

Table of content

1. INTRODUCTION	2
2. DEVELOPMENT OF THE GENITALIA	2
3. PUBERTY IN BOYS	6
4. PUBERTY IN GIRLS	9
5. PRECOCCIOUS PUBERTY IN GIRLS (PUBERTAS PRAECOX)	14

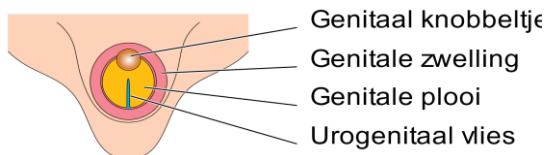
INTRODUCTION

In **girls**, the first sign of puberty is the breast development, influenced by female hormones. This usually starts between the age of 8 and 13 years. There is a large variance in age at start of puberty. On average, 3 years later, menarche occurs. After the first signs of puberty, the height velocity increases. After menarche, a girl still grows 3 to 4 cm.

In **boys**, puberty start a little later, between the age of 9 and 14 years, when the testicular volume becomes 4 ml or more. It take 6 to 9 months after the onset of puberty before growth acceleration occurs.

DEVELOPMENT OF THE GENITALIA

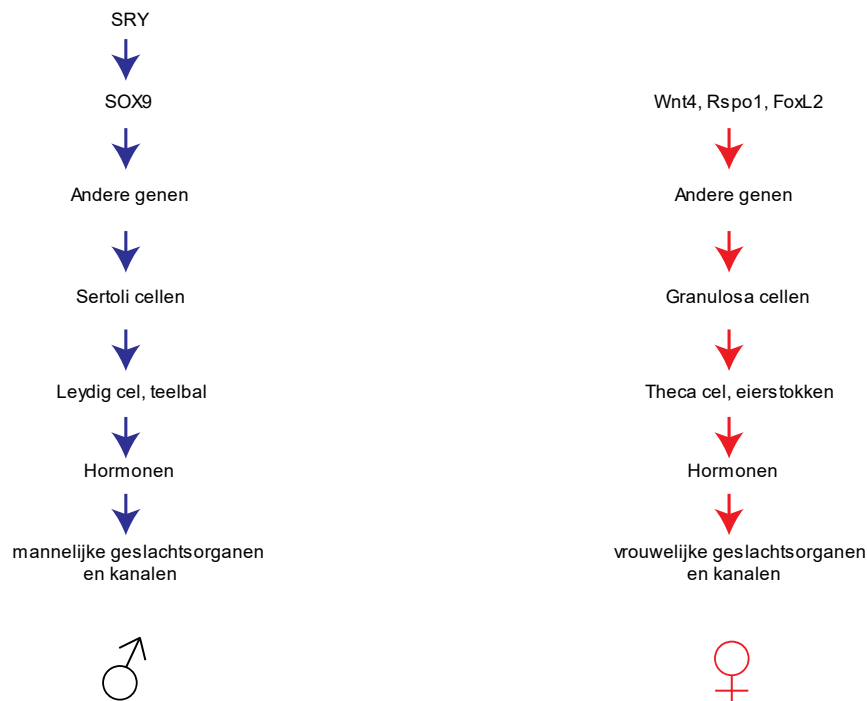
The development of the internal and external genitalia is a complex process with many phases. It is influenced by the chromosomes, genes and hormones.



The first step is the **chromosomal constitution** or Karyotype of the embryo. Boys and man usually have an X and a Y chromosome, while most girls and women have 2 X chromosomes. The chromosomes are inherited through the sperm cell of the father and the oocyte of the mother.

During the 6 weeks after the conception, no difference between the female and male embryo exists. The internal 'gonadal ridge' can develop into testicle or ovary. Externally, it looks the same in both sexes. It contains a small bulb with an opening below.

