Puberty

- Puberty (Latin *pubescere*, to be covered with hair)
- The stage between the onset of secondary sexual characteristics and the completion of physical maturity
- The period in which reproductive capability is attained, manifested by spermatogenesis in males and ovulation in females
Puberty

- In girls starts 8 - 13 (mean 11) years
- In boys starts 9 - 14 (mean 12) years
- In girls starts with BA = 10 year
- In boys starts with BA = 11 year
Puberty in boys

- Psychological / emotional changes
- First sign is testicular enlargement followed by pubic hair development and genital enlargement
- Puberty starts when the testes are 4 ml in size (measured by Orchidometer)
- Adult testes are 20-25 ml in size
Somatic changes in boys

- Growth spurt is later than girls by 2 yr
- Increased muscle mass
- Decreased adipose tissue
- Skeletal changes (↑ BMD)
- 60% have transient gynaecomastia
- Spermatogenesis by 13.5 yr
Puberty in girls

- Psychological / emotional changes.
- First sign is breast enlargement followed by adrenarche and pubarche.
- Pelvic U/S changes of puberty
  - ↑ ovarian volume and follicular size
  - ↑ uterus to cervix ratio
  - ↑ endometrial echo
Pelvic U/S changes

Ovary volume
- prepuberty < 1.5 ml
- postpuberty > 3-4 ml

Follicle size
- prepuberty < 6mm
- postpuberty > 6mm

Uterus to cervix ratio
- prepuberty ≤ 1
- postpuberty > 1

Endometrial echo
- prepuberty = None
- postpuberty = present
Skeletal changes in girls

- Widening of pelvis and carrying angle
- Major increase in BMD
- Increased adipose tissue with typical female distribution
- 95% of growth happened < menarche
- Menarche usually by age 12.5-14.5 yr
- Increased in muscle bulk but not to same extent as males
Precocious Puberty

- Most commonly defined as the onset of puberty before 8 years in girls and before 9 years in boys
- Characterized by rapid growth and advancement of skeletal maturation resulting in compromised adult height
Precocious puberty

- Central, True, GnRH dependent
- Peripheral, Pseudo, GnRH Independent
- Thelarche & pubarche
Central Precocious Puberty

- Result from premature activation of Hypothalamus-Pituitary-Gonadal axis
- The pulsatile GnRH secretion leads to pulsatile secretions of LH and FSH with subsequent release of sex steroids
- Similar to normal mechanism but happened earlier than expected age
Aetiology

- Idiopathic
  most girls (90%)
- Secondary
  most boys (70-80%)
Aetiology

CNS disorders
- Hypothalamic Hamartoma
- Astrocytoma
- Craniopharyngioma
- Ependymoma, germinoma, glioma
- CNS radiation therapy
- Trauma (surgery)
Aetiology

- Inflammation (Brain abscesses)
- Neurological & mental retardation
- Hydrocephalus
- Prolonged sex steroid exposure associated with peripheral puberty
- Prolonged primary hypothyroidism ($\alpha$-TSH stimulates FSH, LH, Prl)
Peripheral precocious puberty

- Suppression of central axis (Hypothalmo-Pituitary-gonadal)
- LH & FSH levels are low
- Sex steroids are high
- Gonads are small in size (unless tumor is present)
Aetiology

- Gonadal: McCune-Albright, tumour, cyst
- Adrenal: CAH, tumours
- Ectopic: hCG secreting tumours
- Exogenous source of hormone
- Familial male dependent (Testotoxicosis)
- Chronic primary hypothroidism ($\alpha$-TSH stimulates testicular enlargement)
Aetiology

**Autonomous gonadal steroid production**

- McCune Albright syndrome
- Familial gonadotrophin-independent
Familial male-dependent precocious puberty (Testotoxicosis)

- Autosomal dominant
- Male – limited
- Mutation in LH receptors → cAMP → autonomous Leydig cell activity and testicular enlargement
- Prepubertal levels of LH, FSH
- Females not affected (FSH is needed)
- Usually misdiagnosed as idiopathic central form (low stimulated gonadotrophin)
- Pubertal testosterone levels
McCune - Albright syndrome (MAS)

- First described by McCune (1937) as osteodystrophica cystica
- Albright (1937) described another 5 cases with osteitis fibrosa disseminata, areas of hyper-pigmentation, endocrine dysfunction with precocious puberty

Albright has described Albright’s hereditary osteodystrophy
McCune - Albright syndrome

- Affects both sexes
- Gonadal autonomy
- Happen more commonly in girls
- In girls, the presenting feature is often menses with / without thelarche
- Menses usually happen < 2-3 yrs of age
Pathogenesis

- Activating mutation within exon 8 of Gs\(\alpha\) gene \textbf{GNAS 1} on 20q13.2, results in increased activity of the Gs\(\alpha\) protein and cAMP in the affected endocrine tissue.
Abnormalities in McCune-Albright syndrome

