

Hormones and Me Growth Problems in Children



Australasian Paediatric Endocrine Group

Growth Problems in Children



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About this Book

Growth Problems in Children should give you a basic understanding of the complex nature of growth and development as well as an overview of the conditions that may affect growth.

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

Merck Serono Australia is pleased 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 2011 with the help of Dr Tim Jones and Dr Glynis Price (Princess Margaret Hospital for Children, WA, Australia), Paediatric Endocrinologists specialising in childhood endocrine disorders and members of the Australasian Paediatric Endocrinology Group (APEG), and Dr Vinutha Shetty (Princess Margaret Hospital for Children, WA, Australia), a Paediatric Endocrine Fellow. Paediatric endocrinologists, A/Prof Margaret Zacharin (Royal Children's Hospital, VIC, Australia) and Dr Ann Maguire (The Children's Hospital at Westmead, NSW Australia) have reviewed the *Hormones and Me* series on behalf of the Australasian Paediatric Endocrine Group (APEG).

This booklet was first updated and reproduced for Australian and New Zealand readers in 2000 with the help of Dr Neville Howard (Children's Hospital Westmead, NSW, Australia). Special thanks to the original authors and editors, Dr Richard Stanhope (Great Ormond Street Hospital for Children and the Middlesex Hospital, UK), Mrs Rosemary Cordell (Child Growth Foundation, UK) and the British Society of Paediatric Endocrinology (BSPE).



Introduction

Growth is the defining characteristic of childhood. Normal growth during childhood depends on a combination of good general health, adequate nutrition and genetics. It is important to remember that there is a wide range of what is considered 'normal' in how children grow and develop. Growing, like learning, does not always follow an even course and can occur in spurts.

Although most children who are below or above average size are otherwise normal, there are some important underlying conditions that can cause abnormal growth. These include chromosome abnormalities (genetic disorders), endocrine gland disorders (hormonal abnormalities), cartilage or bone disorders and general chronic disease. Early detection and treatment of underlying conditions with or without growth supplements can enable many children experiencing abnormal growth to reach their potential.

“Growing, like learning, does not always follow an even course and can occur in spurts.”

Normal Growth

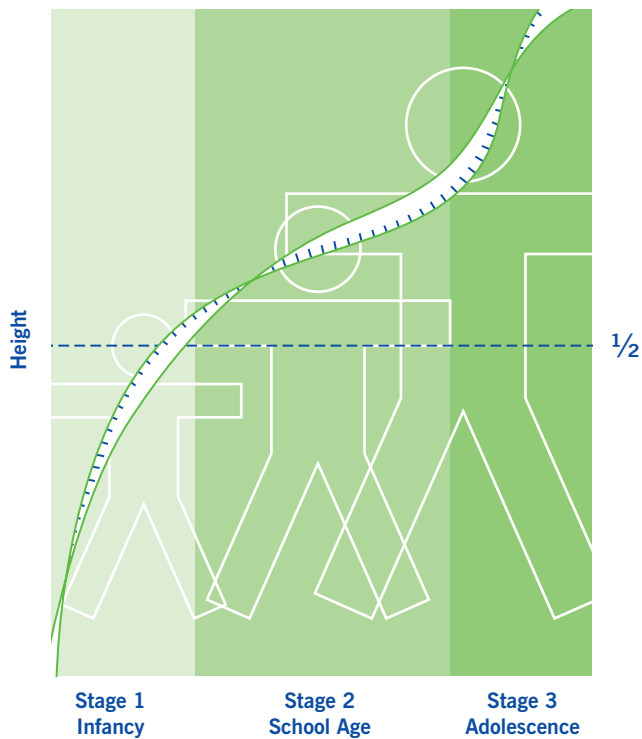
Phases of Growth

Children grow through three phases as can be seen in Diagram 1. Each has a characteristic pattern and each is controlled by a different set of internal mechanisms.

The first phase is from birth through infancy to the pre-school years. This phase is characterised by a rapid growth of all parts of the body including the brain and the nervous system. During this time, the rate of growth steadily decreases so that the fastest speed of growth is at the beginning of this phase in the first three months of life. Hence a newborn baby is growing faster than at any other time in childhood or adolescence, and illness can severely disrupt growth potential during these early months. A number of hormones control this growth phase – the hormone thyroxine is essential for this phase of growth and development to be completed.

The second phase extends through school age of children until adolescence begins. The growth rate during this time is fairly steady at about 5 cm per year. Most of the growth is in the limbs so that the mid-point of the child moves upwards as can be seen in Diagram 2. In this phase, growth hormone is the most important factor controlling growth and development.

Diagram 1 : PHASES OF GROWTH

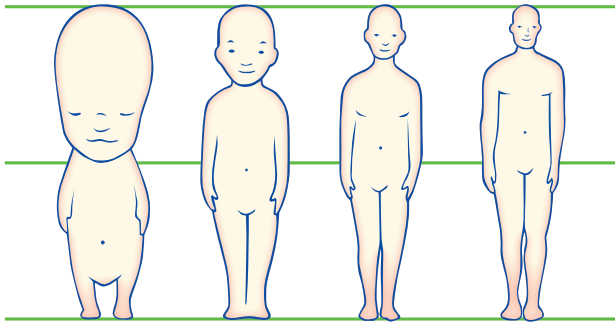


The third phase is the most complicated and stretches through adolescence (puberty) until the bones become solid and adult height is reached. During this phase, the speed of growth picks up rapidly and then falls away to nothing (the growth spurt of adolescence). The sex

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hormones (testosterone and oestrogen), are the major factors controlling this phase but growth hormone and insulin levels are also important.

Diagram 2 : NORMAL GROWTH



The Essentials of Normal Growth

Children grow best when their health, both physical and psychological are optimum. Most important is the provision of adequate nutrition both in quantity and quality so that the energy needs and the specific building blocks are provided to the growing child. Protection from preventable illness is also important (e.g. immunisation against common infectious diseases).

The reasons that our ancestors were shorter than the present generation, relates mostly to the lack of the above essentials for growth in their time.



Assessment of Growth

Every child should be measured regularly. If there are any concerns regarding any child's growth, these should be discussed with the local doctor. The doctor will ask about the child's birth, development and general health, examine the child and may order specific tests to assess the child's growth (see *Table 1*).

“Every child should be measured regularly.”

The measurements taken will depend on the age of the child. Weight, length and head circumference should be measured regularly in infancy. Standing height of the child without shoes is useful from two years of age and should be measured at least every year. If the growth pattern is abnormal, measurements as often as three monthly will give a more accurate view of the pattern and allow calculation of the speed of growth. The heights of both parents should be accurately measured as these can be used to estimate the familial adult height potential of children.

