

PUBERTY

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Physiology of puberty



- **Between early childhood and approximately 8-9 years of age (pre pubertal age) hypothalamic-pituitary-gonadal axis is dormant**
- **Undetectable levels of luteinising hormone LH and sex hormones (Estradiol in girls and testosterone in boys)**
- **Activity of the hypothalamus and pituitary are probably suppressed by poorly unidentified neuronal pathways**
- **Pre pubertal period: 1-3years before puberty; low serum levels of LH are detected during sleep**

Physiology of puberty



- **Low sleep entrained LH secretion occurs in a pulsatile manner.**
- **This reflects endogenous episodic discharge of hypothalamic gonadotrophin releasing hormone (GnRH).**
- **Nocturnal levels of LH increases progressively as puberty approaches.**
- **Pulsatile secretions of gonadotrophins - responsible for the enlargement and maturation of gonads and secretion of sex hormones.**
- **Secondary sexual characteristics appear this is a culmination of the interactions of the hypothalamus, pituitary and the gonads.**
- **During middle or late adolescence - Cyclicity and ovulation occurs.**

Physiology of puberty



- **Positive feedback mechanism-Increase level of oestrogens in mid cycle leads to distinct increase of LH.**
 - **Factors that inhibit or activate the hypothalamic neurons are unknown.**
 - **Several other neurotransmitters are probably important in humans and primates for the development of puberty.**
 - **Estrogens rather than androgens are responsible for the process of bone maturation - ultimately account for the process of bone maturation (epiphyseal fusion) and cessation of growth.**
 - **Estrogens mediate increase secretion of growth hormone which along with direct effects of sex steroids on bone age, is responsible for the pubertal growth spurt.**
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Physiology of puberty



- **Genetic and environmental factors affect the onset of puberty.**
- **Decrease menarchal age – better nutrition and improved general health (difference in blacks and whites, strenuous physical activity associated with delayed puberty or menarche).**
- **Energy balance is closely related to the activity of the GnRH pulse generator and the mechanism initiating and sustaining puberty perhaps via hormonal signals originating from the adipocytes (leptin and other peptides).**

Physiology of puberty



- **Adrenal cortical androgens also play a role in sexual maturation.**
- **Serum levels of dehydroepiandrosterone acetate (DHEA) begin to increase at about 6-8yrs of age before the earliest physical changes of puberty – This phase is called Adrenarche.**
- **Adrenarche typically antedates the onset of gonadal activity (gonadarche) by a few years but the two processes do not seem to be causally related because adrenarche and gonadarche are dissociated in conditions such as central precocious puberty and adrenocortical failure.**

Secondary sexual characteristics - GIRLS



- **The onset of puberty varies and is more closely related with osseous maturation than the chronological age.**
- **In girls, breast bud first sign of puberty(10-11years).**
- **Appearance of pubic hair occurs 6-12 months later.**
- **Interval before menarche is usually 2-2.5 years but can be as long as 6 years.**
- **At least one sign of puberty is present in 95% of girls by the age of 12, by 13 yrs 99%.**

Secondary sexual characteristics -GIRLS



- **Peak height velocity occurs early (at breast stage 2-3), typically between 11-12 years. It always precedes menarche in girls.**
- **Mean age of menarche is 12.75 years.**
- **Wide variation in the sequence of changes involving growth spurt, breast bud, pubic hair and maturation of the internal and external genitalia.**

Secondary sexual characteristics - BOYS

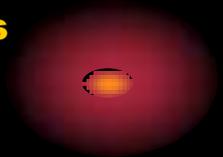


- **Growth of testis (>3cc in volume or > 2.5cm in diameter) and thinning of the scrotum are the first sign of puberty.**
- **Pigmentation of the testis and increase in size of the penis.**
- **Presence of pubic hair, appearance of axillary hair usually occurs in mid puberty.**
- **Unlike in girls acceleration of growth begins after puberty is well underway.**
- **Maximally at genital stage 4-5, typically between the age of 13 and 14 years of age**
- **In boys growth spurt occurs 2 yrs later than in girls and growth might continue beyond the age of 18 years.**

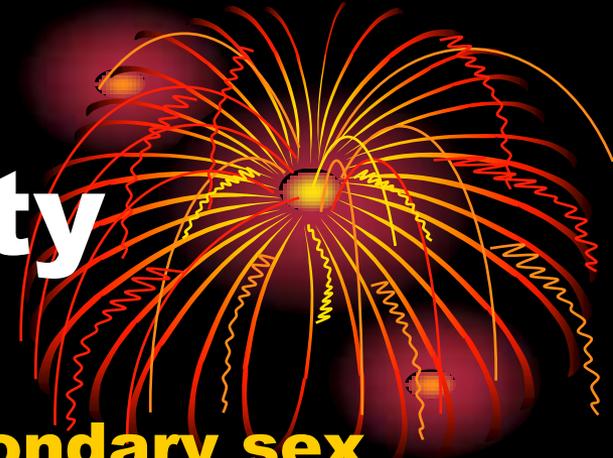
Disorders of puberty



- **A. True isosexual precocious puberty**
 - **Gonadotrophin-dependent sexual precocity or true precocious puberty**
 - **Gonadotrophin-independent precocious puberty**
 - **Tumor related precocious puberty**
- **B. Pseudoprecocious puberty**
- **C. Partial or incomplete precocious puberty**
 - **Premature pubarche or premature adrenarche**
 - **Premature development of the breast or premature thelarche**
 - **Premature gynaecomastia**



