Gonadal disorders

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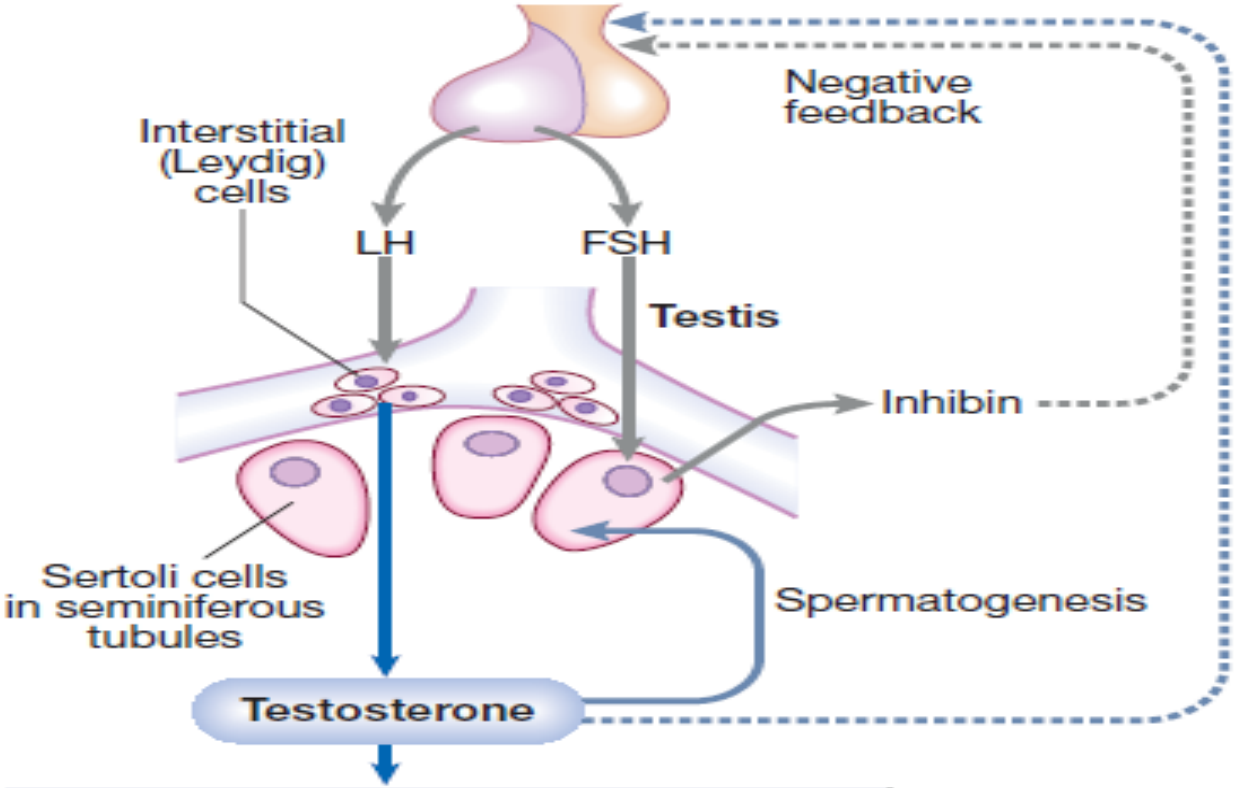
