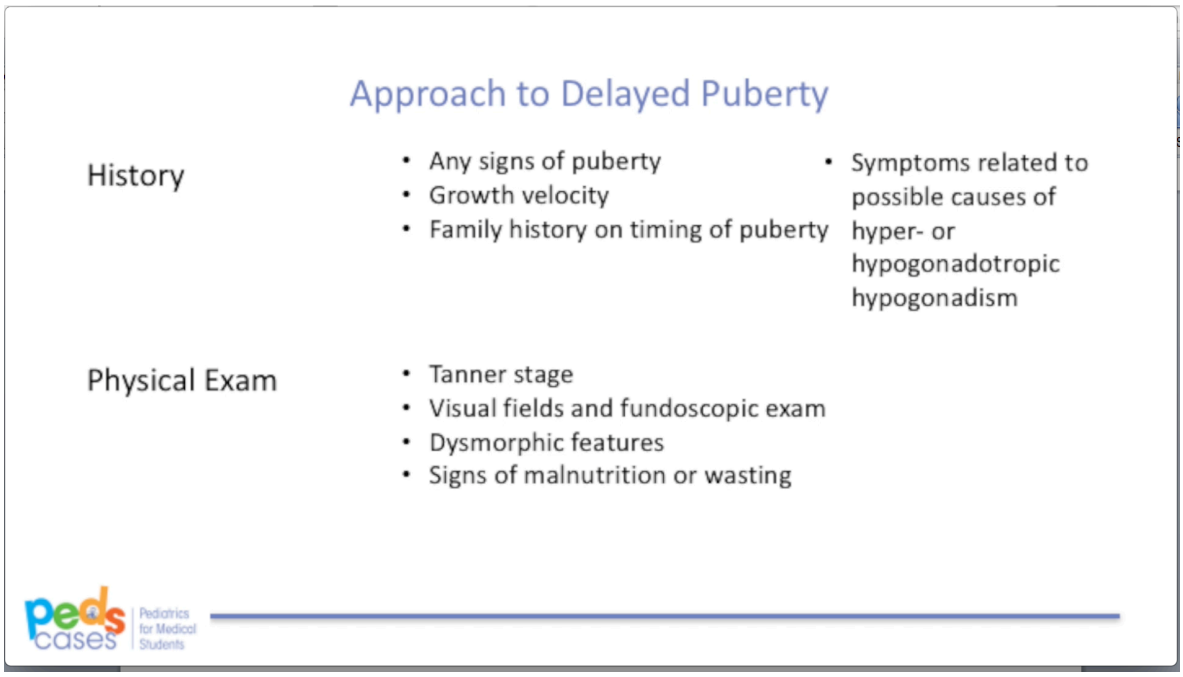
There are also physiologic causes of hypogonadotropic hypogonadism. This means that there are no issues with the hypothalamus, pituitary or gonads, but the HPG axis does not work properly due to systemic illness or physical and/or psychological stress that affect the function of the axis. These are therefore termed physiologic or functional causes.

It could be due to a chronic illness in an organ or system of major significance, like leukemia. The body is already expending so much energy to fight against the disease in order to stay alive, so it cannot afford to use any more resources to allow for further growth and reproductive maturation.

Individuals with eating disorders, such as anorexia nervosa, can also have a negative energy balance and difficulty entering puberty.

In functional hypothalamic amenorrhea or FHA, there is an absence of menstruation or amenorrhea. This can manifest as primary amenorrhea in women who have never started menstruation or secondary amenorrhea in women who were previously menstruating. FHA can be related to weight-loss, stress or exercise. Here again, the body is not prepared to develop any reproductive functions because it is in an overall negative energy state.

Thankfully once we take care of these physiologic problems, the child should be able to go into puberty.



Slide 11:
So how do we approach a child with concerns for delayed puberty?

