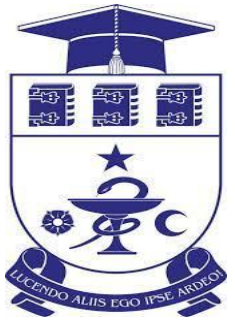
Gonadal disorders

Stela Vudu, MD



Learning objectives

Physiological menstrual cycle
Estrogen physiology and action
Definition and causes of hypogonadism
Diagnosis of hypogonadism
Primary hypogonadism - Turner Syndrome
Secondary causes of hypogonadism
Available treatments for hypogonadism
PCOS

Women reproductive system

extra-hypothalamic central nervous system (CNS)
hypothalamus
pituitary
ovaries
sex steroid–sensitive end organs
sites of estrogen transport and metabolism

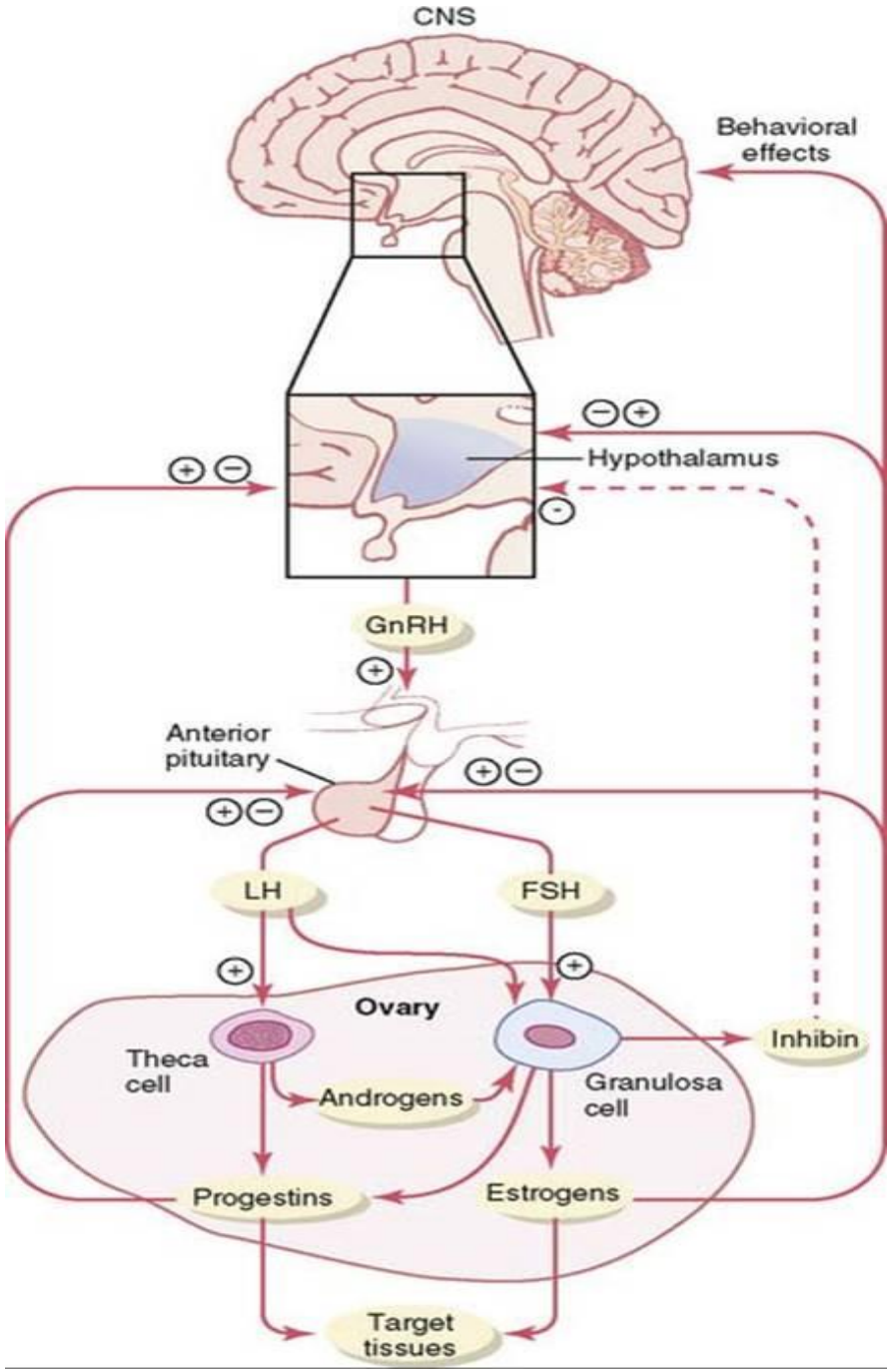


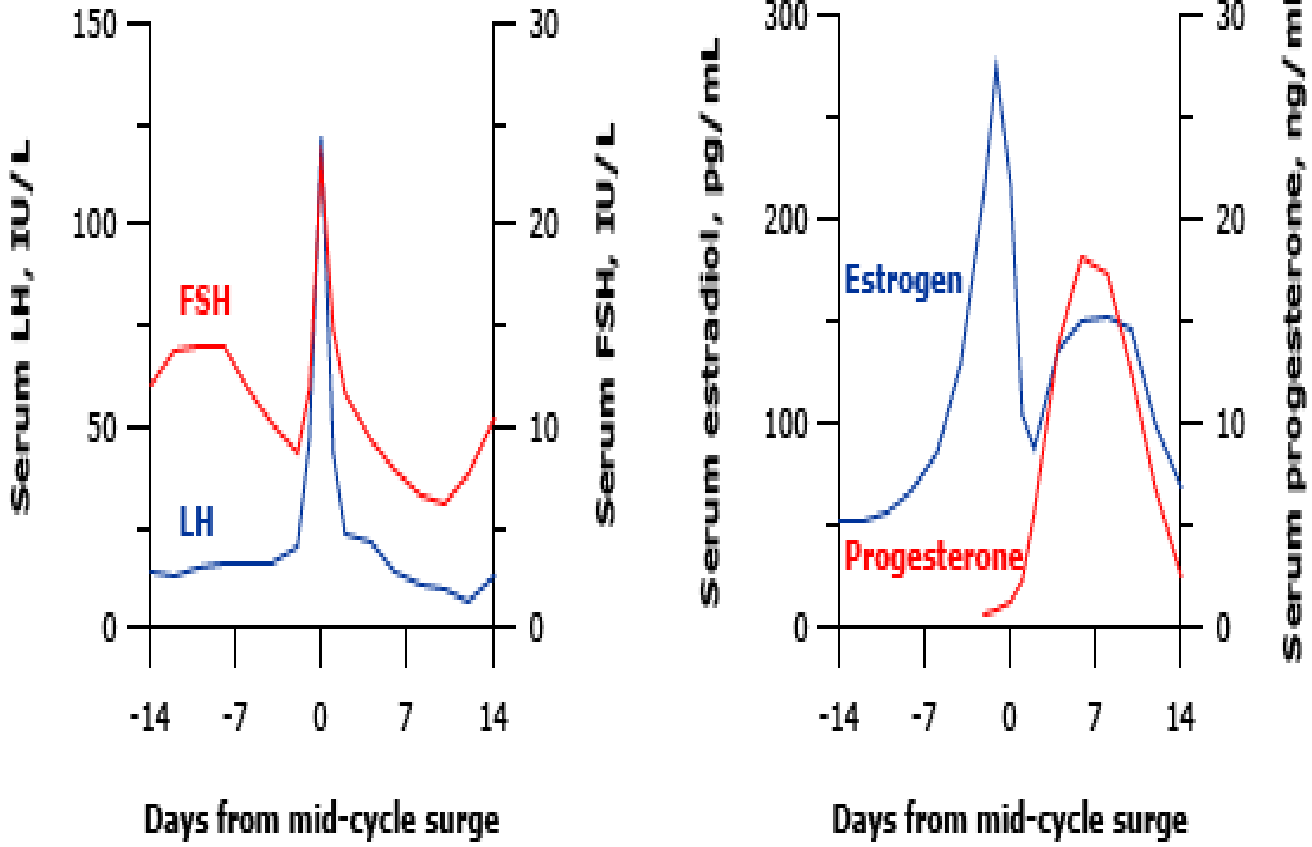
Fig. 1 The female hypothalamic–pituitary–gonadal axis.

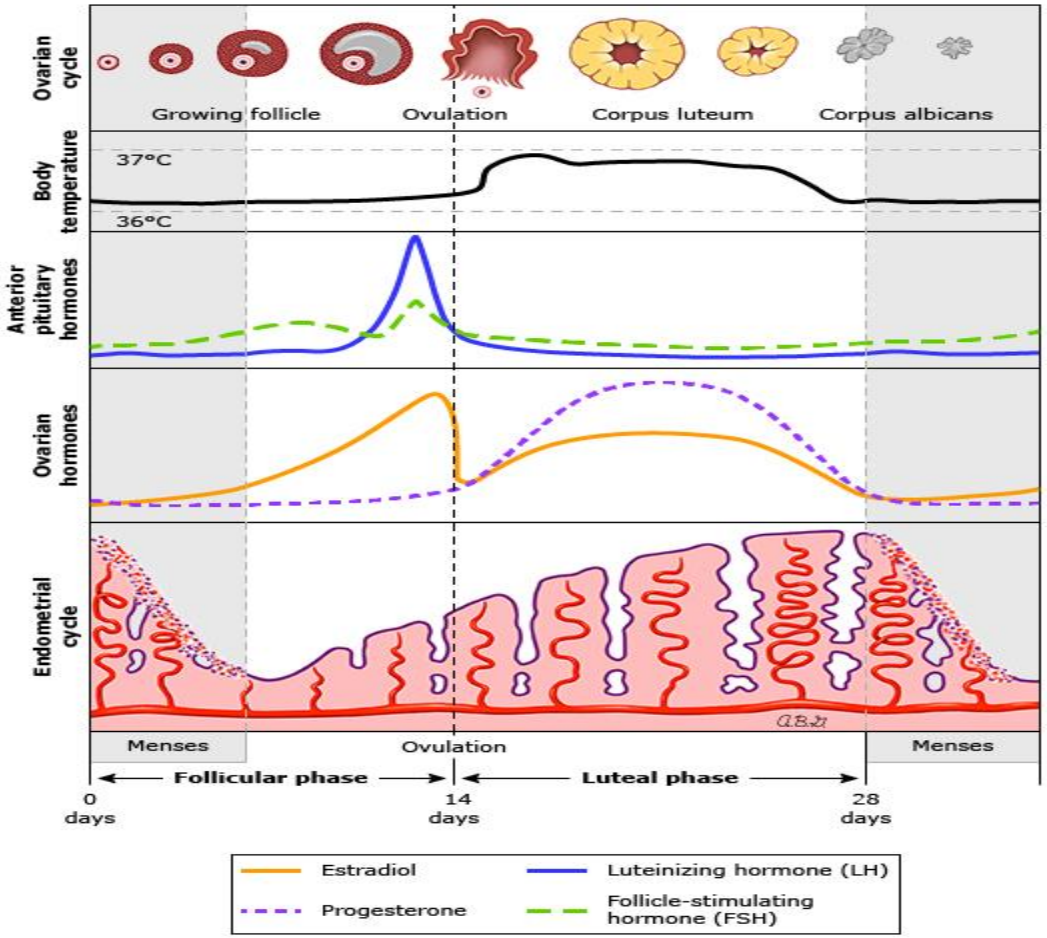
- The hypothalamus produces and secretes (GnRH) into a system of blood vessels that link the hypothalamus and the pituitary gland. GnRH stimulates the pituitary gland by attaching to specific molecules (i.e., receptors).
- After the coupling of GnRH with the receptors, a cascade of biochemical events causes the pituitary gland to produce and secrete two hormones, (LH) and (FSH).
- LH and FSH are secreted into the general circulation and attach to receptors on the ovary, where they trigger ovulation and stimulate ovarian production of the hormones E and P.
- These female hormones cause monthly menstrual cycling and have multiple effects throughout the body.

Menstrual cycle

- The normal menstrual cycle is a tightly coordinated cycle of stimulatory and inhibitory effects that results in the release of a **single mature oocyte** from a pool of hundreds of thousands of primordial oocytes.
- The first day of menses represents the first day of the cycle (day 1). The cycle is then divided into two phases: follicular and luteal.
- The follicular phase begins with the onset of menses and ends on the day before the luteinizing hormone (LH) surge.
- The luteal phase begins on the day of the LH surge and ends at the onset of the next menses.

Hormonal changes during normal menstrual cycle





Corrine K Welt, MD. **Physiology of the normal menstrual cycle**

Estrogen

Estrogen (E) is the principal female hormone secreted mainly by the ovaries.