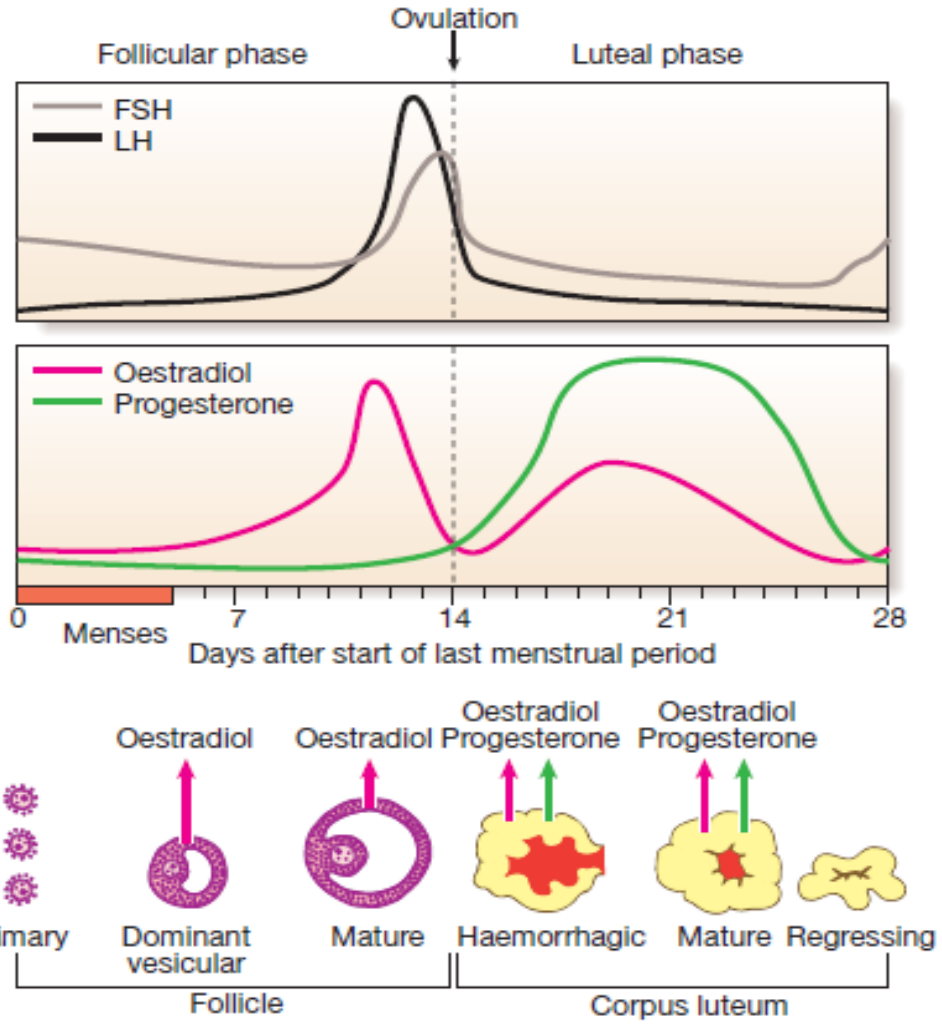
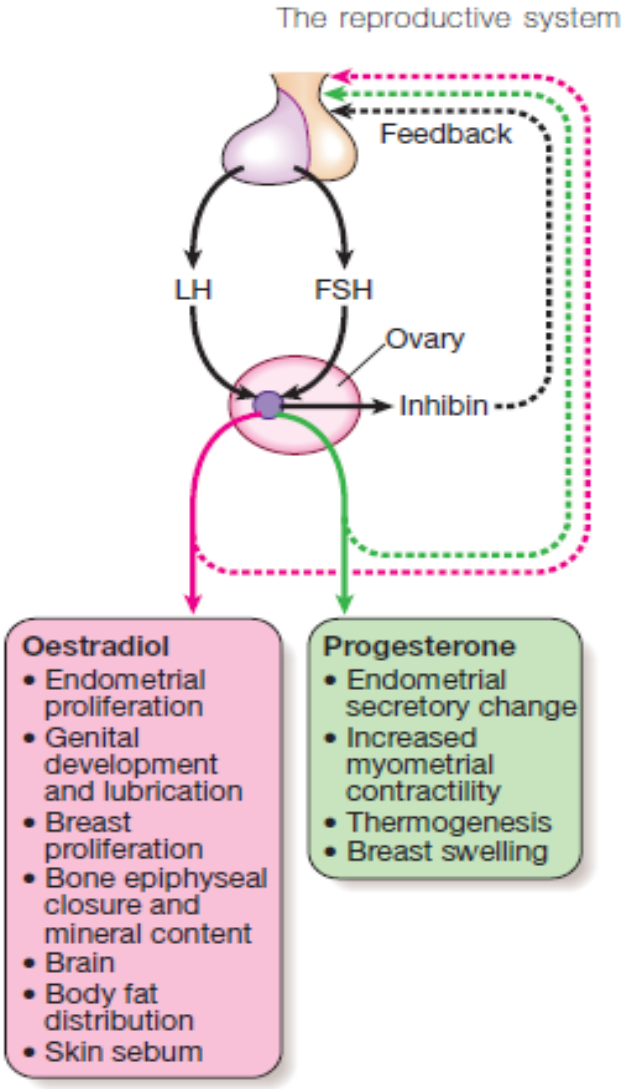
Male reproductive physiology



