DELAYED PUBERTY IN BOYS: A GUIDE FOR PARENTS AND PATIENTS

How is delayed puberty in boys defined?
Boys can start puberty at a wide range of ages, with 95% starting between the ages of 9 and 14, so we consider puberty delayed when it has not started by age 14. The earliest sign of puberty in boys is enlargement of the testicles, followed by growth of the penis and pubic hair. Puberty happens when the pituitary starts making more of two hormones, called LH and FSH, which cause the testicles to grow and produce the male hormone testosterone. The growth spurt usually starts a year or so after the genitals start to enlarge, generally by age 15.

What causes delayed puberty in boys?
By far the most common cause is constitutional delayed puberty (CDP). These boys are generally healthy and will eventually go through puberty if given enough time. In about 2/3 of cases, it is inherited from one or both parents. The mother may have had delayed puberty if she started her periods after age 14, and the father may have had delayed puberty if he started his growth spurt late (after age 16) or if he continued to grow after he graduated from high school. Boys with chronic illnesses such as inflammatory bowel disease, sickle cell disease, or cystic fibrosis often mature late.

A smaller number of boys with delayed puberty have a lifelong deficiency of the puberty hormones LH and FSH, a problem we call isolated gonadotropin deficiency (IGD). This is usually a condition present from birth, and many boys with IGD are born with a penis which is smaller than it should be. Other pituitary hormones in this condition are made normally, and usually growth is normal. Failure to start puberty by age 17 is one sign a boy might have IGD. Another clue is that some boys with IGD also have a poor sense of smell, a condition referred to as Kallmann syndrome. Finally, a few boys with delayed puberty have a problem with the testicles themselves. Because it is easy to determine the size of the testicles on a physical exam, having very small testicles or testicles which cannot be readily felt is a clue to the condition. There are several causes, including previous surgery for undescended testicles or cancer treatments which can injure the testicles.

What are the signs and symptoms of delayed puberty in boys?
The key finding is that the penis and testicles do not enlarge by age 14, which is easily noted on physical exam. Often the testicles have just started to grow but the penis is still small, which suggests that other signs of puberty will appear in the next 6-12 months. Most boys with CDP are short compared with their peers but because they have a delayed growth spurt, they usually catch up to other boys by the time they are 18 and have heights in the normal range as adults.

How is delayed puberty diagnosed?
Sometimes just the physical exam is enough, but many doctors will order some tests to confirm what they suspect and to make sure that the problem is not in the testicles. The most common tests to order are testosterone, LH, and FSH first thing in the morning, when the levels in early puberty are usually higher. Adult testosterone levels vary from 250-800 ng/dL and most boys with delayed puberty have testosterone levels of less than 40. An x-ray of the hand and wrist to determine the bone age is often ordered to help predict adult height, and is typically at least 2 years behind the chronological age, which means that there is more time remaining for growth.
How is delayed puberty treated in boys?

When the problem is constitutional delayed puberty, the problem will resolve with waiting and reassurance. However, late-maturing boys are often impatient to start growing and do not want to wait another 6-18 months for the pubertal growth spurt to start naturally. Therefore, many pediatric endocrinologists may offer a brief course of testosterone to “jump-start” puberty. It is most often given in the form of a monthly injection for several months; different doctors use different doses and number of injections. When the boy is seen back after the injections, there is usually a very nice gain in height and weight as well as growth of the penis and pubic hair, and puberty will in most cases progress without any further treatment. Studies show that a brief course of testosterone will have no effect on the adult height but will allow the boy to get there faster.

When the problem is either isolated gonadotropin deficiency or damage to the testicles, testosterone is still the treatment of choice, but the dose will need to be increased over time and it will need to be continued well into the adult years.