There are 3 types of estrogen:

Estradiol – produced by granulosa cells of the ovary

Estrone – produced from the peripheral conversion of androstenedione.

Estriol – secreted by the placenta during pregnancy.

Estrogen

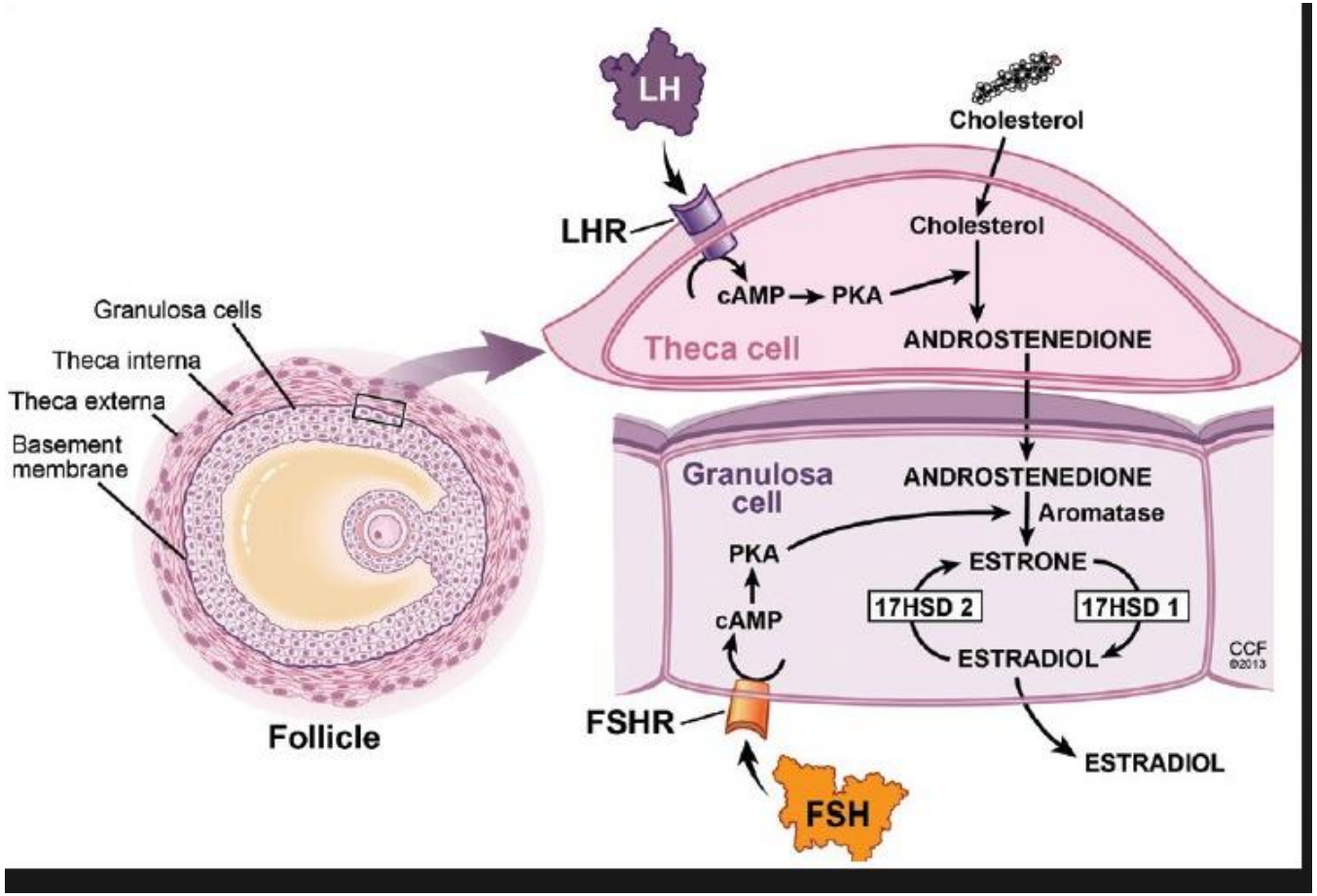
Estradiol daily production rate in women is 40-400 mcg.

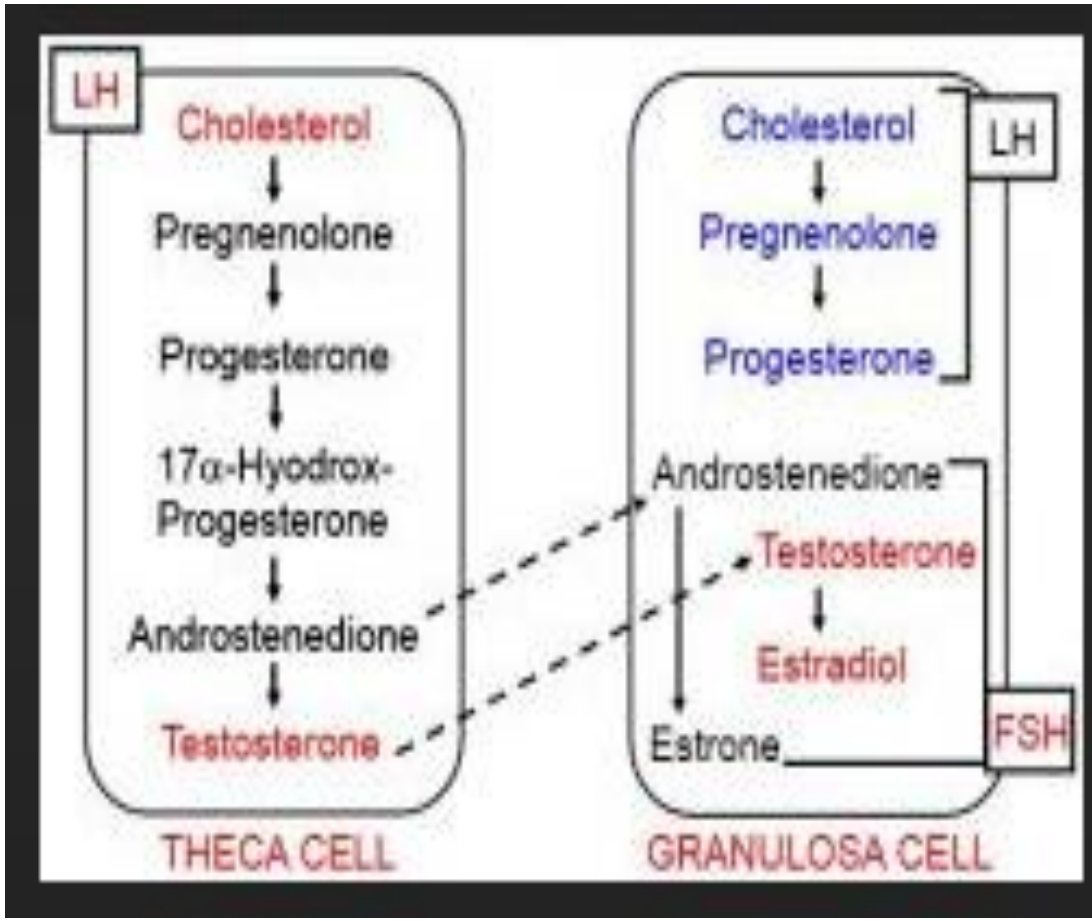
Estrogen circulates mainly bound to 2 plasma proteins:

Hormone-binding globulin (SHBG) and albumin.

In young adult women, only 2-3 % is biologically active, the rest is bound to SHBG and albumin.

Estrogen synthesis





Doshi SB, Agarwal A. The role of oxidative stress in menopause. J Mid-life Health 2013;4:140-6

Estrogen sources

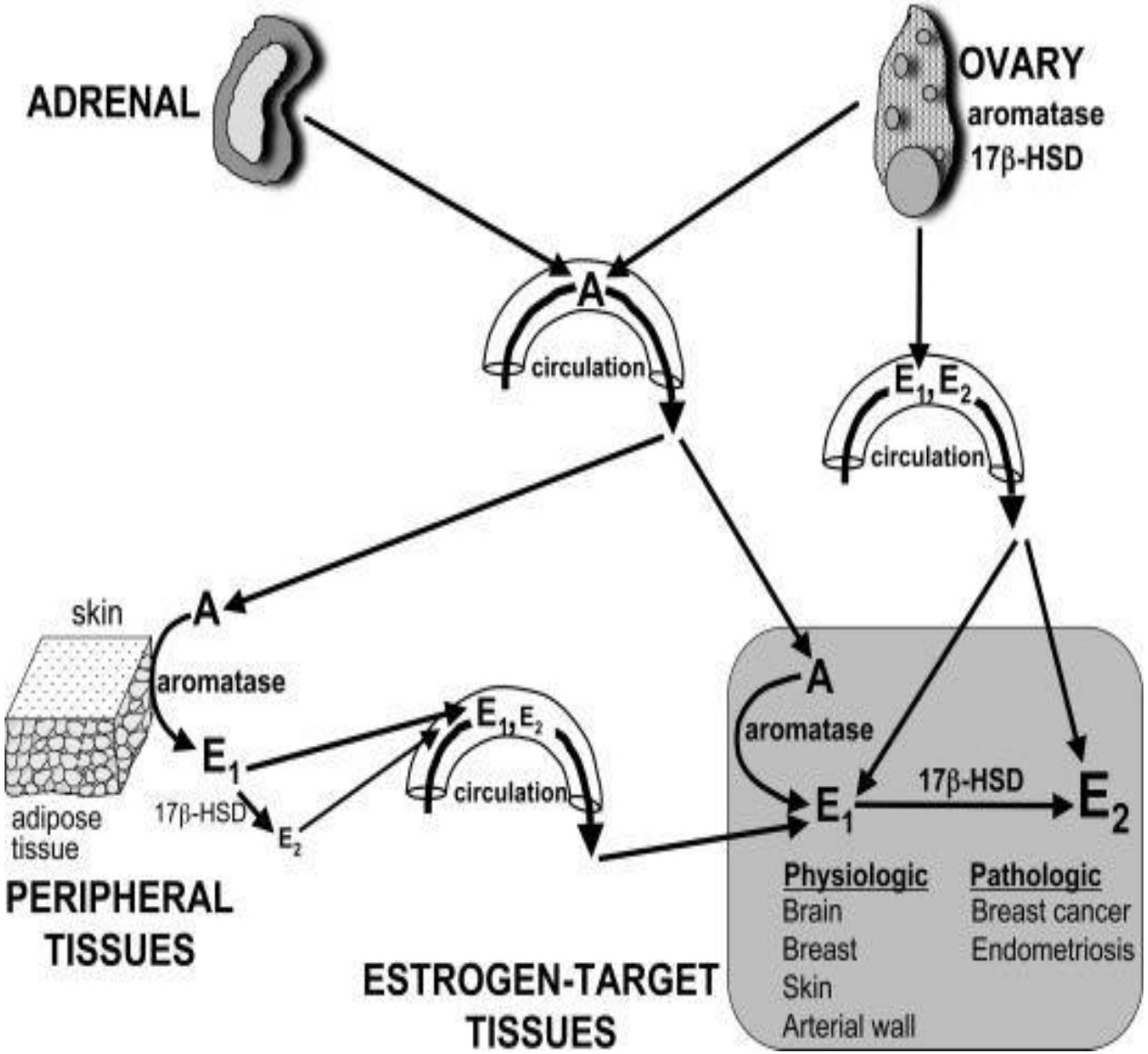


Fig. Origins of estrogen in women.