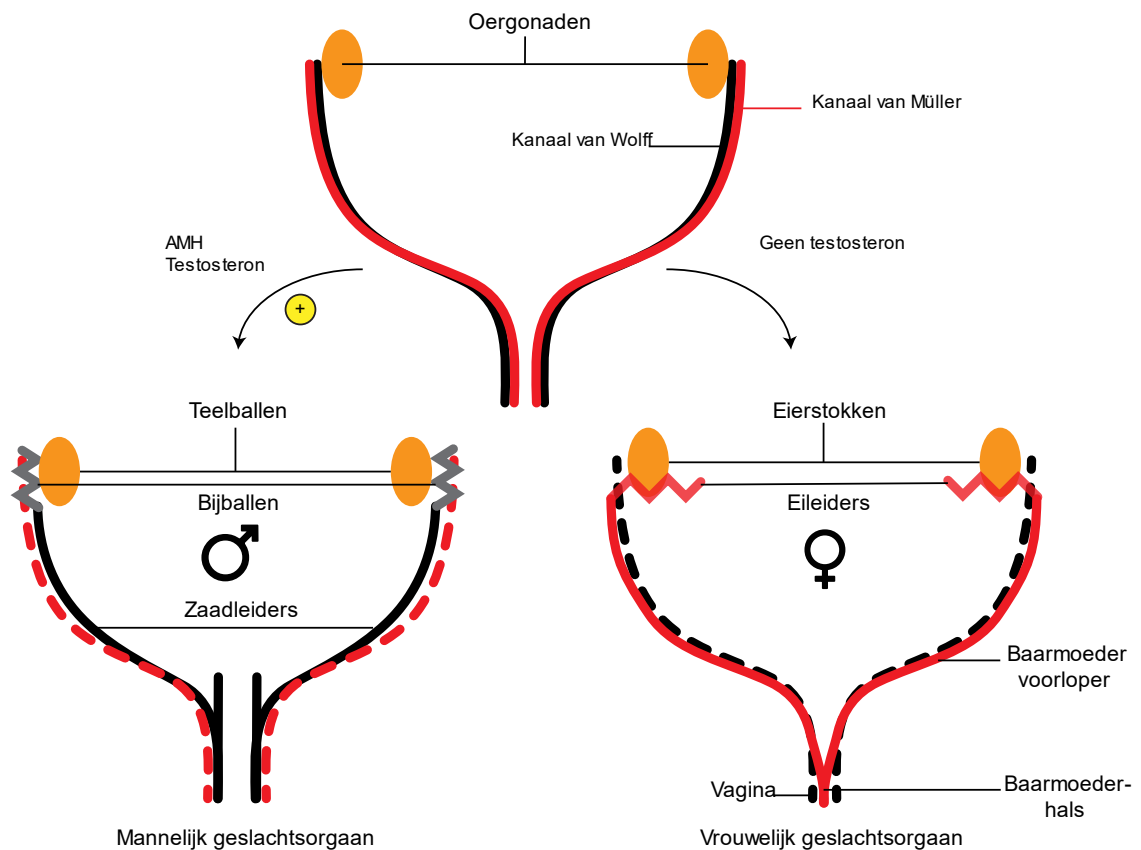
Between the 6th and 8th week, the development of the genitalia will continue uniformly male or female.



Development of the male reproductive organs

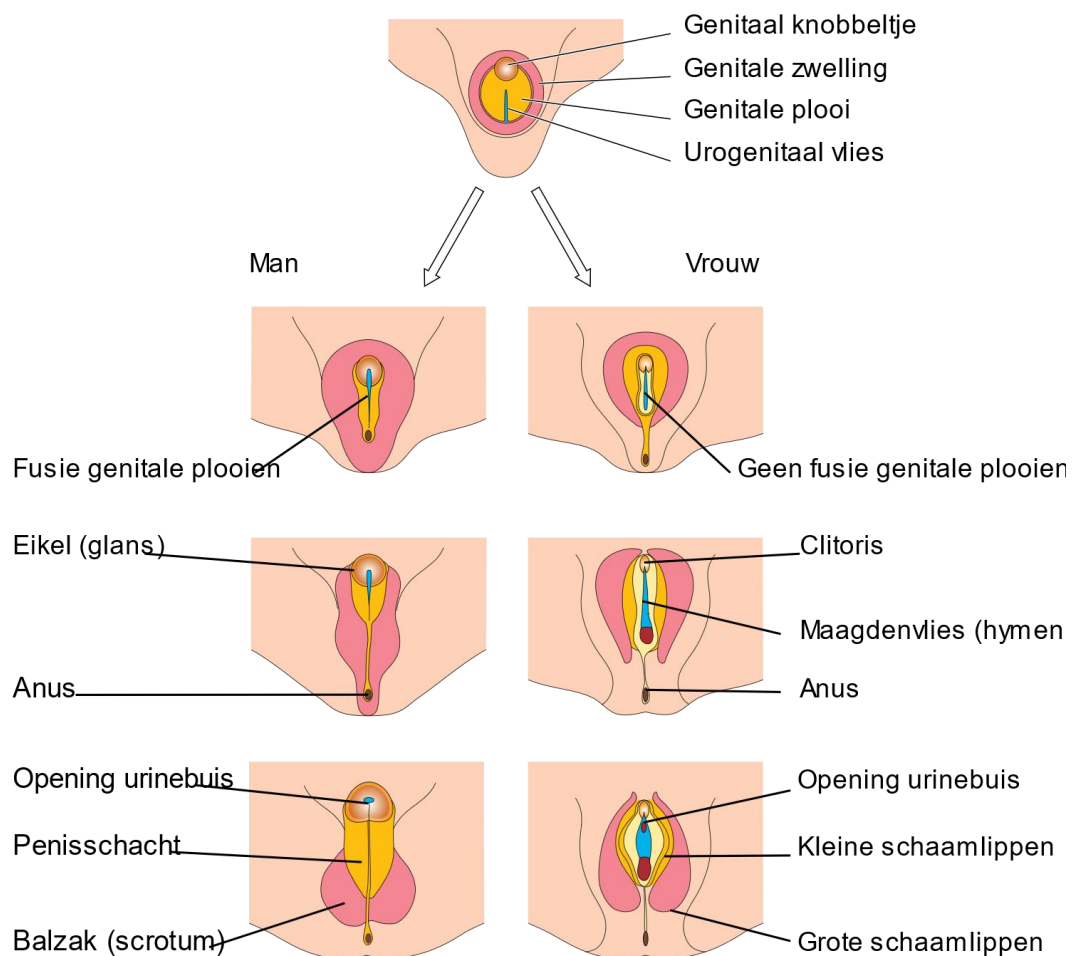
If the embryo has an XY chromosomal constitution, this will typically develop into a boy. On the Y chromosome, a gene ('SRY gene') ensures the development of the 'genital ridge' into a testicle. In absence of this gene, this development does not continue or is aborted in an intermediary phase. The SRY gene on the Y chromosome activates several other genes, according to a 'domino effect'. This initiates the development in the 'genital ridge' of '**Sertoli cells**', only present in the testes. These cells produce hormones and other products, initiating 4 important processes :