**Endocrine**

- Precocious Puberty
- Goitre / Hyperthyroidism
- Acromegaly / Gigantism
- Cushing’s syndrome
- Hyperprolactinemia
- Hypophosphatemic rickets
Abnormalities in McCune-Albright syndrome

Non-endocrine

- Cafe-au-lait spot
- Fibrous dysplasia of bone
- Facial asymmetry
- Elevated hepatic transaminases
- G.I polyposis
- Cardiomyopathy
- Arrhythmias
McCune-Albright syndrome

- Estradiol level may be normal or high depending on the stage of development of follicular cyst
- Menstrual flow represents estrogen withdrawal following regression of large follicular cyst
- Basal and stimulated levels of LH / FSH are suppressed in early stage
- After many cycles of cysts appearance and regression, maturation of Hypothalamic function develop (secondary central precocious puberty)
Treatment

- Sequential removal of ovarian cyst
- Complete removal of ovaries
- $17\alpha$- Medroxyprogesterone (Provera)
- Estrogen antagonists (Tamoxifen)
- Aromatase inhibitors (Testolactone)
- Cyproterone Acetate (Androcur)
- LHRH agonist (central stage)
Variants of normal puberty

- Thelarche
- Thelarche Variant
- Adrenarche (Pubarche)
Thelarche

- Premature breast enlargement with absence of growth spurt
- Bone age is not accelerated
- Pre pubertal pelvic U/S findings
- Onset between 6m to 4 y of age
- Increased sensitivity of the breast tissue to low levels of sex steroids
- Benign nature and need no therapy
Adrenarche

- Occurs when the adrenal side of puberty is turned on prematurely in the absence of gonadal activation
- Premature appearance of pubic and axillary hair, acne, body odor & oily skin
- Idiopathic
Adrenarche

- Elevated adrenal androgens
- Normal LH / FSH & gonadal steroids
- Need to exclude late-onset CAH
- Need to exclude adrenal tumours
- Need to exclude PCOS
Non-Classical CAH

Presentations

- Seldom detected in infancy (unless by screening)
- Pubarche and advanced growth (mid-childhood)
- Amenorrhea, oligomenorrhea, acne and hirsuitism (Adolescent girls)
- Infertility
Non-Classical CAH

- Mineralocorticoid usually unaffected
- Needs glucocorticoid replacement and anti-androgen therapy
- 17 OHP secretion is diurnal
PCOS

- Usually confused with non-classical CAH
- Adolescent-onset of ovarian hyperandrogenism
- High testosterone, low SHBG, High LH/FSH ratio
- Menstrual dysfunction
- Hirsutism and acne
- Obesity
- Ovarian cysts
- Acanthosis nigricans
- Insulin resistance
PCOS

May occur concomitantly with late onset CAH

Treatment
- Cyclic estrogen and progesterone
- Contraceptive pills
- Weight loss
- Metformin
- Androgen-blockers
  - Cyproterone Acetate
  - Flutamide
  - Spirinolactone
Evaluation of Precocious Puberty

- History
- Physical examination
- Growth percentiles
- Calculation of target height
- Bone Age assessment
- Predicted adult height (PAH)
- Basal LH, FSH and sex steroids
- GnRH stimulation test
Evaluation of Precocious Puberty

- hCG: hepatoblastoma, germinoma
- 17 OHP & 11 DOC: CAH
- MRI Brain: Hamartoma, optic glioma
- U/S Testes
- Ovarian and pelvic U/S
- Adrenal U/S
Treatment of CPP

- How early is the onset of puberty?
- How much advancement of the bone maturation?
- What is the predicted adult height (PAH)?
- Comparison of PAH to MPH?
- How fast the progression of physical changes?
- GnRH stimulation test?
Treatment of CPP

- GnRH agonist
- Treatment of underlying pathology
Goals of treatment

- Decrease the progression of pubertal changes
- Decrease bone maturation
- Increase the predicted final adult height
- Psychosocial and behavioral therapy
GnRH agonists

- First reported in 1981
- The treatment of choice of CPP
- Alteration of peptide sequence of native GnRH with more potency, affinity to the receptors
- Acts continuously with down regulation of GnRH receptors
GnRH agonist

Daily S/C preparation
- Desoriline
  4-8 ug/kg/d
- Busereline
  20-40 ug/kg/d
- leuprolide
  20-50 ug/kg/day
- Nafarelin(intranasal)
  800-1600ug/kg/day

Depot-preparations
- Leuprolelin acetate
  (Lucrin)
  0.3 mg / kg (7.5 mg)
- Tryptorelin
  (Decapeptyl)
  50-100ug/kg
- Goserelin (Zoladex)
Response to therapy

- Suppression of endogenous LH / FSH should be confirmed by GnRH test after 3m and then bi-annually
- Testosterone and E₂ with in 1-2 Wk
- Regression of Pubertal changes
Adverse effects

