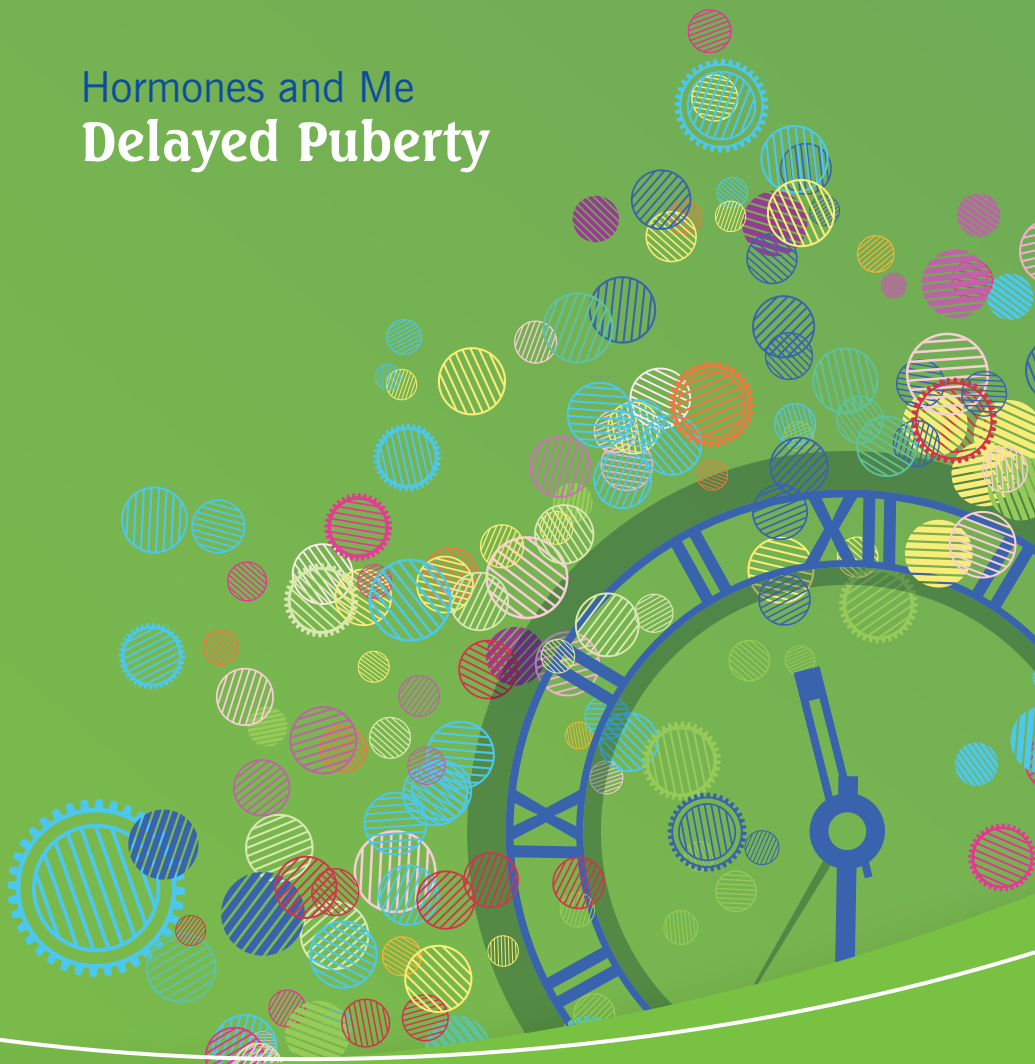


Hormones and Me Delayed Puberty



ANZSPED

AUSTRALIA AND NEW ZEALAND
SOCIETY FOR PAEDIATRIC
ENDOCRINOLOGY AND DIABETES

Delayed Puberty

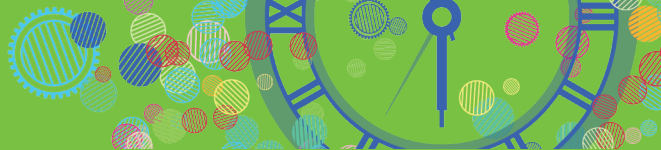


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About this Book

This booklet, *Delayed Puberty*, aims to give you a basic understanding of the course of puberty and development, and how this may be delayed in some adolescents.

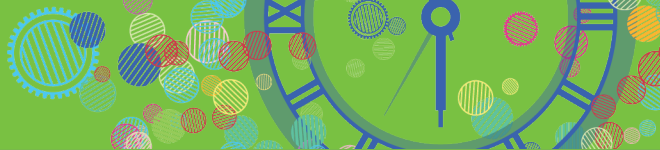
We encourage you to discuss any additional questions or areas of concern with your doctor after reading this booklet.