1. Ensuring the accurate development of the testes
2. The preliminary structures of the ovaries and uterus ('Müllerian channels') are not useful in the male foetus and will be destroyed by a hormone AMH (Anti Müllerian Hormone) produced by the Sertoli cells.
3. Development of the male internal genital structures ("Wolff channels") to epididymis, vas deferens and seminal vesicles.
4. Development of the male hormone (testosterone) producing cells (= Leydig cells).



The Leydig cells start producing male hormone (testosterone) from the 8th week of pregnancy. This hormone, and its derivative, dihydrotestosterone, stimulates the growth of the genital bulb into a penis. During this process, a part of the skin will be folded into a tube, becoming the urethra. The tube is formed from bottom to the top, so the opening arrives at the tip of the penis. If this process is incomplete, the opening of the urethra will be somewhere halfway or even at the bottom of the penis. This is called 'hypospadias'.

Both genital folds will grow, influenced by testosterone and fuse at the midline to form the scrotum. Later, the testes will descend in the abdomen and settle into the scrotum.



Development of the female reproductive organs

When the embryo has 2 X chromosomes, and all the genes necessary to ensure the accurate development of the ovary are functional, the 'genital ridge' will develop into an ovary. No 'sertoli cells' but 'granulosa cells' will occur. These cells produce products ensuring the development of oocytes. Since the granulosa cells do not produce AMH (Anti Müllerian Hormone) the preliminary structures of the female internal genitalia (Müllerian channels) can develop into Fallopian tubes and uterus. Because there is no production of male hormone in the ovary, the preliminary male genital structures ("Wolff channels"), will disappear.

In addition, the external view of the external genitalia of the foetus changes little. The genital bulb grows a little to form the clitoris. The genital folds form the labia.

PUBERTY IN BOYS

Puberty is the phase in life when a person achieves the possibility to reproduce. In boys, it is characterised by growth and development of the testis, the development of the male sexual characteristics, growth spurt and changes in behaviour.

On average, puberty in Belgian boys start at the age of 11.5 years, but a large variance exists. Puberty can start between the age of **9 and 14 years**. When puberty start before the age of 9 years this is considered as precocious puberty (pubertas praecox). When the testicular volume is still below 4 ml at the age of 14 years, this is considered as a late puberty (pubertas tarda).

Puberty start when the hypothalamus, a part of the brain, releases the hormone LHRH, mainly at night. The LHRH stimulates the nightly peak production of LH, FSH in the pituitary gland and testosterone in the testis. Later on, peak production of LH also occurs during the day.

In clinical practise, onset of puberty in boys is determined when the **testis obtain a volume of 4 ml**. This is not easy to observe at home. Doctors use an "orchidometer", a chain with little balls of different volumes to compair with the boys'testis.



Orchidometer with testicle models of different volumes. The blue eggs have a volume up to 4 ml, comparable to boys before the onset of puberty. The model 4 ml marks the start of puberty. Most adult men have a testicular volume between 15 and 25 ml.

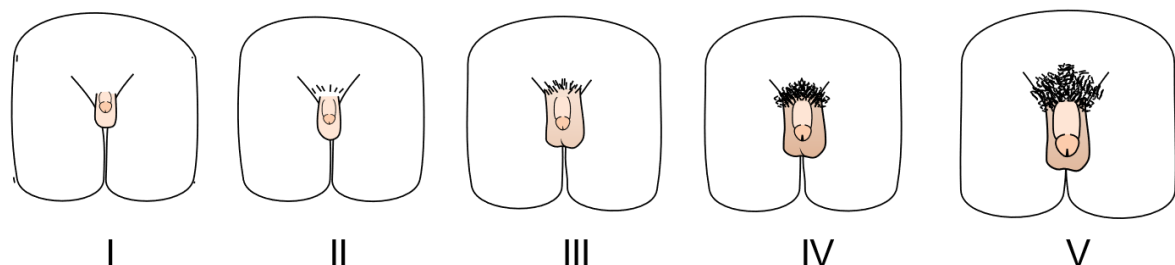
The testicular volume increases because the vas deferens, responsible for the production of **sperm cells**, become long and thicker. The first sperm cells appear in the morning urine at the average age of 13-14 years, in an early stage of puberty.

