PUBERTY AND ITS DISORDERS

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Puberty is the process of reproductive and sexual development and maturation that changes a child into an adult.

- During childhood, the HPO axis is suppressed and levels of GnRH, FSH and LH are very low.
- From the age of 8–9 years GnRH is secreted in pulsations of increasing amplitude and frequency. These are initially sleep-related, but as puberty progresses, these extend throughout the day. This stimulates secretion of FSH and LH by the pituitary glands, which in turn triggers follicular growth and steroidogenesis in the ovary. The oestrogen produced by the ovary then initiates the physical changes of puberty.

- The exact mechanism determining the onset of puberty is still unknown, but it is influenced by many factors including race, heredity, body weight and exercise.
- Leptin plays a permissive role in the onset of puberty.
- The physical changes occurring in puberty are breast development (thelarche), pubic and axillary hair growth (adrenarche), growth spurt and onset of menstruation (menarche).

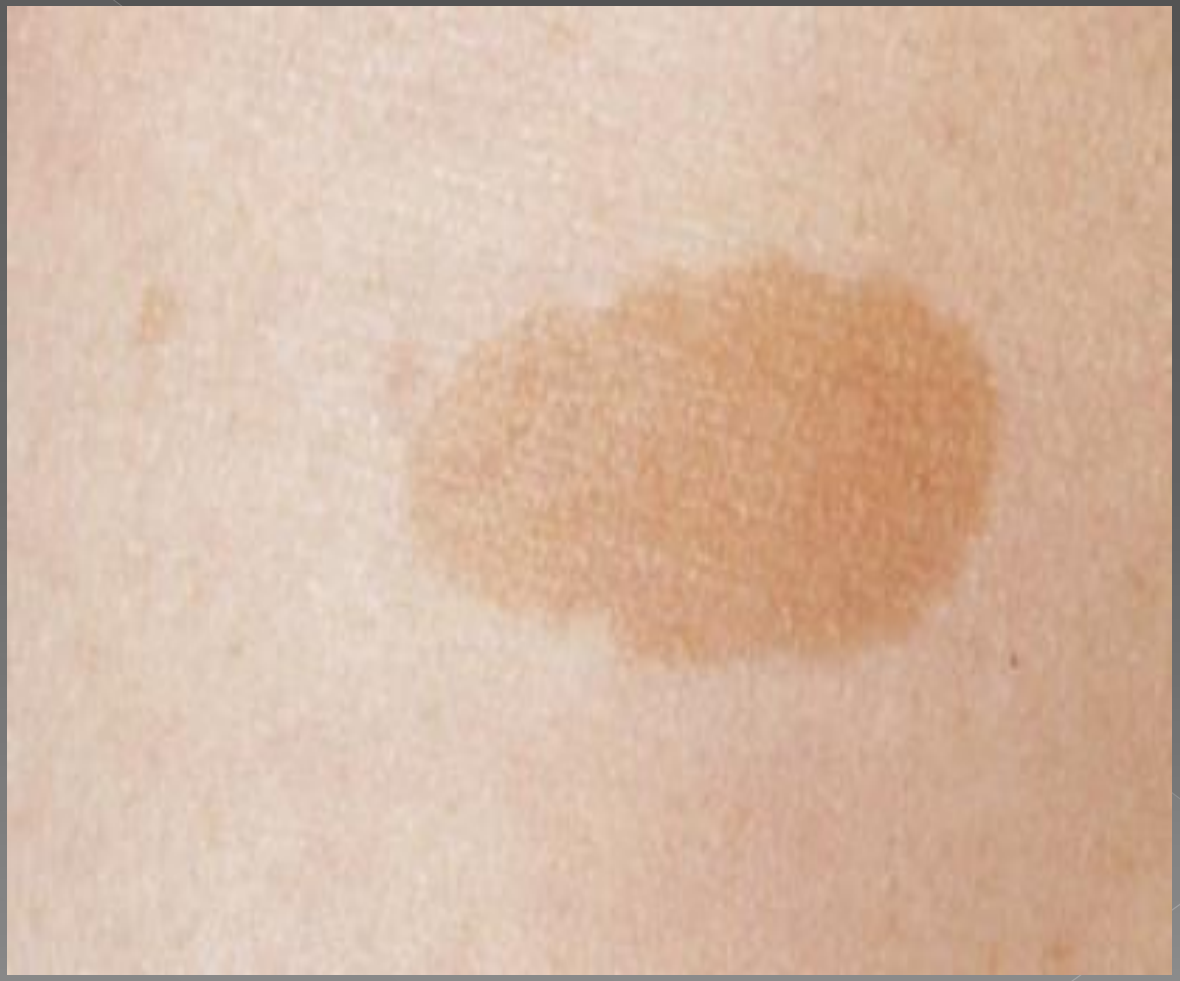
- The first physical signs of puberty are **breast budding** and this occurs 2–3 years before menarche.
- The appearance of pubic hair is dependent on the secretion of **adrenal androgens** and is usually after thelarche.
- In addition to increasing levels of adrenal and gonadal hormones, growth hormone secretion also increases, leading to a **pubertal growth spurt**.
- The mean age of **menarche** is 12.8 years and it may take over 3 years before the menstrual cycle establishes a regular pattern.
- Initial cycles are usually anovulatory and can be unpredictable and irregular.