The biologically active estrogen estradiol (E2) is produced in at least three major sites:

1) direct secretion from the ovary in reproductive-age women;

2) by conversion of circulating androstenedione (A) of adrenal and/or ovarian origins to estrone (E1) in peripheral tissues; and

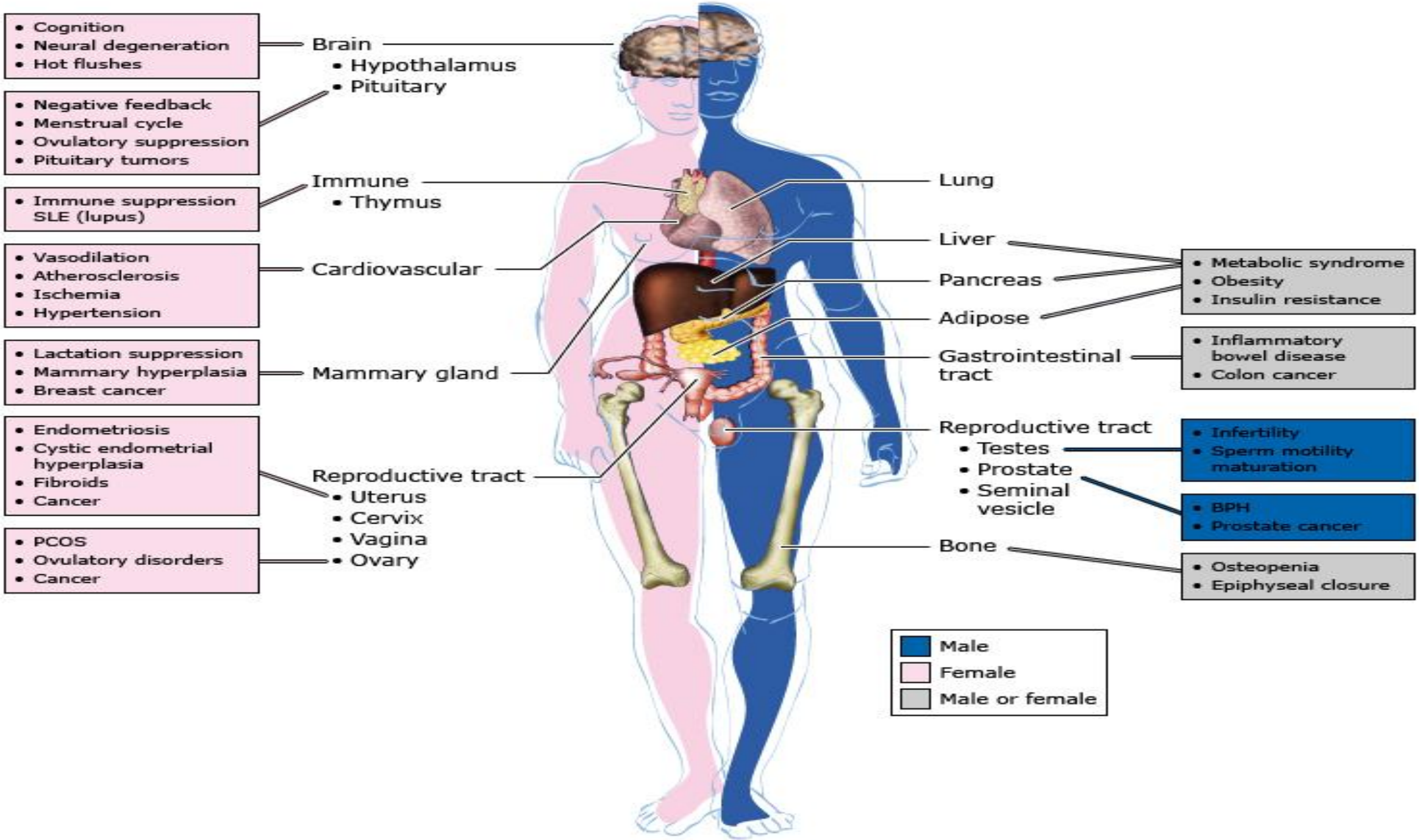
3) by conversion of A to E1 in estrogen-target tissues.

In the latter two instances, estrogenically weak E1 is further converted to E2 within the same tissue.

The presence of the enzyme aromatase and 17-HSD is critical for E2 formation at these sites.

E2 formation by peripheral and local conversion is particularly important for postmenopausal women and for estrogen-dependent diseases such as breast cancer, endometriosis, and endometrial cancer.

Serdar E Bulun. Regulation of aromatase expression in estrogen-responsive breast and uterine disease: From bench to treatment. Pharmacological Reviews 57(3):359-83


• Cognition
• Neural degeneration
• Hot flushes
Brain
• Hypothalamus
• Pituitary
• Negative feedback
• Menstrual cycle
• Ovulatory suppression
• Pituitary tumors
Immune
• Thymus
• Immune suppression
SLE (lupus)
• Vasodilation
• Atherosclerosis
• Ischemia
• Hypertension
Cardiovascular
• Lactation suppression
• Mammary hyperplasia
• Breast cancer
Mammary gland
• Endometriosis
• Cystic endometrial hyperplasia
• Fibroids
• Cancer
Reproductive tract
• Uterus
• Cervix
• Vagina
• Ovary
• PCOS
• Ovulatory disorders
• Cancer
Lung
Liver
Pancreas
Adipose
• Metabolic syndrome
• Obesity
• Insulin resistance
Gastrointestinal tract
• Inflammatory bowel disease
• Colon cancer
Reproductive tract
• Testes
• Prostate
• Seminal vesicle
• Infertility
• Sperm motility maturation
• BPH
• Prostate cancer
Bone
• Osteopenia
• Epiphyseal closure
Male
Female
Male or female

Activin and inhibin

- **Activin**
- Source: gonads, pituitary, placenta
- Stimulates FSH release
- Participates in androgen synthesis through enhancing LH action in the ovary

- **Inhibin**
- Source: gonads, pituitary, placenta, corpus luteum.
- Supresses FSH synthesis and secretion (more than LH)

Hypogonadism

Definition – a clinical syndrome that results in hormone deficiency and decreased function of the gonads.

Causes of female hypogonadism

Primary hypogonadism (ovarian dysfunction)

- **Congenital abnormalities:**

  Turner syndrome

  Other chromosomal abnormalities

  Mutation in the FSH/LH receptor genes

- **Acquired diseases:**

  Chemo- and radiotherapy

  Alkylating agents

  Infections

  Environmental toxins

  Autoimmune

  Idiopathic

Secondary hypogonadism (hypothalamic/pituitary dysfunction)

- ***Hypothalamic dysfunction:***

  isolated GnRH deficiency

  inflammatory/infiltrative disease

  brain tumors

  cranial irradiation

  brain injury

- ***Pituitary dysfunction:***

  hyperprolactinemia (PRLoma)

  other pituitary tumors

  other tumors

  pituitary apoplexy

  genetic causes

Turner syndrome (primary hypogonadism)

- Turner syndrome is one of the more common chromosome anomalies in humans and represents an important cause of short stature and ovarian insufficiency in females.

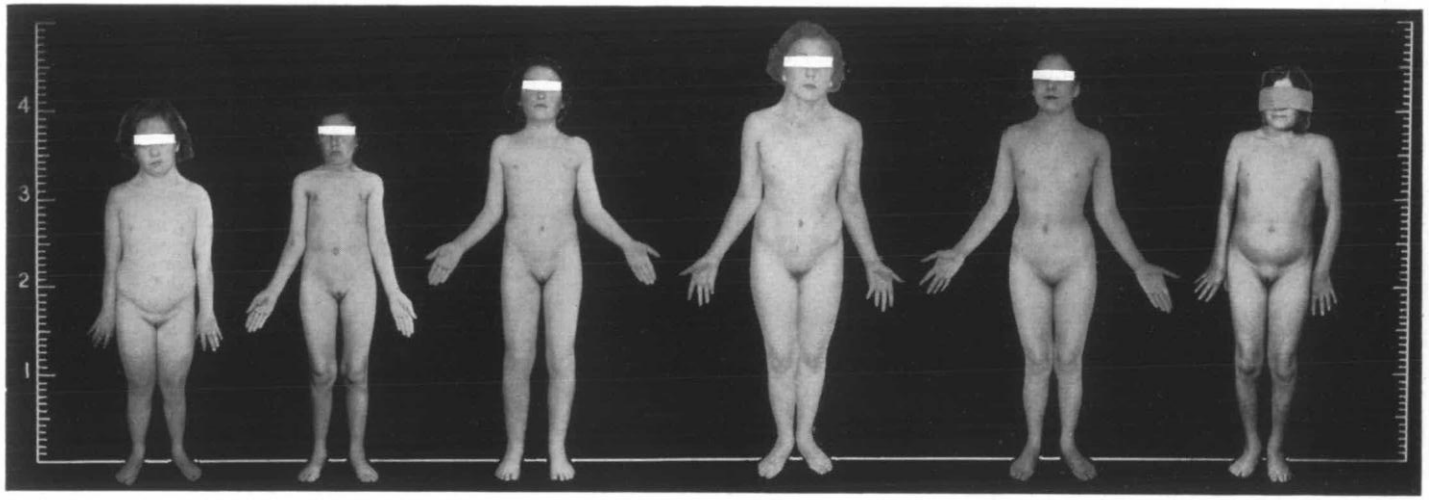
- Common disorder: 1 in 2000 to 2500 females.
- The X chromosome is derived from the mother in 2/3 of patients and from the father in the remaining 1/3.

- It is characterized by :
  ↓ estradiol
  ↑ FSH, LH

Turner syndrome

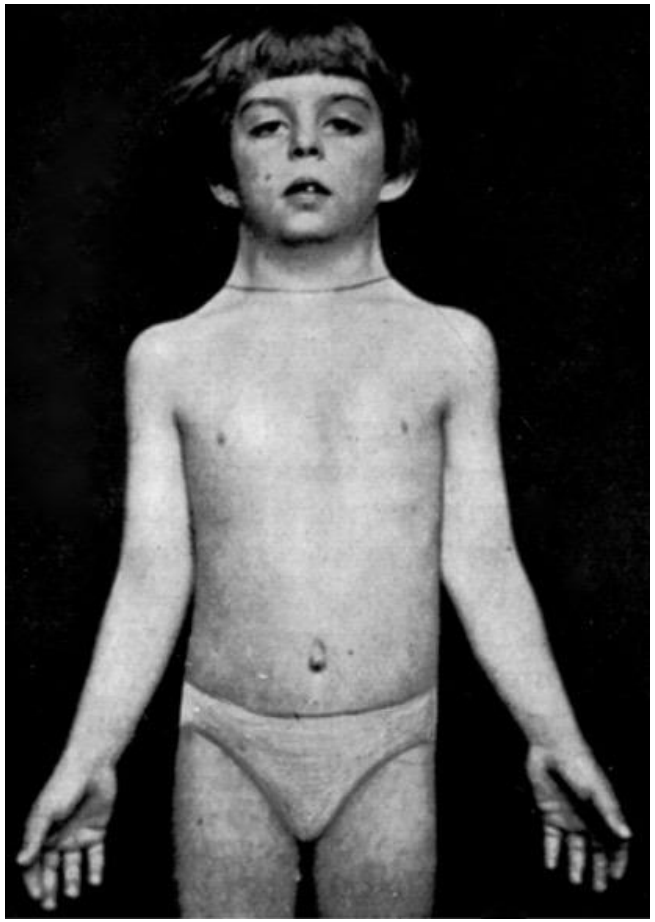
Henry Turner, 1938

Otto Ullrich, 1930



Case 3 Case 7 Case 6 Case 2 Case 1 Case 5

Fig. 1. Patients illustrating the syndrome of infantilism, webbed neck, and cubitus valgus.



HENRY H. TURNER, A SYNDROME OF INFANTILISM, CONGENITAL WEBBED NECK, AND CUBITUS VALGUS, *Endocrinology*, Volume 23, Issue 5, 1 November 1938, Pages 566–574, https://doi.org/10.1210/endo-23-5-566

Ullrich O: Über typische Kombinationsbilder multipler Abartungen. Z Kinderheilk Eur J Pediatr. 1930;49(3):271-276.