The increase in testosterone blood levels causes physical changes. The penis becomes larger and the glans gets its typical shape. The scrotum becomes thinner, larger and more red in colour. The testicular volume continues to increase. There is appearance of hair

above the penis (pubic region) and on the scrotum. The growth of hair increases and spreads to the belly button and inguinal area. These pubertal changes are described in **Tanner stadia**: de G (genital development) stadia G1 to G5, an de P (pubic hair) stadia P1 to P5.

stadium	description
P1	prepubertal
P2	Some lightly pigmented hairs at the bottom of the penis
P3	hair becomes thicker and darker, upward expansion
P4	Inverse triangle
P5	Adult stage with spreading towards belly button and upper legs
P6	Further expansion of hairs on the midline to the belly button

stadium	description
G1	prepubertal
G2	Testicular volume m4 ml of more – scrotum increases, thinner and more red
G3	penis becomes larger – testicular volume increases
G4	penis has grown in length and width – glans strongly developed – greater testicular volume
G5	Adult shape – testicular volume is at least 12 ml



Appearance of **axillary hair**, and later on chest, legs, chin and upper lip.

The **axillary sweat glands** start to develop causing a male sweat smell. The sebaceous glands are also stimulated by testosterone. This causes an oily skin. . The sebaceous glands swell and can become infected, causing acné.

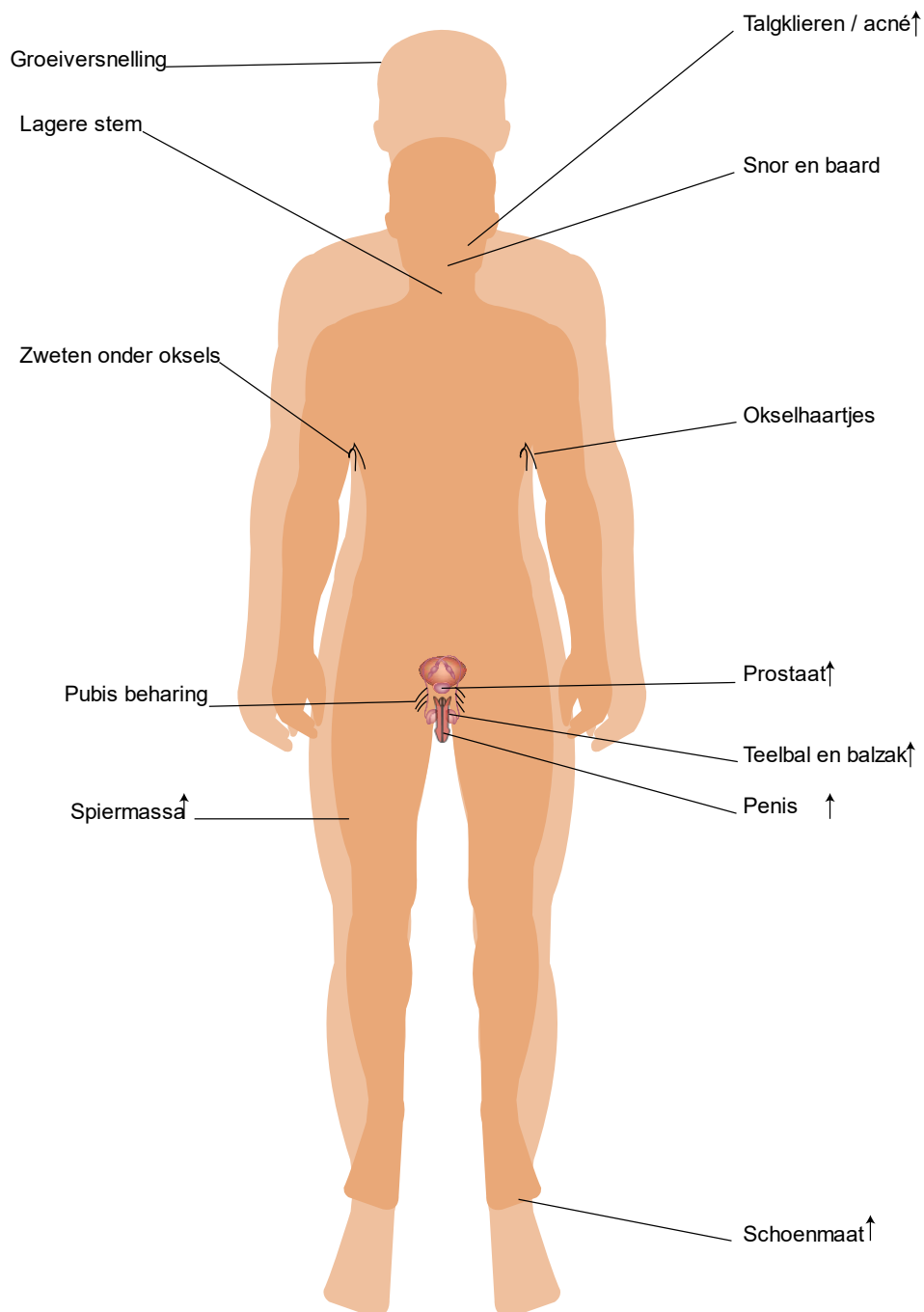
The Adam's apple grows and the vocal cords extend, causing the voice to drop and to lower.