- Facial, axillary and body hair growth
- Scalp balding
- Skin sebum production
- Penis and scrotal development
- Prostate development and function
- Laryngeal enlargement
- Muscle power
- Bone metabolism/epiphyseal closure
- Libido
- Aggression

Female reproductive physiology





Presenting problems in reproductive disease

- Delayed puberty
- Amenorrhoea
- Male hypogonadism
- Infertility
- Gynaecomastia
- Hirsutism
- Polycystic ovarian syndrome
- Turner’s syndrome
- Klinefelter’s syndrome

Delayed puberty

- Delay Onset of physical features of sexual maturation by age of 14 in boys and 13 in Girls.
- Genetic factors have major influence in determining timing of onset of puberty-that age of menarche (onset of menstruation) is often comparable within sibling and mother–daughter pairs and within ethnic groups

Causes of delayed puberty

1. **Constitutional delay**
2. **Hypogonadotrophic hypogonadism (secondary hypognoadism)**
3. **Hypergonadotrophic hypogonadism (primaray hypogonadism)**

Constitutional delay of puberty

- Most common cause of delayed puberty
- Affected children healthy and short .
- History of delayed puberty in siblings or parents.
- Bone age is < chronological age.
- considered normal variant, as puberty will commence spontaneously.

Hypogonadotrophic hypogonadism (secondary hypognoadism)

- **Structural hypothalamic/pituitary diseases**
- **Functional gonadotrophin deficiency:**
  - Chronic systemic illness (B. asthma, coeliac disease, cystic fibrosis, renal failure)
  - Psychological stress,Anorexia nervosa,Excessive physical exercise
  - Other endocrine disease (e.g. Cushing's syndrome, primary hypothyroidism)
- **Isolated gonadotrophin deficiency** (Kallmann's syndrome)

Hypergonadotrophic hypogonadism (primary hypogonadism)

- **Developmental/congenital gonadal disorders**:
  - Cryptorchidism in males
  - Klinefelter's syndrome
  - Turner's syndrome
- **Acquired gonadal damage:**
  - Chemotherapy/radiotherapy to gonads
  - Trauma/surgery to gonads
  - Autoimmune gonadal failure
  - Mumps orchitis, T.B, Haemochromatosis

Investigations for delayed puberty

- Key measurements are LH and FSH, testosterone (in boys) and oestradiol (in girls).
- If gonadotrophin concentrations(LH,FSH)are low, then differential diagnosis lies between **constitutional delay and hypogonadotrophic hypogonadism.**
- A plain X-ray of wrist and hand for bone age,CBC, RFT, LFT, TFT and coeliac disease autoantibodies to look for possible cause of constitutional delay of puberty
- If hypogonadotrophic hypogonadism is suspected, neuroimaging and further investigations are required
- if gonadotrophin concentrations are elevated- chromosomal analysis is required

Management

- Puberty can be induced using low doses of oral oestrogen in girls or testosterone in boys.
- In children with hypogonadism, underlying cause should be treated and reversed if possible.

Amenorrhea

Primary amenorrhoea

Diagnosed in female who never menstruated; occurs as manifestation of delayed puberty or consequence of anatomical defects of reproductive system, such as endometrial hypoplasia or vaginal agenesis.

Secondary amenorrhoea

Cessation of menstruation in female who previously had periods. Secondary amenorrhoea is consequence of either ovarian or hypothalamic/pituitary dysfunction.

Causes of secondary amenorrhoea

- **Physiological**
  - Pregnancy
  - Menopause
- **Pituitary/hypothalamic dysfunction (Hypogonadotrophic hypogonadism)**
- **Ovarian dysfunction**
  - premature ovarian failure
  - Polycystic ovarian syndrome
- **Uterine dysfunction**

Asherman's syndrome(endometrial adhesions after uterine curettage, surgery or infection with T.B)