Precocious Puberty



- **Definition - Appearance of secondary sex characteristics before the age of 8 yrs in girls and 9 yrs in boys.**
- **True or central precocious puberty due to the premature activation of hypothalamic-pituitary-gonadal axis - isosexual precocious sexual development.**
- **Pseudoprecocious puberty: due to a secreting tumor inducing only the development of secondary sexual characteristics.**
- **Partial or incomplete precocious puberty: premature adrenarche, premature thelarche.**

Gonadotrophin-dependent sexual precocity or true precocious puberty

- **Premature activation of the hypothalamic gonadotrophin releasing hormone (GnRH) pulse generator.**
- **Increase in amplitude and possibly episodic secretion of pituitary LH and follicle stimulating hormone (FSH).**
- **Absence of neurologic lesion - idiopathic precocious puberty.**

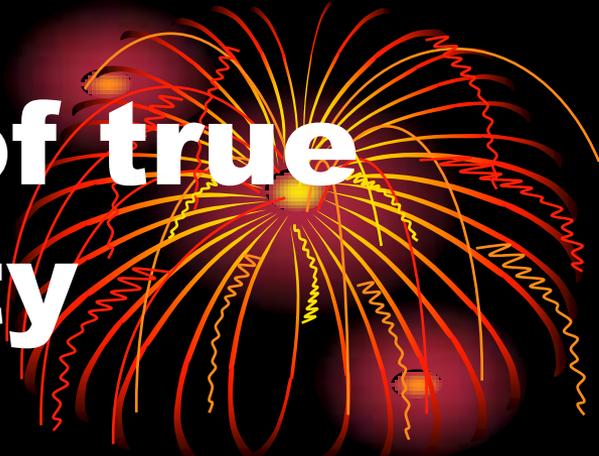


Clinical features



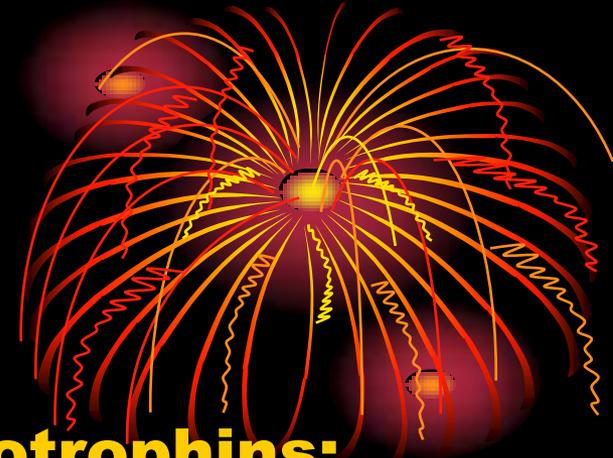
- **Precocious puberty is usually seen between the age of 4-8 yrs.**
- **Occasionally observed before the age 4 years.**
- **Development of the pubertal signs appropriate to the sex of the child.**
- **Girls:**
 - **Appearance of mammary glands, modification of the vulva and menstruation.**
 - **Early menstruation may occasionally be the only symptom.**

Clinical features of true precocious puberty



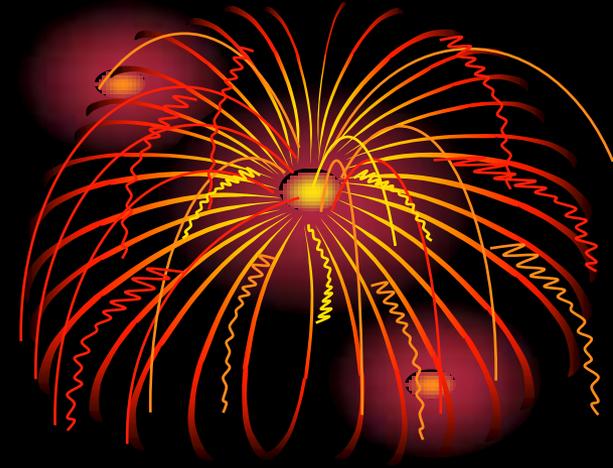
- **Boys:**
 - **Increase size of the penis, frequent erections, bilateral increase in testicular volume (testicular volume index >4).**
 - **Muscle development, acne, seborrhoea and pubic hair growth.**
- **Both sexes: Height increase due to growth acceleration and advance bone age.**

Endocrinological assessment



- **Basal plasma or urinary gonadotrophins:**
 - Normal or increased, usually in the range of pubertal values.
 - In 30 to 50% of cases in the prepubertal range.
- **FSH and LH response to GnRH generally in the pubertal range but can be in the prepubertal range.**
- **Ratio of peak LH over FSH are >1 .**
- **LH pulses during sleep are augmented in idiopathic and tumoral precocious puberty.**