Precocious puberty

- **This is defined as the onset of puberty before the age of 8 in a girl or 9 in a boy.**
- It is classified as either central or peripheral.
- **Central precocious puberty** is gonadotrophin dependent.
- The aetiology is often unknown, although up to 25% are due to central nervous system (CNS) malformations or brain tumours.
- **Peripheral precocious puberty**, which is gonadotrophin independent, is **always pathological.**

- **Peripheral precocious puberty** is far less common than central precocious puberty and is usually induced by excess production of sex steroids.
- Causes include the following.
- •• Androgen secretion from a virilizing adrenal tumour.
- •• Late-onset CAH.
- •• Oestrogen-secreting tumour causing rapid breast development. If a large ovarian cyst is present, this may be part of McCune–Albright syndrome, with associated classical features of irregular café-au-lait spots and cystic bone lesions called polyostotic fibroid dysplasia.
- •• Exposure to exogenous hormones, e.g. inadvertent ingestion of birth control pills by children causing excess levels of oestrogens; topical androgen exposure.

café-au-lait spots



Investigations

- A number of hormonal studies may be carried out in children with precocious puberty. However, they are of limited value and should be focused on specific clinical entities.
- **Estradiol** is usually elevated in girls with precocious puberty and very high levels may suggest a tumour.
- **Dehydroepiandrosterone** is always elevated in children with premature adrenarche; **testosterone** when markedly elevated would suggest an androgen-secreting tumour; and in those children who are considered to have late-onset CAH, the diagnosis can be confirmed by measuring **17-hydroxyprogesterone**.
- Radiological studies have somewhat limited value, although **pelvic ultrasound** may be used if an abdominal tumour is suspected and brain MRI may be used in those children with extreme precocious puberty, where the chances of a positive finding are around 20%.

Treatment

- The majority of girls with central precocious puberty do not require hormonal treatment, because most development is extremely slow and will result in maturity at an age which would be expected even though onset has been early. It is therefore important to review children with precocious development of secondary sexual characteristics 6 months later to see whether there has been rapid development of secondary sexual characteristics or not.
- In these cases, there is a high chance that sexual maturity will be reached by age 9 and therefore suppression of the progress of puberty would be sensible.

- Children with extremely early puberty are often tall at the time of diagnosis and they tend to finish their growth early but achieve normal adult height. It is appropriate in these young children to suppress the development of secondary sexual characteristics.
- The standard treatment for central precocious puberty is GnRH analogues, which may be given nasally or by intramuscular injection. Three-monthly preparations are available and therefore four injections a year is all that is required to suppress puberty. GnRH analogues can then be administered until such time as the child reaches approximately age 11, when withdrawal will result in the normal resumption of pubertal changes.
- Peripheral precocious puberty, when due to an ovarian or adrenal tumour, requires surgical intervention; however, for girls with androgen excess due to CAH, suppression of the adrenal with hydrocortisone will reverse the changes.

Delayed puberty

- When there are no signs of secondary sexual characteristics by the age of 14 years this is termed delayed puberty.
- It is due to either a central defect (hypogonadotrophic hypogonadism) or a failure of gonadal function (hypergonadotrophic hypogonadism)

- Delay in puberty occurs in only 2.5% of the population but the identification of those children who do have a significant aetiology for this may be extremely important.
- It is mandatory to take a detailed history as the presence of chronic medical conditions or excessive athletic participation may be an explanation for delay in the onset of puberty.
- In females, approximately 50% will have constitutional delay with no explanation and the vast majority will commence the onset of puberty by age 18.
- A further 40% have been found to have a genetic defect. In the presence of secondary sexual characteristics, menstruation ought to occur within 2 years of the establishment of Tanner stage 2 breast change.