Clinical assessment

- Underlying cause suspected from associated clinical features and patient's age.
- Hypothalamic/pituitary disease and premature ovarian failure result in symptoms of oestrogen deficiency (hot flushes, sweating , emotional lability, anxiety)
- A history of galactorrhoea(prolactinoma).
- Significant weight loss can cause amenorrhoea by suppression of gonadotrophins.
- Weight gain may suggest hypothyroidism, cushing's syndrome
- Hirsutism, obesity and irregular periods suggest PCOS.
- presence of other autoimmune disease raises possibility of autoimmune premature ovarian failure

investigations

- Pregnancy - excluded by HCG
- Serum LH, FSH, oestradiol, prolactin, testosterone, T4 and TSH
- High concentrations of LH and FSH with low or low-normal oestradiol suggest primary ovarian failure
- Low levels of LH, FSH and oestradiol suggest hypothalamic or pituitary disease and pituitary MRI is indicated.
- Elevated LH, prolactin and testosterone levels (PCOS)
- Ovarian autoantibodies(premature ovarian failure)
- a karyotype for younger women to exclude Turner's syndrome

Male hypogonadism

Clinical features :

- loss of libido, lethargy , muscle weakness, and decreased frequency of shaving, gynaecomastia, infertility, osteoporosis,and anaemia of chronic disease.

Investigations:

- Diagnosis by low serum testosterone level. Distinction between hypo- and hypergonadotrophic hypogonadism is by measurement of random LH and FSH.
- Patients with hypogonadotrophic hypogonadism should be investigated for pituitary disease .
- Patients with hypergonadotrophic hypogonadism should have testes examined for cryptorchidism or atrophy, and karyotype performed for klinefelter's syndrome.

Management

- Testosterone replacement

Infertility

- Infertility affects 1 in 7 couples of reproductive age.
- In women, it may result from anovulation or abnormalities of reproductive tract that prevent fertilisation or embryonic implantation.
- In men, infertility may result from impaired sperm quality (reduced motility) or reduced sperm number(Azoospermia or oligospermia)
- In many couples, more than one factor causing subfertility is present, and in large proportion no cause can be identified.

Causes of infertility

Female factor (35–40%)

- **Ovulatory dysfunction**:
  - Polycystic ovarian syndrome
  - Hypogonadotrophic hypogonadism
  - Hypergonadotrophic hypogonadism
- **Tubular dysfunction**:
  - Pelvic inflammatory disease (chlamydia, gonorrhoea)
  - Endometriosis
  - Previous pelvic or abdominal surgery
- **Cervical and uterine dysfunction**:
  - Congenital abnormalities
  - Fibroids
  - Asherman’s syndrome

Causes of infertility

Male factor (35–40%)

- **Reduced sperm quality or production:**
  - Varicocele
  - Hypergonadotrophic hypogonadism
  - Hypogonadotrophic hypogonadism
- **Tubular dysfunction:**
  - Varicocele
  - Congenital abnormality of vas deferens/epididymis
  - Previous sexually transmitted infection (chlamydia, gonorrhoea)
  - Previous vasectomy

Unexplained or mixed factor (20–35%)

Clinical assessment

- History of previous pregnancies
- Relevant infections and surgery
- Sexual history must be explored(infrequent intercourse).
- Irregular and/or infrequent menstrual periods are indicator of anovulatory cycles (PCOS)
- In men, testes examined to confirm that both are in scrotum and to identify any structural abnormality, such as small size or presence of varicocele.

Investigations

- Investigations performed after couple has failed to conceive despite unprotected intercourse for 12 months, unless there is obvious abnormality like amenorrhoea.
- Both partners investigated.
- male -semen analysis to assess sperm count and quality
- women with regular periods, ovulation confirmed by elevated serum progesterone concentration on day 21 of menstrual cycle.
- Transvaginal ultrasound to assess uterine and ovarian anatomy.
- Tubal patency examined at laparoscopy or by hysterosalpingography

Gynaecomastia

- is presence of glandular breast tissue in males.
- results from imbalance between androgen and oestrogen activity(androgen deficiency or oestrogen excess)
- most common are physiological:

➢ newborn baby(maternal and placental oestrogens)

➢ pubertal boys (oestradiol concentrations reach adult levels before testosterone)

➢ elderly men(low testosterone concentrations).

Causes of gynaecomastia

- Idiopathic
- Physiological
- Drug-induced(Cimetidine, Digoxin, spironolactone)
- Hypogonadism
- Oestrogen excess

➢ Liver failure (impaired steroid metabolism)

➢ Oestrogen-secreting tumour (testis)

➢ Human chorionic gonadotrophin-secreting tumour (testis or lung)

Gynaecomastia

Clinical assessment

- Palpation of breast tissue to be distinguished from prominent adipose tissue (lipomastia) around nipple observed in obesity.
- Features of hypogonadism and testes examined for evidence of cryptorchidism, atrophy or a tumour.