Endocrinological assessment



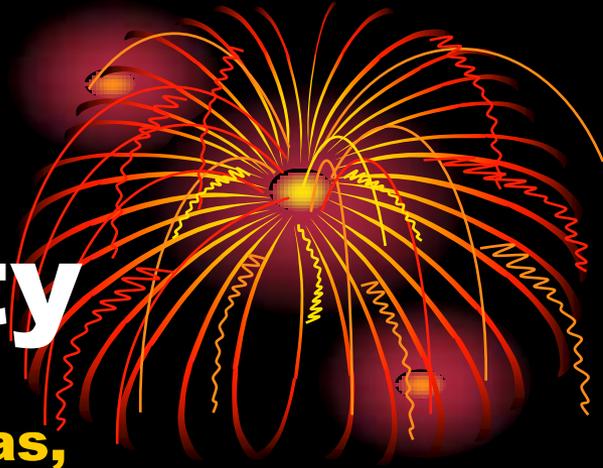
- **Vaginal smears: oestrogenisation.**
- **Plasma estradiol in girls: Usually 2-3 times higher than in pre pubertal child.**
- **Boys: Increased plasma testosterone for chronological age.**
- **Adrenal androgens, DHEA are normal before the bone age of less than 7. After 7 years, they correlate with bone age.**
- **Plasma insulin-like growth factor I (IGF-1) or somatomedin - C levels are elevated for chronological age and correlate well with stages of puberty and bone age.**
- **Growth hormone increase to provocative test.**

Etiology of isosexual precocious puberty



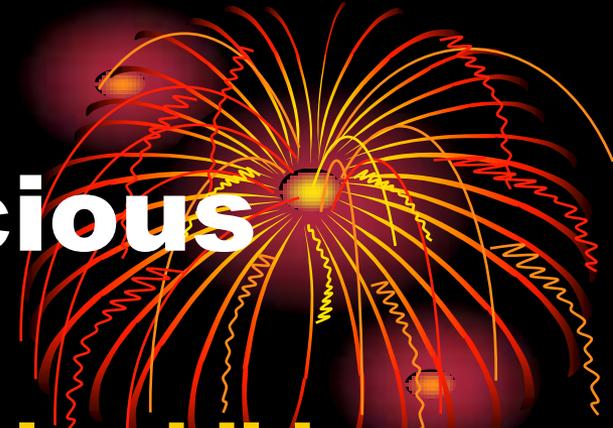
- **70% of girls – Idiopathic.**
- **Intracranial tumors are more frequent in boys.**
- **Exogenous administration of sex steroids (oral preparations/dermatological lotions).**
- **Complete neurological examination: fundi oculi, visual fields, EEGs, x-rays of the skull, CT scans, MRI to exclude an intracranial tumor.**
- **Pelvic Ultrasound: presence of uterus and enlarged ovaries.**
- **X rays: Bone dysplasia.**

Etiology of true precocious puberty



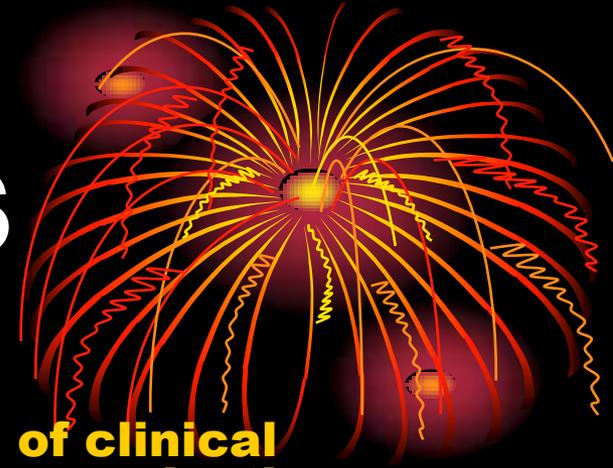
- **A. Intracranial tumors: dysgerminomas, astrocytomas, glioneuromas, craniopharyngioma, hamartoma, optic nerve glioma, post radiotherapy especially in young children etc.**
- **B. Congenital malformations: stenosis of aqueduct of Sylvius, hydrocephaly, microcephaly, craniostenosis, porencephaly.**
- **C. Traumatic causes: perinatal, accidental.**
- **D. Post infectious causes: meningitis, encephalitis, toxoplasmosis, syphilis.**
- **E. Other causes: hypothyroidism, late treated congenital virilizing adrenal hyperplasia, idiopathic epilepsy, Von Recklinghausen neurofibromatosis.**
- **F. Idiopathic: sporadic and familial forms.**