Clinical abnormalities in Turner syndrome

Skeletal growth disturbances

Short stature 95-100 %

Growth failure 90-95 %

Defective dental development 75 %

Characteristic facies with micrognathia 60 %

Short neck 40 %

Kyphosis 50 %

Widely spaced nipples 30-35 %

Short metacarpals 35 %

Lymphatic obstruction

Edema of hands/feet 20-30 %

Low posterior hairline 40 %

Webbed neck 25 %

Germ cell chromosomal defects

Infertility 95 %

Ovarian failure 90 %

Gonadal dysgenesis 85-90 %

Gonadoblastoma 5 %

Clinical abnormalities in Turner syndrome

Other features

Cardiac malformations up to 50 %

Aortic valve abnormalities up to 30 %

Renal anomalies up to 30%

Hypertension 30 %

Ocular abnormalities up to 50%

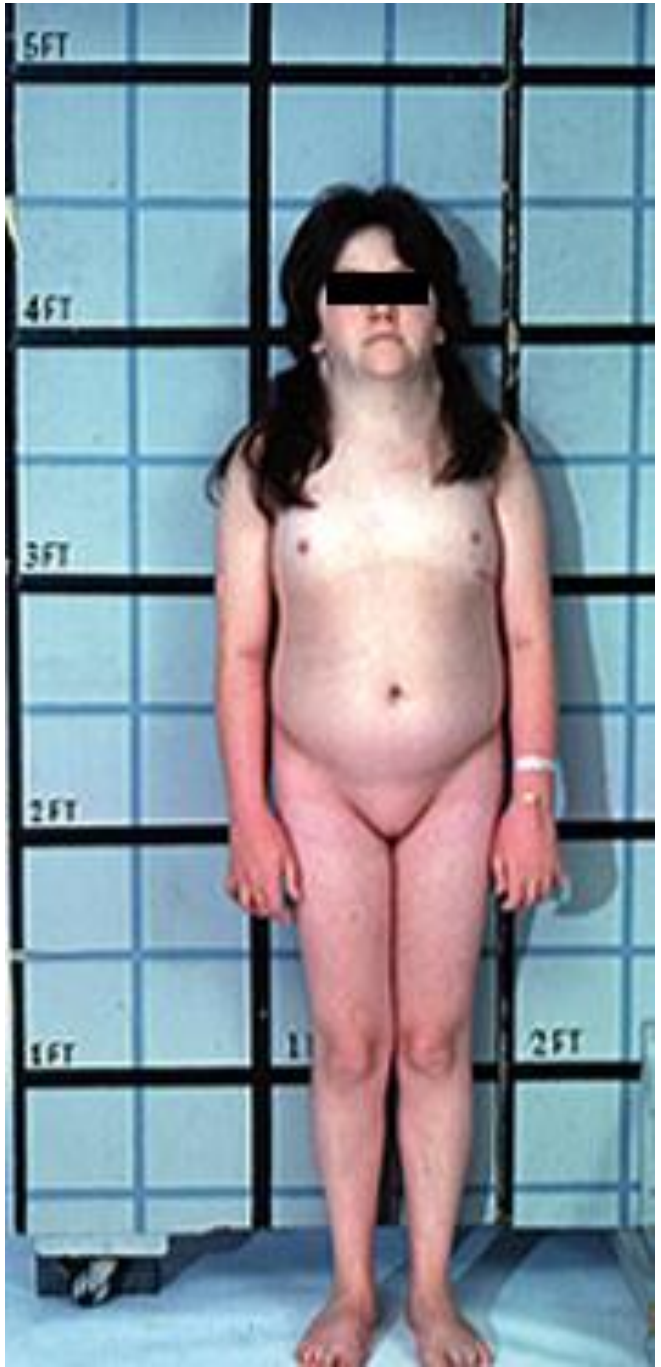
Ears and hearing up to 70%

Skin 25 %

Autoimmune (Thyroiditis, celiac disease, vitiligo) up to 30 %

Diabetes mellitus 5 to 25 %

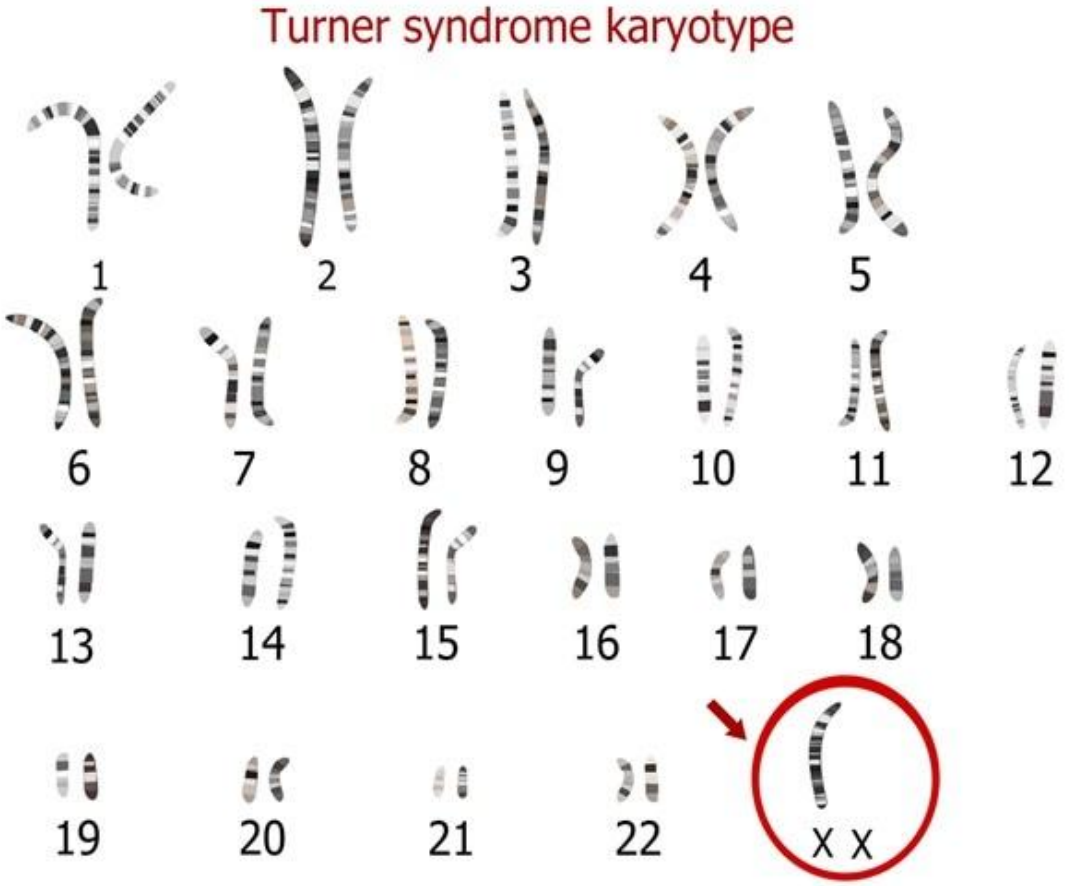
Fatty liver disease/autoimmune process of the liver



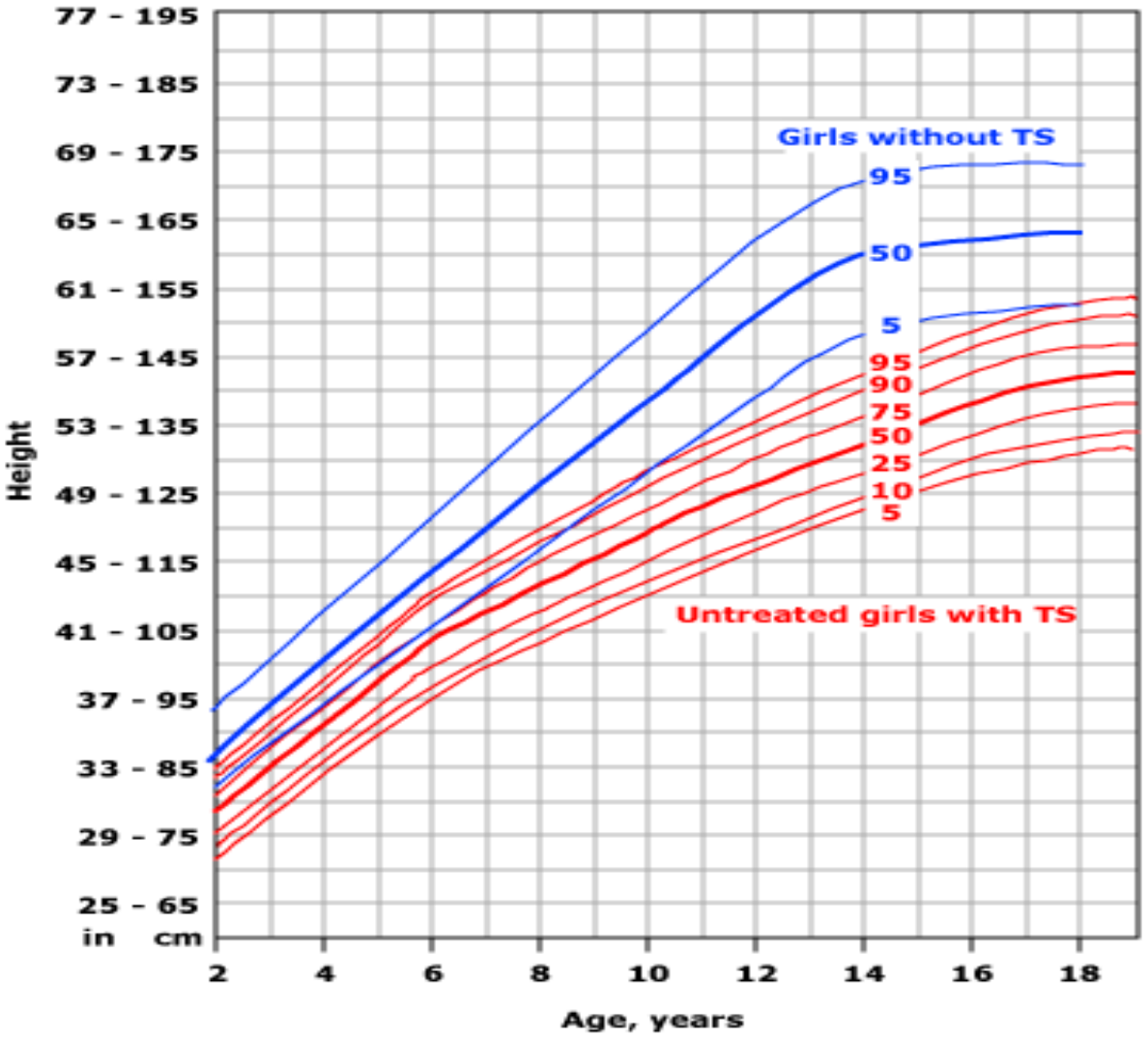
Eleven-year-old with classical appearance of 45,X Turner syndrome,
including short stature, lack of breast development, and shield chest with widely spaced nipples.
Additional features may include webbed neck, cubitus valgus, and shortened fourth metatarsals.

Diagnosis

- Karyotype: 45, X – 40-50 %
- 45,X + mozaicism – the rest (45,X/46,XX or 45,X/47,XXX or 45,X/46XY)



Treatment



- Recombinant human growth hormone start when height falls below the 5th percentile for age, it usually occurs at 2-5 years of age.
- Higher doses of growth hormone are required compared with standard doses used for growth hormone deficiency.
- Initial dose of growth hormone: 50 mcg/kg/day, given once daily, s/c
- OR calculated based on BSA (1.33 mg/m^2/day as a starting point).

Treatment

- Start **low-dose** estrogen **(**one-tenth of the adult replacement dose) to initiate puberty at age 11 to 12 years, without compromising adult height.
- Increase gradually the dose during the next two to four years.
- Progestin therapy should begin after approximately 2 years of estrogen monotherapy (typically around 13 to 14 years of age)

Treatment

- Monitoring and treatment of cardiovascular disease
- Monitoring and treatment of hearing loss
- Strategies for managing learning difficulties if present
- Psychosocial support

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  Idiopathic

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  brain injury

- ***Pituitary dysfunction:***

  hyperprolactinemia (PRLoma)

  other pituitary tumors

  other tumors

  pituitary apoplexy

  genetic causes

Clinical manifestations

- Deficient secretion of the gonadotropins FSH and LH results in hypogonadotropic hypogonadism (secondary hypogonadism).
- It results in ovarian hypofunction and decreased estradiol secretion.
- *The clinical consequences of estradiol deficiency in women with secondary hypogonadism are similar to those seen in women with primary hypogonadism.*

Clinical manifestations

- Irregular periods or amenorrhea
- Anovulatory infertility
- Hot flashes
- Vaginal atrophy
- Breast tissue decreases
- Bone mineral density declines.

Diagnosis

- A normal menstrual cycle is a more sensitive indicator of intact pituitary-gonadal function than any biochemical test.
- If the woman has oligomenorrhea or amenorrhea, serum LH or FSH should be measured. In addition - measurement of serum estradiol.
- LH ↓, FSH ↓, estradiol ↓.

Treatment

- Treatment of LH and FSH deficiency depends whether or not fertility is desired.
- Women with hypogonadism due to pituitary disease who are not interested in fertility should be treated with *estradiol-progestin replacement therapy.*
- Treatment with estradiol can be offered *transdermally*, so estradiol is absorbed into the systemic circulation.

Treatment

- *Oral* estradiol is an effective and inexpensive alternative.
- Women with an intact uterus must also take a progestin to avoid the risk of endometrial hyperplasia or carcinoma.
- Women with secondary hypogonadism who wish to become fertile should be offered *ovulation induction with gonadotropins*.

PCOS

AMENORRHEA ASSOCIATED WITH BILATERAL POLYCYSTIC OVARIES*

IRVING F. STEIN, M.D., AND MICHAEL L. LEVENTHAL, M.D.,
CHICAGO, ILL.
(From Michael Reese Hospital and Northwestern University Medical School)

ACCORDING to leading authoritative works on gynecology, the bilateral polycystic ovary is most commonly found in association with *uterine bleeding* (Fig. 1). This association has been recognized by the medical profession and is not infrequent in occurrence. Endometrial hyperplasia, multiple follicle cysts with granulosa cell lining, and a notable absence of corpora lutea in the ovary are the significant pathologic findings in such cases. The bleeding in these patients is readily explained by the fact that the increase in number of follicles lined by granulosa cells produces an excess of secretion of estrogenic hormone.