Investigations

- Ultrasonography or mammography is required.
- Blood sample for testosterone, LH, FSH, oestradiol, prolactin and HCG.

Hirsutism

- Excessive growth of terminal hair (thick, pigmented hair in androgen-dependent distribution in women (upper lip, chin, chest, back, lower abdomen, thigh, forearm).
- Hypertrichosis is generalised excessive growth of vellus hair (thin, non-pigmented hair Found all over body from childhood).

Causes of hirsutism

Ovarian	PCOS	95%
	Androgen-secreting tumours	<1%
Adrenal	Congenital adrenal hyperplasia	1%
	Cushing's syndrome	<1%
	Androgen-secreting tumours	<1%
	Acromegaly	<1%
	Severe insulin resistance	<1%
Idiopathic	Normal US and endocrine profile	3%

Investigations

- Androgens level :testesterone ,DHEA
- LH,FSH
- Prolactin
- 17-oH-progesterone .
- CT or MRI of the adrenals and ovaries(androgen-secreting tumours)
- If there are clinical features of cushing's syndrome, further investigations should be performed

Causes of hirsutism and clinical features

Cause	Clinical features	Investigation
Idiopathic	familial	Normal
Polycystic ovarian syndrome	Obesity Oligomenorrhoea/ amenorrhoea Infertility	LH:FSH ratio > 2.5:1 Minor elevation of androgens Mild hyperprolactinaemia
Congenital adrenal hyperplasia	Pigmentation History of salt-wasting in childhood, ambiguous genitalia, or adrenal crisis when stressed	Elevated androgens rise in 17-OH-progesterone
Androgen-secreting tumour of ovary or adrenal cortex	Rapid onset Virilisation: clitoromegaly, deep voice, balding, breast atrophy	High androgens Low LH and FSH CT or MRI usually demonstrates a tumour
Cushing's syndrome	Clinical features of Cushing's syndrome	Normal or mild elevation of adrenal androgens

Polycystic ovarian syndrome

- affects up to 10% of women of reproductive age.
- Genetic factors - affects several family members
- clinical features vary between individual patients but diagnosis is usually made during investigation of hirsutism or amenorrhoea/ oligomenorrhoea or infertility
- There is no universally accepted definition but diagnosis of PCOS requires presence of two of following three features:

✓ Menstrual irregularity

✓ Clinical or biochemical androgen excess

✓ Multiple cysts in ovaries (transvaginal ultrasound)

Features of PCOS

Mechanisms	Manifestations
Pituitary dysfunction	High serum LH High serum prolactin
Anovulatory menstrual cycles	Oligomenorrhoea Secondary amenorrhoea Cystic ovaries Infertility
Androgen excess	Hirsutism Acne
Obesity and Insulin resistance	hyperglycaemia Dyslipidaemia Hypertension

Management of PCOS

should be directed at presenting complaint but all PCOS patients who are overweight should be encouraged to lose weight, as this can improve several symptoms, including menstrual irregularity, and reduces the risk of type 2 diabetes

Management of PCOS

Menstrual irregularity and infertility

- weight reduction
- Metformin, by reducing insulin resistance, may restore regular ovulatory cycles in overweight women, it is less effective than clomifene at restoring fertility.
- Progestogens can be administered to induce regular shedding of endometrium and withdrawal bleed

