Hypogonadism

Hypogonadism can refer to either:

1. The failure of the testes to produce adequate testosterone resulting in the signs & symptoms of androgen deficiency or
2. Impaired spermatogenesis resulting in infertility which may be presenting with normal testosterone production but testosterone production is necessary for normal spermatogenesis, normal adult male produces approximately 7 mg of testosterone /day. Testosterone production is dependent on an intact hypothalamus, pituitary gland & leydig cells in the testis which is under the control of LH, spermatogenesis is by Sertoli cells in the testis which is under the control of FSH, negative feedback suppression of LH is mediated principally by testosterone, while secretion of another hormone by the testis, inhibin suppresses FSH.

Classification of hypogonadism:

Secondary hypogonadism: Hypogonadotrophic hypogonadism (↓LH, ↓FSH)

- Structural hypothalamic–pituitary disease
- Functional gonadotrophin deficiency
  - Chronic systemic illness (e.g. asthma, malabsorption, cystic fibrosis, renal failure)
  - Psychological stress
  - Excessive physical exercise
  - Hyperprolactinaemia
  - Other endocrine disease (e.g. Cushing’s syndrome, Primary hypothyroidism)
- Isolated gonadotrophin deficiency (Kallmann’ syndrome)

Primary testicular failure: Hypergonadotrophic hypogonadism: (↑LH, ↑FSH or ↑FSH alone)

- Mumps orchitis (bilateral), gonococcal infiltration, T.B, testicular tumor, haemochromatosis, cirrhosis of liver, idiopathic, chemotherapy, radiotherapy to gonads
- Klinefelter’s syndrome (47 XXY, male phenotype)
- Turner’s syndrome (45 X0, female phenotype)

Clinical features:

- It depends on the age of the patient at the time of the onset of the disease.
- If it occurs before puberty the external genitalia & the secondary sex characteristics fail to develop. In these circumstances the epiphysis of long bones don’t close at the usual age & the patient may grow into an excessive height. (Long arms & long legs in comparison to trunk height-eunuchoid proportion) the typical prepubertal eunuch develops into a tall man with a hairless face, a high-pitched voice, small genitalia & an immature personality some pubic hair is present & is the result of adrenal androgen production – the adrenarche.
- When the onset of the diseases post pubertal the changes are less striking, growth is not affected & there is regression rather than disappearance of the secondary sex characteristics. The external genitalia undergo partial atrophy, here early symptoms will be loss of libido, impotence & tiredness & the late symptoms are decreased shaving, ↓ body hair & ↓ muscle power.
- In some patients particularly when the deprivation is sudden as after surgical castration, these may be (menopausal symptom) such as hot flushes & profuse sweating. Unless replacement therapy is provided.
- Also according to underlying pathology in Kallmann’s syndrome with hypothalamic disease & isolated GnRH deficiency, there is associated anosmia. Also pituitary tumor may present with symptoms of the tumor such as visual field defect.
In Klinefelter’s syndrome due to sex chromosomal abnormality, the affected male has an extra x-chromosome resulting in 47XXY sex chromosome.

The main clinical features are eunuchoid body proportion, sterility due to azospermia, hypogonadism, gynaecomastia due to the loss of testosterone, allows unopposed effects of estrogen & often there is mental retardation.

**Testicular feminization syndrome:**

- In some cases there is complete androgen resistance (testicular feminization) the phenotype is female & the condition is due to defective androgen receptors in target tissues. The testes may be found in groins, pubic hair is absent, breasts develop normally & the pt. may present with primary amenorrhea.

**Investigations of Hypogonadism:**

- The plasma testosterone, LH & FSH should be measured, in hypothalamo-pituitary disease LH & FSH are low. But the pulsatile release of LH & FSH make it difficult to assess the results of single blood sample. The ability of the pituitary to synthesize & release LH & FSH can be tested by giving GnRH (100 µg I.V) & measuring plasma LH & FSH at 0, 20 & 60 minutes. Failure to respond indicates no readily releasable pool of gonadotroph LH & FSH, such pts may respond to the pulsatile administration of GnRH e.g. Kallmann’s syndrome which there is congenital GnRH deficiency. To test the ability of the hypothalamus to produce GnRH so the LH & FSH response to the anti-estrogen (clomiphene citrate) is measured.
- Clomiphene 3mg/kg/d max dose 150 mg/day is given for 10 days with serial measurement of LH & FSH.
- In primary gonadal disease testosterone is low, LH & FSH are high. In cases if there is gynaecomastia then oestradiol should be estimated (it may be exogenous, from adrenal or testicular tumor).
- A karyotype should be performed if indicated, bone age should be assessed in boys with delayed puberty.