Paul Kaplowitz, MD and the PES/AAP-SoEn Patient Education Committee
How is delayed puberty in girls defined?
Puberty starts when the pituitary gland begins to produce two hormones, LH and FSH, which cause the ovaries to enlarge and begin producing estrogens. The growth spurt starts shortly after breasts begin to develop, and the first menstrual cycle begins about 2-3 years later. A girl who has not started to have breast development by the age of 13 is considered to be delayed.

What causes puberty in girls to be delayed?
1) Some girls with delayed puberty are simply late maturers, but once they start, puberty will progress normally. This is called constitutional delayed puberty, and is more common in boys than girls. Often this is something that is inherited from the parents, so it is more likely to occur if the mother started her periods after age 14 (the average is about 12 ½) or if the father was a “late bloomer”.

2) Decreased body fat is a major cause of pubertal delay in girls. It can be seen in girls who are very athletic, particularly in gymnasts, ballet dancers, and competitive swimmers. It can also be seen in girls with anorexia nervosa, who engage in extreme dieting or binging and purging, because they fear becoming too fat even when they are abnormally thin. Finally it can be seen in a number of chronic illnesses where body fat is often decreased.

3) Some girls with delayed puberty may have problems with their ovaries. The ovaries are either not developing properly or being damaged. This is referred to as primary ovarian insufficiency. The major cause present at birth is Turner syndrome, in which all or part of one of the 2 X chromosomes is missing. Most of these girls are also extremely short for their age, and may have certain distinctive physical features, such as webbing of the neck, a high-arched palate, or arms which bend outward when extended. However, in most cases, Turner syndrome is diagnosed well before age 13 due to short stature. The major acquired cause of ovarian insufficiency is damage to the ovaries due to radiation, usually to treat leukemia or certain other kinds of cancer. Occasionally, girls may have their ovaries damaged by the body’s immune system.

4) Finally, some girls fail to start puberty because of a lack of the pituitary hormones LH and FSH, called gonadotropins. This can occur when there are other pituitary deficiencies as well, including growth hormone, or it can be an isolated finding (particularly in a girl who is delayed but not short).

How is delayed puberty in girls diagnosed?
The endocrinologist will order blood tests to measure levels of LH, FSH, and estradiol and in some cases other tests. Very high levels of LH and FSH will indicate that the ovaries are not working properly, and the pituitary is trying to stimulate them to work harder. If the cause of the ovarian insufficiency is not clear, a chromosome study or karyotype will be done to see if all or some cells are missing all or part of an X-chromosome. If the LH, FSH, and estradiol are all low, the problem could be either decreased body fat (if one of the risk factors listed above is present) or a permanent deficiency of LH and FSH. Other tests may be ordered if deficiency of multiple pituitary hormones is suspected, and on occasions, a brain MRI may be helpful. A hand x-ray for a bone age is often done, which is typically delayed by 2 or more years, which means that there is still additional time to grow.
How is delayed puberty in girls treated?
In girls with constitutional delayed puberty, breast development will eventually start on its own. Giving estrogens for 4-6 months is sometimes used to help get things started sooner. For girls with delayed puberty and decreased body fat, sometimes eating more and gaining weight will help get puberty started. For girls with primary ovarian insufficiency or a permanent deficiency of gonadotropins, long-term estrogen replacement is needed and can be given either in the form of a daily tablet of estradiol or as a patch which needs to be applied to the skin twice a week. Doctors usually start on a low dose, and often increase the dose about every 6 months. After 12-18 months, it is typical to start a second hormone called a progestin (e.g. Provera) which will, after a few months, result in a period usually within a couple of days of stopping the progestin. You may ask your endocrinologist to discuss with you and your child what is known about your child’s potential for fertility.