Assessment of Abnormal Growth

Table 1 : DETAILED MEDICAL HISTORY

General Examinations

- measurement of length, height, weight and head circumference
- body proportions, usual physical features, pubertal status
- general health
- height of parents

Screening Investigations

Blood Tests

- full blood count, ESR
- blood chemistry (creatinine, electrolytes, calcium, phosphate)
- coeliac screen
- hormone function (e.g. thyroid hormone levels, IGF1 & IGFBP3)
- chromosome studies

Urine Tests

- microscopic examination
- chemical assessment

Imaging

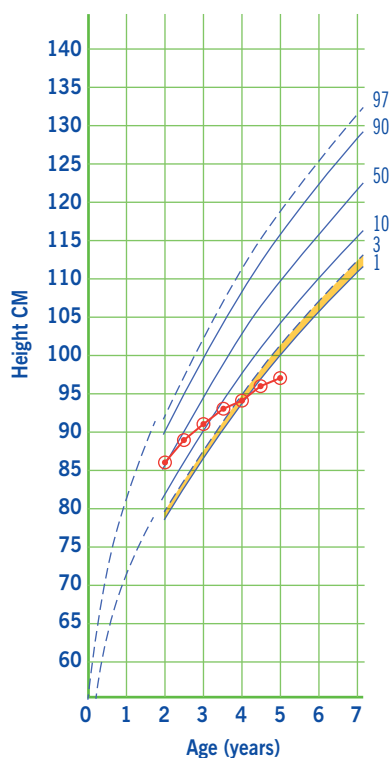
- X-rays to assess bone structure and maturity

Centile Charts

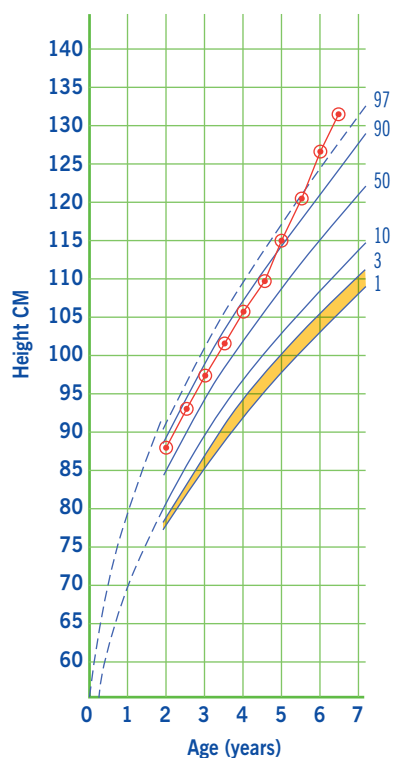
Centile charts are graphs that show the average pattern of growth during childhood. Measurements of height (or length in infants), weight and head circumference should be plotted throughout childhood on the centile chart appropriate for the age and sex of the child. A series of measurements demonstrating the trend in growth is more valuable than

one single measurement. The child's growth should usually follow the curve of the centile graph (see *Diagram 1*). Crossing centile lines is a warning sign of abnormal growth (see *Diagram 3*).

Diagram 3 : CENTILE CHARTS



A boy's growth chart with an example of short stature and abnormal growth



A girl's growth chart with an example of tall stature and excessive growth

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Table 2

Causes Of Short Stature	Causes Of Tall Stature And Rapid Growth
• Genetic or familial short stature • Constitutional growth delay • SGA / Intrauterine growth retardation (IUGR) - Placental failure - Drugs and infections - Various syndromes (e.g. Russell Silver) • Bone abnormalities (e.g. Achondroplasia) • Turner Syndrome • Other genetic problems • Poor nutrition - Poor intake - Poor absorption of food (e.g. Coeliac Disease) • Chronic Systemic illness - evident (e.g. asthma) - hidden (e.g. inflammation of the bowel) • Hormone problems - Growth hormone deficiency - Other hormone deficiencies • Unexplained	• Genetic or familial tall stature - Chromosomal abnormalities (e.g. Klinefelter Syndrome) • Genetic problems (e.g. Marfan Syndrome) • Other syndromes (e.g. Sotos Syndrome) • Hormone problems - early puberty - growth hormone excess - thyroid hormone excess • Over nutrition • Unexplained



Short Stature

Short stature – defined as having a height below the 3rd percentile for age and sex – is a common problem affecting up to 5 children out of every 100. Although this may be the normal pattern of growth for an individual child, underlying causes of poor growth should be considered. The process of growth is dependant on adequate nutrition, normal bone structure and biochemistry, normal thyroxine, growth hormone and other hormones as well as general health. Disruption of normal growth may therefore be an indication of many abnormal conditions (see *Table 2*). The following sections will look at the major causes of short stature in childhood.

“Children are a reflection of their parents”

Familial Short Stature

Children are a reflection of their parents. Parents who are short usually have children whose height is in the lower range of normal. Conversely tall parents usually have children who are tall. As a general rule, a child's potential adult height is the average of the parent's heights with a correction for the parent of the opposite sex to the child. See *Table 3* for a formula to calculate a child's potential height.

Table 3

To calculate the potential height of a boy, the mother's height is given an additional 13cm and averaged with the father's height. This mid parental or "target height" can be plotted on a growth chart to estimate the centile the boy should grow along.

e.g. FATHER 180cm

MOTHER 157cm + 13cm = 170cm

AVERAGE 175cm = potential height = 50th height centile

(See *Diagram 3*)

To estimate a girl's height, subtract 13cm from the father's height and follow the same steps as above.

Constitutional Short Stature with Slowed Maturation

Constitutional delay of growth is the most common cause of short stature in childhood. This is a variant of normal and is usually associated with a delay in maturation and with late puberty. Constitutional short stature often runs in families and members of the family may have a history of being 'late bloomers' with regard to growth and puberty.

Children with constitutional short stature usually have normal weight and length at birth. Between 6 and 30 months of age, their growth slows down and falls below the 3rd centile line. After this dip, growth returns to normal and they remain parallel to, but below the 3rd centile line on their growth chart. Intellectual development remains normal for age. Assessment of bone maturity on X-ray will show that bones are behind in skeletal maturation.



Problems may arise especially around the time of adolescence. While the child's friends experience the onset of puberty and its associated growth spurt, the child with constitutional short stature will fall further behind his or her peers in growth. This child will eventually enter puberty normally and given time, children with constitutional short stature usually reach their genetic height potential. Reassurance and open communication can help deal with the emotional stress of being small.