Gonadotrophin – independent precocious puberty



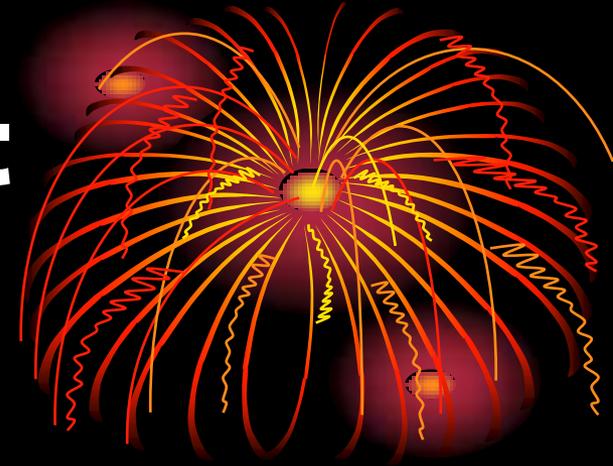
- **Testotoxicosis: affects male children with bilateral enlargement of the testis.**
- **Concentrations of testosterone is in the pubertal range.**
- **Premature Leydig cell and seminiferous tubule maturation.**
- **LH and FSH response to GnRH is of the prepubertal type, with low gonadotrophins and absence of pubertal pulsatile LH levels at night .**

TESTOTOXICOSIS



- **Characterised by the lack of suppression of clinical symptoms of puberty and plasma testosterone by the administration of GnRH agonist.**
- **Possible pathogenic mechanisms:**
 - **Increased bioactive LH, increased sensitivity of Leydig cells to LH, circulating stimulating immunoglobulins with LH activity, local production of hCG or GnRH-like peptides.**
 - **A heritable in born error in the intra testicular regulation of Leydig cell function, or abnormal differentiation of fetal to adult Leydig cell that retain enhanced responsiveness to low LH activity.**
 - **None of the hypotheses has been confirmed.**
- **Familial disorder apparently inherited as sex-linked autosomal dominant trait.**
- **Proposed therapy: medroxyprogesterone, spironolactone, ketoconazole, testolactone, cypoterone acetate.**

McCune – Albright syndrome



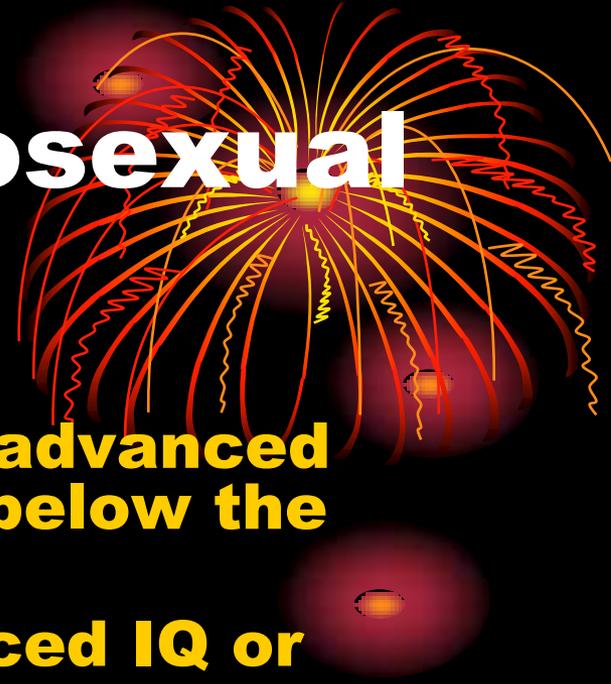
- **Exclusively observed in girls.**
- **Fibrous bony dysplasia (femoral and tibial diaphyses most frequently affected and the skull shows hyperosteostic lesions).**
- **Skin pigmentation: café-au-laits spots which are usually unilateral (rarely cross the mid line) but can be bilateral.**
- **Mechanism: hyperfunction of the hypothalamus with increased GnRH secretion often associated with acromegaly, hyperthyroidism, Cushing syndrome (doubted by some authors).**
- **Resistance to GnRH-agonist therapy has been observed.**
- **Treatment: medroxyprogesterone acetate and testolactone.**

Secreting follicular ovarian cysts



- **Can occur without evidence of McCune–Albright syndrome. Cysts can be large and autonomous.**
- **LH response to GnRH is also blunted with low levels of LH.**
- **Pathogenesis of the development of functional ovarian cysts in pre pubertal girls has not been elucidated.**
- **Sequence of hormonal changes occurs rapidly; transient elevation of circulating estradiol, breast development, endometrial hyperplasia with subsequent atresia of the ovarian follicle or cyst and withdrawal breakthrough bleeding.**
- **Treatment: cysts can be transient and regress spontaneously (able to secrete significant amounts of estradiol). Surgical excision should be delayed except when malignancy is suspected.**
- **Prognosis: patients usually undergo normal pubertal maturation at the normal age.**

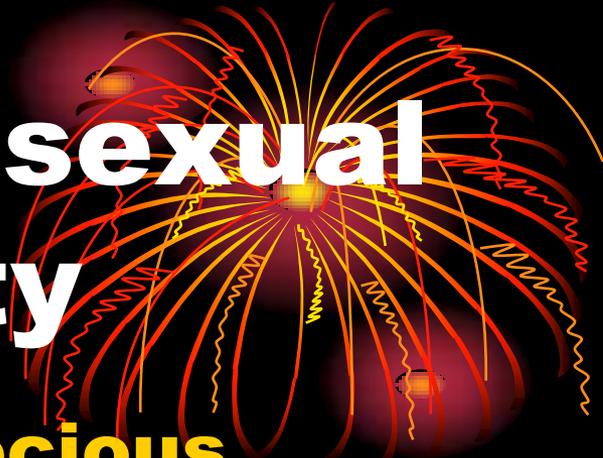
Evolution of true isosexual precocious puberty