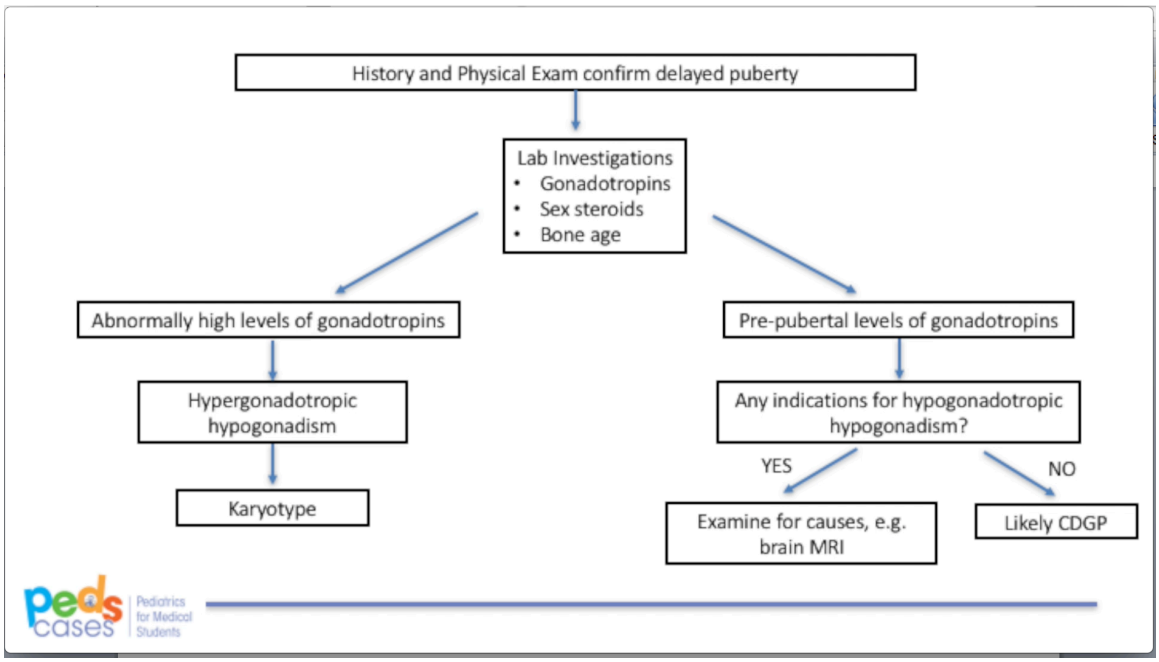
On history, it is important first to ask what they mean by delayed puberty? Are they referring to absent breast development, lack of hair, or something else?

Finding out about their growth velocity is key on a focused history. Individuals with Constitutional Delay of Growth and Puberty, the most common cause of delayed puberty, show a normal velocity on their height trajectory.

Next, we need to know if there are any other late boomers in the family. Genetics is a major determinant of the timing of puberty. If the patient comes from a family where everybody went into puberty early, then he or she is likely to be early. If the patient comes from a family where everybody was late, then he or she is likely to be late.

It can also be helpful to ask questions directed at possible causes of hypogonadotropic hypogonadism and hypergonadotropic hypogonadism. If suspecting hypergonadotropic, we can ask about the gonads, for example, if there was ever any irradiation or mumps. If suspecting hypogonadotropic, we can ask about symptoms of undernutrition, any chronic illnesses, and intracranial pathologies.

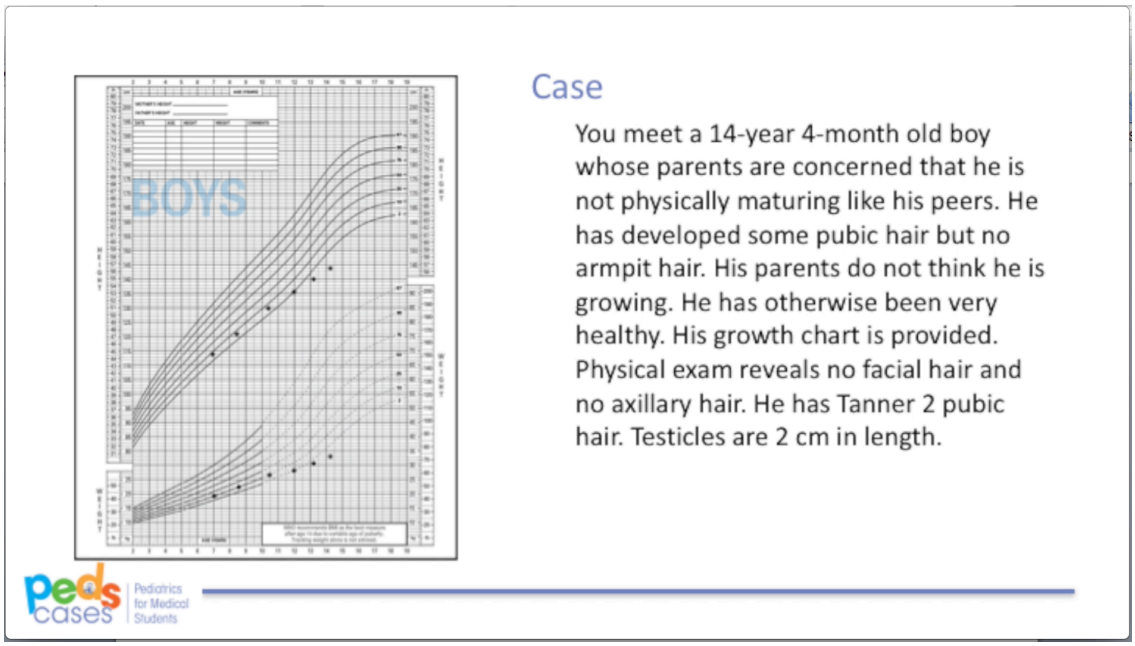
In terms of physical exam, we should confirm that the patient has not entered puberty by Tanner staging the breast development and pubic hair in girls, genital development and pubic hair in boys.
Again, it is recommended to perform visual fields and fundoscopic exam to rule out the possibility of a cerebral mass or tumor that could cause hypogonadotropic hypogonadism.
We can also look for any dysmorphic features that are often seen in genetic syndromes such as Turner Syndrome, and signs of malnutrition or wasting to see if there is a physiologic cause.