If reassurance is not enough, there are treatments available. If lack of pubertal development is the major concern, hormone therapy with a male hormone (testosterone) in boys or female hormones (oestrogen) in girls, can initiate puberty. These forms of therapy require careful monitoring by a paediatric endocrinologist.

Genetic Disorders Causing Short Stature

Human Genetics (Growth Genes)

The genetics of growth in humans is extremely complex and not all inherited traits have been identified yet. There are however, many genes on the human chromosomes that affect the way the body proportions develop making no two children grow in the same fashion or look identical (with the exception of identical twins). Clearly, some growth traits are recessive and appear only when two parents carry the trait but do not show it themselves. The parent's genetic makeup influences the growth of their children much more than that of previous generations or lateral relatives (cousins) so that the growth characteristics of the father and mother are most relevant in determining the growth of their children.

Turner Syndrome

Turner Syndrome is one of the most common genetic (chromosome) abnormalities in girls, affecting 1 in every 2500 girls born. It is caused by an abnormality of the sex chromosomes so that one of the pairs of X chromosomes found in women is partly or completely missing. This results in short stature and problems with ovarian development. Some affected girls have other physical features. Any girl with short stature should have a chromosome study done to test for Turner Syndrome.

“Any girl with short stature should have a chromosome study done for Turner Syndrome”

Girls with Turner Syndrome benefit from growth hormone treatment starting as early as possible and later need hormone replacement therapy (HRT) with female hormones to complete their sexual development. They will need assessment by other specialists to exclude problems that are associated with Turner Syndrome, e.g. defects in heart, kidney and hearing.



Noonan Syndrome

Noonan syndrome is a less common genetic abnormality affecting around 1 in 2000 babies born. It affects both girls and boys and often runs in families.

Children with Noonan Syndrome have characteristic facial and body features, poor growth, sometimes a delay in adolescence and often abnormalities of the heart chambers or valves. All children with Noonan Syndrome should see a children's cardiologist for heart investigations.

Although children with Noonan Syndrome may have normal weight and length at birth, their growth rate and final height is often less than average. Special height charts are available for children with Noonan Syndrome and from this a paediatric endocrinologist will be able to estimate the child's final height. Growth hormone may be used to try and improve adult height in some children with Noonan Syndrome. Hormone replacement therapy (HRT) may be necessary if puberty does not occur spontaneously.

Down Syndrome

Down Syndrome is one of the most common chromosome abnormalities affecting around 1 in 1000 babies born worldwide – male and female alike. Down Syndrome is the result of having 3 instead of 2 chromosomes number 21, an abnormality which occurs at the moment of conception. Children with Down Syndrome have a variety of features affecting various body systems and have a characteristic facial appearance. They experience poor growth and special growth charts are available for children with this syndrome. The growth problem in this syndrome can sometimes be worsened by an underactive thyroid gland or by

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problems with the pituitary gland. Children who grow poorly on the Down Syndrome centile charts need investigation by a paediatric endocrinologist to identify their hormone deficiencies.

Other Genetic Causes

There are many other syndromes and recognizable patterns of growth that are rare but have a genetic basis. These conditions can be recognised by a paediatric endocrinologist or specialist in human genetics. Often there are specific tests to confirm the doctor's suspicions of the diagnosis. Growth patterns in this group of disorders vary widely but the diagnosis can be most useful in predicting the outcome for the individual child. Some of these conditions can benefit from growth hormone treatment.



Growth failure at birth

Small for Gestational Age (SGA) / Intrauterine Growth Retardation IUGR)

“Small for Gestational Age” (SGA) is a term used for babies whose weight and /or length at birth, are less than expected (compared with appropriate population standards for both gender and gestation), regardless of the cause. It refers to the size at birth, irrespective of the growth rate within the womb. For a baby born at full term, this is less than 45 cm long and less than 2.5 kilograms weight. Tables of length and weight are available for premature babies. Low birth length is a stronger predictor of subsequent short stature than weight.

Intrauterine growth retardation (IUGR) is a term used when babies do not grow at a normal rate within the womb and hence are born with a weight and length that are inappropriately low for the duration of pregnancy. Small for gestational age does not necessarily equate with intrauterine growth restriction. SGA includes babies with constitutional smallness or “small normal” babies who have not experienced IUGR. As small maternal size is a factor in maternal constraint, smaller women tend to deliver smaller babies.

The growth of a baby within the womb depends on maternal health and nutrition, the placenta that supplies food and oxygen to the foetus and the genetic information stored within the baby's cells. Sometimes the cause of SGA/IUGR remains a mystery, however there are some conditions in the mother that are commonly linked to poor foetal growth. These include high blood pressure, diabetes mellitus, or infections during pregnancy, smoking and the abuse of alcohol or other drugs. Babies with genetic

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or chromosomal abnormalities often have SGA/IUGR. Recent evidence suggests that changes can be made after conception, depending on maternal health, that may influence foetal growth and outcome (called epigenetic programming).

Most babies born with SGA/IUGR show catch-up growth over the first two or three years of life, however in around one third of cases this does not occur. The majority of premature infants born at less than 32 weeks will show growth failure with a severity related to the degree of prematurity and the presence of chronic lung disease. There is catchup of length and weight in the majority by 5 years of age. Children who do not experience this catch-up growth may benefit from growth hormone therapy to help them reach their genetic height potential.

Russell Silver Syndrome

Russell Silver Syndrome describes a group of children born SGA and associated with IUGR, who display a number of specific physical characteristics as well as poor growth. These children tend to be small and thin with triangular faces, prominent foreheads and small chins. Often the limbs are of different lengths and the fifth fingers are very small. There are many other physical traits associated with this syndrome and the number of characteristics varies from child to child. The cause of Russell Silver Syndrome is unknown, although some genes linked with this condition have now been identified. Most cases of Russell Silver are sporadic, which means they occur in people with no history of the disorder in their family. However sometimes Russell Silver Syndrome does run in families and can occur again in the next pregnancy.