**Management:**

- Depends on the cause, the androgen deficiency should be replaced by one of the following drugs & routes.
  - Depot testosterone ester (sustanon) 250-500 mg by intramuscular injection every 2-4 weeks, monitor its effects on the basis of symptoms plus packed cell volume (every 6-12 month), other preparations are testosterone undecanoate 80-120 mg orally twice daily, another preparation is testosterone implant 600-800 mg s.c every 3-6 months & probably this is the best method for obtaining normal blood levels.
  - Undesirable effects of testosterone are edema secondary to sodium retention acne & premature closure of epiphysis, oral testosterone cause intrahepatic cholestatic jaundice, serious complications: hepatoma & peliosis hepatis (blood filled cysts in the liver), it can aggravate prostatic carcinoma, prostatic specific antigen (PSA) should be measured in men older than 50 years and monitored annually thereafter.
  - For treatment of infertility in secondary hypogonadism gonadotrophin therapy should be given, in post pubertal male is usual to give human chorionic gonadotrophin (HCG) 3000I.U intramuscularly weekly to stimulate testosterone production by the interstitial cells, for the first 6 months & then HCG weekly together with FSH (usually as pergonal, human menopausal gonadotrophin which contains equal amount of LH & FSH 75I.U intramuscular three times per week. this combination should be continued for 9-12 months), if there is hypothalamic cause for the hypopituitarism then pulsatile GnRH therapy with a portable infusion pump may be effective 1-10 µg/pulse every 60-90 minutes.
  - There is no effective therapy for infertility resulting from primary gonadal failure.
  - However it is important to exclude causes such as sulphasalazine therapy when the effects are reversible.

**Gynaecomastia:**

It is enlargement of the male breast, may occur unilaterally or bilaterally. Gynaecomastia is very commonly observed during the new-born period, puberty & in elderly. For e.g.: approximately 50% of normal boys at puberty & 40% of elderly men have been noted to have gynaecomastia. If significant gynaecomastia develops between late puberty & elderly one should search carefully for an underlying disorder that can account for the breast enlargement.
Causes of gynaecomastia:

- Estrogens stimulate & androgen inhibit breast development therefore disorders that alter the usual ratio of oestrogen to androgen can result in gynaecomastia.

Classification of the causes of gynaecomastia:

1. Physiologic: newborn, puberty, elderly.
2. Pathologic
   - ↑ Estrogen secretion
   - Increased conversion of androgen to estrogen: Liver disease, adrenal disease, nutritional (refeeding after starvation), thyrotoxicosis.
   - Decreased androgen secretion: primary hypogonadism, secondary hypogonadism.
   - Androgen resistance: testicular feminization.
3. Drugs:
   - Hormones–Estrogen, androgen, hCG, antihypertensives like reserpine, methyldopa, spironolactone.
   - Psycho tropics e.g.: phenothiazine, butyrophenon, marijuana, methadone, heroin, tricyclics antidepressants, and diazepam.
   - Cardiac drugs: digitalis.
   - Gastrointestinal: cemitidine, metoclopromide.
   - Cytotoxic: cyclophosphamide, vincristine.
   - Miscellaneous: penicillamine, ketokonazole.

Approach to a patient with gynaecomastia:

- It is essential to be sure that (true) gynaecomastia is present. The most frequent error is to confuse the fatty breast of the obese pt. which lacks the glandular elements with gynaecomastia .the diagnosis of gynaecomastia is based on the palpation of subareolar glandular tissue.
- Particular attention should be paid to the testis as either small testis or a testicular mass suggests the likely mechanism for gynaecomastia, in addition a careful search for signs of liver disease, thyrotoxicosis, other evidence of feminization & galactorrhea is indicated. Finally in all pts with gynaecomastia, a complete drug history is essential.
- Many laboratory studies can be useful in the evaluation of gynaecomastia when it’s well selected on the basis of history & physical exam. In the pubertal boy for e.g.: lab. Studies are usually not indicated , while liver function tests , serum estrogen , testosterone, , LH & hCG concentration & adrenal androgen levels are sometimes useful in the evaluation of pt.s with gynaecomastia e.g.:if LH is high & testosterone is low the diagnosis is usually testicular failure , but if LH & testosterone are both low the diagnosis is most likely ↑primary estrogen production ( for e.g.: a sertoli cell tumor of the testis )& if both LH & testosterone are elevated the diagnosis is either an androgen –resistance state or a gonadotrophin –secreting tumor .
- Regression or significant improvement in gynaecomastia occurs in a substantial number of pt.s, gynaecomastia usually improves after stopping an offending drug or after correcting a hormonal deficiency or excess .pubertal gynaecomastia spontaneously regress & drug therapy is not indicated. Long standing cases of gynaecomastia or large breasts will rarely regress entirely after the causal disorder has been corrected. In these cases cosmetic mastectomy may be very helpful .the risk of breast cancer in men is proportional to the amount of breast tissue present & therefore is increased in pt.s with substantial gynaecomastia.
Female Endocrinology

- The sexual disorders in the female as with the male can be classified into those arising from either hypothalamic-pituitary or primary gonadal defects, the presentation is often with menstrual abnormality such as primary or secondary amenorrhea.