The testosterone (direct and after conversion to oestrogens) stimulates the production of growth hormone, causing a growth acceleration occurring 6-9 months after the onset of

puberty. During the first 2 years of the pubertal growth spurt, boys can grow 8 to 14 cm/year. The growth velocity gradually decreases and most boys stop growing at the age of 18 years. The total increase in length from the beginning of puberty until adult height is approximately 28 cm when puberty start at 12 years. The pubertal growth spurt is higher when puberty start early. Boys who start puberty at 14 years of age usually have an increase in length of 22–24 cm.

The growth acceleration begins mostly at the hands and the feet, sometimes causing an increase in shoe size of 5 to 7 sizes. During the first years of puberty, the legs and arms will grow slightly faster than the trunk. Only in the later stages of puberty, the shoulders and chest increase in size.

Testosterone and its derivatives also have an effect on the brain. During puberty, many changes occur in the brain causing a decrease in emotional and impulse control.



PUBERTY IN GIRLS

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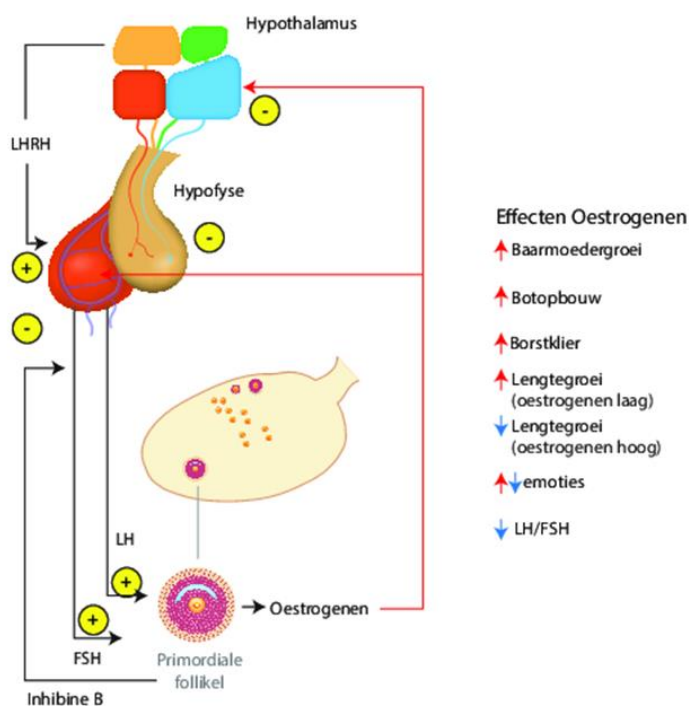
Page

9 of 19

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Puberty is the phase in life when a person achieves the possibility to reproduce. In this phase, many changes in girls will take place : growth and development of the ovaries and uterus, development of female sexual characteristics, growth spurt and behavioural changes. Puberty has started in girls when breast tissue starts to grow. In Belgium, this is on average at the age of 10 years, but a large variance exists, between the age of **8 to 13 years**. When puberty starts before the age of 8 years in girls, this is considered as precocious puberty (pubertas praecox). When there is no breast development at the age of 13 years, this is considered as a late puberty (pubertas tarda).

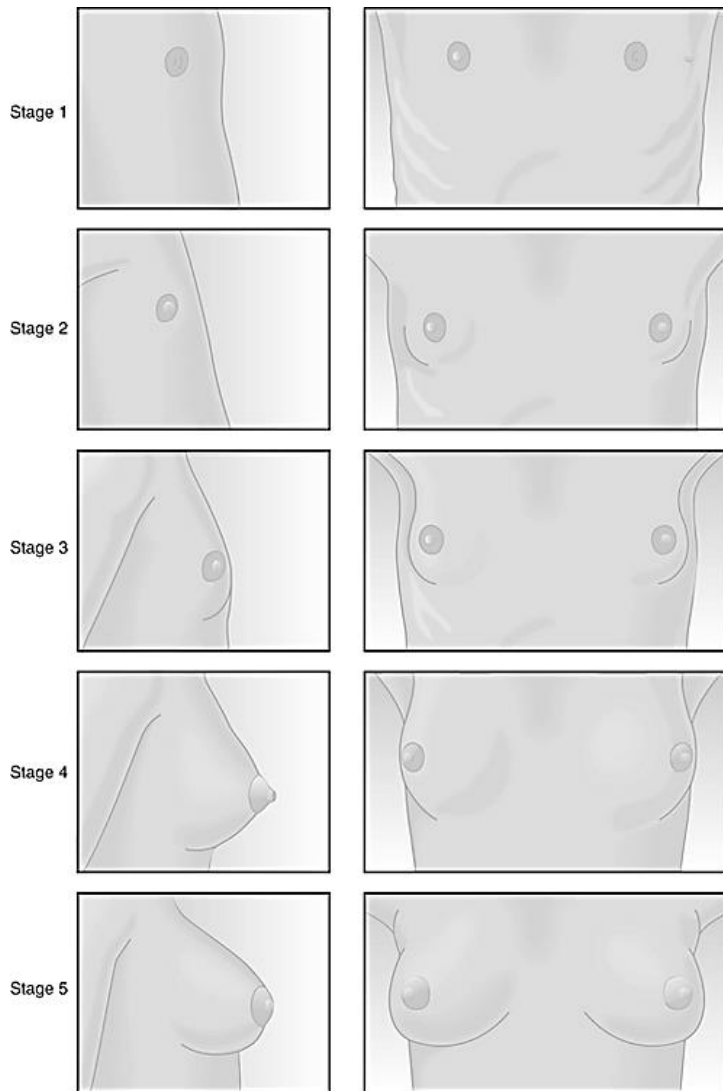
Puberty start when the hypothalamus, a part of the brain, releases the hormone LHRH, mainly at night. The LHRH stimulates the nightly peak production of LH, FSH in the pituitary gland. These peaks cause the ovaries to grow, from 1 ml tot 20 ml volume, and to produce more female hormones (and a little male hormone).