Merck is proud to bring you this booklet from the Hormones and Me educational series. We hope that you find it a valuable and helpful resource.

This booklet was revised in 2024 by Dr Gabby Atlas (Royal Children's Hospital) and Prof Margaret Zacharin (Royal Children's Hospital) on behalf of the Australia and New Zealand Society for Paediatric Endocrinology and Diabetes (ANZSPED), previously APEG.

The previous booklet was reviewed in 2018 by Prof Margaret Zacharin (Royal Children's Hospital, VIC, Australia) – a Paediatric Endocrinologist specialising in childhood endocrine disorders and a member of the Australasian Paediatric Endocrinology Group (APEG).

This booklet was first updated and reproduced for Australian and New Zealand readers in 2000 by Dr Geoffrey Byrne, (Princess Margaret Hospital, WA, Australia). Special thanks to the original authors and editors, Dr Richard Stanhope (Great Ormond Street Hospital for Children and the Middlesex Hospital, UK), Mrs Vreli Fry (Child Growth Foundation, UK), Professor Leuen Hughes (Addenbrookes Hospital, UK) and the British Society of Paediatric Endocrinology (BSPE).



Introduction

Puberty is a time of great transformation for any adolescent, even when it follows a 'normal' course. There are changes to almost all aspects of a young person's life; academic demands increase, social relationships become more complex, independence to some may seem daunting and the physical changes of puberty can be challenging.

When puberty comes early or late, this can cause further difficulties. Family and friends need to be supportive of the young person as he or she comes to terms with 'being different' from peers.

This booklet has been written to help you understand more about 'normal' puberty as well as its variants, particularly delayed puberty.

“Delayed puberty is an extremely common condition in both boys and girls.”

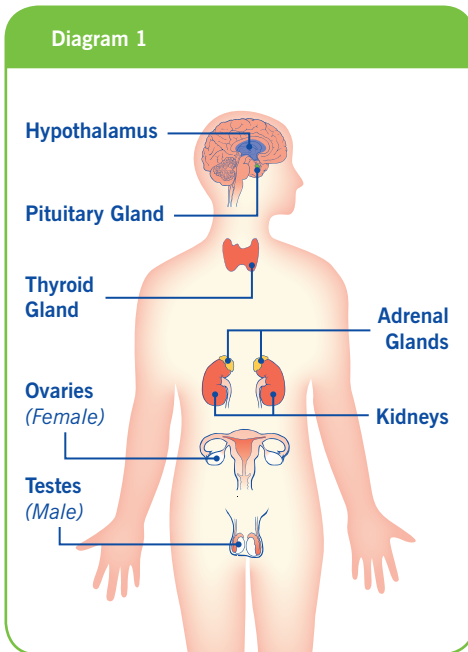
Hormones

Hormones are chemicals that carry messages from one part of the body to another via the blood stream. Hormones are produced by endocrine glands (such as the pituitary gland) and play a vital role in regulating growth, development and metabolism. The body makes many hormones (e.g. thyroid, growth, sex and adrenal) that work together to maintain normal body functions.

The Control of Hormone Secretion

The regulation of hormone production begins in a part of the brain called the hypothalamus, located just above the pituitary gland (see *Diagram 1*). The hypothalamus sends chemical messages to the pituitary, a pea-sized

gland at the base of the brain. In turn, the pituitary, responds to these messages by producing a number of different hormones. The pituitary is often referred to as the 'master gland', as it regulates the release of most of the body's hormones. Some of these hormones have a direct action on the body (e.g. growth hormone) whilst some stimulate other hormone producing glands in the body, such as the thyroid gland, adrenal glands and sex hormone glands (ovaries and testes) (see *Diagram 1*).



Hormones Controlling Puberty

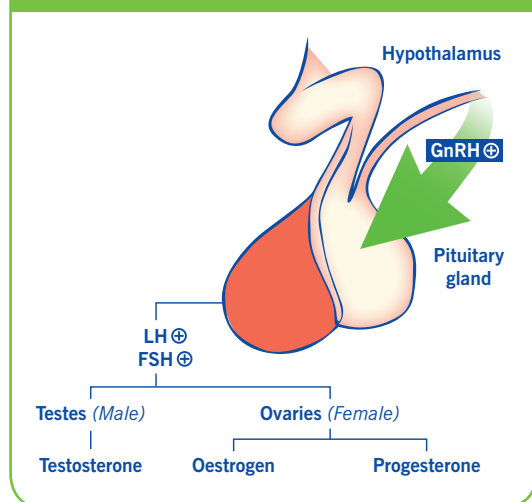
There are a number of hormones, which directly trigger and control the course of normal puberty.

