Congenital Adrenal Hyperplasia
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# PUBERTY AND CONGENITAL ADRENAL HYPERPLASIA

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## General

Puberty is defined as the acquisition of reproductive capability and is attained through a series of physical changes which have their onset in more than 50% of boys and girls by their twelfth birthday. The appearances which consist in girls of changes in the breast tissue and the appearance of pubic hair, in boys the change of the size of the testes and penis along with the appearance of pubic and axillary hair are brought about by a number of mechanisms.

In association with these changes, the puberty growth spurt contributes about 30 cms in boys and 25cms in girls to the adult height of the individual. Between the sexes there is a slight difference of the timing of the puberty growth spurt, occurring quite early on in puberty around the age of eleven years in girls and later in boys, around the age of thirteen to thirteen and a half.

## Hormonal Control of Puberty

The system regulating puberty is known as the Hypothalamic-pituitary-gonadal axis. The hypothalamus is an area of the brain which produces hormones and is situated at the centre of the base of the brain.

In this system the hypothalamus secretes a hormone called Gonadotropin-releasing hormone (GnRH) in little bursts every 90 minutes which stimulates the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. These hormones appear in a pulsatile form as shown in the graphs in Figure: 1.

LH and FSH are sometimes called the sex hormones. Before 8-9 years of age the system is switched off but thereafter becomes more active at night initially and then during the day and night once puberty is established.

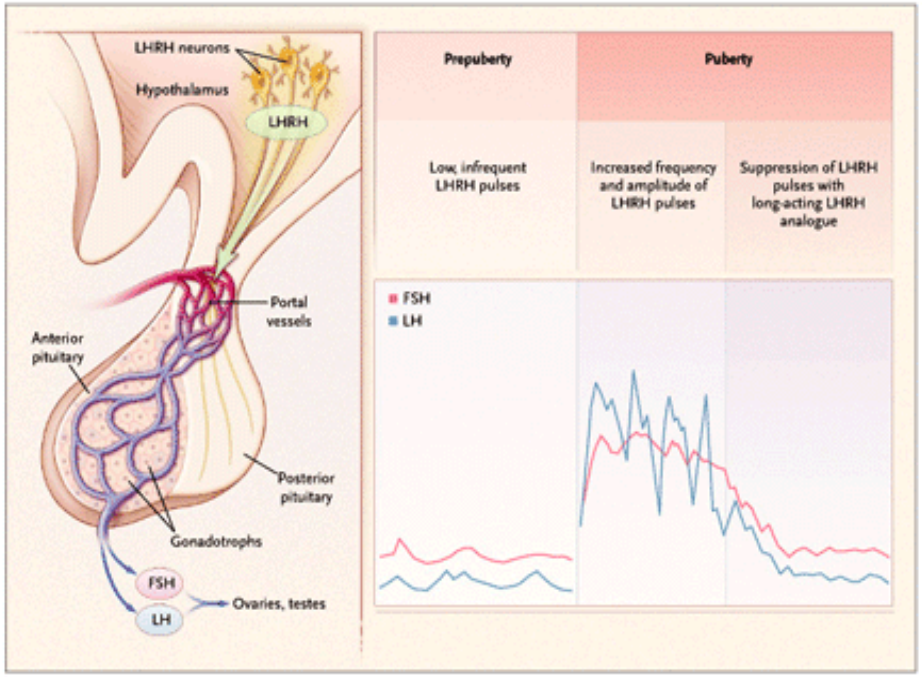


**Figure: 1**

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The graphs below illustrate further the pulsatile production of LH and FSH during the stages of puberty. The graph Figure: 2 traces the LH and FSH over a 24 hour period in a prepubertal child. The data show that there is no activity.