According to the same authoritative works, little or no mention is made of bilateral polycystic ovaries accompanied by *amenorrhea*, and inasmuch as we have encountered a series of cases exemplifying the latter conditions, we desire to present the results of our study of them.

PCOS

- Polycystic ovary syndrome (PCOS) - heterogeneous, complex genetic trait
- unclear, and likely multiple, etiology
- an important cause of ovulatory and menstrual irregularity, subfertility and infertility, clinically evident hyperandrogenism, and metabolic dysfunction in women.

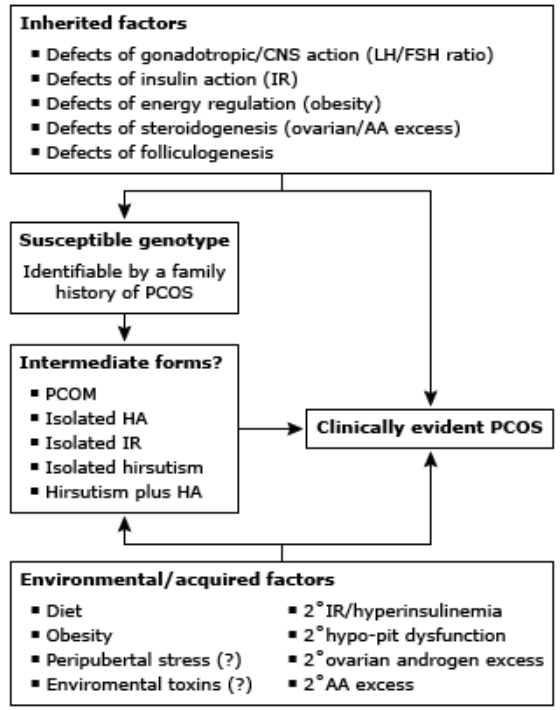
PHENOTYPES OF PCOS

- **Phenotype A** (also known as "full PCOS" or "classic PCOS") includes biochemical or clinical hyperandrogenism, oligoovulation, and polycystic ovarian morphology
- **Phenotype B** (also known as "classic PCOS") includes hyperandrogenism and oligoanovulation
- **Phenotype C** (also known as "ovulatory PCOS") includes hyperandrogenism and polycystic ovarian morphology
- **Phenotype D** (also known as "non-hyperandrogenic PCOS") includes oligoanovulation and polycystic ovarian morphology

High-risk groups associated with an increased prevalence of PCOS

- Oligoovulatory infertility
- Obesity and/or insulin resistance
- Type 1, type 2, or gestational diabetes mellitus
- A history of premature adrenarche
- First-degree relatives with PCOS
- Certain racial/ethnic groups (eg, Mexican American)
- Use of antiseizure medications – valproate

Potential mechanisms underlying the development of PCOS



Inherited factors act to create a susceptible genotype, most commonly identifiable by a positive family history for PCOS or related features. This susceptible genotype, in isolation or in association with environmental or acquired factors, may result in intermediate forms of functional hyperandrogenism. Continued exposure to environmental factors, or an increasing load of genetic variants favoring its occurrence, leads to the development of clinically evident PCOS.

PCOS: polycystic ovary syndrome; CNS: central nervous system; LH: luteinizing hormone; FSH: follicle stimulating hormone; IR: insulin resistance; AA: adrenal androgen; PCOM: polycystic ovarian morphology; HA: hyperandrogenemia.

Clinical picture

- **Menstrual dysfunction** characterized by infrequent or absent menses. However, some women with PCOS have abnormal uterine bleeding as a result of their chronic anovulation. The ovulatory dysfunction typically results in infertility and the need for ovulation induction in those who wish to conceive.

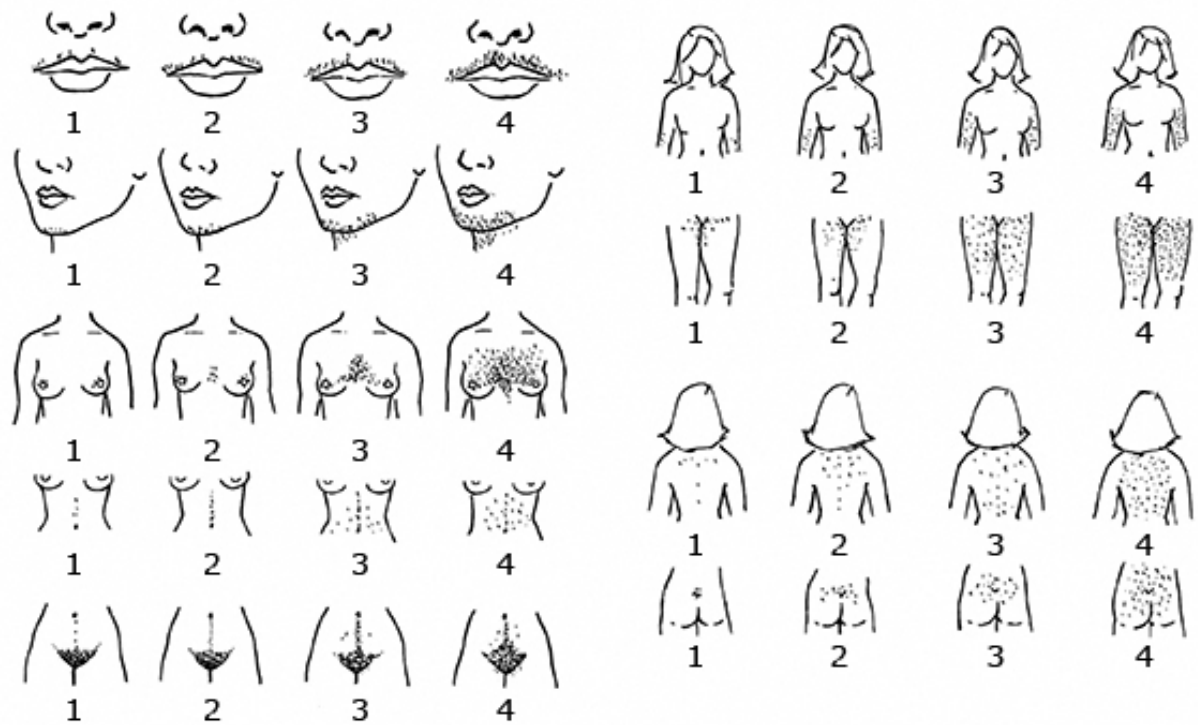
- **Hyperandrogenism**, which may include clinical signs (hirsutism, acne, alopecia) and/or elevated serum androgen concentrations.

- **Typical polycystic appearance of the ovaries** on transvaginal ultrasound. However, this ultrasound appearance is nonspecific as it may also be seen in normal-cycling women.

Clinical picture

- A clustering of risk factors for diabetes and cardiovascular disease, including obesity (and insulin resistance), glucose intolerance, and dyslipidemia.
- Other clinical manifestations that may be seen include sleep apnea and nonalcoholic steatohepatitis (NASH).
- Women with PCOS may be more likely to have mood disorders (depression and anxiety). In addition, PCOS appears to be associated with an increased risk of eating disorders, in particular, binge eating.

Grading of severity of hirsutism in women



Ferriman-Gallwey hirsutism scoring system. Each of the 9 body areas that is most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile), and these are summed to provide a hormonal hirsutism score. "Focal" hirsutism (score 1 to 7) is a common normal variant, whereas generalized hirsutism (score of 8 or more) is abnormal in the general United States population. The normal score is lower in Asian populations and higher in Mediterranean populations.

Visually scoring hirsutism

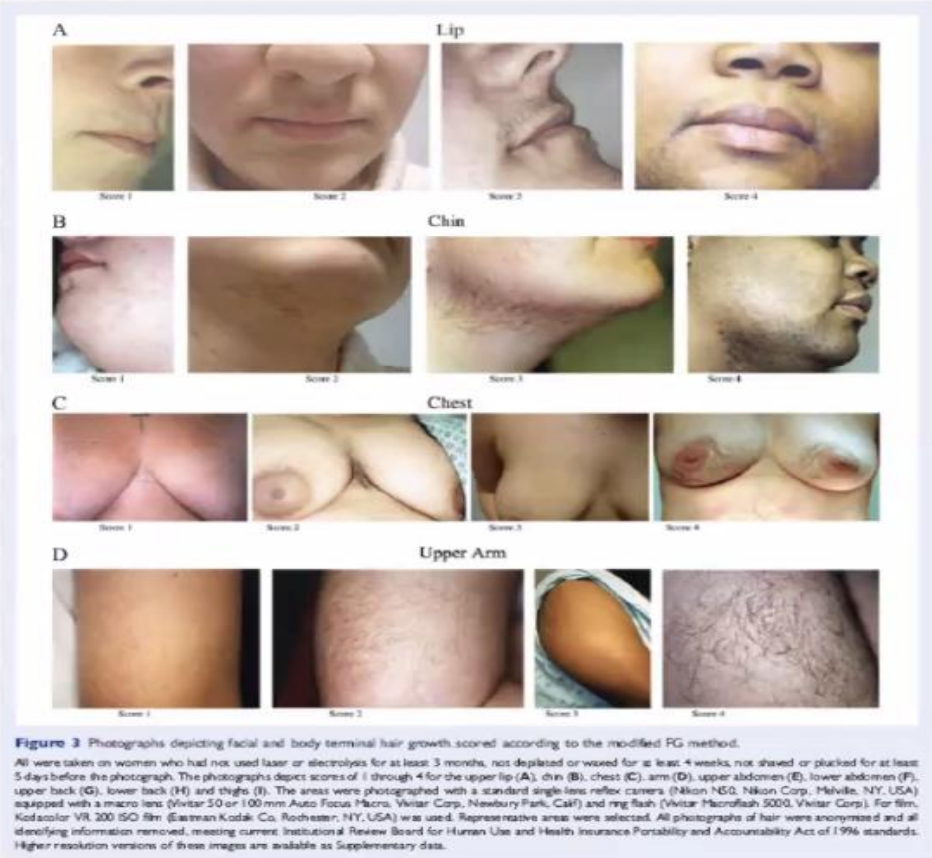


Figure 3 Photographs depicting facial and body terminal hair growth scored according to the modified FG method.

All were taken on women who had not used laser or electrolysis for at least 3 months, not depilated or waxed for at least 4 weeks, not shaved or plucked for at least 5 days before the photograph. The photographs depict scores of 1 through 4 for the upper lip (A), chin (B), chest (C), arm (D), upper abdomen (E), lower abdomen (F), upper back (G), lower back (H) and thighs (I). The areas were photographed with a standard single-lens reflex camera (Nikon N50, Nikon Corp., Melville, NY, USA) equipped with a macro lens (Vivitar 50 or 100 mm Auto Focus Macro, Vivitar Corp., Newbury Park, Calif) and ring flash (Vivitar Macroflash 5000, Vivitar Corp.). For film, Kodacolor VR 200 ISO film (Eastman Kodak Co, Rochester, NY, USA) was used. Representative areas were selected. All photographs of hair were anonymized and all identifying information removed, meeting current Institutional Review Board for Human Use and Health Insurance Portability and Accountability Act of 1996 standards. Higher resolution versions of these images are available as Supplementary data.

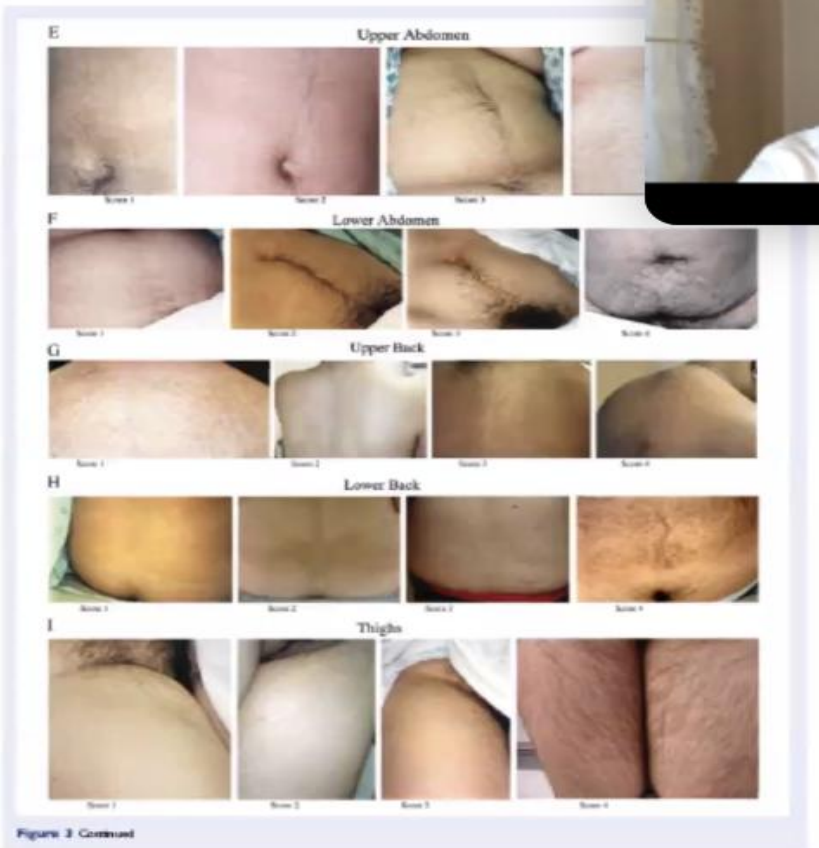


Figure 3 Continued

Yildiz et al., Hum Reprod Update 2010

Diagnosis

Most expert groups use **Rotterdam criteria** to make the diagnosis of PCOS.