Gonadotrophin Releasing Hormone (GnRH)

This hormone is released by the hypothalamus and controls the release of the ‘gonadotrophins’; luteinising hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland. The release of this hypothalamic hormone is the most important control mechanism regulating pubertal development and fertility. Both LH and FSH in turn act on the ovaries (girls) or testes (boys), to initiate the release of oestrogen or testosterone. Oestrogen and testosterone are often referred to as “sex hormones” and they are responsible for the development of pubertal characteristics (growth and secondary sexual characteristics)

as well as changes in behaviour (see *Diagrams 2 and 3*).

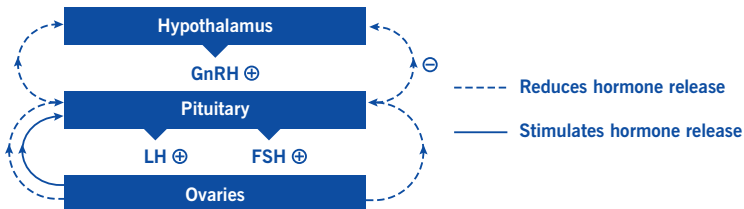
Diagram 2



Hormones and Me

Delayed Puberty

Diagram 3



Gonadotrophins

Follicle Stimulating Hormone (FSH)

This hormone is released by the anterior lobe of the pituitary gland. It stimulates the ovaries and testes to produce eggs and sperm respectively.

Luteinising Hormone (LH)

This hormone is also released by the anterior lobe of the pituitary gland. It stimulates the release of female and male sex hormones from the ovaries and testes.

Sex hormones

Oestrogen

A female sex hormone, which is secreted by the ovaries. It is responsible for breast development in girls, and maturation of the uterus.

Testosterone

A male sex hormone (an androgen) which is secreted by the testes. Other milder androgens from the adrenal glands (located near the kidneys) stimulate pubic and underarm hair growth at the time of puberty in both boys and girls.



Typical Puberty

The early changes of puberty usually occur between the ages of 10–13 years. They are noticeable in girls by the budding of breasts and then pubic hair, with menstrual periods starting between 11–14 years of age. Boys usually develop testicular enlargement and then pubic hair (9–14 years). Underarm and facial hair and deepening of the voice occur typically between 13–16 years.

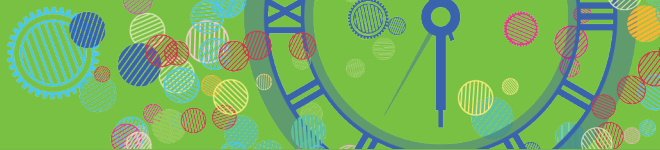
“The difference between the average age of onset of puberty between girls and boys is only 6 months, although it is often thought to be several years!”

In girls, the growth spurt occurs early in puberty and commences at the same time as the onset of breast development, with growth slowing down after the onset of the first period. In contrast, boys have a growth spurt which occurs later, commencing halfway through puberty. The difference between the average age of onset of puberty between girls and boys is only 6 months, although it is often thought to be several years! This is probably because the early events of puberty in boys are hidden whereas breast development in girls is much more socially obvious. In addition, the later growth spurt in boys only maintains this common misconception. The growth spurt of puberty depends on both growth hormone and sex hormone secretion.

Delayed Puberty

The hormonal changes at puberty start very gradually. It is only when the level of sex hormones reaches a threshold that the development of sexual characteristics is stimulated and puberty is described as having commenced. However, the hormonal events of puberty have usually started several years prior to the onset of the appearance of secondary sexual characteristics.

It is when these changes begin earlier than 8 years in a girl and 9 years in a boy that an assessment needs to be made by a specialist, to determine what is causing the early pubertal development.



Common Variations of Pubertal Development

Early Normal Puberty

In many countries including Australia, children appear to be going through puberty at a younger age than in previous generations. This is known as the secular trend in growth and development. The earlier age of puberty happening nowadays can most likely be explained by the improvements in nutrition and living circumstances and the lack of chronic disease in childhood. This trend seems to be particularly true for girls, with many showing signs of breast development at 8 years of age or later.