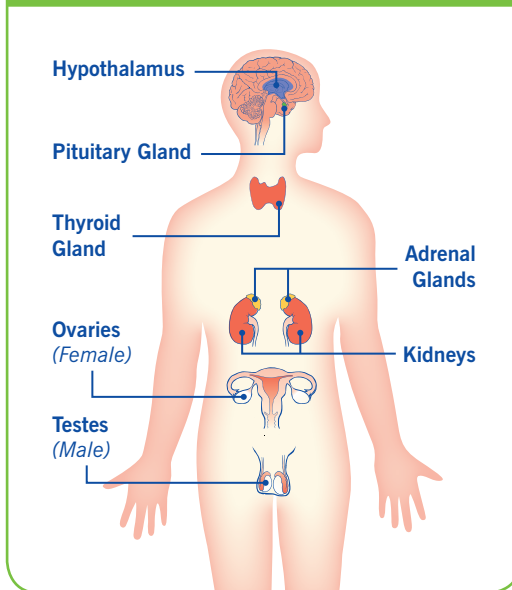
Most children with Russell Silver Syndrome develop normally except in size. They tend to put on weight in middle childhood and experience normal puberty although this may be a little earlier than their peers. Improved care including the prevention of low blood sugar levels, nutritional supplements during childhood and growth hormone therapy will help children with Russell Silver Syndrome reach their full potential. Growth hormone therapy may improve short and long term growth in this syndrome.

Hormone Disorders

Not only does normal growth depend on good health and nutrition, but the normal secretion of growth stimulating hormones from endocrine

glands. The two most important hormones required for growth are growth hormone and thyroid hormone. A deficiency in one or both of these hormones will result in poor growth and short stature. The main hormone disorders causing short stature in children are Growth hormone deficiency, Pituitary gland failure, Hypothyroidism, and Cushing's syndrome, which will be described in the following section.

Diagram 4 : THE HUMAN BODY



Growth Hormone Deficiency

Growth hormone deficiency is estimated to affect 1 child out of 5000 and is more commonly recognised in boys. It occurs when the pituitary gland at the base of the brain fails to produce adequate levels of growth hormone. The pituitary gland releases growth hormone (as well as many other hormones) in response to chemical messages from the hypothalamus, the part of the brain to which it is connected (see *Diagram 4*).



Low levels of growth hormone may be due to a problem within the hypothalamus, the link between the hypothalamus and the pituitary gland or within the pituitary gland itself.

Growth hormone is released by the pituitary gland in spurts over a 24 hour period, mostly at night during sleep and after exercise. Once released into the blood stream, growth hormone acts on the liver, kidneys and other tissues including bones to produce other chemicals known as somatomedins (or insulin-like growth factors). These somatomedins act with growth hormone to promote growth. As well as promoting growth, growth hormone has an important role in the metabolism of fat and carbohydrate and helps to maintain blood sugar levels.

Causes of Growth Hormone Deficiency

It is not always possible to determine the exact cause of growth hormone deficiency. There may have been damage to the pituitary gland or its connections at birth or it can occur following a head injury or infection. When the cause is unknown the term idiopathic growth hormone deficiency is used.

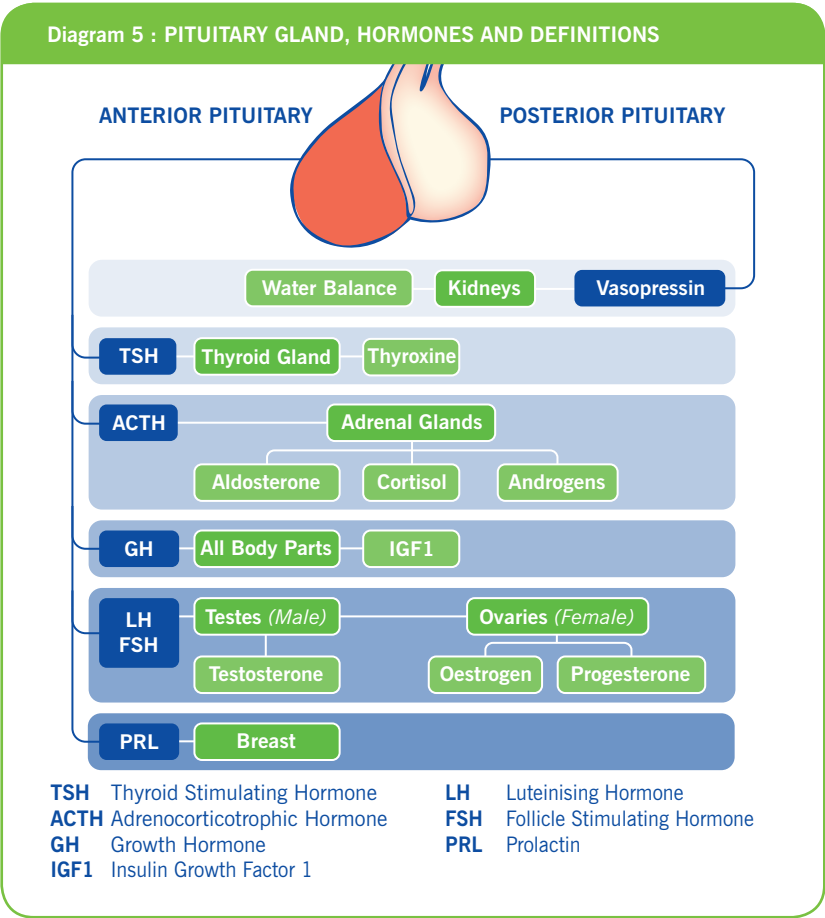
Other causes of growth hormone deficiency include problems with the development of the pituitary gland or the hypothalamus. Sometimes growth hormone deficiency may be inherited or linked to a genetic syndrome. In some cases, damage to the pituitary gland or hypothalamus is caused by trauma, a brain tumour, surgery or radiotherapy used to treat brain tumours and leukaemia.

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It is rare for children to have a complete lack of growth hormone. In most cases there is some growth hormone present but this is insufficient to maintain normal growth.

Diagram 5 : PITUITARY GLAND, HORMONES AND DEFINITIONS





How is Growth Hormone Deficiency Diagnosed?

Children with growth hormone deficiency are small compared to other children of their age and their growth rate is poor, so they fall behind their peers (see *Diagram 3*). They tend to be chubby and to have young looking faces due to delayed bone development in the skull as well as in the limb bones.

Any child with suspected growth hormone deficiency should be assessed by a paediatric endocrinologist. This growth specialist will take medical history, details of the child's birth, development and general health. It is important to provide as many measurements of the child's height and weight as possible so a detailed growth chart can be plotted.

A thorough physical examination of the child including accurate measurement of height, weight and body proportions will be performed. X-rays of the child's left hand will be taken to determine maturation of the skeleton. Blood tests will be taken to look for levels of other pituitary hormones, which may also be low. These include thyroid stimulating hormone (TSH), the sex hormone stimulating hormones (FSH and LH) and the adrenal stimulating hormone (ACTH), insulin like growth factors (IGF1) and their binding proteins (IGFBP3), (see *Diagram 5*).