2 out of 3 of the following criteria are required to make the diagnosis:

- Oligo- and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries (by ultrasound)

The diagnosis of PCOS is only **confirmed** when other conditions that mimic PCOS are excluded (eg, disorders that cause oligo/anovulation and/or hyperandrogenism, such as thyroid disease, NCCAH, hyperprolactinemia, and androgen-secreting tumors).

Treatment

- *First line treatment in overweight and obese women is weight loss –*

❖it may normalize menstrual cycle and restore ovulation

❖has a metabolic benefit.

- Subsequently, treatment will depend upon whether pregnancy is pursued or not.

Women not pursuing pregnancy

OCs in the treatment of PCOS

Noncontraceptive benefits

- Decreased dysmenorrhea, menorrhagia, anemia
- Decreased risk of osteoporosis
- Decreased risk of ectopic pregnancy
- Protection from the risk of endometrial/ovarian cancer

……

Side effects

- Abnormal menstrual bleeding
- Nausea, breast tenderness, headache, mood changes

……

Women not pursuing pregnancy

COCP and anti-androgen

In combination with the COCP, antiandrogens should only be considered in PCOS to treat hirsutism, after six months or more of COCP and cosmetic therapy have failed to adequately improve symptoms
In combination with the COCP, antiandrogens could be considered for the treatment of androgen-related alopecia in PCOS
In PCOS, antiandrogens must be used with effective contraception, to avoid male foetal under virilisation Potential liver toxicity requires caution

Women pursuing pregnancy

- Weight loss in obese women.
- Ovulation induction.
- First line : Letrozole - an aromatase inhibitor or clomiphene citrate.
- Second line: Follicle-stimulating hormone injections
- Second line: Ovarian drilling
- Third line: In vitro fertilization.

Menopause

- Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathologic or physiologic cause.
- Menopause occurs at a median age of 51 years.
- It is a reflection of complete/near complete ovarian follicular depletion, resulting ↓ estrogen and ↑ FSH.

Menopause

- Natural menopause between 40 and 45 years is "*early menopause*”.
- Natural menopause < 40 years is "*primary ovarian insufficiency*”.
- *Perimenopause* is the menopausal transition occurring after the reproductive years, but before menopause, and is characterized by irregular menstrual cycles, endocrine changes, and symptoms such as hot flashes.

Factors affecting age at menopause

- **Genetics** – genome-wide association studies have identified a number of regions associated with age at menopause.
- **Smoking** — The age of menopause is reduced by approximately 2 years in women who smoke.
- **Ethnicity** — natural menopause occur earlier among Hispanic women and later in Japanese American women when compared with White women.
- **Other** – type 1 DM, night shift work, in utero exposure to diethylstilbestrol (DES).

Menopausal transition.

- Menstrual cycle.
- *Early transition.* Normal intermenstrual interval during the reproductive years is 25-35 days; during the menopausal transition, this may increase to 40-50 days.
- *Late transition.* Afterwards it progresses to skipped cycles, episodes of amenorrhea, and an increasing frequency of anovulatory cycles.

Menopausal transition.

- *Menstrual bleeding* – the transition is characterized by a gradual decrease in menstrual bleeding, however, some women experience heavy or prolonged bleeding, due to anovulatory cycles and prolonged exposure of the endometrium to unopposed estrogen.
- Women with obesity and uterine fibroids are also more likely to experience heavy bleeding.

Clinical picture

- **Hot flashes – 80 % of women**

❖Hot flashes are generalized, lasting 2-4 minutes, often associated with profuse perspiration, sometimes followed by chills, and a feeling of anxiety. Hot flashes usually occur several times per day.

❖Hot flashes are particularly common at night.

❖Hot flashes are mediated by thermoregulatory dysfunction at the level of the hypothalamus and are induced by estrogen withdrawal.

❖Estrogen administration restores the "thermoregulation" to normal and stops hot flashes.

Clinical picture

- Sleep disturbance
- Depression
- Cognitive changes (forgetfulness, difficulties with word retrieval, and "brain fog").
- Genitourinary syndrome of menopause (decreased vaginal lubrication and sexual dysfunction). Symptoms are responsive to estrogen therapy, in particular, vaginal estrogen therapy.

Long-term consequences of estrogen deficiency

- Bone loss (postmenopausal osteoporosis)
- Cardiovascular disease
- Skin changes
- Impaired balance
- Osteoarthritis (limited data)
- Body composition

Diagnosis

- In women over age 45 years the diagnosis of the menopausal transition or "perimenopause" is based upon a change in intermenstrual interval with or without menopausal symptoms
- A high serum follicle-stimulating hormone (FSH) concentration is **not** required to make the diagnosis.
- Menopause is diagnosed as 12 months of amenorrhea in the absence of other biologic or physiologic causes.

Diagnosis

- In women between the ages of 40 and 45 years the diagnosis of the menopausal transition or early menopause is the same as that for women over 45 years, except that other causes of menstrual cycle dysfunction must first be ruled out (eg, hCG, PRL, TSH).
- Women under age 40 years with a change in intermenstrual interval and menopausal symptoms should not be diagnosed with either the menopausal transition or menopause. They have primary ovarian insufficiency (premature ovarian failure).

DIFFERENTIAL DIAGNOSIS

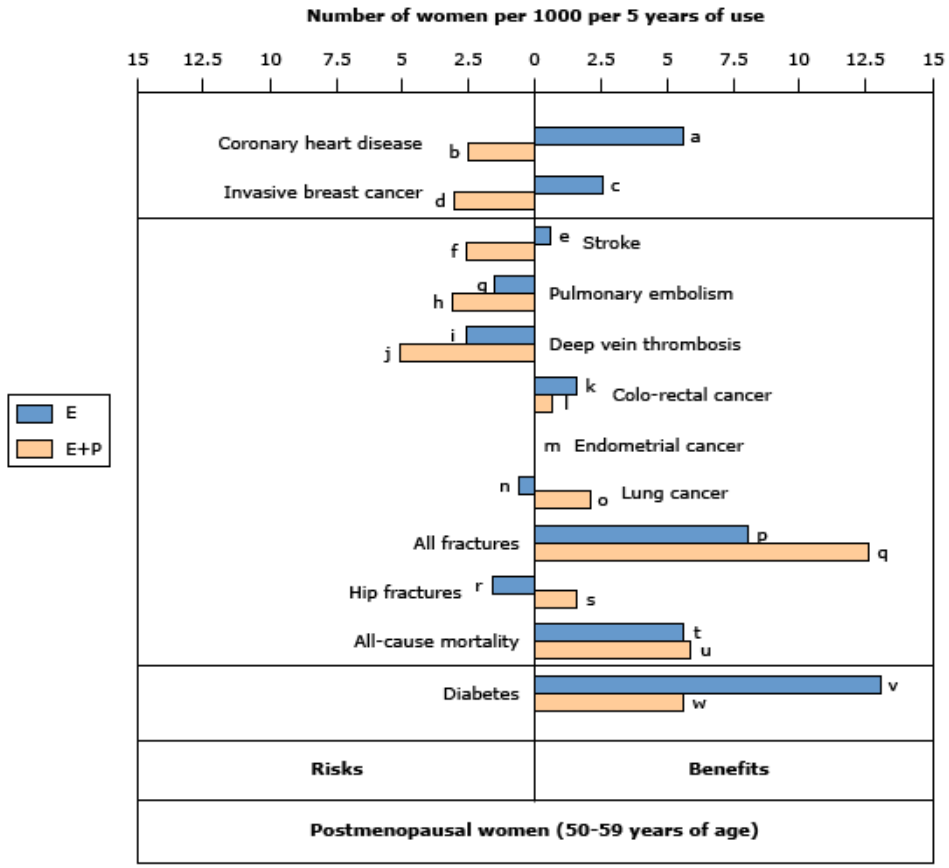
- Hyperthyroidism
- Pregnancy
- Hyperprolactinemia
- Pheochromocytoma
- Malignancy
- Medications (SSRI, tricyclics)

Treatment

Menopausal hormone therapy (MHT) –

- *Primary goal – to relieve vasomotor symptoms (hot flashes).* Other symptoms that respond to estrogen include sleep disturbances, depression/anxiety, and, in some cases, joint pains.
- MHT is suggested for healthy, peri/postmenopausal women with moderate to severe vasomotor symptoms impacting quality of life and who are within 10 years of menopause (or <60 years of age).
- For most women, the benefits of MHT outweigh the risks .

Risks and benefits of menopausal hormone therapy (MHT)



Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015.

Menopausal hormone therapy (MHT)

- Standard recommendations for duration of use are 3 – 5 years.
- All types and routes of estrogen are equally effective for hot flashes.
- *17-beta estradiol* is preferred over other estrogens (such as conjugated equine estrogens) because it is structurally identical to the main estrogen secreted by the ovary.
- The transdermal route is particularly important in women with hypertriglyceridemia, active gallbladder disease, or known thrombophilias.

Menopausal hormone therapy (MHT)

- For women with an intact uterus who are starting MHT and therefore require a progestin, *micronized progesterone* is a first-line progestin.
- It is effective for endometrial hyperplasia
- It is metabolically neutral
- It does not appear to increase the risk of either breast cancer or CHD.

Contraindications to MHT

- History of breast cancer
- CHD
- Previous VTE event or stroke
- Active liver disease
- Those at high risk for these complications.

Nonhormonal pharmacotherapy

- SSRIs (paroxetine, citalopram)
- Serotonin-norepinephrine reuptake inhibitors SNRIs (venlafaxine)
- Anti-epileptics (gabapentine)

Complementary and alternative therapies

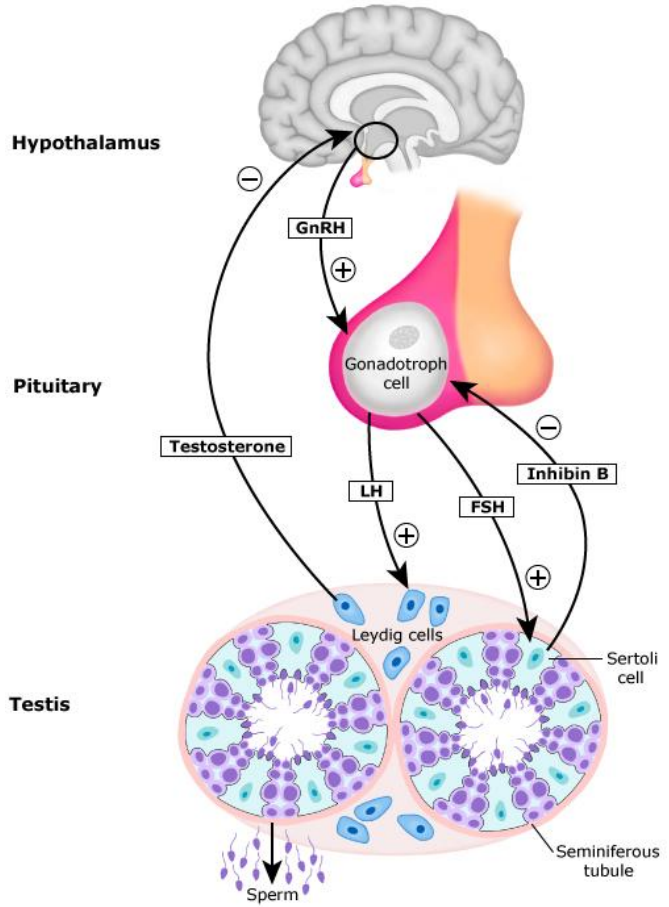
- **Plant based therapies** – phytoestrogens - found most in soybeans, chickpeas, and lentils, but also in flaxseed, grains, fruits, and vegetables.
- **Herbal therapies (***Cimicifuga racemosa***)**
- **Weight loss**
- **Cognitive behavioral therapy**

Male hypogonadism

Learning objectives

- Hypothalamic-pituitary-testicular axis
- Testosterone physiology and action
- Definition and causes of hypogonadism
- Diagnosis of hypogonadism
- Available treatments for hypogonadism
- Primary hypogonadism - Klinefelter Syndrome

Hypothalamic-pituitary-testicular axis



MECHANISMS OF TESTOSTERONE ACTION

testosterone	testosterone	testosterone
• Direct bind to androgen receptor (AR) • **Source:** testis, adrenals (small amount). • Daily production: 5-7 mg • Pulsatile secretion under LH control	• Conversion to **DHT** by **5-α reductase** • Binds to AR • **Role:** For action on external genitalia, prostate and sexual hair • **Source: extratesticular (most)** skin, liver, testis. • T:DHT=10-15:1	• Conversion to **estradiol** by **aromatase** • Binds to ER • **Source:** adipose tissue (most), skin, bone, brain, testis (20%). • **Role:** bone growth and density, body fat, sexual function.