This means some girls will start to have menstrual periods while still in primary school. In most cases such instances of early puberty are merely a variation of normal. After assessment by a specialist, if puberty and height are normal, no specific treatment is usually required. Often simply explaining the situation to the girl and her family is all that is needed, although sometimes a child psychologist is required as well. Involving the teacher is another good strategy to help the child cope at school.

Delayed Puberty

Delayed puberty is defined as lack of any pubertal development by 13 years of age for girls and 14 years for boys. Delayed puberty is most often due to a constitutional (familial) delay or is associated with chronic disease.

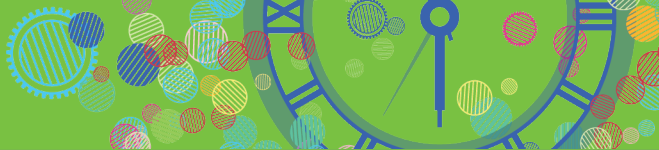
Delayed Puberty

Constitutional delay is a normal variant of puberty which doesn't require specific treatment, however when delayed puberty is associated with a chronic disease or hormone deficiency the underlying cause should be treated.

“Delayed puberty is defined as lack of any pubertal development by 13 years of age for girls and 14 years for boys”.

Delayed puberty usually isn't a problem, however some boys may experience behaviour and self-esteem issues, more so than girls. Boys with delayed puberty may be teased about their lack of development or left out of sporting teams. Girls with delayed puberty may feel different to their peers, and feel left out of discussions about periods, clothes and other such topics of conversation. Whilst these concerns may seem trivial, on occasions they can lead to significant behavioural problems, including truancy.

It is important to identify and address such issues, with the help of a child psychologist if needed, early on.



Growth During Puberty

Growth

Children grow at a relatively constant rate throughout childhood, until just before the start of puberty when the speed of growth (growth rate) slows down to its lowest point; that is the beginning of breast development in girls, and the appearance of pubic hair and testicle growth in boys. After puberty starts, the growth rate rapidly increases, which is known as the 'pubertal growth spurt'. If puberty is "late" or "delayed", the very low growth rate that occurs just before puberty will continue until puberty starts, and as such the adolescent will grow at a much slower rate than those of the same age with normal timing of puberty.

The pubertal rapid growth phase or pubertal growth spurt, lasts for about 2 years, and starts around 2 years earlier in girls than in boys. During puberty the peak growth rate for girls is 6–11 cm per year starting at around 11.5 years of age. The peak growth rate for boys is 7–12 cm per year starting at around 13.5 years of age.

After the pubertal growth spurt growth continues at a slow rate for several years, until the growth plates (the gaps at each end of the long bones, which allow the bone to grow) are fused and the bones cannot get any longer (see p13 for further information on growth plates). For girls, most of their height is achieved after 18–24 months of having periods, at which time their skeletal development is mature and their growth plates are fused. An x-ray of the wrist, called a bone age, can determine whether the growth plates are mature and have fused (usually a bone age of >13.5 years in girls and >15.5 years in boys). This is termed "near final height" because at this bone age they would have achieved 97.5% of their final adult height.

Hormones and Me

Delayed Puberty

Delayed puberty

Diagram 4a shows the growth of a boy who had both short stature AND delayed puberty, similar to that reported by his father (i.e. familial growth delay). He was 16 years old when he commenced his growth spurt. Prior to that he did not display any secondary sexual characteristics (testicular enlargement, pubic hair etc) and his height had progressively fallen away from the lowest 3% of the population.

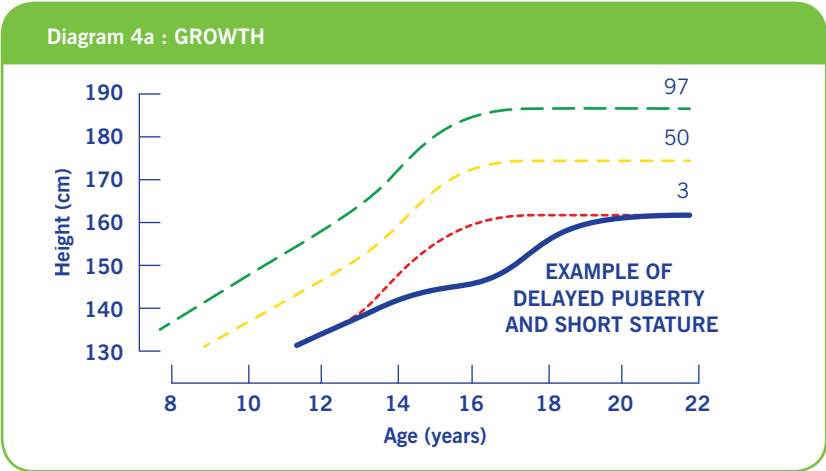
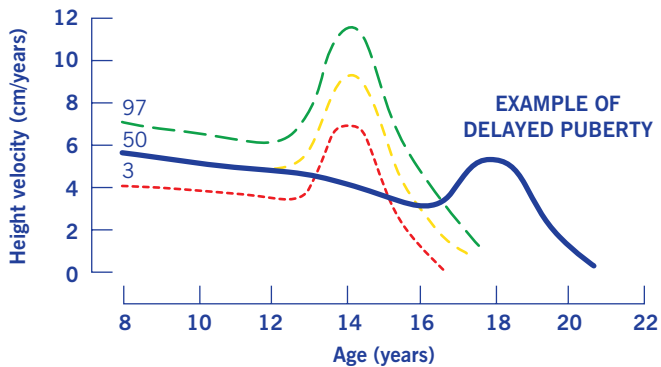