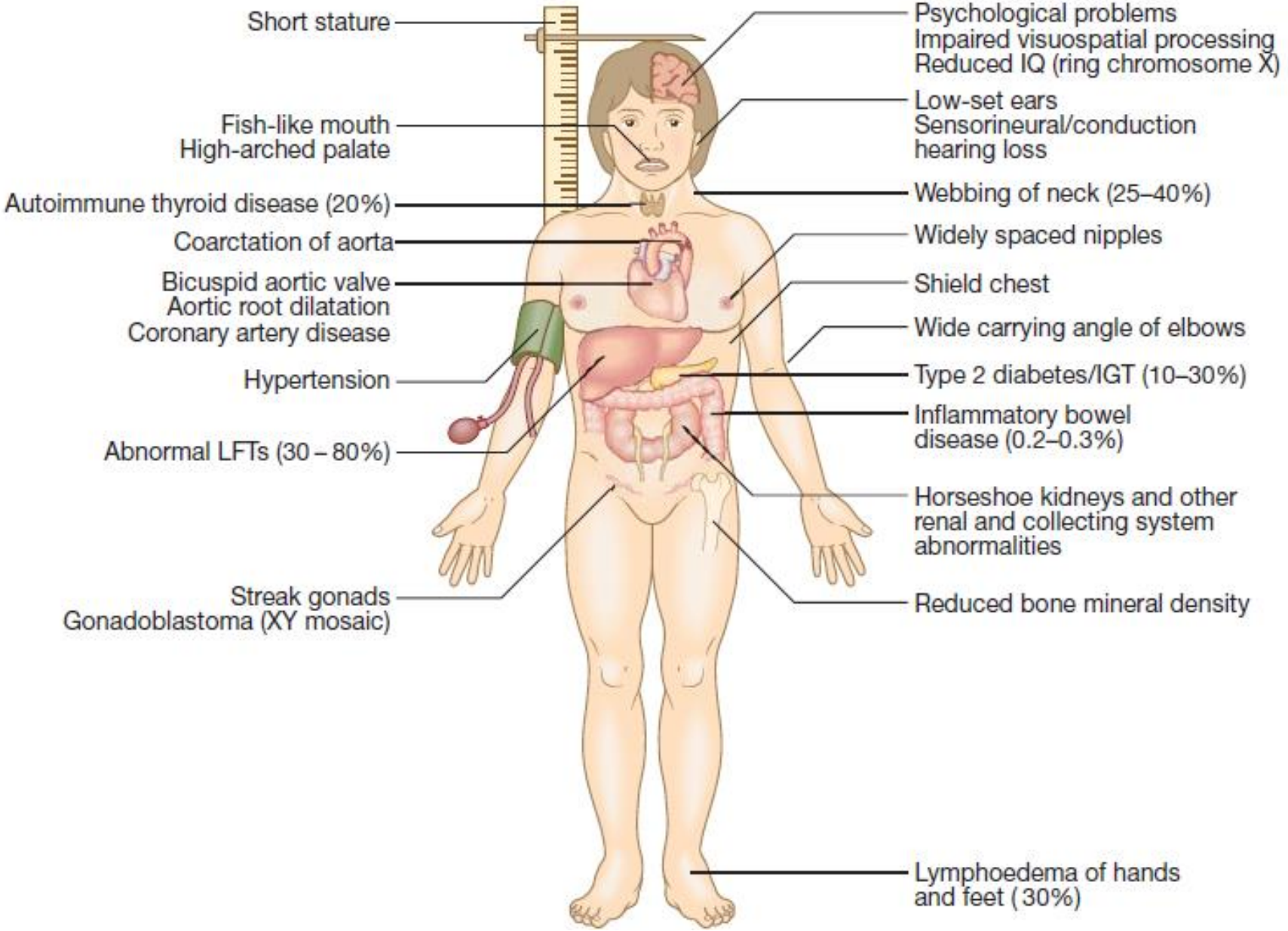
Management of PCOS

Hirsutism

- cosmetic measures, such as shaving, bleaching and waxing
- Electrolysis and laser treatment
- Metformin is less effective at treating hirsutism than at restoring menstrual regularity
- If conservative measures are unsuccessful, anti-androgen therapy e g Spironolactone is given

Turner's syndrome

- Turner's syndrome affects around 1 in 2500 females.
- classically associated with 45XO karyotype
- other cytogenetic abnormalities mosaic forms (45XO/46XX or 45XO/46XY) .


Short stature
Fish-like mouth
High-arched palate
Autoimmune thyroid disease (20%)
Coarctation of aorta
Bicuspid aortic valve
Aortic root dilatation
Coronary artery disease
Hypertension
Abnormal LFTs (30 – 80%)
Streak gonads
Gonadoblastoma (XY mosaic)
Psychological problems
Impaired visuospatial processing
Reduced IQ (ring chromosome X)
Low-set ears
Sensorineural/conduction
hearing loss
Webbing of neck (25–40%)
Widely spaced nipples
Shield chest
Wide carrying angle of elbows
Type 2 diabetes/IGT (10–30%)
Inflammatory bowel
disease (0.2–0.3%)
Horseshoe kidneys and other
renal and collecting system
abnormalities
Reduced bone mineral density
Lymphoedema of hands
and feet (30%)