- **However, any child presenting at any stage because of concern over failure to establish either secondary sexual characteristics or menstruation should be investigated at that time.**
- There are often extremely good reasons why a mother will bring her daughter for investigation and this often relates to the fact that a sibling completed her pubertal development at an earlier age or she herself went through puberty at an earlier age.
- **While investigations may not lead to a diagnosis of abnormality, proof of normality is extremely important.**

Hypogonadotrophic hypogonadism

- This is central and may be constitutional, but other causes must be excluded: these include anorexia nervosa, excessive exercise and chronic illness, such as diabetes or renal failure.
- Rarer causes include a pituitary tumour and Kalmans syndrome.
- Associated with delayed puberty and **primary amenorrhoea**.

Hypergonadotrophic hypogonadism

- This is caused by gonadal failure. The gonad does not function despite high gonadotrophins.
- Associated with Turner syndrome and XX gonadal dysgenesis.
- Premature ovarian failure can occur at any age, including prior to pubertal age, and may be idiopathic, but can also be part of an autoimmune or metabolic disorder or following chemo- or radiotherapy for childhood cancer.
- Associated with delayed puberty and primary amenorrhoea.
- Hypergonadotrophic hypogonadism can also occur later in life and will cause secondary amenorrhoea after normal sexual development.

Evaluation and management

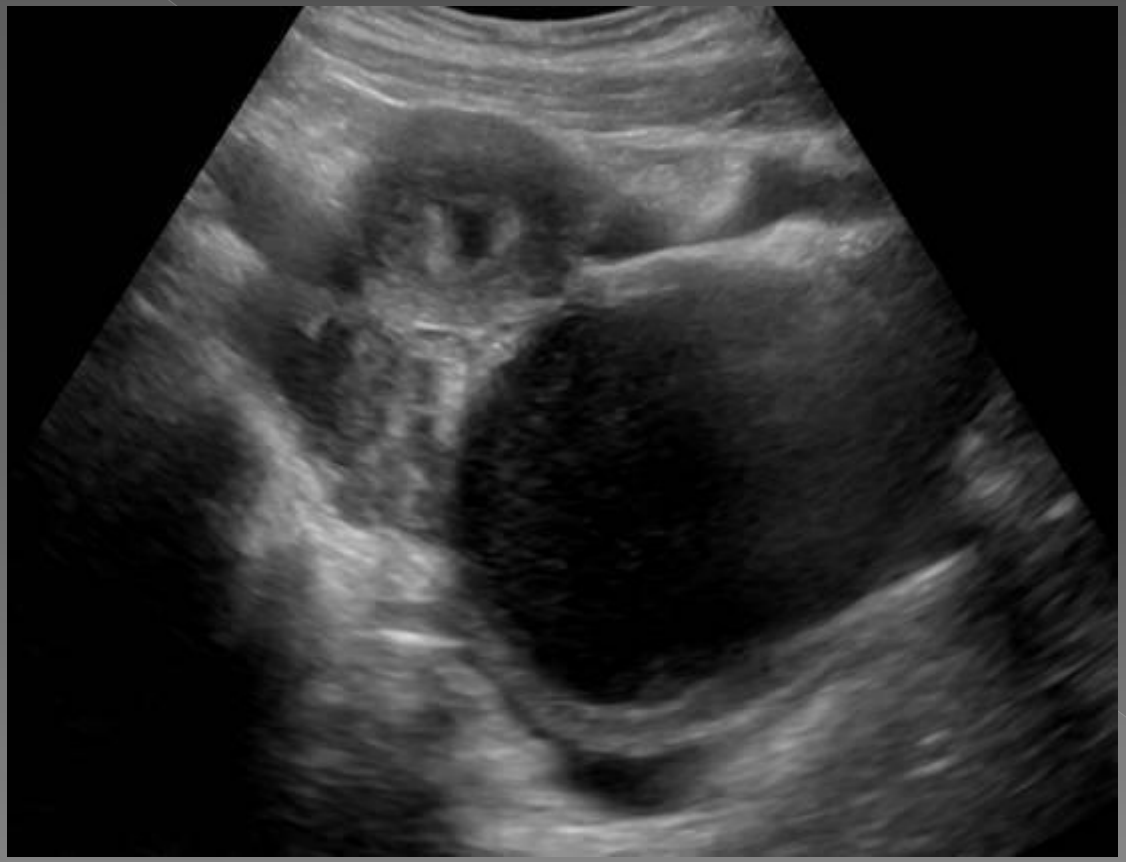
- Having understood the classification, it becomes apparent that most of the conditions are rare and constitutional delay is undoubtedly the most common diagnosis.
- **However, as the rest of the diagnoses have serious implications, the diagnosis of constitutional delay should only be made when all other syndromes have been excluded.**
- It is vital to record a full history and examination, including most importantly the development of secondary sexual characteristics and height.
- Secondary sexual characteristics should be classified according to the staging system of Tanner. Individuals can then be classified according to their secondary sexual characteristics.