Diagram 4b depicts the growth “velocity” also known as “growth rate” for the same boy. It shows that when the growth spurt is delayed the peak growth rate is lower than expected, however the final height achieved is in fact the same as expected.

Diagram 4b : VELOCITY



Bone Age

At either end of a child's long bones, there are gaps, called growth plates, which allow the bone to grow. During childhood, these gaps gradually get smaller and by the time puberty is complete they disappear, the growth plates 'fuse' and the bones cannot get any longer. Once all of the growth plates are fused, the potential for further growth, or height gain, is minimal.

Bone age is a measurement of biologic age rather than actual or chronologic age. It is a useful measurement which allows assessment of remaining growth potential for a child or adolescent. A simple X-ray is taken of the left hand and wrist, and this is compared with a set of photographic standards to assess how mature the child's bones are, or in other words, how open the growth plates are.

Delayed Puberty

Measuring bone age allows the doctor to predict how much further growth is possible. For example if the bone age is younger than the actual, or chronological age of the child, there is potential for more growth to occur. Think back to the boy in Diagrams 4a and 4b; if his bone age was two years younger than his actual age, he would be expected to continue growing for two years more than most boys and thus should finish growing at 19 years of age instead of 17 years like most boys.



Delayed Puberty

Approximately 95% of girls and boys have commenced puberty by 13 years and 14 years respectively. After this puberty is considered to be delayed.

DELAYED PUBERTY : NO PUBERTAL DEVELOPMENT OR GROWTH SPURT

13 years in girls

14 years in boys

Causes of Delayed Puberty

Puberty may be delayed due to a number of reasons, summarised under the following two types:

Constitutional Delay

As mentioned earlier, the most common cause of delayed puberty is 'constitutional delay', a variant of normal puberty and growth whereby the bone age will be delayed, indicating that further growth is possible. Where there is a history of delayed puberty in parents, siblings or extended family it is known as 'familial delay'. If there is no family history, it is known as 'idiopathic delay'. A history of delayed puberty can be assessed in females by asking when the first period was, whereas a history of delayed puberty in males is often not so easy to ascertain. A male can usually state roughly the age at which his growth spurt took place. This gives a good idea that he was in late puberty at that time.

Medical (rarer) causes

Delayed puberty may be caused by a medical condition. In such cases growth velocity will be slow, and bone age may be normal or delayed. Medical review and investigation will be required. Medical conditions which may lead to delayed puberty include:

- Chronic (long term) illnesses; such as kidney disease, severe asthma, cystic fibrosis, rheumatoid arthritis, coeliac disease, inflammatory bowel disease or hypothyroidism.
- Failure of the ovaries or testes to produce enough of the sex hormones also known as sex steroids (oestrogens, testosterone) required for puberty; a common problem for girls with Turner Syndrome or boys with Klinefelter Syndrome, this also occurs after some treatments for childhood cancer, or in rare conditions where the ovaries become scarred, e.g. galactosaemia. With some of these problems, puberty



may be delayed or might start then fail to progress normally to a full adult appearance.

- Failure of the pituitary gland to make gonadotrophins (FSH and LH); such as hormone deficiencies that are sometimes inherited or following some treatments for childhood cancer.
- Delayed progression of puberty and menstruation in individuals with eating disorders, and in some ballet dancers, gymnasts and athletes; often related to weight or energy expenditure.

Medical Assessment

In the initial assessment of any adolescent with delayed puberty, the doctor will need information on their medical history, general health, growth and the onset of puberty in parents and other family members. The combination of short stature with delayed puberty reduces the number of possible causes, therefore the adolescent's height will be carefully measured and compared with any previous measurements. A medical examination will be needed to rule out any medical conditions, such as chronic illness and to determine the absence, or stage of pubertal development. Boys will have their testicular development assessed by comparing the size of the testes with a set of standard measurements. In girls, the presence of ovaries and ovarian size can be assessed by an abdominal ultrasound of the pelvis.