- **Marked excessive growth and advanced bone age may result in height below the normal range.**
- **Patients do not have an advanced IQ or developmental quotient.**
- **No abnormal sex drive for their chronological age.**
- **Tendency to play and seek the company of children of the same height and strength.**
- **Dyssynchrony in age and body appearance which are associated with social and psychological problems.**

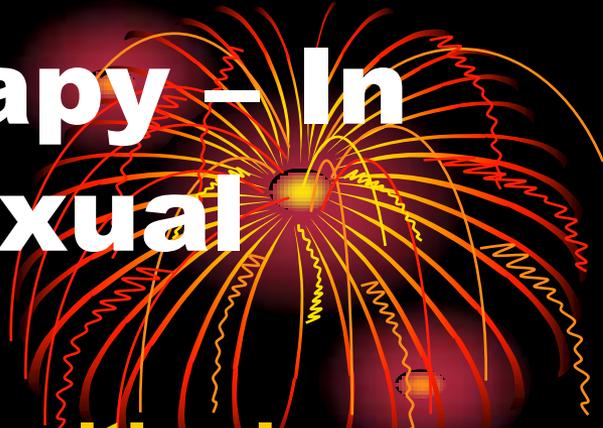
Therapy - True isosexual precocious puberty

- **Depends on whether precocious puberty is gonadotrophin dependent or gonadotrophin independent.**
- **Gonadotrophin dependent: use of drugs that decrease the secretion of pituitary gonadotrophins or block the peripheral action of sex steroids.**
- **Aim of treatment: reverse the development of sex characteristics and decrease the acceleration of growth and bone age.**



Indications for therapy – In Cases of True Isosexual precocious puberty,

- **Girls – Age of less than 8 years with a bone age of less than 13 years.**
- **Boys – Age of less than 9 years, with a bone age of less than 15 years, Plasma testosterone concentration above 1ng/ml.**
- **Both sexes: Rapid progression over a period of 6 – 12 months of symptoms, growth rate and bone age**
- **Idiopathic precocious puberty :-**
- **Slowly progressive variant with occasional retention cysts – might just require careful follow up**



Therapy – True Isosexual precocious puberty



- **Medroxyprogesterone acetate, cyproterone acetate and superactive GnRH agonists.**
- **Antigonadotropic and antiandrogenic drugs while reversing or arresting the progression of the secondary sexual characteristics do not suppress height.**
- **Medroxyprogesterone acetate decreases the secretion of gonadotrophins and the size of the mammary glands and penis. Menstruation ceases.**
- **Medroxyprogesterone has no effect on growth and bone age.**
- **Side effects:- Weight gain and secondary appearance of cushing's syndrome linked to its glucocorticoid effect, virilisation, disorganisation of gonads and decreased numbers of germ cells.**

Therapy - True isosexual precocious puberty



- **Antiandrogenic drugs: danazol and cyproterone acetate. Former abandoned because of its virilising effects in girls.**
- **Cyproterone acetate has antiandrogenic action and competes with testosterone and dihydrotestosterone at the level of cellular receptors.**
- **Glucocorticoid and other effects are similar to medroxyprogesterone acetate.**
- **Long term effect on fertility are not known.**
- **Reversibility of inhibition of spermatogenesis is dose dependent and usually occurs in 6 months.**
- **Normal cycles resume in 1-12 months in girls who had onset of menarche before treatment after discontinuation of treatment.**

Therapy – Isosexual precocious puberty



- **GnRH agonists induce desensitization of the pituitary receptors- First choice of treatment in idiopathic precocious puberty in girls and boys.**
- **Initially they have short term stimulatory effects followed by suppression of pituitary gonadotrophin secretion.**
- **Routes of administration:-S/C, I.M, Intranasal. Low compliance with intranasal administration.**
- **Plasma gonadotrophins concentrations and FSH and LH responses to native GnRH and sex steroids plasma levels decrease within two weeks to level within the prepubertal range.**
- **Regression of secondary sexual characteristics to the prepubertal state.**
- **Gonadotrophin and sex steroid secretion and the clinical progression through puberty appear to resume normally after the discontinuation of long-term GnRH treatment.**

Therapy – Tumor related precocious puberty



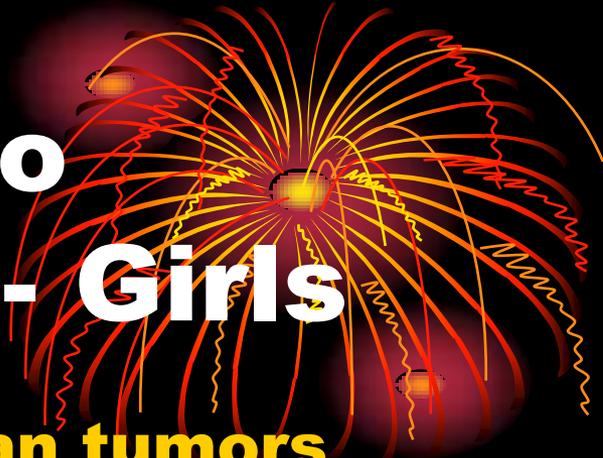
- **Histological diagnosis of the tumor must be confirmed.**
- **Surgical ablation is highly recommended.**
- **Total ablation not possible: tumor might be radiosensitive.**
- **Hamartoma: medical therapy.**
- **Pedunculated hamartoma resection can be done by microsurgery.**