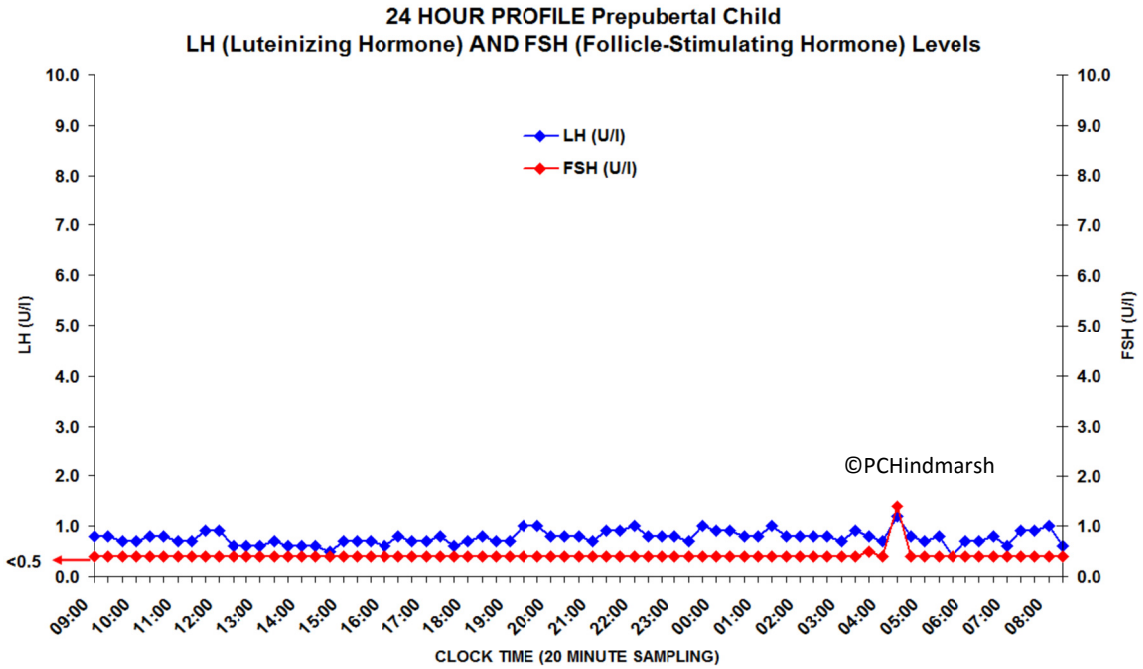


**Figure: 2**

In the graph Figure: 3 we can clearly see that the LH and FSH activity has become more active at night but not during the day, this happens when a child has entered the first stage of puberty.