Paul Kaplowitz, MD and the PES/AAP-SoEn Patient Education Committee
**Congenital Adrenal Hyperplasia (CAH): A Guide for Parents and Patients**

**What is CAH?**
CAH is a disease caused by a lack of an enzyme in the adrenal glands. The adrenal glands are glands that sit on top of your kidneys. The adrenals make 3 types of hormones; mineralocorticoids, cortisol and androgens. Mineralocorticoids (the main hormone is aldosterone) control salt balance in your body. Cortisol is a natural steroid. It normally rises in the early morning and whenever you are sick or stressed. It maintains your body’s homeostasis (equilibrium) and is essential for life. Androgens are sex hormones and are responsible for hair under the arms and in the pubic area. In CAH, the adrenal gland is not able to make cortisol, but instead makes too much androgens. CAH is caused by inheriting 2 abnormal genes from both of your parents for an enzyme (specific type of protein) that is needed to make cortisol. The most frequent enzyme affected is called the 21-hydroxylase. Absence of this enzyme results in very high levels of the hormone 17-hydroxyprogesterone.

In the most severe form of the disease (salt-wasting), someone with CAH will lose too much salt in their urine as they do not make enough mineralocorticoids. The females may be virilized from too much androgens. In the non-salt wasting form, which is milder, the patient is able to maintain salt balance, but still has too much androgens. Both types present either shortly after birth or within a few weeks after. A much milder form presents later in childhood with early pubic hair or adult type body odor. This is called non-classical CAH.

**How frequent is CAH?**
In the general population, the most severe form of CAH (classical) occurs in approximately 1 of 15,000 people. This is an autosomal recessive condition and requires that a defective gene be inherited from each parent, but the parents, who are called carriers, are not affected. When both parents have a defective gene, there is a 25% chance of having an affected child in each pregnancy. The non-classical form of CAH occurs in around 1 of 100 people.

**How is CAH Diagnosed?**
The classical form of CAH (salt-wasting and non-salt wasting) is screened on the newborn screen in every state in the United States. The newborn screen measures the level of 17-hydroxyprogesterone, a hormone that is eventually made into cortisol in unaffected people. In the most common form of CAH, 17-hydroxyprogesterone cannot be broken down effectively and it builds up to very high levels. In baby boys, the disease is not usually suspected at birth. The diagnosis is made when the newborn screen results come back high or the baby becomes sick in the first month of life. In a baby girl the diagnosis may be suspected if her genitalia show evidence of exposure to high levels of androgen, or a disorder of sexual development. In such a case, the infant may have an enlarged clitoris, labia that are fused together or may have genitalia that look very similar to a male except that the testes are missing. If an infant has a disorder of sexual development or the newborn screen for CAH comes back high, your baby’s doctor, will draw blood from your infant to measure the level of 17-hydroxyprogesterone and salt level in the blood. Sometimes, other hormones are measured as well.

**How is CAH Treated?**
Since the basic defect is a block in the synthesis of the hormone cortisol, the main treatment for classical CAH is to replace cortisol. The most common medication used is called hydrocortisone. This is usually given three times per day. A mineralocorticoid called fludrocortisone is also used to increase holding onto sodium (salt) and getting rid of potassium in the urine. Sometimes in infants extra salt is also given. Since people with classical CAH cannot make cortisol efficiently, they must take extra hydrocortisone.
when they are sick to maintain their body’s balance (homeostasis). This is very important to remember as an ill patient (fever, vomiting) with classical CAH that does not get extra steroids may become sicker and may even die. Patients with non-classical CAH can make cortisol normally, so do not always need treatment. If patients with non-classical CAH have significant effects from too much androgen, they are sometimes treated with a small dose of steroids.

Can CAH be Prevented?
CAH cannot be prevented. However, experimental treatment is available to pregnant women who are carrying affected female fetuses. This involves treating the pregnant mother with steroids as soon as she knows that she is pregnant. This treatment may result in decreased male hormone levels in the fetus and therefore, less virilization of the genitalia. Since all of the side effects are not fully known, this remains an experimental and controversial treatment.

