PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Puberty and Pubertal Disorders – Part 1: Normal Puberty.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

# Puberty and Pubertal Disorders – Part 1: Normal Puberty

Developed by Ruojin Bu and Dr. Elizabeth Rosolowsky for PedsCases.com.
April 10, 2018

## Introduction:

Hi everyone. Welcome to the first episode of a three-part series on puberty and pubertal disorders. My name is Ruojin Bu and I'm a medical student at University of Alberta. This entire series was developed in collaboration with Dr. Elizabeth Rosolowsky, a pediatric endocrinologist at the University of Alberta.

Puberty can be both an exciting and a scary time for many pediatric patients. It can be a source of pride for some, embarrassment for others.

In this first episode, we will explore the physiology and clinical presentations of normal puberty. Then in part two of our series, we will discuss an approach to precocious puberty and in part three, an approach to delayed puberty.

## Slide 2:

By the end of this video, the learner should be able to:

- Describe the major hormonal changes of normal puberty
- Recognize the physical signs of normal puberty
- Assess the stages of pubertal development
- Describe the relative timing of pubertal milestones

## Slide 3:

Let's start with a case. During your rotation in a family medicine clinic, you see a 5-year 6-month old girl for concerns regarding the appearance of pubic hair. From history, you learn that her pubic hair started growing 6 months ago. She is otherwise very healthy. On exam, she is on the 30th percentile for height and 20th percentile for weight. Her growth chart appears to have a normal trajectory. She has Tanner stage 1 breasts and Tanner stage 2 pubic hair.

Is this 5 and 1/2 year old girl in puberty? What are the physical signs of normal puberty and how do we evaluate them?

Developed by Ruojin Bu and Dr. Elizabeth Rosolowsky for PedsCases.com.
April 10, 2018.

We will return to this case at the end of the video, but first, let's talk about the basics-what is puberty?

**Slide 4:**
Puberty, as we understand it, is not a single, sudden event. It is a developmental process leading to reproductive maturity and fertility.

Puberty is characterized by:
-the appearance of secondary sexual characteristics, which we will discuss further in this video
-the pubertal growth spurt resulting in final adult height
-the psychological, cognitive and social changes that may extend beyond the completion of physical changes of puberty, and are beyond the scope of this video

**Slide 5:**
The physiology of puberty is very complex, but nevertheless, we can begin by becoming familiar with the components of the hypothalamic-pituitary gonadal axis.

The hypothalamic-pituitary-gonadal axis or HPG axis is an important driver of sexual development and reproduction in both boys and girls. The axis consists of the hypothalamus, pituitary gland and gonads. We know that there are several key hormones that are involved in the interaction between these three components, and there are internal and external cues that influence the function of the axis.

In the hypothalamus of the brain, there are neurons that synthesize a hormone called gonadotropin-releasing hormone or GnRH. GnRH is transported through a group of blood vessels called the hypophyseal portal system to the anterior pituitary, where there are cells that make gonadotropins. "Tropin" means "stimulating", so a gonadotropin is a hormone that stimulates the gonads. These gonadotropins are luteinizing hormone, abbreviated LH, and follicle stimulating hormone, abbreviated FSH. Once arrived, GnRH stimulates the gonadotropin-producing cells of the anterior pituitary to release LH and FSH hormones into the bloodstream. LH and FSH travel to the gonads -- ovaries in females and testes in males -- and stimulate the production of sex steroids. The principal sex steroids are estradiol in females and testosterone in males. The sex steroids are able to moderate the release of GnRH from the hypothalamus and gonadotropins from the pituitary through a negative feedback loop.

**Slide 6:**
The HPG axis has alternating periods of activity and inactivity throughout an individual's lifetime.

During the 2nd and 3rd trimester of pregnancy, the fetal HPG axis is quite active, playing a major role in fetal sexual differentiation and maturation. We see a robust secretion of GnRH from the hypothalamus, causing the release of LH and FSH from the pituitary, followed by the production of testosterone and estradiol from the fetal gonad. Right before birth, however, the activity of the axis is dampened, likely due to the negative inhibitory effects of the circulating sex steroids.