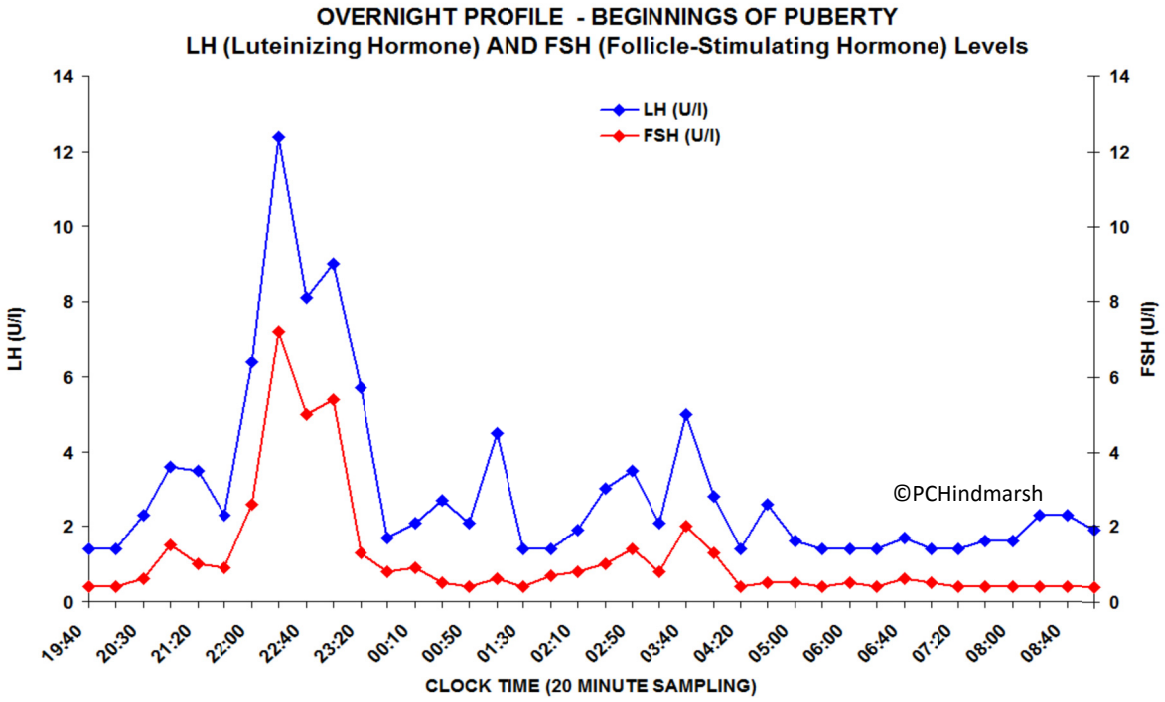


**Figure: 3**

In the later stages of puberty (Figure: 4) we can clearly see that LH and FSH production is very pulsatile throughout the full 24 hour period.

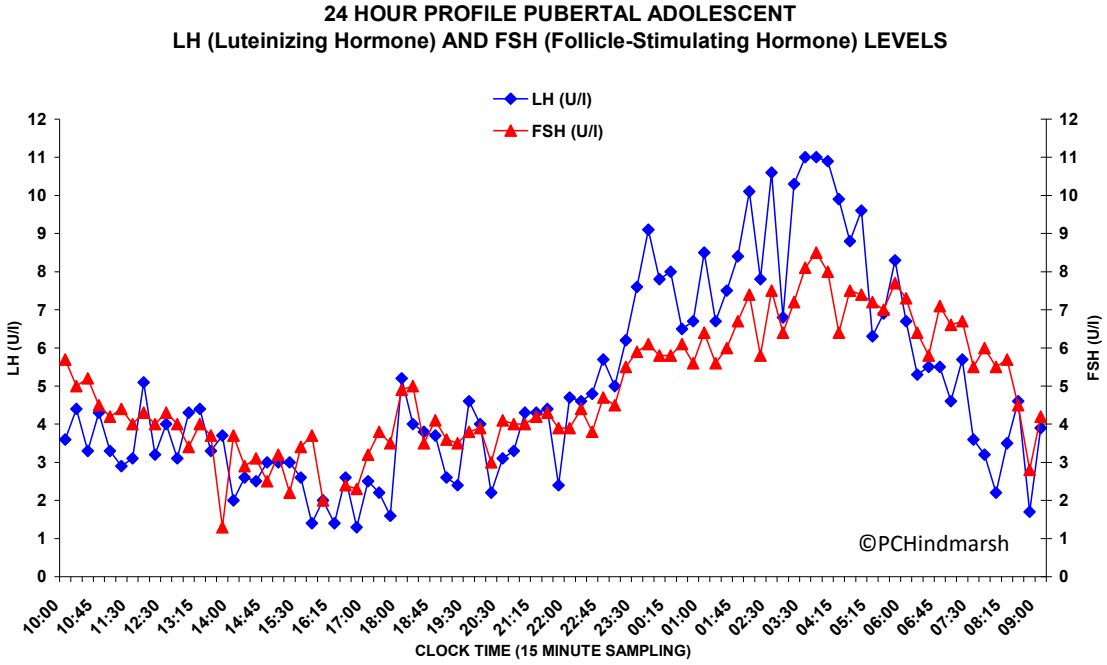


**Figure: 4**

The LH and FSH then impact on either the testes or the ovaries to produce an increase in size of the testes in boys and the development of follicles in girls. We can measure this in boys by comparing changes in size with a special set of beads known as an Orchidometer, or Prader's balls as can be seen in Figure 5. The string of 12 different sized beads increase in size from 1 ml to 25 ml, the beads are compared with the size of the testicles and the volume is matched as closely as possible to the size of the bead.

The size and volume of the beads indicate the staging of puberty as follows:

Prepubertal: 1 ml - 3 ml (shown in Figure: 5 as black beads)

Pubertal: 4 ml - 12 ml

Adult: 12 ml - 25 ml


**Figure: 5**

## Ultra Sound Scans

### Girls

In girls by using ultrasound we can measure change in the appearance of the ovary to a multicystic appearance as shown in Figure: 6 Usually we start doing this type of scan from the age of 10 years in all girls with CAH as part of annual review