-Kathleen Bethin, MD, PhD and Teresa Quattrin MD, PES/AAP-SoEn Patient Education Committee
Polycystic Ovary Syndrome

What is polycystic ovary syndrome (PCOS)? It is a health condition that some girls have, with symptoms of excess body hair (hirsutism), severe acne, and menstrual cycle problems. The excess body hair can be on the face, chin, neck, back, chest, breasts, or abdomen. Problems with the menstrual cycle can be heavy, long-lasting periods, months without any periods, or periods that happen too often. Some girls, but not all, have several small cysts on their ovaries. About 60-70% of girls with PCOS are overweight or obese, but some are normal weight or thin. Sometimes girls may have mothers, aunts, or sisters who have a history of the same problems, or family members with type 2 diabetes. Sometimes PCOS is called “ovarian hyperandrogenism”. This means that the ovaries make too much androgens. Androgens are the hormones that cause hair growth and acne in puberty and adults.

What causes PCOS? This is not completely known. It does seem to “run” in families. It also seems to be related to being insulin resistant in most girls. Insulin is the hormone that the body uses to take sugar from the blood and put it into the body’s cells for energy. Being insulin resistant means that a girl’s body has to make more insulin to keep her blood sugar, or blood glucose, normal. Being insulin resistant makes the body’s insulin levels higher, and higher insulin levels can make the ovaries produce too much androgens, preventing regular menstrual periods. Some girls who are insulin resistant have problems with blood pressure or cholesterol too, which are risks for heart disease in adults.

Some genetic differences in the ovaries and/or adrenal glands of girls may also cause PCOS.

How is PCOS diagnosed? PCOS is diagnosed by testing adrenal, thyroid, pituitary and ovary hormones to be sure that other diseases are not causing problems with periods, body, hair, and acne and then sometimes by having an ultrasound of the ovaries to look for a string of small cysts along the outsides of the ovaries. There is not a single lab test to absolutely diagnose PCOS: the diagnosis is made by ruling out other diseases and recognizing the combination of problems with periods, acne, body hair, and often, insulin resistance that are seen in PCOS.

How is PCOS treated? Treating PCOS means treating acne, excess body hair, and abnormal menstrual periods if those are present and also treating insulin resistance if it is present. Acne can be treated with medication applied to the skin, antibiotics, estrogen and progesterone medication taken by mouth (which also regulates periods), or a pill called spironolactone which blocks the androgens that cause the acne. Extra body hair can be prevented with estrogen and progesterone medication by mouth or spironolactone. Many girls also try different ways to get rid of the unwanted hair, using laser treatment, waxing, or shaving. A medication called Vaniqua can be applied twice a day to unwanted areas of hair to prevent new hair from growing. It is usually not covered by insurance and must be used every day, or the hair will grow back.

Abnormal menstrual periods can be treated several different ways. Many girls take an oral contraceptive, a pill containing estrogen and progesterone, to regulate periods. Other girls take 5-10 days of a pill called progesterone every 1-3 months to have a period. Other girls choose to use an estrogen and progesterone patch or intrauterine device (IUD). Some girls cannot use some of these medications because of other health conditions they have, so it is important to share your whole medical and family history with your health provider.

Metformin is a medication that may be used to treat PCOS. It helps the body to use insulin better, and can be associated with a small amount of weight loss. It has not yet been approved by the FDA (Federal Drug Administration) to be used for PCOS but it is usually safe and often helps. Other ways to improve insulin resistance are to have at least 150 minutes of physical activity that raises the heart rate every week and to have a healthy diet. The helpful type of diet will not have sweet drinks like sodas in it and will avoid too much concentrated carbohydrates and processed foods.

Although some women with PCOS may have difficulty becoming pregnant, a girl with PCOS can become pregnant, even if she is not having regular periods. Anyone with PCOS who is having sex should use contraception if she does not wish to become pregnant. If a woman with PCOS wants to have a child and is having difficulty becoming pregnant, many options are available to allow pregnancy to occur. Some PCOS medications cannot be used during pregnancy, so discuss your plans honestly with your healthcare provider.

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