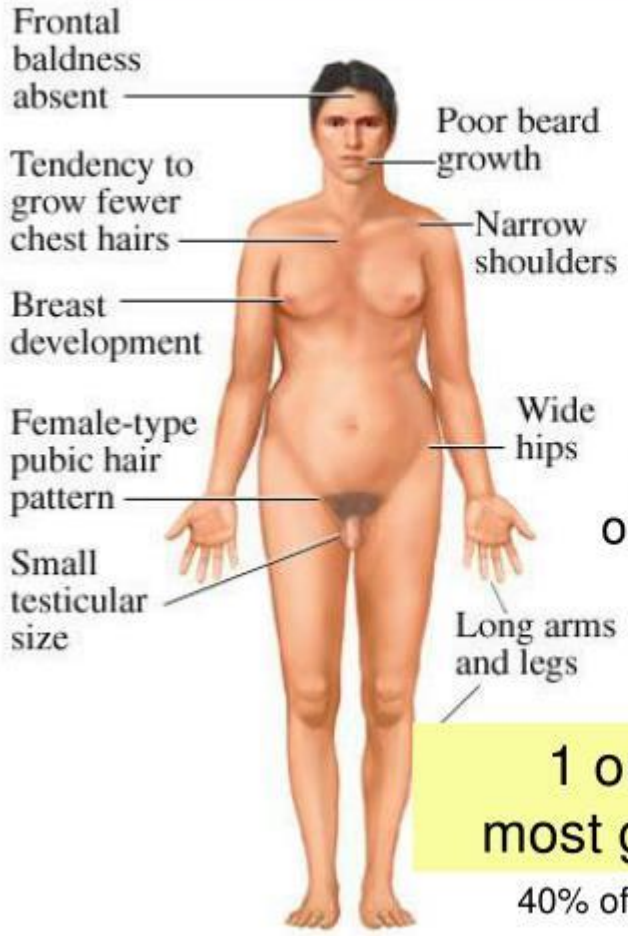
Diagnosis and management

- Diagnosis of turner's syndrome confirmed by karyotype analysis.
- Short stature, responds to high doses of growth hormone.
- Pubertal development can be induced with oestrogen therapy
- Prophylactic gonadectomy is recommended for individuals with 45xo/46xy mosaicism because risk of gonadoblastoma.

Klinefelter's syndrome

- 47XXY karyotype ,affects approximately **1 in 1000** males.
- other cytogenetic variants 46XY/47XXY mosaicism.
- principal pathological abnormality is dysgenesis of seminiferous tubules. By adolescence, hyalinisation and fibrosis are present within seminiferous tubules and Leydig cell function is impaired, resulting in hypogonadism.

47, XXY – Klinefelter syndrome



Gynecomastia –

Male with female features

- ❖small testes,
- ❖inability to produce sperm

Mental retardation

is related directly to the number of supernumerary X chromosomes (-15 IQ unit per 1 extra X).

1 out of 500 or 1000 males; most go through life undiagnosed

40% of embryos survive to birth

Gynaecomastia and delay puberty,small, firm testes,and tall stature

learning difficulties and behavioural disorders, increased risk of breast cancer and type 2DM

those with 46xy/47xxy mosaicism, may pass through puberty normally and be identified only during investigation for infertility

Diagnosis and management

- Klinefelter's syndrome is suggested by the typical phenotype in a patient with hypergonadotrophic hypogonadism and can be confirmed by karyotype analysis.
- Individuals with clinical and biochemical evidence of androgen deficiency require androgen replacement

Kallmann's syndrome

- genetic disorder characterized by failure of episodic GnRH secretion
- Results from disordered migration of GnRH-producing neurons into the hypothalamus.
- Incidence of 1 in 10,000 ♂.
- ♂:♀ ratio = 4:1
- Anosmia in 75%.
- cleft lip and palate, sensorineural deafness, cerebellar ataxia, and renal agenesis.
- **Low testosterone, LH, and FSH levels.**
- Rest of pituitary function normal.
- Normal MRI pituitary gland and hypothalamus; absent olfactory bulbs may be seen on MRI.
- **Management**

✓ Androgen replacement therapy.

✓ When fertility is desired, testosterone is stopped and exogenous gonadotrophins are administered

THANKS