PSEUDO PRECOCIOUS PUBERTY



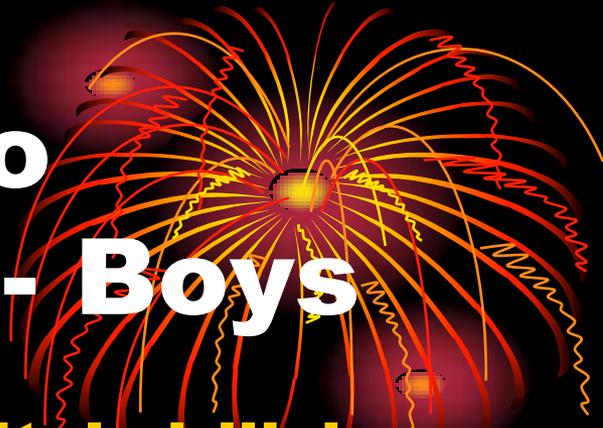
- **Development in accord with the child sex (isosexual pseudo precocious puberty), when not in accord (heterosexual pseudo precocious puberty).**
- **Excessive secretion of androgen secretion in girls – abnormal production of pubic hair and a hypertrophy of the clitoris.**
- **Increase secretion of estrogens in boys – development of mammary glands with pigmented and enlarged areola.**
- **Girls: Exclude ovarian tumor by clinical examination, radiography and ultrasonography.**
- **Boys: Palpation of the testis to exclude tumor, small testes suggest an adrenal cortex origin. Enlarged testes suggest true precocious puberty, testotoxicosis or adrenal hyperplasia.**

Causes of pseudo precocious puberty - Girls



- **Isosexual (feminisation): ovarian tumors (granulosa cell tumors, theca cell tumors, teratoma, arrhenoblastoma), ovarian cysts, adrenal cortex tumors, administration of estrogens and HCG secreting tumors.**
- **Heterosexual (virilization): adrenal cortex tumors, congenital virilizing adrenal hyperplasia, ovarian malignant tumors, adrenal ectopic tissue in ovary, administration of androgens, primary cortisol resistance.**
- **Premature adrenarche and thelarche.**

Causes of pseudo precocious puberty - Boys



- **Isosexual (virilisation): congenital virilising adrenal hyperplasia, adrenal tumors, Leydig cell tumors, teratoma, administration of androgens, gonadotrophin-secreting tumors (chorioepithelioma, teratoma, hepatoblastomas).**
- **Heterosexual (feminisation): adrenal cortex tumors and administration of estrogens.**
- **Partial pubertal precocity: premature adrenarche and pubertal gynaecomastia.**

Treatment of pseudo precocious puberty

- **Diagnosis of ovarian, testicular and adrenal tumors. Laparoscopy or exploratory laparotomy might be necessary to make a diagnosis of granulosa cell tumors.**
- **Surgical ablation of diagnosed tumor.**
- **Malignant tumor: association of chemotherapy and/or radiotherapy.**

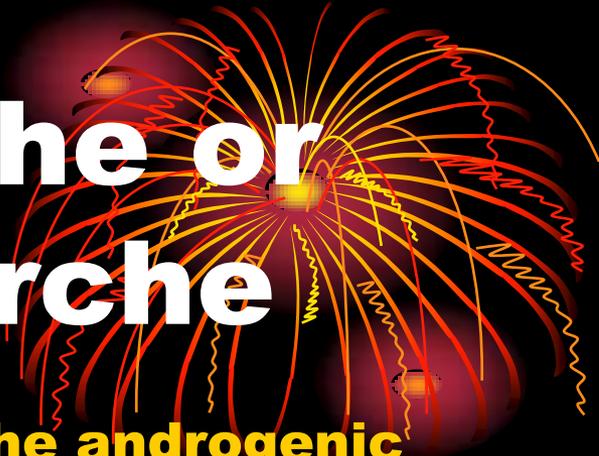


Partial or incomplete precocious puberty



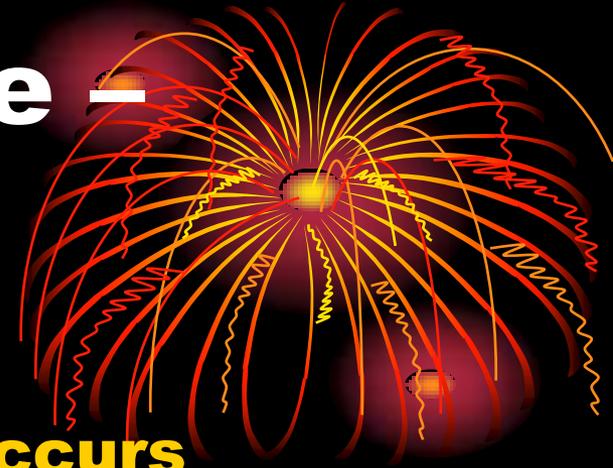
- **Three conditions represent partial precocious puberty:**
 - **Premature and isolated development of pubic and or axillary hair – Premature pubarche.**
 - **Premature and isolated development of the breast – Premature thelarche.**
 - **Pubertal Gynecomastia (boys) – case of normal pubertal development.**