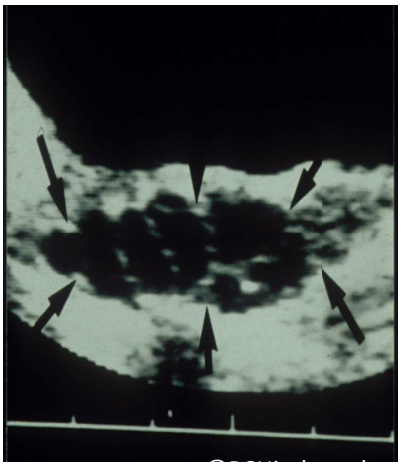

**Figure: 6**

### Boys

You can also use ultra sound to measure the size of the testes and this scan is known as a sonogram. However we tend to reserve using sonograms to check for the presence of adrenal rests. Figure: 7 shows what a normal testes ultra sound looks like.

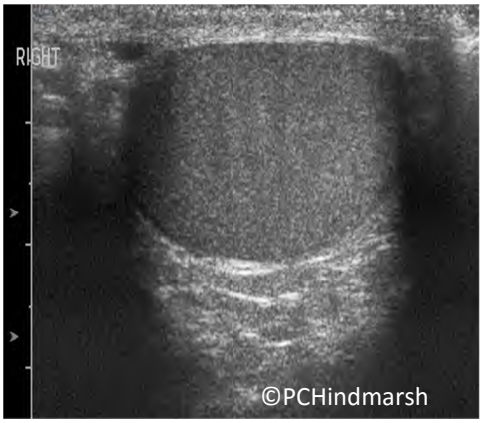


**Figure: 7**

### Sex Steroid Production

The testes and ovary produce the sex steroids testosterone and estradiol (oestradiol) respectively. These hormones have a pulsatile pattern but more of a circadian rhythm with respect to testosterone with higher values in the early hours of the morning and low values in the late afternoon.

The situation with the ovaries is more complex because of the presence of the menstrual cycle which requires a close interaction between LH and FSH as well as the generation of estradiol and progesterone from the ovary leading to ovulation and menstrual periods

The pathway of testosterone and estradiol production uses several of the steps used in the formation of cortisol in the adrenal gland. Like the adrenal gland the gonads use cholesterol as the starting point. However, the gonads do not contain 21 hydroxylase so they cannot form cortisol and instead there is a shift in the pathway towards the formation of testosterone and estradiol.

The diagrams below compare the pathways of a person without CAH (Figure: 8) with a person who has classical congenital adrenal hyperplasia (Figure: 9) which illustrates the block of cortisol that happens resulting in the production of excess adrenal androgens and the resulting feedback onto the pituitary to switch off LH and FSH.