Puberty

- The adolescent or pubescent phase of development provides the individual with reproductive capacity in the female somatic growth accelerates, the breast buds develop (thelarche), pubic hair appears (pubarche) & finally the menarche occurs. This process generally begins in girls between 8-14 years of age, with full development over a 3 years period. The age of onset of puberty is variable & influenced by genetic factors, socioeconomic conditions & general health. Pre-pubertal girls have low serum levels of gonadotropins & sex steroid hormones, during the progression of puberty, the characteristic inhibitory effect of estrogen on gonadotropin (FSH, LH) secretion declines & in the case of LH a positive feedback process develops.
- An early feature of the pubescent girl is the nocturnal pulsatile secretion of LH, the enhanced LH activity stimulates the ovary to secrete increasing amounts of estrogen & secondary sex characteristics subsequently develop.

Precocious puberty

- Isosexual precocious puberty is defined as the premature (<8 years) development of adult genitalia consistent with the chromosomal sex of the child. Girls the majority of cases (80%) are idiopathic. With both (FSH & LH) & (estradiol & progesterone) are in the normal adult range, iso sex precocious puberty also occurs in the Albright syndrome.
- High gonadotropin levels suggest an intracranial lesion or a tumor secreting hCG, hypothyroidism can also be associated with precocious puberty due to increased secretion of gonadotropins.
- If precocious puberty associated with low levels of gonadotropins this suggests an ovarian or adrenal tumor, the adrenal tumor can be detected by CT scan of the abdomen & the ovarian tumors can usually be detected on physical examination or U/S of the pelvis.

Treatment

- Gonadal & adrenocortical tumors should be removed surgically, intracranial tumors may be treated surgically, by radiation & or by chemotherapy.
- The progression of idiopathic precocious puberty can be delayed by medical intervention. This measure avoid psychosocial problem in the young child & may prevent premature closure of the epiphysis with resulting permanent short stature, progesterone acetate (200-300 mg given I.M weekly) it stops breast development & menstruation. However, adult short stature may remain the problem. Agonist of GnRH (Goserelin) injection also effectively stop the progression of precocious puberty without causing the short stature & are the result of choice.

Delayed puberty

Girls who haven’t displayed breast growth by age 14 years are considered to have delayed onset of puberty. but mostly undergo puberty spontaneously. These delays create psychological problems & parental anxiety. Thus reassurance can be provided only once other lesions have been excluded. Delayed puberty also associated with excessive exercise, nutritional disorders such as anorexia nervosa. Chronic system illness (especially those involving G.I.T) & hypothyroidism rarely it is due to hypogonadotropic hypogonadism or to primary gonadal failure. If indicated secondary sex characteristics can be induced with estrogen e.g.: ethinylestradiol, 20 µg given orally daily over a 6 month period. Spontaneous progression of puberty frequently develops during or subsequent to therapy.
**Hirsutism**

Refers to the excessive growth of thick terminal hair in an androgen-dependant distribution in women (upper lip, chin, chest, back, lower abdomen, thigh, forearm.) & is one of the most common presentation endocrine disease. It should be distinguished from hypertricosis, which is generalized excessive growth of vellus hair.

**Causes of hirsutism:**

- Polycystic ovarian syndrome.
- Exogenous androgen administration.
- Androgen secreting tumor of ovary or adrenal cortex.
- Cushing’s syndrome.
- Congenital adrenal hyperplasia.
- Idiopathic.

**Clinical assessment**

- The severity of hirsutism is subjective important observation is a drug & menstrual history, calculation of body mass index, measurement of blood pressure, examination for virilization (clitromegaly, deep voice, male pattern balding, breast atrophy) associated features include acne vulgaris or Cushing’s syndrome. Hirsutism of recent onset associated with virilization is suggestive of an androgen secreting tumor but this is rare.

**Investigation**

- Random blood sample should be taken or testosterone, prolactin, LH&FSH, if testosterone levels are elevated with low LH & FSH then causes other than idiopathic hirsutism & PCOD are more likely, congenital adrenal hyperplasia due to 21-hydroxylase deficiency is diagnosed by a short ACTH stimulation test with measurement of 17 hydroxy progesterone is depends on the cause.

**PCOS**

The primary cause remain uncertain the diagnosis usually made during the investigation of patient presenting with hirsutism or amenorrhea/oligomenorrhea with or without infertility, PCOS require the presence of 2 of the following 3 features:

- Menstrual irregularity
- Clinical or biochemical androgen excess
- Multiple cysts in the ovaries (most readily detected by TV US)

Women with PCOS are at increased risk of glucose intolerance

LH: FSH ratio>2.5-1. There is minor elevation of androgens with mild hyperprolactinemia

**Treatment**

- Weight loss, cosmetic measures, anti-androgens, metformine, glitazone may be helpful