The **female hormones** (oestrogens) increase the glandular tissue in the breasts. The development of the breasts is described in Tanner stadia: the M(mama) of B (breast) development stadia M1 to M5.

stadium	description
M1	prepubertal

M2	Slice of breast tissue palpable – nipple protrudes
M3	Breast increases – nipple and breast shape in 1 area
M4	Nipple and areola form a second hill on the breast
M5	Adult shape



Female hormones increase the volume of the **uterus** 10–20 times and increase the thickness of the vaginal mucosa causing the colour to change from red to light pink.

The oestrogens stimulate the production of growth hormone, causing a **growth acceleration** immediately at the start of puberty. During the first 2 years of the pubertal growth spurt, girls can grow 6 to 10 cm per year. Thereafter, growth velocity slowly decreases and most girls stop growing at the age of 16 years. The total increase in height

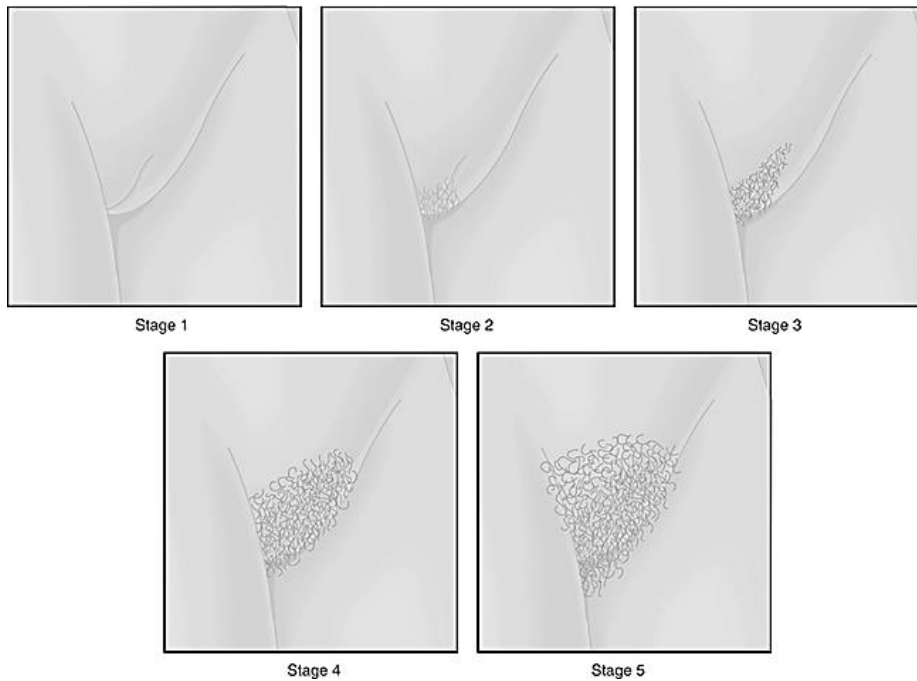
from the beginning of puberty until adult height is on average 18 cm if puberty start at 10-11 years of age. The growth spurt is larger when puberty start earlier and shorter when puberty starts later.

Growth is visible in the beginning at hands and feet, sometimes causing an increase in **shoe size** up to 5 sizes in 2-3 years. During the first years, the arms and the legs grow a little faster than the trunk, compensated during the second half of the pubertal growth spurt. In adult women, the **leg length** is on average 52% of the total length.

Oestrogens stimulates bone development until the age of 25 years. To increase bone mass, it is important to have sufficient intake of calcium (min 1200 mg/day) and vitamine D during this period. Because women lose a lot of bone mass after menopause, due to a lack of oestrogens, even leading to osteoporosis, increasing bone mass at a young age is very important.

The male hormones, produced by the ovaries, stimulate the growth of hair in the pubic region. The progression of this hair growth is also divided in Tanner stadia : P(pubic hair) stadia 1 to 5.

stadium	description
P1	prepubertal
P2	Some light pigmented hairs on the labia
P3	hair becomes thicker, darker and upward expansion
P4	inverse triangle, less extensive than in adult stage
P5	Adult stage



The male hormones also stimulate **axillary hair growth and axillary sweat glands**. Girls can develop axillary sweat smell. Stimulation of the sebaceous glands can cause an oily skin and acné.