**Pathway of a person without CAH**

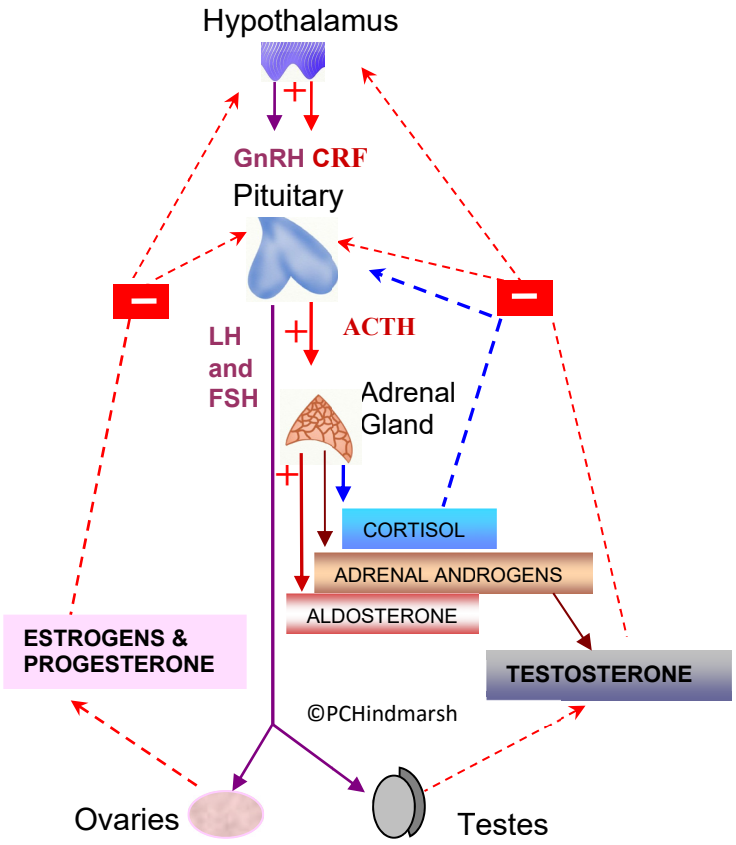


**Figure: 8**

**Pathway of a person with Classical CAH**

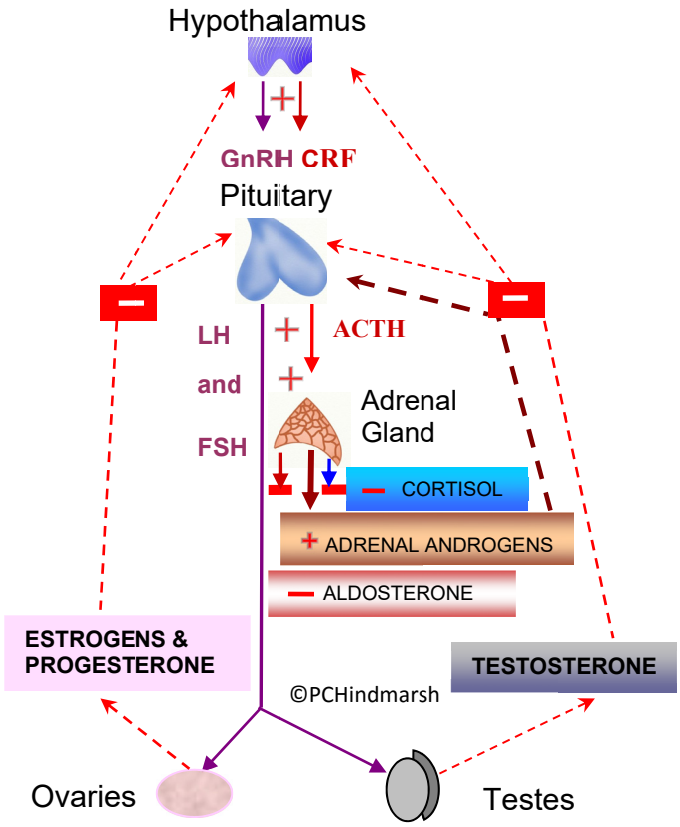


**Figure: 9**

In the male, the hypothalamic-pituitary-gonadal axis is predominant because of its ability to produce testosterone. This gives all the secondary appearances that we associate with puberty. These changes include enlargement of the penis in boys and breast changes in girls along with appearance of pubic hair and hair under the arms. Spottiness is also part of all this!

In girls, however, estradiol is the predominant hormone produced during puberty from the ovary and the male like hormones that are required for pubic hair development do not come predominately from the ovary but from the adrenal gland.

This difference leads to a number of problems and potential confusion as to what system is regulating what in the appearances that we see. However it is important to realise that these two systems do operate particularly in females and they need to be considered separately.

As such when we come to start thinking about puberty in congenital adrenal hyperplasia it is extremely important for us to remember this additional role that the adrenal gland plays in females in particular.

**Feedback system in girls**

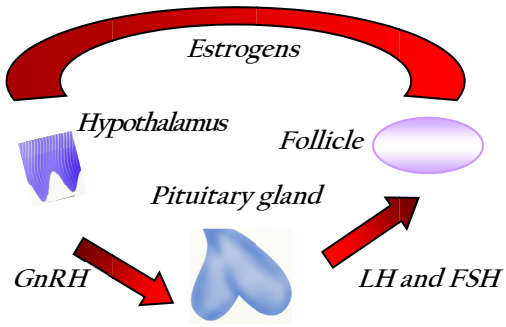


**Figure: 10**

**Feedback system in boys**

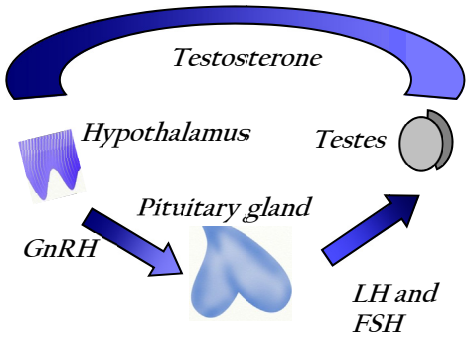


**Figure: 11**

We then add in the hypothalamo-pituitary-adrenal axis making cortisol, androgen and aldosterone as illustrated in the diagram below Figure: 12.