“A medical examination will be needed to rule out any medical conditions, such as chronic illness, and to determine the absence, or stage of pubertal development.”

Investigations

The findings of the initial examination will dictate which investigations your doctor will undertake. The following investigations may be appropriate in some patients but your doctor will decide what is most appropriate for your child.

1. X-ray of the wrist to determine bone age
2. Pelvic ultrasound in girls
3. Measurement of gonadotrophin and sex hormone levels if gonadal failure is suspected.
4. Chromosome assessment to exclude Turner Syndrome in all girls with delayed puberty and/or short stature. Chromosome testing may be needed in some boys if Klinefelter syndrome is suspected.
5. Blood tests to screen for a number of chronic diseases e.g. kidney disease, coeliac disease, inflammatory bowel disease.



Treatment of Constitutional Delay of Puberty

Constitutional delay of growth and puberty is more often seen as a “problem” in boys than girls and there is often a similar history in parents or close relatives. Reassurance may be all that is needed for adolescents who have already commenced puberty and are expected to achieve an adult height predicted by their parents’ heights.

If puberty is very delayed some adolescents, particularly boys, may not cope with being shorter and looking much younger than their peers, or may be embarrassed by the lack of secondary sexual development. Although these adolescents do not have a medical disorder, because of their anxiety and the associated behavioural changes, treatment with sex steroids (also known as sex hormones) may be necessary to increase the growth rate and to gently advance the timing of puberty. Some refer to this as “kick-starting” their puberty. Once puberty has started, treatment with sex hormones is stopped and the adolescent’s normal progression of puberty is allowed to continue.

GIRLS

Treatment of girls with constitutional delay of puberty is not common and must be done by an experienced paediatric endocrinologist. The aim of therapy is to initiate the growth phase of puberty and to induce early breast development. Adolescents must be closely monitored to avoid over-treatment. Treatment involves giving a very small amount of oestrogen (approximately one eighth of the usual adult dose) either daily or every second day, for up to 12 months. Oestrogen can be given as an oral tablet, transdermal patches, or gel. Starting an adolescent girl on “the pill” or oral contraceptive, straight away will significantly accelerate bone maturity and reduce her final height, so this **MUST** be avoided.

BOYS

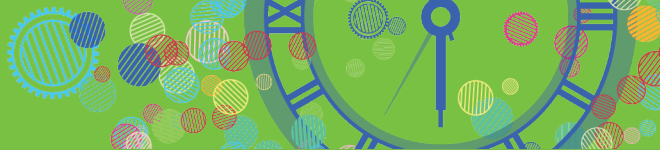
Treatment of boys with constitutional delay of puberty is commonly prescribed under the care of paediatric endocrinologists. Low dose testosterone given in tablet form or as an injection into the muscle, is used to induce puberty over a 6–9 month period of time. Treatment may be started if boys are >14 years of age and still not in puberty. Once puberty is established, treatment is stopped and the boy's normal pubertal progression and growth is allowed to continue. Final height and fertility are not affected.

Risks of treatment

The risks of treatment are minimal, although rarely allergy or side effects of the medications can occur. It should be emphasised that in both sexes, the use of these growth promoting sex steroids increases the rate of growth and shortens the time to achieve adult height, but does not increase final height.

These treatments should be used cautiously to avoid any acceleration in bone maturity with the risk of reducing final height.

Growth hormone treatment of children with constitutional delay of puberty does not accelerate growth more than treatment with sex steroids. Additionally there is no evidence to show that the use of growth hormone in these children results in a significant increase in final height.



Treatment of Other Causes of Delayed Puberty

Treatment of children with chronic illness and delayed puberty should focus on management of the illness and often the re-commencement of normal puberty will follow.

Anorexia Nervosa is a very common condition, seen more often in girls than boys. It requires multi-disciplinary care from a specialised adolescent health team. Part of the care should include assessment of bone health and puberty by an endocrinologist. Delayed puberty or puberty that arrests or regresses is common when weight is very low and a girl's nutrition is poor. Use of oestrogen supplements to help the situation may be advised.