Developed by Ruojin Bu and Dr. Elizabeth Rosolowsky for PedsCases.com.
April 10, 2018.

**Slide 7:**
At birth, the HPG axis becomes active again. We see a surge in GnRH secretion from the hypothalamus. This drives an increase in the production of LH and FSH in the pituitary, leading to high levels of estradiol and testosterone levels that exert a negative feedback control. The levels of circulating gonadotropins and sex steroids can be as high as what is seen in puberty, so sometimes we call this period the "minipuberty of early infancy." But we don't want babies to become reproductive, so fortunately, this axis normally becomes quiet after about 6 months for boys and 18 months for girls.

**Slide 8:**
In the normal physiology of the prepubertal period, we see a net inhibition of the axis. What turns off the activities of the HPG axis is not fully understood, but we are aware that there are a number of different signals that modulate the activities of the axis. These signals can be excitatory or inhibitory in nature. They can come from the central nervous system or the periphery, and may be related to other functions or events happening in the body, such as chronic stress or inadequate nutrition.

We know that the neurotransmitter gamma-amino butyric acid or GABA is found ubiquitously throughout the central nervous system. It acts as a major inhibitory signal in the GnRH neuronal network. Gaba-nergic neurons inhibit the activity of GnRH-producing neurons in the hypothalamus. Consequently, we see a lower level of LH and FSH released from the pituitary, and a lower level of sex steroids made in the gonads. The sexual maturation during the prepubertal period essentially comes to a halt, allowing somatic growth in height and weight to take center stage in childhood.

**Slide 9:**
The onset of the pubertal period is marked by the re-awakening of the HPG axis. What initiates this process is still an active area of research, but we have found that there is a stimulatory neuropeptide called kisspeptin in the arcuate nucleus of the hypothalamus. Kisspeptin may have a role in integrating the incoming signals and amplifying GnRH secretion from the hypothalamus. Interestingly, kisspeptin was discovered in Hershey, Pennsylvania, home of Hershey's chocolate factory, and was named after "Hershey's Kiss", one of its most popular chocolate candies. So after all, puberty does begin with a "kiss" eh?

With an increase in the level of excitatory input, notably kisspeptin, and a decrease in the level of inhibitory input, such as GABA, we see an enhanced GnRH release from the hypothalamus. In turn, more LH and FSH are secreted from the pituitary. Please bear in mind that this is a very simplified explanation of how puberty starts, and a more comprehensive explanation of the mechanisms that control the start of puberty is beyond the scope of this video. Nevertheless, ultimately more sex steroids are made in the gonads. The gonads themselves also increase in size due to the direct stimulation of LH and FSH. We cannot appreciate as readily the enlargement of ovaries in a girl because we cannot see them, but we can see and measure the growth of the testes in a boy.

Developed by Ruojin Bu and Dr. Elizabeth Rosolowsky for PedsCases.com.
April 10, 2018.

**Slide 10:**
Now, it is important to recognize that the hypothalamic neurons that secrete GnRH have an intrinsic pulse-generating capacity. GnRH is released in an alternating up and down, or a pulsatile, pattern. One GnRH pulse produces one corresponding pulse in the secretion of gonadotropin, so LH and FSH are released from the anterior pituitary in the same pattern.

The pulses are characterized by amplitude -- the magnitude of the pulse, and frequency -- the rate at which the pulse is moving. As we will see next, the amplitude and frequency of the GnRH and gonadotropin pulses change from birth to the onset of puberty based on the level of activity in the HPG axis.

**Slide 11:**
When the HPG axis is activated in the fetal period and infancy, we see an increased amplitude and frequency in the pulsatile secretion of GnRH from the hypothalamus and gonadotropins from the anterior pituitary. When the axis becomes quiet in pre-puberty, the pulsatile release becomes less frequent and much smaller. There is a very low level of activity that is not detectable with most assays. At the beginning of puberty, we observe a resurgence in amplitude and frequency when the HPG axis is reactivated.