Premature pubarche or premature adrenarche



- **Due to the premature maturation of the androgenic secretion of adrenal cortex or to the premature change in the sensitivity to androgens of the target tissue receptors.**
- **Condition is observed from the age of six years.**
- **Three times more frequent in girls than in boys.**
- **Moderate increase in height and slight advance in bone age are occasionally seen.**
- **Slight increase in size of clitoris.**
- **Increase plasma concentrations of DHEA and DHEAS.**
- **Adrenal androgens can be inhibited by dexamethasone and stimulated by ACTH.**
- **Evolution is normal and puberty occurs normally.**

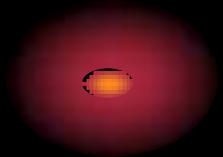
Premature thelarche – Premature breast Development



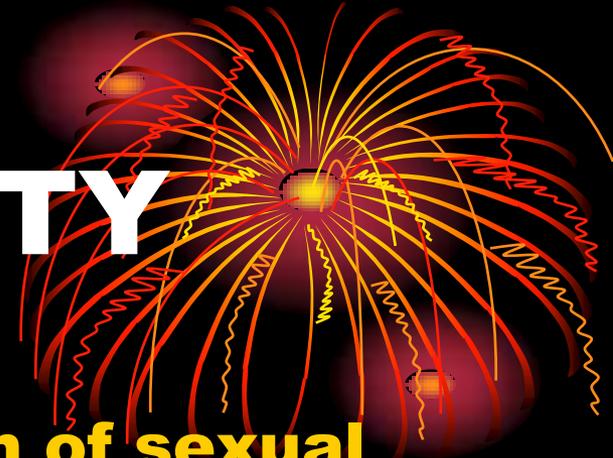
- **Isolated breast development occurs between 1-3 years.**
- **Signs of estrogenisation are absent: no modification of vagina, areolar, labia.**
- **Absence of signs of true precocious puberty.**
- **Plasma estradiol levels are prepubertal.**
- **An increased sensitivity of breast to estrogens is not excluded.**
- **No therapy is needed as spontaneous regression occurs in 70% of cases.**

Pubertal gynaecomastia



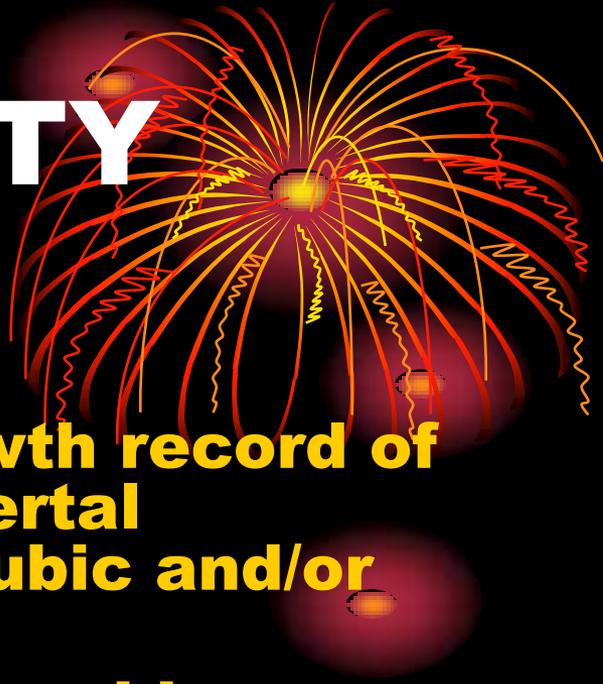
- **Breast development during male puberty is called pubertal gynaecomastia.**
 - **Occurs in 30-65% of boys during puberty and it is observed between the age of 14–14.5 years.**
 - **Etiology is unknown.**
 - **Exclude underlying pathologies like Klinefelter's syndrome and non endocrine tumors (breast cancer, neurofibroma, hemangioma, lipoma – in these cases gynaecomastia is usually unilateral).**
 - **Inbalance between secretion of estrogens and testosterone.**
 - **Gynaecomastia - Due to abnormal sensitivity of the mammary gland to estrogens or exaggerated in situ conversion of testosterone to estrogens.**
 - **Treatment: psychological assistance and surgery.**
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DELAYED PUBERTY



- **Definition:- absence of any sign of sexual development related to the secretion of the gonads.**
- **No breast development after the age of 13 in girls.**
- **Absence of increase in testicular volume(above 4cc or 4cm²) in boys.**
- **Usually 95% of boys and girls after this age already have some sign of pubertal development.**
- **Absence of any sign of sexual maturation – Indication for clinical/biological workup.**