As the blood level of growth hormone fluctuates widely over a 24 hour period it is not reliably measured in a single blood test, rather blood must be taken during a growth hormone surge or at frequent intervals over a period of time. The specialist will recommend provocation or stimulation tests, which will involve a day stay in hospital, or an overnight stay with growth hormone levels measured frequently during sleep. In growth hormone deficiency, there will be a lack of growth hormone production in

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response to two stimulation tests or inadequate peaks of growth hormone production during sleep.

Growth Hormone Treatment

Growth hormone has been used for many years with great success in the treatment of children with short stature for various reasons. In Australia, growth hormone treatment is available for children with growth hormone deficiency. However in growth hormone sufficient children, to qualify for growth hormone treatment, a child's height has to be less than the 1st percentile for age and sex, and growth rate less than 25th percentile. Biosynthetic growth hormone is manufactured using gene technology and is identical to the growth hormone we produce naturally. Before biosynthetic growth hormone was available (prior to 1985), growth hormone was taken from human pituitary glands at autopsy. The use of human growth hormone carried a small risk of infection but this does not occur with biosynthetic growth hormone. However there is a small risk of other side-effects of growth hormone which will be fully discussed with you by your doctor before commencing growth hormone treatment.

“Growth hormone has been used for many years with great success in the treatment of children with growth hormone deficiency”

The aims of treatment are two-fold: firstly to catch up height to the normal range and secondly to increase final height. Provided treatment with growth hormone is started at a reasonably early age (before age 6 years old) both aims can usually be achieved. Later, treatment before puberty is still appropriate but the results are usually less satisfying than when treatment is started early.



The dosage of growth hormone varies according to the child's weight and surface area and will increase as he or she grows. It is given by an injection once daily just under the skin using a syringe or special pen with a fine needle. The injection is best given before bedtime to mimic the natural production of growth hormone as closely as possible.

Refer to page 37 for further information on growth hormone treatment.

Pituitary Gland Failure (Hypopituitarism)

Around half of all children with growth hormone deficiency will also have some deficiency of the hormones involved in sexual development and will need treatment with sex hormones to initiate puberty. Children with deficiencies of multiple pituitary hormones will need sex hormone therapy to experience normal puberty, thyroid hormone (thyroxine), hydrocortisone for adrenal gland failure and often vasopressin (DDAVP) to balance water loss.

Hypothyroidism

Hypothyroidism is a deficiency of the hormones produced by the thyroid gland – thyroxine (T4) and triiodothyronine (T3). These hormones are essential for normal growth and cell function. A deficiency may be present from birth and the main problem may either be the thyroid gland itself or in the hypothalamus or pituitary gland, which are responsible for stimulating the thyroid gland. A routine blood test for hypothyroidism is performed on every newborn baby to ensure early diagnosis and treatment but children may develop a thyroid problem later. This test measures TSH, and is a good test for detecting problems with the thyroid gland. However, this test will not detect central hypothyroidism (hypothyroidism associated with pituitary gland or hypothalamic problems). Therefore a normal newborn screening test does not exclude central hypothyroidism.

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Later in childhood, hypothyroidism is usually caused by an abnormality of the immune system that results in damage of the thyroid gland. Sometimes hypothyroidism is due to failure of the pituitary gland to secrete thyroid stimulating hormone (TSH), (see *diagram 5*). Low levels of thyroid hormones in hypothyroidism result in slowing down of growth during childhood resulting in short stature. Other general symptoms of hypothyroidism include tiredness, constipation, dry skin and intolerance to cold. Treatment with oral thyroid hormone (thyroxine) restores normal thyroid function and normal growth.

Cushing Syndrome

Cushing Syndrome is a condition caused by overproduction of the hormone cortisol or the prescription of this hormone or others like it, e.g. hydrocortisone and prednisone, in conditions where steroids are essential for maintaining health. Conditions such as asthma, inflammatory bowel diseases and rheumatoid arthritis are examples. Cortisol is normally produced by the adrenal glands (located on top of the kidneys) and is vital in the regulation of blood pressure, the immune system, metabolism and growth.

Children with too much cortisol will tend to be overweight, (especially around the face and trunk), have high blood pressure and experience poor growth. They may also develop excess body hair, greasy scalp hair and acne. The condition is diagnosed by measurement of cortisol levels in the blood and urine. Treatment depends on locating the source of the over-activity and removing it. Following this, supplements of adrenal or pituitary hormones may be necessary. Growth in these children then usually resumes but growth hormone treatment is required.



In asthma and other medical conditions treated with steroids such as prednisone, growth failure may occur and the physician will attempt to reduce the steroid prescribed, to improve growth. Some children however, cannot reduce their steroid due to the need for ongoing maintenance treatment of their underlying condition. Growth hormone treatment is sometimes used to improve growth, but may not be successful when the child is using steroids.

Cartilage and Bone Disorders

There are many cartilage and bone disorders which affect growth. Most of the conditions are rare and many are inherited. They are known as skeletal dysplasias. In general, body dimensions are abnormal in these disorders, with relatively short limbs. There is a spectrum of severity of relatively common short limbed dwarfing disorders from the severe Achondroplasia to the milder Hypochondroplasia. The incidence of this group of disorders is around 1 in every 15,000 babies born.

Achondroplasia

This is the most common type of skeletal dysplasia recognisable at birth. Achondroplasia is due to an abnormality of a single gene, which can occur spontaneously when a baby is conceived or be inherited from a parent with achondroplasia. This inheritance of achondroplasia is autosomal dominant, meaning a person with achondroplasia has a 50% chance of passing the defective gene to their child. If the child inherits the gene he or she will have achondroplasia. When a child with this problem is born to normal stature parents a mutation has generally occurred to cause the genetic abnormality.

Children with achondroplasia share many distinctive features including very short arms and legs, normal back length, a large head and characteristic face. Achondroplasia does not affect intelligence.

There is no cure for achondroplasia. But operations to lengthen bones of the arms and legs can be successful and improve height. Growth hormone treatment can be used in the short-term by increasing the rate of growth, but has not been shown to increase final height. The best outlook for final height is likely to be achieved by combination of growth hormone treatment and surgery to lengthen limbs.



Hypochondroplasia

Hypochondroplasia is also a common skeletal dysplasia in which the limbs are less shortened than in achondroplasia. Recognition comes not at birth but from the doctor's measurement of limb length and characteristic X-rays.