Normal secondary sexual characteristics

- The presence of normal secondary sexual characteristics should alert the clinician to the presence of **outflow tract obstruction**. This is the most common cause of primary amenorrhoea in the presence of normal secondary sexual characteristics. It is thus appropriate to carry out investigations to make this diagnosis.
- It is inappropriate to perform any physical pelvic examination on these young adolescents and imaging techniques should be used. It is simple to arrange a pelvic ultrasound scan to assess the pelvic anatomy and only in rare circumstances where this cannot be delineated by ultrasound should it be necessary to use MRI.
- If the uterus is absent, the karyotype should be performed; if this is 46XX, then MRKH syndrome is the most likely diagnosis.

- If the chromosome complement is 46XY, the patient is, by definition, an XY female.
- If the uterus is present on ultrasound, then there may be an associated haematocolpos and haematometra and appropriate reconstructive surgery should be carried out.
- If the pelvic anatomy is normal, then it is essential to assess gonadotrophin and prolactin levels as this would tend to indicate a hypothalamic cause for the amenorrhoea, so-called constitutional delay.
- if resistant ovary syndrome is the diagnosis then gonadotrophin levels will be very elevated.
- Elevation of prolactin levels may suggests a prolactinoma.

Hematometra and Hematocolpos



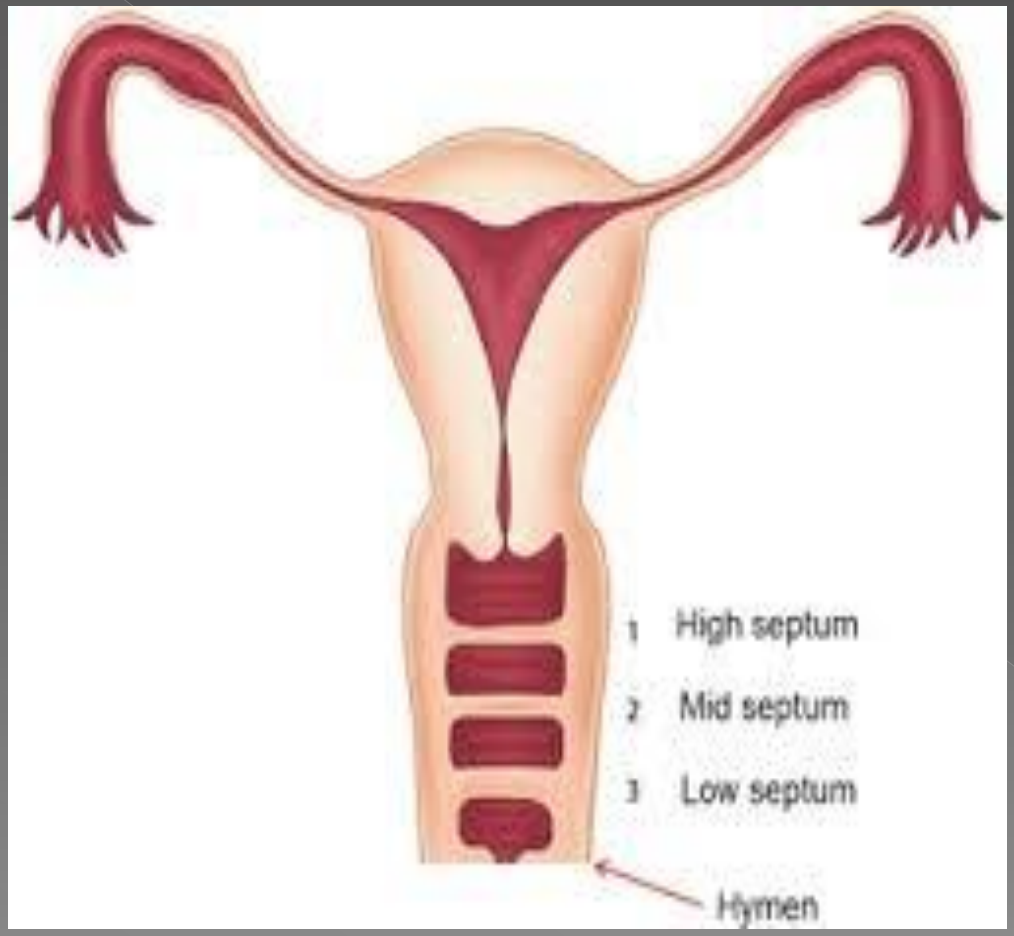
Management

- Patients with an absent uterus require special psychological counselling and their care should be managed in a centre able to offer the complete range of psychological, psychosexual and gynaecological expertise. These young girls will have major problems with future sexual activity and their infertility and require very careful counselling. At the appropriate time a vagina may be created either non-surgically or surgically. In 95% of cases the use of vaginal dilators is successful.