Adolescents with delayed puberty due to the lack of gonadotrophins (FSH and LH) or absence or failure of the gonads to produce the sex hormones, require long-term treatment with sex steroids. Both females and males need these sex steroids to increase growth and produce secondary sexual development. They are also important for both sexes to increase bone density and prevent future osteoporosis (bone fragility). Girls' bones are generally smaller than those of a boy, with a finer structure. Thus, with the passage of time and adult health problems, although the rate of bone loss is the same in women and men, a woman's bones are more prone to osteoporosis in later years.

“The adolescent should be encouraged to discuss all aspects of the diagnosis and the need for and timing of treatment with the specialist.”

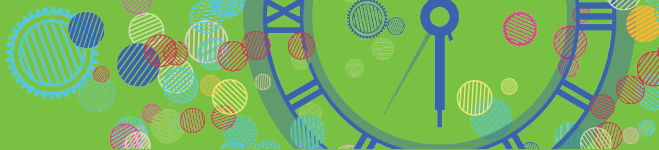
Long Term Treatment

People who will never produce their own sex steroids, such as those with gonadotrophin deficiency or non-functioning gonads, will require life-long sex hormone replacement therapy (HRT). In these cases, long term HRT is needed to maintain general health and energy, normal cardiovascular function and lipid status, normal sexual function and the quality of skin muscle and bone, and therefore definitely cannot be stopped at the end of pubertal development and growth.

The adolescent should be encouraged to discuss all aspects of the diagnosis and the need for and timing of treatment with the specialist. The adolescent in consultation with their parents should, wherever possible, decide the best time to start treatment.

Girls are usually started on a low dose of oestrogen given by oral tablets, transdermal patches or gel. The dose will be gradually increased depending on the rate of pubertal development and growth. It is important that the initial dose is not too high, otherwise the breasts may develop abnormally, and can have an unusual shape which may be permanent. The oral contraceptive pill **SHOULD NOT** be used to induce puberty, but may be used later down the track. Within a year of starting oestrogen, progesterone is added to commence the menstrual cycle. Continuous treatment with oestrogen is important to increase bone density during puberty, therefore even at this stage the oral contraceptive pill is usually not suitable because it only contains oestrogen in 21 of the 28 tablets for each month.

Boys are usually started on a low dose of testosterone, given by oral tablets, injections or gel to initiate secondary sexual development. The dose is increased based on growth rate and the speed of pubertal



development. Once growth and puberty are almost completed then testosterone injections, implants, patches or gels are used for ongoing lifelong hormone replacement. As testosterone injections may need to be given more frequently than once per month some young men choose to have an implant of testosterone placed under the skin every 5–6 months. However, there is now a long acting slow release testosterone preparation available, given by intramuscular injection once every 3 months. This is a satisfactory alternative for boys who need long term or permanent testosterone replacement. It should not be used for treatment of simple constitutional delay of puberty as it is too strong and may advance the bone age too quickly. It may fuse the bone ends too fast and lose a small amount of growth potential. Testosterone patches, which can be placed on the back or buttocks are now available, and are an option although their use is limited if skin irritation occurs.

Questions and Answers

Is there anything wrong with an adolescent who has delayed puberty?

Constitutional delay of growth and puberty is a condition and not a disease. The body clock has slowed down, physical development and maturity is delayed. If no treatment is offered, puberty will progress normally, at a much later age than average, but final height will be achieved normally.

Do all adolescents with delayed puberty need treatment?

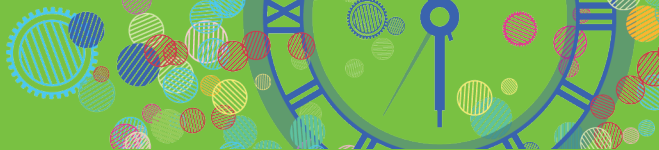
No, this depends very much on the individual adolescent. Some children are severely affected by their relative short stature and delayed sexual development. If the adolescent is experiencing psychological difficulties, particularly if they are being constantly teased and physically bullied, then treatment should be offered. However, the decision to accept any treatment should be discussed openly between the specialist, the adolescent and the parents.

Will delayed puberty affect normal sexual function?

No, if it is just a constitutional delay in puberty. It is just that reaching adult sexual maturation may take a little longer than usual. In constitutional delay of growth and puberty, sexual drive, sexual function and fertility should be entirely normal once the adolescent has matured. However, if there is a long term problem such as a chromosome disorder or pituitary disorder then long term treatment will be required.

Will an adolescent with delayed puberty grow up to be as tall as their friends?

Yes, with or without treatment. In constitutional delay, the timing of the growth spurt will be extremely delayed. Although the adolescent will eventually reach a height appropriate for their parent's heights, it will take



longer than their friends. Indeed, adolescents with delayed puberty may be growing until their early twenties. The specialist can advise how tall an affected adolescent may become by looking at an X-ray of their hand and wrist. Treatment will probably make no difference to the final adult height.