Final adult height in this condition is generally less than expected in the family. In the short-term, growth hormone treatment improves height but whether final (adult) height is improved is controversial.

Other Skeletal Dysplasias

There are many rare conditions of cartilage and bone development which lead to short stature and poor growth. The particular features can be recognised by paediatric endocrinologists and X-rays used to more clearly define the diagnosis. Some of the conditions (e.g. hypophosphatemic rickets) respond to chemical treatments. Others do not respond to treatment and the use of growth hormone treatment in this group is of controversial value.

Growth Disorders Secondary to Systemic Diseases

Disorders affecting specific systems like the gastrointestinal tract, heart, lungs, kidneys and blood can affect growth. Often the diagnosis is made before the short stature is noted, but even in the asymptomatic short child, it is important to rule out hidden disorders. The following section will describe the common systemic disorders causing short stature.

Disorders of Food Absorption

Any condition that impairs the ability to absorb food resulting in poor nutrition can cause inadequate growth. Food provides the energy source for growth and the specific chemicals that are the building blocks of growth. Coeliac disease and Crohn's disease are two most likely conditions causing short stature due to poor nutrition.

There are a number of other gut problems in this category, but unlike coeliac disease and Crohn's disease, the symptoms of the problem will be very obvious. Hence coeliac disease and Crohn's disease are more likely to show up as a child with poor growth.

“Coeliac disease and Crohns disease are two of the most common conditions causing short stature due to poor nutrition”

Coeliac Disease

Children with coeliac disease are sensitive to a protein called gluten, which is present in many grains including wheat foods. The gluten damages the delicate lining of the small bowel making it unable to absorb vital nutrients. As well as experiencing poor growth, children with coeliac disease can become very malnourished and develop gut symptoms.



Coeliac disease is diagnosed by a blood test measuring specific antibodies followed by a biopsy of the small intestine which can be done using an endoscope. Once diagnosed, it is important to eliminate gluten from the diet. Growth returns to normal with a new diet. Advice about gluten-free eating is available from the Coeliac Society of Australia.

Crohn's Disease

Poor growth is usually present in children with Crohn's disease. It involves long-term inflammation of the bowel wall, which leads to poor absorption of nutrients and there are usually gut symptoms. Inflammation can usually be well controlled with medication and a gastroenterologist should supervise management. Occasionally, surgery is required. Growth returns to normal if the poor absorption can be effectively controlled.

General Chronic Disease

Almost all chronic disease in childhood can cause short stature for reasons that are not always clear. Some of the conditions in which poor growth can occur are listed in table 4. Some times it is the treatment as well as the disease itself that interferes with normal growth. Long-term therapy with prednisone and other steroids, which are used to control inflammation in many chronic diseases (e.g. asthma), can result in growth disorders. (See *Cushing Syndrome* page 25).

“Almost all chronic disease in childhood can cause short stature for reasons that are not always clear”

Anorexia nervosa, a common eating disorder, most frequently seen in adolescent girls, can be associated with serious growth failure – partly due to poor growth secondary to lack of nutrition, and partly due to failure to start or continue with puberty.

Table 4 : CONDITIONS OF CHRONIC ILLNESS ASSOCIATED WITH POOR GROWTH

- Anaemias & other blood disorders
- Malnutrition
- Asthma, Cystic Fibrosis and other Lung conditions
- Heart Disease
- Coeliac, Inflammatory Bowel Disease & other intestinal disorders
- Kidney Disease
- Liver Disease
- Rheumatoid arthritis
- Metabolic disorders
- Other Long-term Disorders

Mostly, the diseases will be obvious but sometimes poor growth is the presenting problem. Hence the doctor will order blood tests for these conditions when a short child is investigated (*see Table 1*).

Psychosocial Short Stature

Children in situations where home life is severely disrupted or unhappy, often experience emotional stress and poor growth. The growth failure is due to a combination of factors including, a decrease in the secretion of growth hormone, the body's response to growth hormone and poor nutrition.

If intervention by a social worker or psychologist fails, the only solution to this disorder may be to remove the child temporarily from the disrupted social situation and provide normal emotional, physical and nutritional support elsewhere. Growth in these children then recovers rapidly.



Tall Stature

Tall stature generally has less disadvantage than short stature. Only very tall or rapidly growing children require assessment. The most likely cause of tallness is genetic trait from one or both parents. The genetic tendency in height can be calculated by estimating the same sex mid parental height (see *Table 3*).

The assessment of tall stature follows much the same lines as for poor growth. After careful body measurements an estimation of final (adult) height is made by X-raying the hand and wrist for the level of skeletal maturation and using the height and a set of tables to predict the final height. When the predicated final height is much greater than the parent's height, consideration is given to further investigation and to interventions than may limit growth and reduce final height.

Otherwise normal, but very tall boys and girls can possibly have their adult height reduced by advancing maturation (and adolescence) with the appropriate sex hormones in high dosage – testosterone in boys and oestrogen in girls. This therapy is undertaken rarely nowadays.

Occasionally tall stature is due to inherited disorder such as Marfan Syndrome, genetic disorders such as Klinefelter Syndrome or Sotos Syndrome, early puberty (precocious puberty) or an endocrine disorder.

Genetic Disorders Causing Tall Stature

Marfan Syndrome

Marfan Syndrome is a rare inherited disorder that may affect many organ systems including bones, eyes, heart and blood vessels. Children with Marfan Syndrome have excessively long limbs with long thin fingers and very mobile joints. They are long babies at birth. They may be near-

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sighted (myopic) and at risk of more serious eye disorders. All children with Marfan Syndrome are tall and loose jointed and they may require limitation of their height to improve the mechanics of their loose joints. The diagnosis can be made by DNA (genetic) studies. Some of the most worrying problems occurring in Marfan Syndrome are abnormalities of the heart valves and dilation of the main arteries. All children with Marfan Syndrome need regular check-ups with specialists in various fields to ensure early detection and treatment of any problems.

Klinefelter Syndrome

This syndrome occurs in about 1 in 580 boys and promotes more rapid growth and tall stature particularly after 8 years of age. The problem is genetic and relates to the boy having 1 extra X chromosome, 47XXY.

Other problems can include some learning difficulties and abnormalities in physical development. All men with Klinefelter Syndrome have reduced fertility due to reduced sperm counts and adolescent boys have smaller testicles than normal.

Many boys with Klinefelter Syndrome benefit from male (testosterone) hormone treatment in childhood and / or later in life to promote male physical and behavioural characteristics.