Testosterone transportation

- 0.5-3 % is free (unbound)
- > 50 % bounds to albumin = bioavailable T (easily dissociates from A.)
- 44 % bounds to SHBG (NOT bioavailable, NOT active).

Androgen action in men

- Normal development of the fetal male phenotype during embryogenesis
- Regulation of gonadotropin secretion by the hypothalamic-pituitary system
- Stimulation of sexual maturation at puberty and maintenance during adulthood
- Initiation and maintenance of spermatogenesis
- Normal sexual function, including *normal libido, erectile function, and sexual satisfaction*

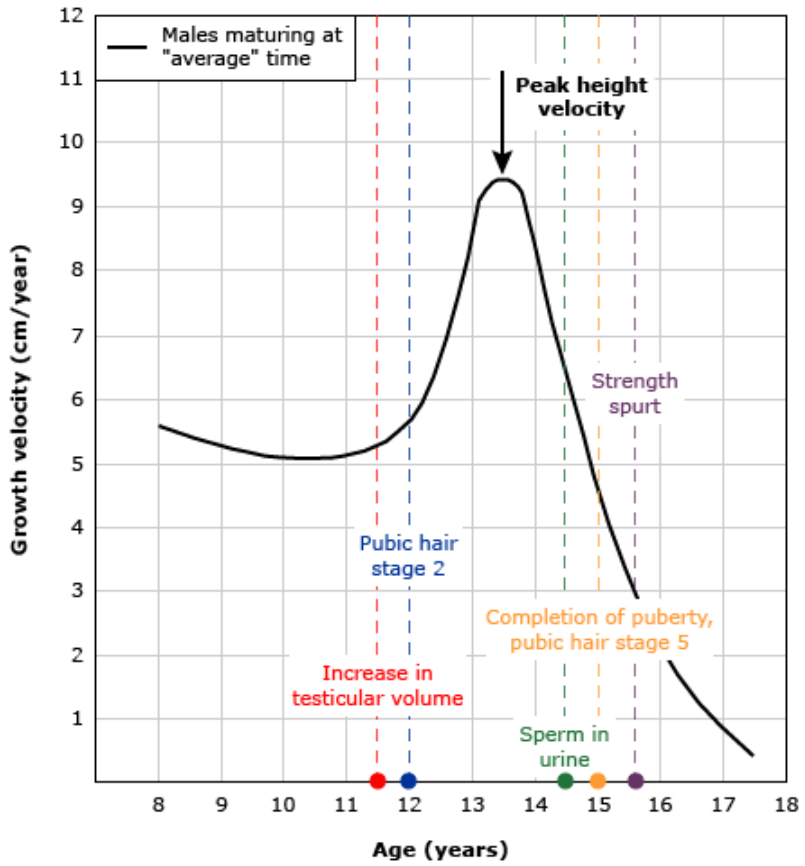
Androgen action in men

- Increasing muscle mass and bone mass at puberty and maintenance during adulthood
- Closure of long-bone epiphyses resulting in cessation of growth at puberty
- Maintenance of lower fat mass (compared with women and hypogonadal men)
- Increasing and maintenance of erythropoiesis and hematocrit

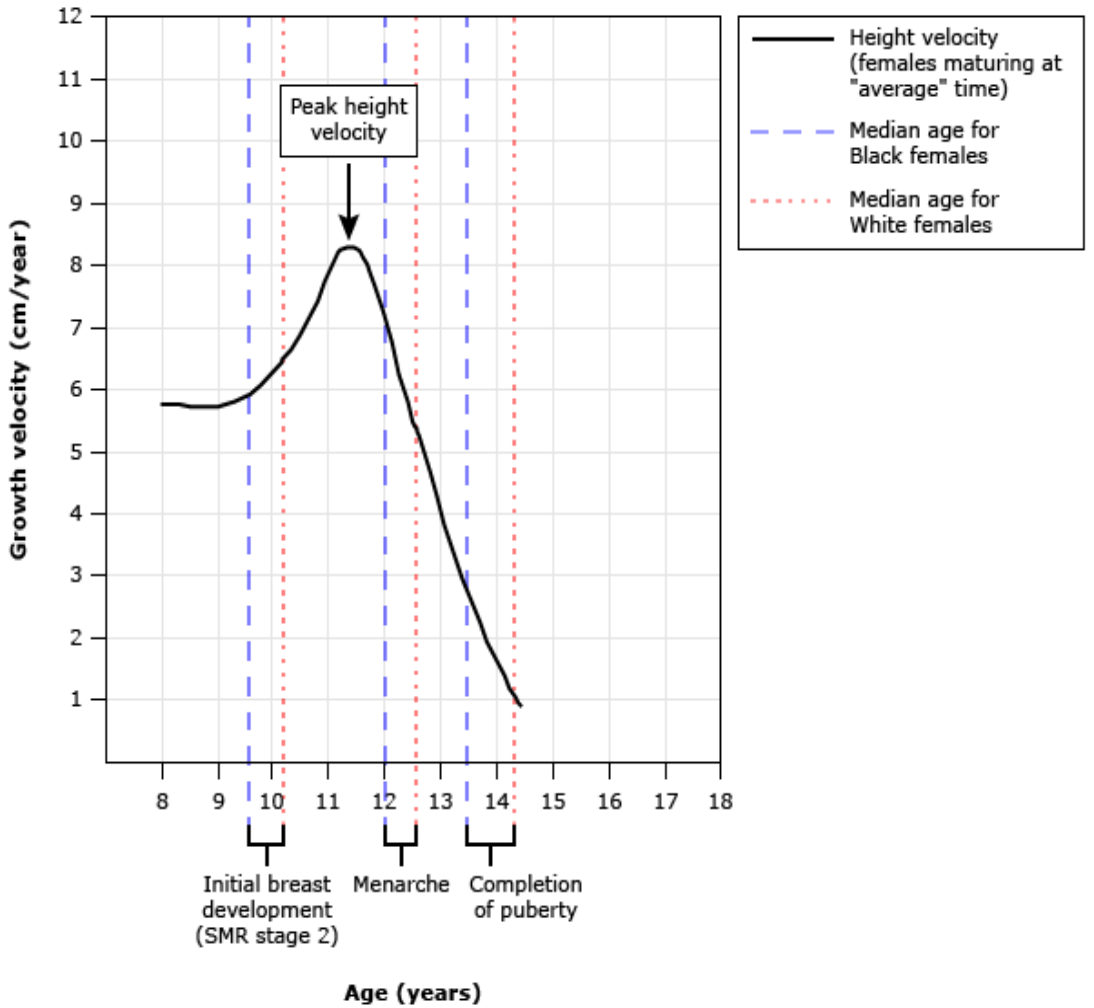
Structure of the testis

- *Interstitial compartment* - **Leidig cells** – testosterone.
- *Seminiferous tubule compartment* (80 - 90 % of testicular volume) – **Sertoli cells** – inhibin B and germ cells in various stages of spermatogenesis.

Prader orchidometer for measuring testicular size. Each bead is labeled with its volume, ranging from 1 to 25 mL. Prepubertal sizes are 1 to 3 mL, pubertal sizes are 4 to 12 mL, adult sizes are 12 to 25 mL.



Karpati AM et al, Stature and pubertal stage assessment in American boys: the 1988-1994 Third National Health and Nutrition Examination Survey. J Adolesc Health 2002; 30:205-12.



Data from: Biro FM, Huang B, Lucky AW, et al. Pubertal correlates in black and white US girls. J Pediatr 2006; 148:234, and from: Tanner JM, Davies PS. J Pediatr 1985; 107:317.

Male hypogonadism

Hypogonadism in a male refers to a decrease in one or both of the two major functions of the testes:

sperm production

or

testosterone production.

Causes of male hypogonadism

Primary hypogonadism (dysfunction of testes)

- **Congenital abnormalities:**

  Klinefelter syndrome

  Other chromosomal abnormalities

  Mutation in the FSH/LH receptor genes

  Cryptorchidism

- **Acquired diseases:**

  Radiation

  Alkylating agents

  Infections (mumps)

  Ketoconazole

  Environmental toxins

  Trauma, testicular torsion

  Autoimmune

  Chronic systemic illness (cirrhosis, chronic renal failure)

  Idiopathic

Secondary hypogonadism (hypothalamic/pituitary dysfunction)

- ***Congenital:***

Isolated GnRH deficiency

- Without anosmia
- Kallman syndrome
- Associated with adrenal hypoplasia congenita

GnRH deficiency associated with mental retardation/obesity

- Laurence-Moon-Biedl syndrome
- Prader-Wili syndrome

Idiopathic forms of multiple anterior pituitary hormone deficiencies

- ***Acquired:***

Tumors, head trauma, pituitary apoplexy

"Functional" gonadotropin deficiency

- Hypothyroidism, hyperPRLemia, diabetes, Cushing disease.
- Post-androgen abuse
- Drugs – marijuana, opioids, anabolic steroids, glucocorticoids

Clinical picture

- Failure to undergo or complete puberty
- Decrease in energy
- Decrease in libido
- Decrease in muscle mass
- Decrease in body hair
- Hot flashes
- Gynecomastia
- Infertility

Diagnosis

- A morning serum **total testosterone** 8 - 10 am.
- If a man is suspected of having an abnormality in testosterone binding to SHBG, measurement of *free testosterone by equilibrium dialysis* should be performed.
- The 2 most common situations of abnormal T binding :

✓Obesity – ↓ SHBG

✓Aging – ↑ SHBG

Diagnosis

- If the testosterone is subnormal, **it should be repeated**, and serum LH and FSH concentrations should be measured to distinguish primary from secondary hypogonadism.

- A semen analysis is also part of the evaluation of hypogonadism if the patient is pursuing fertility or has been diagnosed with infertility.

Diagnosis

- The patient has primary hypogonadism if T and/or the sperm count are below normal and the serum LH and/or FSH concentrations are ↑.
- The patient has secondary hypogonadism if the T and/or the sperm count are below normal and the serum LH and/or FSH concentrations are normal or ↓.

Additional tests

Possible causes:

- Ask and examine for clues to possible causes of hypogonadism (see the slide ‘causes of hypogonadism’)…
- Anosmia or hyposmia suggests Kallmann syndrome
- Peripheral vision abnormalities suggest a mass lesion in the pituitary gland or hypothalamus.

Additional tests

- Karyotype
- **Pituitary function testing (**cortisol at 8 AM and free thyroxine, prolactin**)**
- Pituitary MRI
- **Genetic testing (*ANOS1, KISS1R, GNRHR etc*)**

Differential diagnosis

Primary hypogonadism

- ❖A greater fall in sperm production than in testosterone secretion
- ➢The seminiferous tubules are damaged to a greater degree than the Leydig cells.
- ❖Associated with gynecomastia, because ↑ FSH and LH stimulate testicular aromatase, which increases the conversion of T to E.

Secondary hypogonadism

- ❖Similar decrease in sperm and testosterone production
- ➢ The primary reduction in LH secretion results in a ↓ in testicular testosterone production and, therefore, in intratesticular testosterone, which is the principal hormonal stimulus to sperm production.

Treatment

The following recommendations are consistent with the *Endocrine Society Clinical Practice Guidelines:*

Testosterone replacement therapy is recommended in men who are hypogonadal (clinical symptoms and signs consistent with testosterone deficiency and a subnormal morning (8 to 10 AM) serum testosterone concentration on **3 separate occasions.**

Choice of testosterone regimen

- **Transdermal** testosterone is recommended for most hypogonadal men, especially **a gel**, because it usually produces normal serum T and most patients find it the most convenient.

- Some men prefer **injections** of long-acting testosterone esters because of the freedom from daily application.