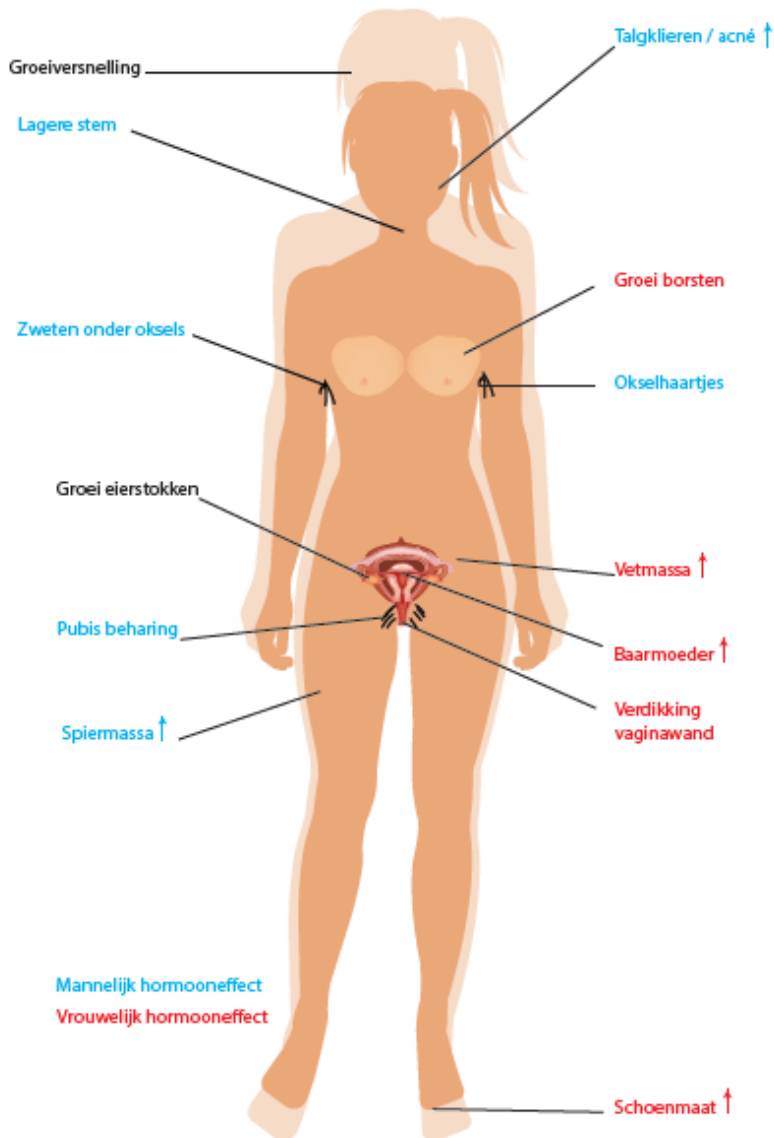
Also in girls, the vocal cords become extended and the **voice** slightly lower, but seldom noticed.

Sex hormones also have an effect on the **brain**. During puberty, many changes occur in the brain causing a decrease in emotional and impulse control.

Some years after the onset of puberty, the ovaries start to produce **progesteron**.

When oestrogens and progesterone are produced in peaks, the first menstrual bleeding occurs : **menarche**. This usually arrives around the age of 13 years, 2-3 years after the onset of puberty. The skeletal age is also 13 – 14 years and indicates the end of skeletal growth. Most girls can still grow 2-5 cm after the occurrence of menarche..

In the first years after menarche, the bleedings are irregular in timing as for blood loss.



PRECOCIOUS PUBERTY IN GIRLS (PUBERTAS PRAECOX)

Normally, puberty occurs between the age of 8 and 13 years in girls. The first sign is progressive development of breast tissue. If the ovaries produce sufficient female hormones to initiate breast development before the age of 8 years, this is considered as precocious pubertal development.

Causes of precocious puberty in girls

Precocious puberty occurs 10 to 20 times more frequent in girls than in boys. Compared with data from 40 years ago, puberty in girls starts 1 year earlier and more girls develop

breasts before the age of 8 years. Specialists suspect a link with increasing weight in children. Fat tissue can produce low quantities of female hormones. Another hypothesis suspects the presence of environmental chemicals, mimicking the effect of female hormones.

In most cases, the normal puberty mechanism is activated too early (**central pubertas praecox**). In less than 5% of the girls with precocious puberty, the production of female hormones started in the ovaries without a signal from the brain (**peripheral pubertal praecox**)

The **causes** of precocious puberty often remain unknown. Some congenital conditions or tumours in the brain increase the chances of developing an early puberty. In some families, children develop puberty early, indicating that a genetic factor is playing a role. Precocious puberty is also more frequent in children from international adoption.

A peripheral precocious puberty can be caused by genetic changes due to chronic activation of the gonads (f.e. Mc Cune-Albright syndrome) or by tumours producing female hormones (granulosa cell tumours, germ cell tumours). Another cause is accidental intake of female hormones (medication of older sisters or mother)

Possible causes of precocious puberty in girls

Central	Unkown cause	
	International adoption	
	Congenital brain defects	Hydrocephalus
		Spina bifida
		Brain malformations
	Acquired Brain laesions	Tumours
		Cerebral palsy
		Meningitis and encephalitis
		Irradiation
	Genetic causes	Very rare gene anomalies (KISS1, KISSR, MKRN3, DKL)
		Chromosomal anomalies

Peripheral	Tumours	Granulosa cell tumours
		Germ cell tumours (dysgerminoma, teratoma,..)
	Activating mutations	Mc Cune-Albright

Symptoms of precocious puberty in girls?