In girls found to have an XY karyotype, again careful counselling is necessary about the malignant potential of their gonads, this being reported in around 30%. It is therefore necessary for them to have their gonads removed and this should be performed at a time when counselling is complete. Sharing the information of the karyotype with the patient should be done at the time when the relationship between the clinician and the patient warrants it. All patients should be informed of their karyotype when appropriate.

In outflow tract obstruction, surgical management depends on the level of obstruction. The simplest form is an imperforate hymen and in this condition a cruciate incision in the hymen allows drainage of the retained menstrual blood. Transverse vaginal septa are much more difficult to deal with and require specialist reconstruction to create a vagina which is subsequently functional.

Transverse vaginal septa



- If investigations suggest that constitutional delay and development of secondary sexual characteristics is complete, there is no need to suggest any treatment other than annual review. These young women very much appreciate the opportunity to return for monitoring until such time as their menstruation commences.
- In some circumstances it may be useful to promote menstruation using the oral contraceptive pill for one cycle to prove that menstruation can occur and this can be extremely reassuring.
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- If the diagnosis of resistant ovary syndrome is suspected, then diagnosis can really only be made by ovarian biopsy and subsequent histology confirming or illustrating the absence of oocytes.
- Finally, elevated prolactin levels should provoke the clinician to perform imaging of the pituitary fossa, probably best done by CT, to determine the presence or absence of a microadenoma and management subsequently with bromocriptine.

Absence of secondary sexual characteristics

- In this situation, it is extremely important to make an assessment of the patient's height.
- If the patient is of normal height for age, measurement of gonadotrophin will reveal levels that are either low or high. Low levels of gonadotrophins confirm the diagnosis of hypogonadotrophic hypogonadism, while elevated levels should provoke the clinician to perform a karyotype.
- The 46XX patient will have premature ovarian failure, resistant ovary syndrome or gonadal agenesis, whereas the XY female will have 46XY gonadal agenesis or testicular enzymatic failure.
- If stature is short, gonadotrophin levels will either be low (associated with an intracranial lesion) or high (which, following a karyotype, almost certainly indicates Turner's syndrome or a Turner mosaic).

Management

In patients with hypogonadotrophic hypogonadism, treatment should be to manage any acquired problem.

Weight-related amenorrhoea may require the input of specialist psychiatrists and psychologists.

In isolated GnRH deficiency, seconadary sexual characteristics will need to be induced using hormone replacement therapy. These patients can be informed that they are fertile and that ovulation induction in the future can be performed.

Hormone replacement therapy is essential and regimens exist for the induction of secondary sexual characteristics over 3–5 years. Oestrogen should be used alone for about 2 years, and then 2–3 years of gradual introduction of progestogens, thereby establishing normal breast growth over a time frame that is equivalent to normal.

Any attempt to accelerate breast growth by using higher doses of oestrogen will result in abnormal breast growth and this should be avoided at all costs. Controversy currently exists over the choice of oestrogen, and the mode of administration. Increasing evidence would suggest that transdermal estradiol is the preferred medication, but compliance in teenagers is an issue. It is likely that both oral and transdermal regimens will continue for some time.

- Patients with Turner's syndrome are a special group. Turner's syndrome occurs in 1 in 2500 female births and is the **commonest cause of primary amenorrhoea**.
- After the diagnosis is made, paediatric endocrinologists will use growth hormone as early as possible to improve final adult height attainment, and recent studies suggest this can be very successful. Previous recommendations to delay the induction of puberty until age 15 to maximize height attainment would seem unjustified.
- Induction of puberty should begin at age 12 and is associated with improved cognitive function. Recent studies have shown that patient's with Turner's syndrome have increased risk of thrombosis, and transdermal estradiol has been shown to be safer and to improve overall body composition .

- Patients with an XY dysgenesis or enzymatic failure should have gonadectomies performed to avoid malignancy.
- It must always be remembered that any chronic medical illness which prevents normal growth will result in delayed onset of puberty and these causes must be considered in any patient presenting in this way.


Thank
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