Slide 12:
If we continue to suspect delayed puberty in a patient after a focused history and physical exam, we would proceed with investigations. We start by measuring the concentrations of the gonadotropins, LH and FSH, in the blood as well as estradiol or testosterone. We could also check the bone age to see if the child has completed as much growth as their chronological age might suggest. Delayed puberty is typically accompanied by a delayed bone age.

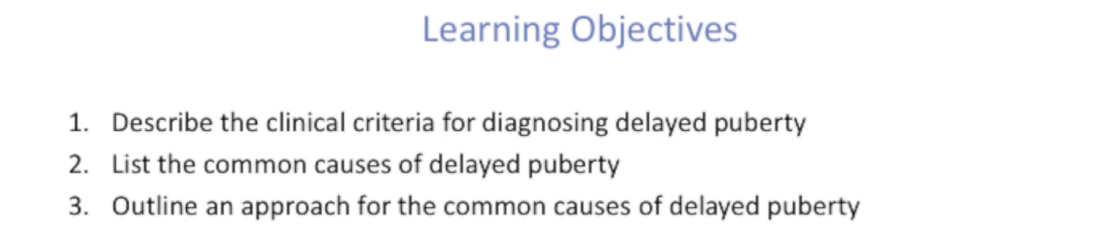
Like precocious puberty, the decision tree splits off, again at the level of gonadotropins. If we see LH and FSH levels are very high, we are dealing with hypergonadotropic hypogonadism. Given that the most common cause is Turner syndrome in girls and Klinefelter syndrome in boys, karyotyping the patient would be warranted.

Now if the levels of gonadotropins are below the pubertal range, this may require a second-line evaluation for causes of hypogonadotropic hypogonadism. If the history and physical exam are normal, we are led to believe that the cause may be Constitutional Delay of Growth and Puberty, which does not require any further work-up. If there are any red flags for hypogonadotropic hypogonadism raised, we would investigate further for underlying causes. We may consider a brain MRI to look for CNS abnormalities that could cause hypogonadotropic hypogonadism.



Slide 13:
Now back to our case.

The boy's lab results came back and showed that he has delayed bone age and pre-pubertal levels of LH and FSH. He appears to be healthy on the basis of history and physical exam, and you strongly suspect Constitutional Delay of Growth and Puberty. You understand that the commonly accepted management for CDGP is a wait-and-watch approach, so you proceed to provide him and his family reassurance and arrange for a follow-up to see the boy in 6 months.



Slide 14:
Let's review our learning objectives for this video. Hopefully by now you are able to:

1. Describe the clinical criteria for diagnosing delayed puberty
2. List the common causes of delayed puberty
3. Outline an approach for the common causes of delayed puberty

We have to come to the end of our three-part series on puberty and pubertal disorders. Thanks for watching.

References

- Lahoti A and Sills I. Update on puberty and its disorders in adolescents. *Adolesc Med State Art Rev* 2015; 26(2): 269-290.
- Palmert MR and Dunkel L. Clinical practice. Delayed puberty. *N Engl J Med* 2012; 366(5): 443-453.