The amplitude and frequency of gonadotropins, particularly the LH, can serve as an indicator for the onset of puberty. When do you think it would be possible to measure LH and FSH levels? If you said during the infancy period and the puberty period, you would be correct. However, there is a caveat. The early pubertal rise in amplitude and frequency of pulsatile gonadotropin secretions initially occurs when an individual is asleep at night. The levels of LH and FSH are low when the child is awake. This means that measuring the level of gonadotropins during the day is not a reliable way to detect early puberty.
As the HPG axis further matures, the pulsatile secretions begin to take place more frequently during the day so LH and FSH measurements may become more indicative of puberty.

**Slide 12:**
The hormonal changes that we've talked about is what drives the normal, physiologic puberty or true puberty. It is also known as the gonadotropin-dependent puberty because it relies on the activation of the HPG axis. So how do we recognize true puberty clinically?

In a girl, we look specifically for the appearance of a visible breast bud, also known as thelarche. The breast bud refers to the breast tissue that appears in the region deep to the areola. It is important to palpate for the breast tissue because sometimes lipomastia, or subcutaneous fat in the breast region, can mimic the appearance of breast tissue.

In a boy, true puberty is recognized when the volume of the testicle is greater than or equal to 4 mL, or the length of the ovoid testicle is equal to or longer than 2.5 cm. The volume of the testicle can be measured with a special instrument called an orchidometer. We can see from the picture that it looks similar to a beaded necklace with each bead representing a different testicular volume. A volume of 4 mL or more signifies true puberty. In addition to

measuring the volume with an orchidometer, we can also choose to measure the length of the ovoid body with a measuring tape.

**Slide 13:**
There are additional clinical signs of puberty that we may observe.

Including:
Axillary hair, body odor, pubic hair (sometimes called pubarche, referring to the onset of pubic hair), acne, peak height velocity, changes in body composition. Menarche or the onset of menses can be observed in girls. The growth of facial hair can be observed in boys.

Now, you might wonder, what if a girl only has pubic hair but no breast development? What if a boy has acne, axillary hair and pubic hair but no testicular enlargement? Please be reminded that true, gonadotropin-dependent puberty is suggested on the basis of breast development in a girl and testicular enlargement in a boy. Having one or multiple of these physical signs without having breast development or testicular enlargement does not mean that the child is going through TRUE puberty. If axillary or pubic hair development occurs in a girl without breast development or in a boy without testicular enlargement, then the cause of these clinical signs may be due to a gonadotropin-independent process and is not considered TRUE puberty.

**Slide 14:**
Although the timing of pubertal onset and the rate of sexual maturation can be different from person to person, the sequence of events through puberty is quite predictable.

We can describe the progression from early pubertal to full adult appearance using the Tanner Staging, also known as the Sexual Maturity Rating. It is a widely-used system developed by a British pediatrician named James Tanner. The system consists of 5 stages, with stage 1 representing a complete prepubertal state and stage 5 representing the final adult appearance. In girls, the staging is based on the growth of breast and pubic hair. In boys, the staging is based on the growth of the genitals and pubic hair. It takes 3 to 5 years to go from Tanner 1 to Tanner 5 staging.

**Slide 15:**
Let's start by going through Tanner staging in girls.

In stage 1, there is no breast development. Only the papilla, or nipple, sits above the chest wall. There is no pubic hair present.
In stage 2, a little bit of breast tissue appears deep to the areola, which we call the "primary mound," along with an increase in the diameter of areola and papilla. There is sparse, short straight hair primarily along the labia.
In stage 3, the breast, or the primary mound, and areola continue to enlarge but there is no separation in contour. The hair begins to curl, appears considerably darker and has spread onto the mons pubis.

In stage 4, the areola and papilla project off the breast tissue to form a secondary mound. Collectively, we call this “mound-on-mound”. More hair appears but there is no hair on the medial surface of the thighs.
Lastly in stage 5, we see mature female breasts with a further extension of the papilla above the level of areola. Hair has now spread onto inner thighs and the classic feminine adult hair distribution of an inverse triangle is present.