Table 5 : SEX CHROMOSOMES IN HUMANS	
Boys/men	46 XY
Girls/women	46 XX
Turner syndrome	45 X (or variants)
Klinefelter syndrome	47 XXY (or variants)



Sotos Syndrome

This syndrome is an example of a number of rare conditions where rapid growth and tall stature are associated with an abnormality of the nervous system. Children with Sotos syndrome have delayed intellectual development associated with large brains and head size and characteristic facial features that a paediatrician can recognise. Fortunately, bone maturation advances faster than normal and although they become tall adults, these children do not remain as huge as they appear in early years. No growth treatment is required.

Other Genetic Causes

There are a number of rarer genetic disorders which result in tall stature. These are either chromosomal disorders (e.g. 47XYY Syndrome) or specific gene defects, which result in a characteristic appearance along with rapid growth and tall stature. These conditions can be recognised by a paediatric endocrinologist or a specialist in human genetics. Often there are specific tests to confirm the doctor's suspicions of the diagnosis. Growth patterns in this group of disorders vary widely but the diagnosis can be most useful in predicting the outcome for the individual child.

Premature Sexual Maturation

Premature sexual maturation is a term that describes a group of children who grow rapidly (out pace their peers), and cross centile lines on the growth chart in an increasing direction (see *Diagram 3*). The increased growth rate is accompanied by pubertal changes e.g. the appearance of breasts and genital growth. These changes are due to the sex hormones of puberty being produced abnormally early. Another term for this diagnosis is precocious puberty. There are many causes for this problem,

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including a genetic tendency to early adolescence. The doctor can advise on the treatments available to arrest rapid growth and sexual maturation if necessary.

Any child who is growing and maturing rapidly requires medical assessment as some of the causes have very serious implications.

Other Hormonal Causes

Excessive growth hormone produced by the pituitary gland is usually due to a tumour and will cause rapid growth and advance bone maturation. Often this rare condition is associated with headaches, problems with eyesight and other nervous system complaints. Urgent medical assessment by a specialist is needed.

“Any child who is growing and maturing rapidly requires medical assessment as some of the causes have serious implications”

The first sign of thyroid hormone excess may occasionally be rapid growth as thyroxine, the main hormone from the thyroid gland, promotes growth of long bones. An overactive thyroid causes other symptoms including a large thyroid (goitre), a rapid heart rate, fatigue and nervousness with behaviour problems including poor attention span. Medical or surgical treatment of the overactive thyroid condition corrects the growth problem.



Growth Hormone Treatment

Some children with poor growth benefit from the administration of growth hormone. The doctor's recommendation to begin a child on a course of growth hormone is based on many factors including a complete evaluation of the child's growth pattern, general health, medical and family history, the results of appropriate laboratory tests and the diagnosis. In addition, the child must fulfil conditions set by the Government so that the supply of the hormone can be provided through public health system.

Availability of Growth Hormone

All growth hormone is called somatropin and is produced by a process called biosynthesis. There are several brands of growth hormone available and although they vary in formulation, all brands of growth hormone have been shown to be effective in promoting growth in hormone deficient children.

Dosage and Administration

The dosage of growth hormone is calculated from the weight and height of the child. This means the dose will increase as the child grows. In certain circumstances the doctor may increase the dose if the child does not respond adequately.

“Please discuss the options available with the doctor”

Growth hormone is given by an injection just under the skin. To mimic the body's natural production, it is recommended that growth hormone be given before bedtime each night.

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Storage of Growth Hormone

Incorrect storage can reduce the effectiveness of the growth hormone injections. As growth hormone is susceptible to temperature extremes, please store it according to the manufacturer's guidelines. If travelling with growth hormone, please seek the advice of your Health Care Professional on appropriate storage requirements.

Supply of Growth Hormone

Growth hormone is provided in 3 month supplies once the Government authority has been granted. Supplies are delivered to a patient's nominated community or hospital pharmacy. The height and weight of a child on growth hormone treatment will need to be measured on a 3 monthly basis and the doctor will need to provide details of the child's response to growth hormone every 6 months, to obtain further supplies.

Growth Hormone Injections

Growth hormone can be given via needle and syringe, injector pen, or electronic auto-injector. Please discuss all options available with your Health Care Professional to determine which devices are available in your country and the delivery option that is best suited to you.

Coping with Injection Problems

It is never easy explaining to children that injections are for their own good but there are ways of making the process easier. Try to develop a routine by injecting at the same time every day, giving the child a familiar toy to hold and using the same location such as a sofa or bed. Take time to create a relaxed atmosphere and explain the process to the child.



It is recommended that the child does not see the injection preparation process and therefore it is usually best for it to be done out of sight. The establishment of a quick, “no-fuss” procedure often ensures that children grow to accept their injections readily. For those who are anxious about giving/seeing the injection, options are available to help overcome this hurdle. The doctor or endocrine nurse can provide you with information about injection techniques and hospital growth clinics offer support programmes and other advice.

Questions and Answers

About Growth Hormone Treatment

How does growth hormone work?

Growth hormone increases the size, number and protein content of cells in the growing body. The amount of muscle, bone and connective tissues increases whilst the skeleton lengthens and widens. At the same time body fat is reduced. The child starting on growth hormone loses fat without losing weight and gains muscle strength and bone structure. Some children find their appetite increases and increased food intake adds to the effect of the growth hormone.

Are there any side-effects to growth hormone treatment?

Like all medicines, growth hormone therapy may occasionally cause unwanted side effects, such as skin reaction at the injection site and less often, headaches, swelling of the arms or legs and limping. Children with bone disorders (e.g. hip problems, scoliosis) need to be closely monitored, because rapid growth can aggravate these problems. To avoid this the doctor may start the child on a small dose of the hormone and gradually increase it until the full dosage is reached. Other rarer side-effects can occur, though these usually only happen in children who have a separate pre-existing condition (e.g. Turner Syndrome) and therefore an increased risk of developing these rare effects. If you are concerned that your child may be experiencing side effects as a result of growth hormone therapy, you should contact your doctor or endocrine nurse as soon as possible.



Why would the doctor recommend growth hormone treatment?

To be considered for growth hormone therapy, a child is usually less than the first centile for height on a growth chart and growing extremely slowly. Treatment is started based on many factors, including a complete evaluation of his/her growth pattern, general health, medical and family history, bone age x-ray, test results and diagnosis. There are usually three reasons for starting therapy:

1. To achieve “catch-up” growth to bring the child in line with peers
2. Improve self-esteem and reduce social discrimination
3. Long-term to significantly improve adult height

Aims 1 and 2 are always part of the recommendation.