**The Hypothalamo-pituitary-adrenal axis**

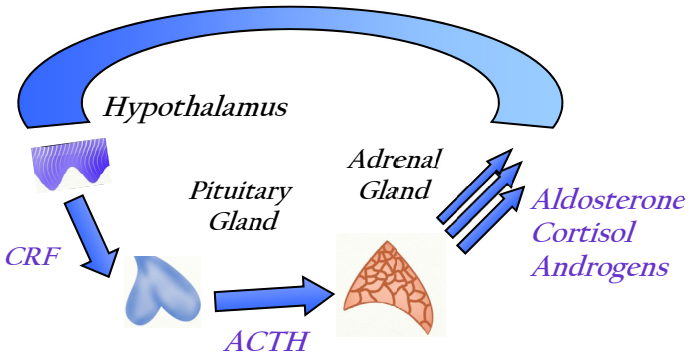


**Figure: 12**

**Order of Puberty**

The pubertal changes in boys and girls take place in an order sequence that reflects the increase production of LH and FSH from the pituitary gland. In the early stages of puberty in both sexes the production of LH and FSH is at night only (see Figure: 3) and this is associated with a small but significant increase in the circulating concentrations of the sex steroids.

These only produce early changes of puberty but in order to progress to full menstrual cycles and to develop an adult size testes in boys the LH and FSH production has to switch from being predominantly at night to taking place during both the day and night time (Figure 4). This is also associated with an increase in the sex steroid production and the completion of the changes that take place in puberty.

The Table Figure: 13 shows the sequence of events that take place and as we have said these need to take place in a progressive manner. As illustrated, in boys the predominant factor is the production of testosterone from the testes and this leads to the appearance changes. In girls, however, the adrenal gland produces the androgens that are necessary to give pubic and axillary hair changes but it is the ovary in its production of estradiol that leads to breast changes and the associated growth spurt.

You can see, therefore, that it is possible for someone to display some pubic and axillary hair as they are able to make some androgen but as they have an ovarian problem, they have no breast development. Equally we know that in people with pituitary problems where only hydrocortisone is given and estrogen replaced the girls do not develop adequate pubic and axillary hair because they are lacking in adrenal androgens due to the pituitary problem.

**Boys—development of external genitalia**

**Stage 1:** Prepubertal.

**Stage 2:** Enlargement of scrotum and testes; scrotum skin reddens and changes in texture.

**Stage 3:** Enlargement of penis (length at first); further growth of testes.

**Stage 4:** Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker.

**Stage 5:** Adult genitalia.

**Girls – Breast development**

**Stage 1:** Prepubertal.

**Stage 2:** Breast bud stage with elevation of breast and papilla; enlargement of areola.

**Stage 3:** Further enlargement of breast and areola; no separation of their contour.

**Stage 4:** Areola and papilla form a secondary mound above level of breast.

**Stage 5:** Mature stage: projection of papilla only, related to recession of areola.

**Boys and Girls—pubic hair**

**Stage 1:** Prepubertal (can see velus hair similar to abdominal wall).

**Stage 2:** Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia.

**Stage 3:** Darker, coarser and more curled hair, spreading sparsely over junction of pubes.

**Stage 4:** Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs.

**Stage 5:** Adult in type and quantity, with horizontal distribution ("feminine").

**Figure: 13 Stages of Puberty**

**What happens in CAH when the adrenal glands make too many adrenal androgens?**

In CAH the situation becomes quite complicated because of the additional adrenal androgen production from the adrenals in both males and females especially when control of the condition is poor.

For males, poor control in CAH will lead to a situation which looks rather similar to puberty known as precocious puberty and this starts earlier than normal puberty because of the increase in adrenal androgens. These are relatively weak androgens compared to testosterone but would be sufficient to produce an increase growth rate, appearance of pubic and axillary hair and also an enlargement of the penis. However, because there is feedback of the adrenal androgen on the pituitary gland the production of LH and FSH will be switched off so that there is no increase in the size of the testes. So from a simple examination using the beads (see Figure: 5) we can tell that the androgens are from the adrenal gland because the testes are not enlarged.