- Essential for the diagnosis is the presence of **breast tissue** (stage B2 or further, see text on pubertal development in girls) before the age of 8 years. It is not always easy to differentiate between breast tissue and fat tissue in girls who are overweight. Breast tissue feels firmer and lies directly behind the nipple. Often, the nipple points protrudes and changes in colour.
- Female hormones makes the **mucosa** from the labia thicker, causing a **lighter colour**.
- Often, but not always, some **pubic hair** appears in the genital region (P2 or more) and in the armpit.
- The **sweat glands** become active and can produce 'adult' sweat smell. The skin and hair become fatter due to the stimulation of the sebaceous glands.
- Female hormones stimulate the production of growth hormone, causing girls to **grow faster**. This can be visualised by putting all growth data on a growth curve.

Undesirable aspects of precocious puberty

The high levels of female hormones at a young age closes the growth plates and results in short stature

Girls with precocious puberty often feel different than other children and sometimes they are being bullied at school. They have more psychological problems and show more risk behaviour at a young age. Some studies show associations between early puberty and other conditions, like diabetes, and cardiovascular disease in adults.

Treatment of precocious puberty in girls

The **goal** of the treatment is to synchronise the physical and psychological development with chronological age and avoid short stature by early closing of the growth plates.

The type of treatment depends on the cause of the precocious puberty

- Central precocious puberty:

In most cases, the origin is a **central precocious puberty** with the hypothalamus producing high peaks of LHRH. For this form, medication (LHRH analogues) can block the LHRH from interacting with the pituitary gland. The currently available LHRH analogues need to be injected in the muscle or subcutaneously, and different forms with different duration of action exist. Some formulas work for a couple of hours, but the pharmaceutical industry succeeded in binding these molecules to a gel permitting very slow release of the active substance during 1.3 or even 6 months.

Usually, the treatment is very effective. The breast development stops and a reduction of the breast volume is often obtained. The emotional fluctuations and ‘puberty behaviour’ decrease. The closure of the growth plates is delayed, with a positive effect on adult height, especially in girls with puberty onset before the age of 6 years. In older girls, the effect on adult height is variable.

The most common adverse events of the treatment are pain, redness and swelling of the injection site, exceptionally, an allergic reaction to the medication can occur. After the first injection, 5-10% of the girls experience a vaginal bleeding that does not reoccur with continuation of the treatment. After stopping the treatment, puberty development continues and most girls have menstruations within 2 years

During the treatment, the bone density may decrease, but this will restore after stopping the treatment

- Peripheral precocious puberty

The **peripheral precocious puberty** can be treated with medication reducing the production of female hormones in the ovaries or tumour ad/or blocking the effect of female hormones. If a tumour causes the production of female hormones, this can be surgically removed.

Additional examinations

Bone age: female hormones accelerate the bone maturation and increase the skeletal age (bone age). In children with precocious puberty, bone age will be more advanced than the chronological age.

MRI (magnetic resonance imaging) of the brain: precocious puberty can be caused by significant brain anomalies, especially when puberty start before the age of 5 years. Luckily, in more than 90% of the girls with precocious puberty, the brain MRI is normal. Nevertheless, in order not to miss a serious (brain) problem, most doctors prefer to do the brain MRI.

Hormonal blood levels

When girls go into puberty, the LH levels rises, first at night and later on also during the day. When the precocious puberty is 'peripheral', the LH level will be suppressed. An LH level above 1.0 mIU/L usually indicates the beginning of puberty. The female hormone (oestradiol) concentrations also rise, first at night and then during the day, but still can be low in the beginning. In peripheral precocious puberty, the oestradiol is usually highly elevated, compared to values in prepubertal children. Oestradiol stimulates the production of growth hormone and IGF-1 (see text on growth hormone). The IGF-1 concentrations in the blood rise early in puberty, and are sometimes the first sign indicating the onset of puberty.

Because basal values of LH, FSH and oestradiol do not always provide clarity on the onset of puberty, usually, an LHRH stimulation test will be proposed.

LHRH test: this test investigates whether the hormonal axis that initiates puberty is active or not. A blood sample is taken to measure basal values of the hormones LH, FSH and oestradiol. The hormone LHRH is then given intravenously. At different times, blood samples are taken to measure if LH and FSH values rise.

In prepubertal girls, FSH will rise more than FSH, while the opposite occurs in girls in puberty. Exceptionally, very low values of LH are measured with no rise after LHRH administration. This situation occurs when the levels of female hormones, oestradiol, are very high, as may be the case in peripheral pubertas praecox or administration of female hormones, oestradiol.

Some clinical features look like precocious puberty, but are not related :

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Page

- Increase in fat mass in the breast region : **adipomasty**
- In babies and toddlers, an isolated breast development sometimes can be noticed (see **premature thelarche**)
- Some girls develop axillary and genital hair without breast development (see **premature adrenache**)
- **Premature menarche**: vaginal bleeding without other signs of pubertal development