**Slide 16:**
Now let’s turn our attention to Tanner staging in boys.

Tanner Staging of genital development in boys involves changes to the penis, testes, and scrotum.
In stage 1, the testes, scrotum and penis have a prepubertal size and proportion.
In stage 2, there is an enlargement of the testes greater than 4 mL in volume or 2.5 cm in length and thinning of the scrotal skin.
In stage 3, the testes and scrotum enlarge further, and the penis grows significantly, especially in length.
In stage 4, the penis continues to increase in length and circumference, the testes and scrotum continue to enlarge and the scrotal skin darkens in color.
At stage 5, the genitalia reach the size and shape of an adult male.

The growth of pubic hair in boys courses through a similar progression as in girls with the hairs first appearing at the root of penis, as observed in stage 1, and finally spreading to the inner thighs, as observed in stage 5.

**Slide 17:**
Tanner Staging also provides information regarding the expected sequence and timing of other events that happen in puberty. There is a number of salient events occurring during puberty, so when does each event occur relative to each other?

Moving from left to right is the normal sequence of pubertal events seen in the majority of girls.

For girls, the onset of breast development or thelarche marks the first event of true puberty, occurring in Tanner stage 2. This is followed by the appearance of pubic hair, typically within a year. Next we see an acceleration in height. Menarche usually happens 2 to 2.5 years after breast development. Menarche may occur between Tanner stages 3 and 5.

**Slide 18:**
In boys, testicular enlargement is seen as the first event, characterizing Tanner stage 2. Then, we may see the growth of pubic hair within a year, followed by a rapid increase in height. The deepening of voice is rather a late event. Peak height velocity and voice change typically occur during Tanner stages 4 and 5.

**Slide 19:**
When comparing girls and boys, we see that puberty starts on average at a younger age in girls. The average age for breast development, marking the onset of puberty, is 10 and half years with a normal range of 8 to 13 years.

For boys, the average age for the onset of testicular enlargement is 11 years, with a normal range of 9 to 14 years. The timing of the peak height velocity also differs between girls and boys. It occurs in the first half of pubertal development for girls, before menarche.

For boys, the peak height velocity occurs in the second half of puberty. Furthermore, for girls, the peak height velocity (average 8.3 cm/year) is less than the peak height velocity for boys (9.5 cm/year).

So what are the clinical implications of these differences?
First, if the normal range of puberty for girls is 8 to 13 years and for boys 9 to 14 years, then we can set cut-offs for early puberty as being before the age of 8 years for girls and 9 years for boys. Conversely, we can set cut-offs for delayed puberty as being no breast development for girls over the age of 13 years and no testicular enlargement for boys over the age of 14 years.

Second, because boys attain their peak height velocity later than girls and also attain higher peak height velocity compared to girls, men are in general ultimately taller than women, with about a 10 cm height difference on average.

**Slide 20:**
Let's now return to our earlier case.

This is a 5-year 6-month old girl with 6 months of pubic hair development. She is very healthy. She has Tanner 1 breasts, so no breast development, and Tanner 2 pubic hair, where there are a few, short straight hairs mostly along the labia.

Based on this information, we would surmise that she is not going through TRUE puberty since she has no breast development. She has pubarche, or development of pubic hair only. Please stay tuned for part 2 of our series to learn more about how we can approach this case.

**Slide 21:**
To quickly recap the learning objectives for this video, hopefully you are now able to:
- Describe the major hormonal changes of true puberty
- Recognize the physical signs of true puberty
- Assess the stages of pubertal development
- Describe the relative timing of pubertal milestones

Well, this wraps up our video on Puberty Part 1 with a focus on true puberty. We invite you to watch part 2 of our series on an approach to precocious puberty and part 3 on an approach to delayed puberty found on PedsCases.com.

Developed by Ruojin Bu and Dr. Elizabeth Rosolowsky for PedsCases.com.
April 10, 2018.

Thank you for watching!

**Slide 22:**

References:


- Herbison AE. Control of puberty onset and fertility by gonadotropin-releasing hormone neurons. Nature Reviews Endocrinology 2016; 12(8): 452-466.
- Roa J, Tena-Sempere M. Energy balance and puberty onset: emerging role of central mTOR signaling. Trends Endo & Metab 2010; 21(9):519-528.



Developed by Ruojin Bu and Dr. Elizabeth Rosolowsky for PedsCases.com.
April 10, 2018.