In girls what would happen is that the adrenal androgen production would lead to an increase of body hair and sometimes an enlargement of the clitoris. Again because LH and FSH are suppressed by the adrenal androgens there would be no estradiol production and there would be no breast development.

Although people often refer to these changes as puberty, strictly speaking they are not because the LH and FSH are suppressed and the drive to the change is not from the changes in LH and FSH production but from the over production of adrenal androgens. The figure below summarises all this. Normal puberty would see the pituitary gland make LH and FSH which would tell the testes or ovaries to make testosterone or estrogen. These would then modulate the activity of the pituitary but would not suppress LH and FSH production.

If instead CAH was poorly controlled then there would be a lot of adrenal androgen such as androstenedione and testosterone which will feedback on the pituitary and suppress LH and FSH and therefore switch off or suppress gonad activity, as illustrated in the diagram below, Figure: 14.

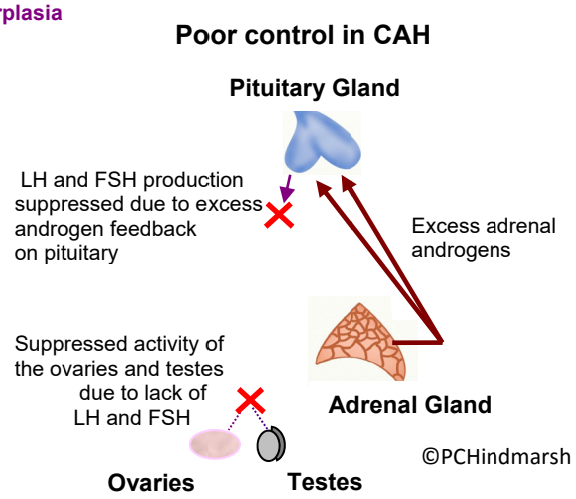


**Figure: 14**

The diagram below illustrates the normal production and feedback of the sex hormones

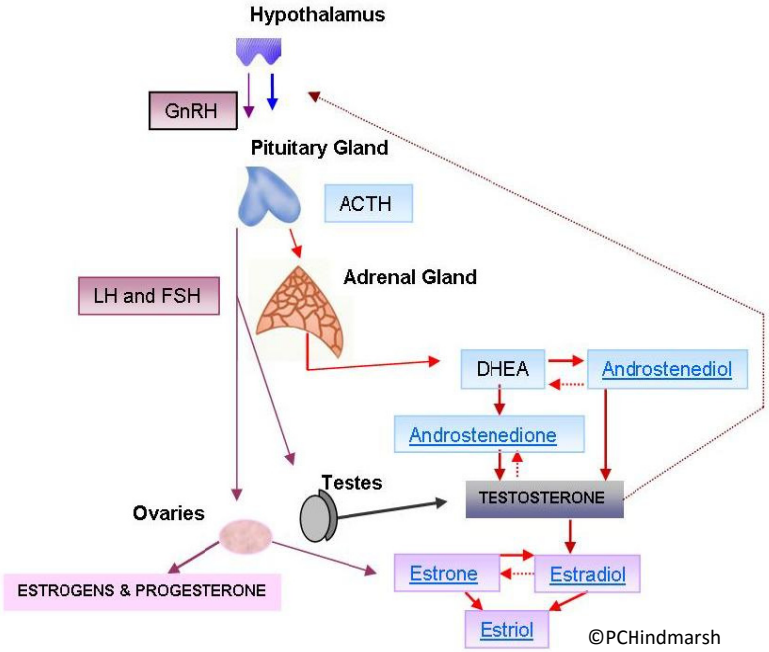


**Figure: 15**

### Symptoms and signs of precocious puberty

Excess androgen due to under treatment in CAH can lead to precocious puberty and if the following signs and symptoms develop before the age of 9 years old in boys and 8 years old in girls, contact your child's endocrinologist.

**Both Genders**

Fast growth – rapid increase height
Body odour
Appearance of pubic or axillary hair
Under arm hair usually appears around the age of 11 years old.
Acne

**Boys**

Facial hair (usually on the upper lip)
Deepening voice
Enlarged penis or testicles

**Girls**

Breast growth
Menstruation (First period)