Choice of testosterone regimen

- **Oral** alkylated androgens (methyltestosterone) are associated with **adverse liver effects**.
- **Oral** testosterone undecanoate, a product that bypasses the first-pass hepatic effect, includes a boxed warning about possible **increases in BP and CV events** (MI, stroke).

Potential adverse effects

- Prostate cancer screening in men > 50 y.
- Benign prostatic hyperplasia (BPH)
- Erythrocytosis
- Venous thromboembolism
- Cardiovascular risks
- Skin irritation

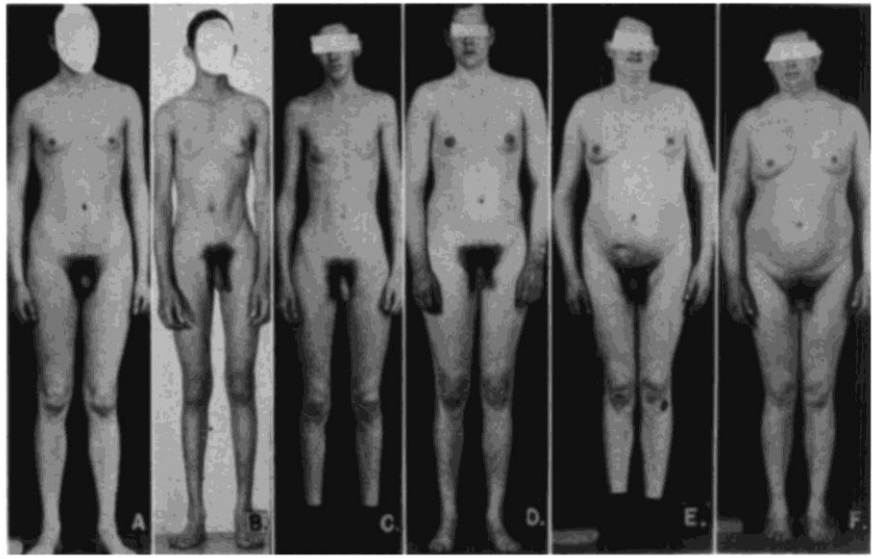
Contraindications to use

- Prostate cancer
- Breast cancer
- Hematocrit > 50 %
- Severe and untreated sleep apnea
- Uncontrolled heart failure

Klinefelter syndrome

- Klinefelter syndrome is the most common cause of primary hypogonadism.
- The prevalence of Klinefelter syndrome is 1 to 2.5 per 1000 boys and men (0.1 to 0.25 %).
- Only 25 to 50 % of patients with Klinefelter syndrome are diagnosed during their lifetimes.

Klinefelter syndrome



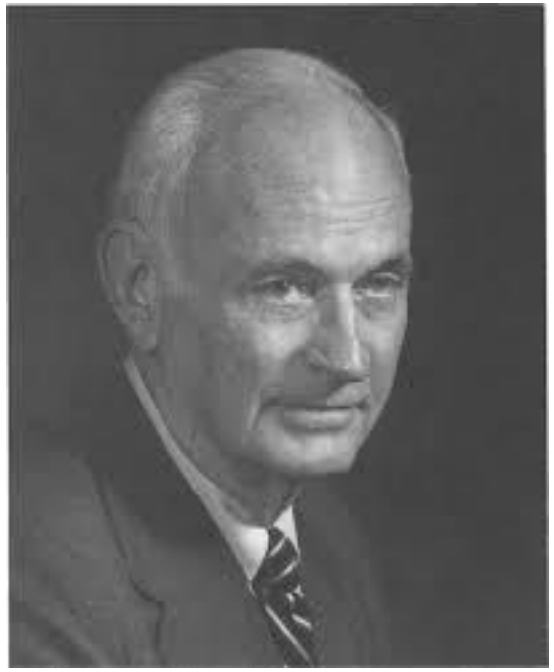


Fig. 1. MASCULINE BODY CONFIGURATIONS and relatively normal development of the accessory sexual organs, except for the breasts. A, *case 1; B, case 2; C, case* 3; D, *case 6; E, case 8; F, case* 9.
From: Syndrome Characterized by Gynecomastia, Aspermatogenesis without A-Leydigism, and Increased Excretion of Follicle- Stimulating Hormone. HARRY F. KLINEFELTER, JR., EDWARD C. REIFENSTEIN, JR., M.D. AND FULLER ALBRIGHT, M.D., November1942, The Journal of Clinical Endocrinology.

Pathogenesis

- Klinefelter syndrome results from supernumerary X chromosomes in an XY male ($X_{1+n}Y$).
- 80 - 90 % - 47,XXY. The extra X chromosome is due to maternal or paternal meiotic nondisjunction of the X chromosome during gametogenesis (ova or sperm production).
- 10 % have mosaicism (47,XXY/46XY) with 47,XXY present in some tissues and the normal karyotype in other tissues. Mosaic Klinefelter syndrome is due to post-fertilization mitotic nondisjunction during early fetal development.
- Very rarely, men may have more than two X chromosomes (eg, 48,XXXY).

Clinical picture

Children:

- Learning disability > 75 %
- Delayed speech development > 40 %
- Autism spectrum disorder 30-50 %
- Psychiatric disorder > 25 % (anxiety, depression)
- ↓ penis size 10 -25 %
- Cryptorchidism 25-40 %

Clinical picture

Puberty

- They do not begin or complete pubertal development :

✓failure of testes to grow normally

✓incomplete virilization (scant pubic and facial hair)

✓gynecomastia

✓tend to be taller than expected based on mid-parental height and have legs that grow out of proportion to arm length.

Clinical picture

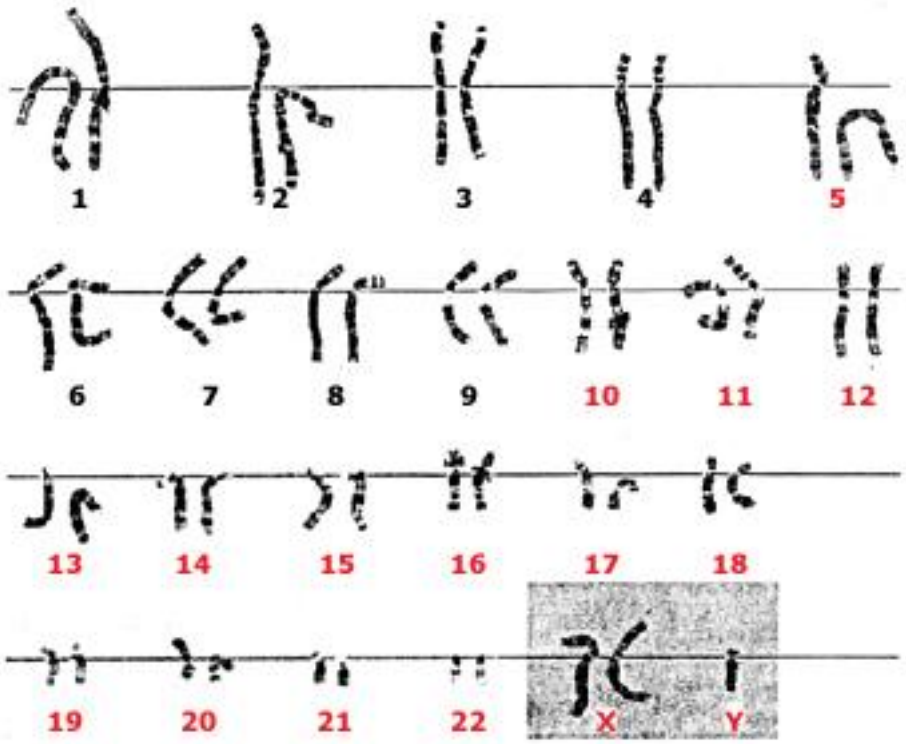
Adults

- ✓Infertility due azoospermia
- ✓Signs and symptoms of androgen deficiency (gynecomastia, sexual dysfunction, or osteoporosis).
- ✓Very small, firm testes (≤4 cc each) due to progressive fibrosis and destruction of both functional (steroidogenic and spermatogenic) compartments of the testes.

Morbidities in Klinefelter syndrome

- Metabolic syndrome 40-50 %
- Type 2 DM 10-40 %
- Osteoporosis 40 %
- Tremor (Parkinson-like syndrome) > 25 %
- Psychiatric disorder (anxiety and depressed mood) > 25 %

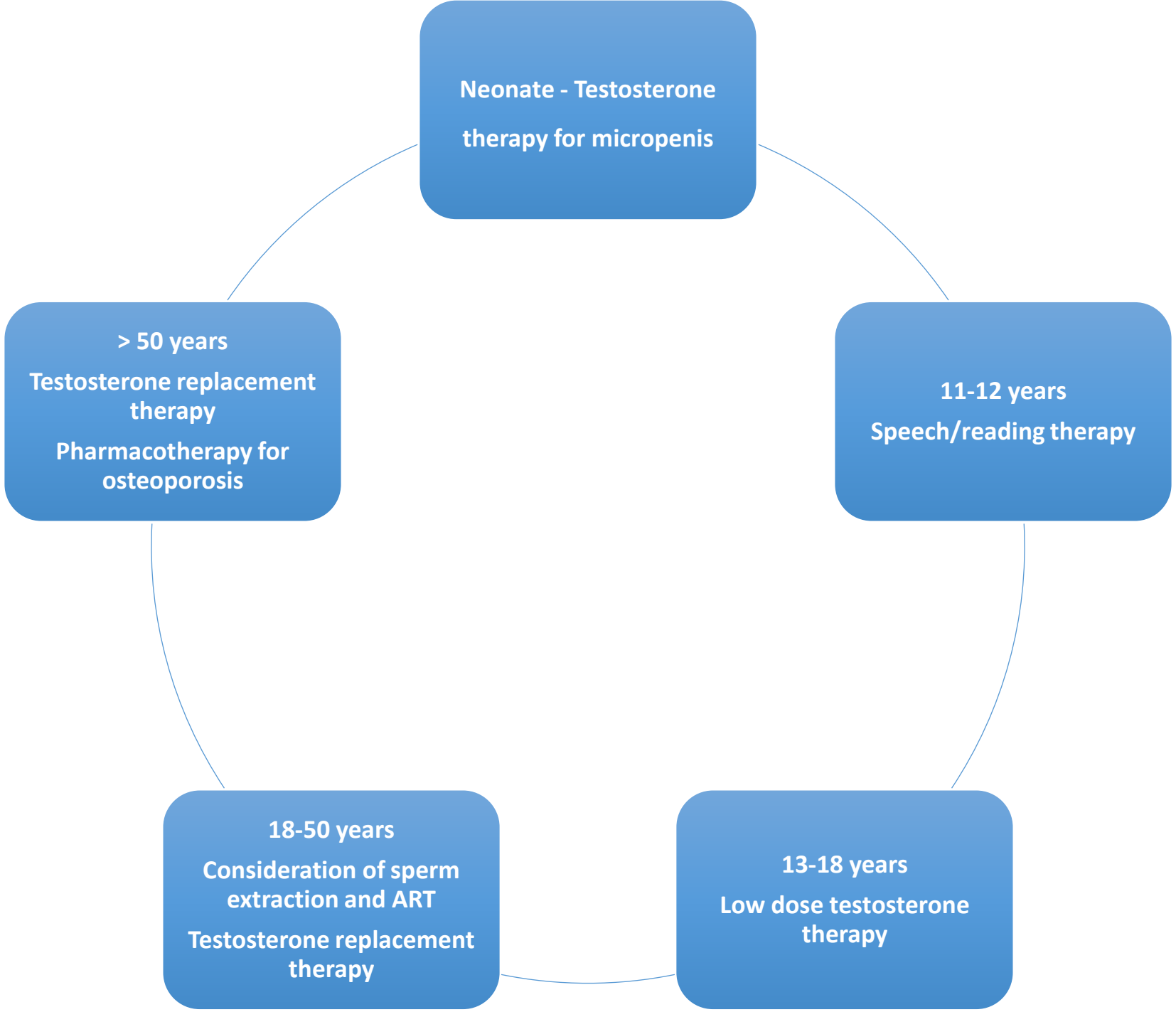
Diagnosis –
sex chromosome karyotyping of serum white blood cells



Management

➢ **Informing the patient and family about the diagnosis**.

- The diagnosis must be provided in a *sensitive* manner that discloses the *genetic* basis
- Inform that *it is not inherited*
- Say that is *no fault* of either parent or of the patient.
- Inform about potential consequences: a very high likelihood of *permanent androgen deficiency and infertility*.


Neonate - Testosterone
therapy for micropenis
11-12 years
Speech/reading therapy
13-18 years
Low dose testosterone therapy
18-50 years
Consideration of sperm extraction and ART
Testosterone replacement therapy
> 50 years
Testosterone replacement therapy
Pharmacotherapy for osteoporosis