When is treatment with growth hormone stopped?

In certain conditions such as growth hormone deficiency, treatment with growth hormone should be life-long even after reaching final adult height. Currently, growth hormone has been approved as an indication for treatment in adults but financial support may not be available in some countries. In other conditions, treatment is given until the bones are close to becoming solid. This usually occurs at 13-14 years in girls and 16-17 years in boys, however, bone maturation can occur earlier or later than these ages. In some children, growth hormone treatment is stopped when there has been sufficient “catch-up” growth to bring the child into the normal range for their age.

Should children give their own injections?

Children should feel involved in the administration of their injections, and the initial device choice if possible. If they can give their own growth hormone injection it is easier for them to attend school camps and sleepovers etc. Around the age of 9 years, some children may decide to give their own injections. They should, however, always be supervised by an adult.

Where should injections be given?

Growth hormone injections are given under the skin in the legs, arms abdomen or buttocks. It is important to use different injection sites every day.

What if an injection is missed?

There is no adverse reaction to missed injections, however, for optimal growth outcomes to be achieved, it is important that injections are given regularly, according to the schedule prescribed. Missing injections can lead to less efficient growth. Also, if too many injections are missed, ongoing funding for growth hormone treatment may be affected. Therefore, please talk to your Health Care Professional about what to do in the case of missed injections.

Are there any drugs or treatment that should not be taken during treatment with growth hormone?

Tell the doctor if the child is taking other medication before starting to use growth hormone. Some medications may interfere with the effect of growth hormone, however there are no known drugs which are incompatible with growth hormone as it is made naturally by the body.

[illegible]

Glossary

Anabolic Steroids

Synthetic male sex hormones that promote tissue and bone growth.

Biosynthetic Hormone

Manufactured hormones that are identical to or perform the same function as those made naturally by our bodies.

Cardiologist

A doctor who specialises in disorders of the heart and circulation.

Cartilage

Soft gristle material at the end of long bones, some of which hardens into bones when growth is complete.

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.

Congenital

A feature or condition that is present from birth, but not necessarily hereditary.

Corticosteroids

Steroid hormones produced by either the adrenal gland or synthetic process. Examples include cortisone, hydrocortisone and prednisone.



Cyanotic Heart Disease

Heart conditions in which arterial and venous blood mix. The overall oxygen content of the blood is lower resulting in less oxygen delivery to the body.

Cystic Fibrosis

A hereditary disease that affects secretory glands, (i.e. sweat glands, mucus-secreting glands and pancreas). Children with cystic fibrosis experience frequent chest infections, digestive problems as well as poor growth.

DNA

Stands for Deoxyribonucleic Acid and is the chemical that forms the genetic code.

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. All of the glands together make up what is termed the endocrine system.

Endocrinologist

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

Endoscope

An instrument used to visualise the inside of the body. Most endoscopes consist of a narrow, mobile tube with a light and a camera to transmit the images to the eye or a screen.

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Foetus

The developing baby in the womb from the ninth week of pregnancy until the moment of birth.

Gastroenterologist

A doctor who specialises in the disorders of the digestive tract.

Genetic Potential height

The adult height calculated from the heights of the parents.

Hormones

Blood chemicals that stimulate growth and sexual development and help to regulate the body's metabolism. Normally the body carefully controls the release of hormones as too much or too little may disrupt the body's delicate balance. They are produced by endocrine glands and carry messages from one cell to another via the bloodstream.

Hypothalamus

Part of the base of the brain that controls the release of hormones from the pituitary gland.

Idiopathic

The term used to describe the situation when no reason can be found to explain the cause of a disease or disorder.

Intrauterine

Within the uterus (womb).



Karyotype

The chromosome set of an individual. For example the karyotype of a girl with Turner Syndrome is usually 45X.

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.

Paediatric Endocrinologist

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

Pituitary gland

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

Placenta

The organ which connects the foetus to the wall of the uterus. The placenta provides the foetus with nourishment and eliminates wastes.

Puberty

Essentially the period in a young person's life, both male and female, where they become physically capable of reproduction.

Somatomedins

These are hormones made by the liver that deliver the growth message to the bones and other tissues. Somatomedins are stimulated by growth hormone.

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Subcutaneous Injections

An injection given beneath the skin.

Syndrome

A syndrome is a collection of characteristics that occur together and characterise a particular condition.

Testosterone

Most potent male sex hormone, which is produced in the testes (testicles) and controls male sexual development.

Thyroid Gland

A butterfly-shaped gland in the front of the neck below the larynx, which makes the hormone thyroxine.

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.

X Chromosome

The female sex chromosome.

Y Chromosome

The male sex chromosome.



Support Organisations and Further Reading

Australasian Paediatric Endocrine Group (APEG)

www.apeg.org.au

Association of the Genetic Support

www.agsa-geneticsupport.org.au

Australian Pituitary Foundation

www.pituitary.asn.au

Coeliac Society of Australia

www.coeliac.org.au

Downs Syndrome Australia

<http://www.downsyndrome.org.au/>

Downs Syndrome Association NSW

<http://www.downsyndromensw.org.au/>

Downs Syndrome Association QLD

www.dsaq.org.au

Downs Syndrome Association Victoria

<http://www.downsyndromevictoria.org.au/>

Downs Syndrome Association South Australia

www.downssa.asn.au

Downs Syndrome Association Western Australia

www.dsawa.asn.au

The Endocrine Society

www.endo-society.org

The Hormone Foundation

www.hormone.org

The Magic Foundation

www.magicfoundation.org

Marfan Association Victoria

<http://www.marfanvic.org.au/>

Turners Association

www.turnersyndrome.org.au

UK Society for Endocrinology

www.endocrinology.org



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Please ask your doctor or nurse for further information on the resources available to you.

The *Hormones and Me* series includes:

1. Growth Problems in Children
2. Turner Syndrome
3. Craniopharyngioma
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5. Puberty and its Problems
6. Delayed Puberty
7. Multiple Pituitary Hormone Deficiency (MPHD)
8. Congenital Adrenal Hyperplasia (CAH)
9. Adult Growth Hormone Deficiency
10. Management of Emergency or 'Stress' Situations
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12. Congenital Hypothyroidism
13. Klinefelter Syndrome
14. Disorders of the Thyroid Gland in Children and Adolescents



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Date of preparation: April 2017 | AUS-SAI-0417-0007

Hormones and Me

Growth Problems in Children

This booklet is valuable reading for children who have hormone problems affecting their growth.

It is also recommended reading for their family and friends.