DELAYED PUBERTY (Investigations)



- **A complete family history, growth record of the adolescent, staging of pubertal development with or without pubic and/or axillary hair.**
- **Presence of anosmia or of dystrophic symptoms, determination of bone age – radiogram of left wrist and hand.**
- **Basal plasma concentrations of gonadotrophins, LH, FSH, adrenal androgens, DHEA, DHEAS, testosterone in boys and estradiol in girls.**
- **Buccal smear for chromatin, radiograms of the skull and sella turcica, US, laparoscopy**

DELAYED PUBERTY ETIOLOGY



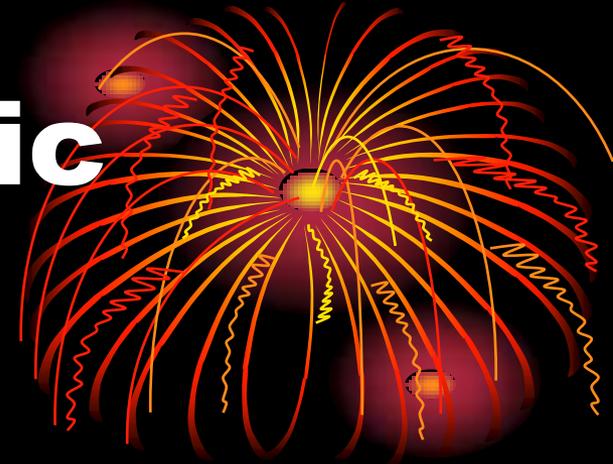
- **Idiopathic delayed puberty with a good prognosis.**
- **Delayed puberty - pathological causes:**
 - **Hypergonadotrophic hypogonadism.**
 - **Hypogonadotrophic hypogonadism.**

Hpergonadotrophic hypogonadism - Primary gonadal deficiency



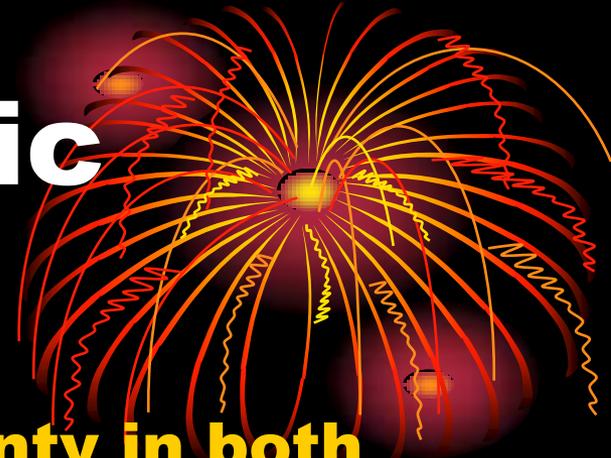
- **May be total or partial.**
- **Basal gonadotrophins are elevated at the age of puberty.**
- **Forms: ovarian dysgenesis or Turner's syndrome, testicular dysgenesis as in Klinefelter's syndrome or anorchidia.**
- **Pubic and axillary hair are usually present because of secretion of adrenal androgens. Bone age is delayed.**
- **Therapy (girls): administration of small doses of estrogens 25 days per month after 13 years. From the second month a progestogen is added from the 15th day.**
- **Therapy (boys): testosterone orally, sublingually or IM.**

Hypogonadotrophic hypogonadism



- **Secondary gonadal deficiency or hypogonadotrophic hypogonadism is more frequent in boys.**
- **Difficult to differentiate from delayed adolescence.**
- **History: chronic or intermittent disease which can affect growth or sexual development, family history (abnormal puberty, fertility problems).**
- **Signs (boys): signs of eunuchoidism, small testicular volume, poorly developed scrotum and infantile voice. Unilateral or bilateral cryptorchidism.**
- **Signs (girls): absent breast development, infantile vulva.**

Hypogonadotrophic hypogonadism



- **Axillary and pubic hair are scanty in both sexes.**
- **Visual and olfactory functions should be examined.**
- **Biological diagnosis at puberty is difficult because basal levels of gonadotrophins are normal or low similar to prepubertal levels especially panhypopituitarism.**
- **Treatment as for hypergonadotrophic hypogonadism (estradiol and testosterone)**
- **Fertility: gonadotrophins, pulsatile administration of GnRH.**

Delayed puberty - Micropenis



- **Micropenis: not per se a disorder of delayed sex maturation. Size of penis is small compared to standards for age, has normal size with absence of sexual ambiguity.**
- **3 main causes: hypopituitarism (GH and gonadotrophins deficiencies), primary testicular defects (hypergonadotrophic hypogonadism), partial insensitivity to androgens.**
- **Treatment depends on the cause: local applications/long acting testosterone prep.**

Delayed puberty – Primary amenorrhoea



- **Definition: the absence of menstruation before the age of 16 years.**
- **Associated with complete, partial or no pubertal development.**
- **Organic lesions of the genital tract should be excluded before any endocrine evaluation.**
- **Anorexia nervosa is a cause of primary amenorrhoea in the adolescent girl.**