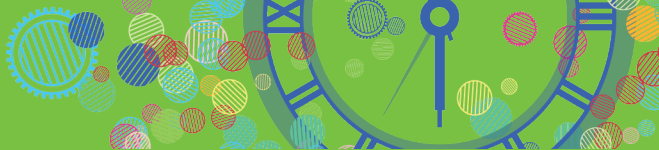
Are there any side effects from treatment?

Both anabolic steroids and testosterone have been used for more than forty years for the treatment of constitutional delay of growth and puberty. This experience has shown that there are very few side effects. Mood swings, behaviour changes and minor acne can occur, but this is more a complication of the start of the adolescent years rather than the result of treatment.

After the start of treatment, what changes can be seen and how soon will they occur?

All boys and girls being treated will start growing faster within a few months of starting treatment. Boys being treated with testosterone treatment will notice their penis growing and may have more frequent morning erections.

This image shows a single sheet of white paper with horizontal blue ruling lines. The lines are evenly spaced and run across the width of the page. There are no margins, text, or other markings on the paper.



Glossary

Chromosome

A thread like structure that carries genetic information in the form of genes composed of DNA. Normally, each human cell contains 23 pairs of chromosomes, one pair of these are the sex chromosomes. Genes and chromosomes are like blueprints for the body's development, and so play a large part in determining a person's characteristics.

Endocrine Gland

A gland that makes hormones and release them into the blood. The pituitary, thyroid, adrenal, testes (testicles) and ovaries are all endocrine glands.

Gonads

A term that refers to the sex glands, they are the ovary in females and the testes in males.

Growth Hormone

A hormone released by the pituitary gland, which promotes growth.

Hormones

Chemicals transported in blood that stimulate growth and sexual development and help to regulate the body's metabolism. They are produced by endocrine glands such as the pituitary, and carry messages from one cell to another via the bloodstream.

Hypothalamus

Part of the base of the brain that sits immediately above the pituitary gland and controls the release of hormones from the pituitary gland.

Menstrual Cycle

The regular shedding of the inside lining of the womb which usually occurs monthly and only in females. This results in bleeding, which is termed menstruation and is often referred to as periods.

Oestrogen

A group of female hormones that are produced by the ovaries from the onset of puberty and continuing until menopause, which controls female sexual development.

Ovaries

Females have two ovaries, which produce the reproductive cells, i.e. eggs.

Ovulation

Usually occurs monthly as part of the menstrual cycle and specifically refers to the ovaries releasing matured eggs.

Paediatric Endocrinologist

A doctor who specialises in the disorders of endocrine glands in children.

Pituitary gland

A gland at the base of the brain, which releases the important hormones related to normal growth, development and fertility, including growth hormone.

Puberty

The process of physical changes when a child's body becomes an adult body and becomes physically capable of reproduction.



Testes

The male reproductive glands, which produce sperm, the male reproductive cells.

Testosterone

The major male sex hormone, which is produced in the testes.

Turner Syndrome

A congenital chromosomal disorder occurring in females caused by the absence of one X chromosome. Short stature is a common symptom in girls with Turner Syndrome.

Ultrasound

A diagnostic tool used to show images of internal body parts.

Uterus

Womb.

Support Organisations and Further Reading

Australian Pituitary Foundation

www.pituitary.asn.au

Australia and New Zealand Society for Paediatric Endocrinology and Diabetes (ANZPED)

www.anzsped.org

The Endocrine Society

www.endocrine.org/patient-engagement

The Hormone Foundation

www.hormone.org

The Magic Foundation

www.magicfoundation.org

Pituitary Foundation UK

www.pituitary.org.uk

Pituitary Network Association (USA)

www.pituitary.org

UK Child Growth Foundation

www.childgrowthfoundation.org

UK Society for Endocrinology

www.endocrinology.org



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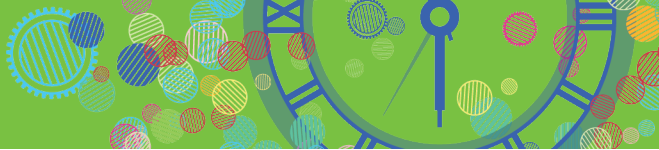
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Puberty and its Problems
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Speak to an appropriate healthcare professional

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Hormones and Me

Delayed Puberty

This booklet is valuable reading for adolescents
with delayed puberty.

It is also recommended reading for their family and friends.