- Anaphylactic reactions: angioedema, urticaria
- Local skin reactions: redness, swelling, itchiness and sterile abscesses
- Flare phenomena
- Under treatment
  Results in stimulation rather suppression of central axis
Combined GnRH agonist and GH

Criteria of combination
- GV suppressed < 25th centile for CA
- No improvement in PAH
- GH 0.3 mg /kg / Wk for 2-3 years

Advantages
- Substantial improvement of both parameters
- Shorten the total duration of Precocious puberty
Treatment of peripheral type

- Medroxyprogesterone acetate (Provera)
- Ketoconazole
- Aromatase enzyme inhibitors (testolctone)
- Androgen antagonists
Medroxyprogesterone

- Structurally similar to glucocorticoid
- Progestational agent which suppresses gonadotrophin
- Useful in the treatment of both types
- Effective in halting the advancement of secondary characters in both sexes
- Effective in preventing menstruation
- No effects on bone maturation
Ketoconazole

- Anti-fungal with side effect of the inhibition of both steroidogenesis and testosterone synthesis at 17,20 Lyase step
- Dose 400-600 mg/day
- Suppression happen with in 48 h
- Potential hepatotoxic
Aromatase Inhibitors

- Aromatase enzyme converts Androstedione to estrone
  Testosterone to estradiol
- The conversion of estrone to estradiol has 5 folds greater affinity for estragon receptors
- Steroidal and non Steroidal inhibitors
Steroidal Aromatase Inhibitors

First generation
  Testolactone

Second generation
  Formastine
  Plomestane
  Atamestane
  Minamestane
  Exemastane
Testolactone

- Testolactone (Teslac) is a competitive steroidal aromatase inhibitors
- Derivative of testosterone (lactone ring substituted for D-ring of steroid nucleus)
- Dose 20 mgr/kg/day initially then 40 mg/kg/day divided into 4 doses over 3-4 wk
- Combined with Spirinolactone is useful in treatment of familial testotoxicosis
Androgen antagonists

- Cyproterone Acetate (70-150 mg/m²/d). halted the progression of Pubertal signs.
- Similar structure to Cortisol, might result in cushingoid features
- Suppresses the ACTH- Adrenal axis
Delayed Puberty

No pubertal changes

- In girls no pubertal changes by age of 13 years or menarche by 15.5-16 years
- In boys no pubertal changes by age of 14 years

OR

- If > 5 years between onset of puberty and menarche in girls or completion of genital growth in males
Aetiology

- Constitutional delay
- Primary gonadal failure
- Hypothalamic - Pituitary defects
Evaluation of delayed Puberty

**History**
- Review rates of weight and height gain
- Evidences of other endocrinopathies
- Current or prior illnesses and their treatment *(irradiation, surgery, chemotherapy, glucocorticoid therapies)*
- Family history of delay, hypogonadism or infertility
- History of Anosmia or hypo osmia
- Evidence of any systemic illnesses
- Exercise pattern and diet histories
Evaluation of delayed Puberty

Examination
- Height, weight and pubertal stage
- Upper / Lower segment ratio
  - ratio < 0.88 = Eunchoidism
- Testicular location, size and consistency
- Breast and genital developments
- Stigmata for Turner’s, Klinefelter’s syndrome
- Neurological examination of fundi, visual field and sense of smell
Evaluation of delayed Puberty

Laboratory evaluation
- Basal LH, FSH, sex steroid levels
- Bone age
- Karyotype analysis
- GnRH test
- hCG test
- Search for other endocrinopathies
Treatment

Male with hypogonadism

- Replacement therapy of Testosterone ester or enanthate (Depot, IM injection)
- Starting dose 50 – 100 mg every 4 Wk X 2 years
- Gradual titration over 3-4 years
- Full adult dose 200 – 250 mg every 2 wk
- Transdermal T scrotal patches or DHT patches
- Testosterone pellet

Higher doses during first year can provoke gynecomastia and early fusion of epiphysis
Treatment

Female with hypogonadism

- Replacement therapy with cyclic estrogen-progesterone therapy
- Starting age of 13-15 years
- Starting treatment with low dose conjugated estrogen at dose initially 0.3 mg X 6m, then 0.625mg for 1-2 years then 1.25 mg/day
- Add progesterone after 12 months unless break through bleeding happened
- Progestrone (provera, norethinsterone) 5 –10 mg/day in first 10 days of each calendar month
- Spontaneous menstruation can happen in patients with Turner syndrome
Treatment

Constitutional delay

- No treatment unless psychosocial
- Oxandrolone (0.25 mg /kg) maximum 10 mg daily
- Testosterone injections 50 – 100 mg monthly for 3-6m
- Oral Testosterone Undecanoate (TU) 40mg/day
Treatment

Hypogonadotrophic Hypogonadism

- Addition of hCG 200-3000 IU/week
- Addition rh FSH or HMG
- Cyclic GnRH analogue

These agents are important to restore fertility and to increase testicular size in male patients