A Rare case of Primary Amenorrhoea

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Definition

- **The absence of menses by 13 years of age when there is no visible development of secondary sexual characteristics or by 15 years of age in the presence of normal secondary sexual characteristics**

Magnitude of the Problem

- **Ovarian Failure** **36%**
- **Hypogonadotrophic Hypogonadism** **34%**
- **PCOS** **17%**
- **Congenital Lesions** **4%**
- **Hypopituitarism** **3%**
- **Hyperprolactinemia** **3%**
- **Weight related** **3%**

Differential Diagnosis of Primary Amenorrhoea with Presence of Secondary Sexual Characters

- **Constitutional delay**
- **Genitourinary Malformation i.e. imperforate hymen, absent vagina with or without functioning uterus**
- **Androgen Insensitivity**
- **Resistant ovary syndrome**
- **Pregnancy**

Differential Diagnosis with Absence of Secondary Sexual Characteristics

- **Hypothalamic disfunction i.e. chronic illness, anorexia nervosa, weight loss, stress**
- **Gonadotrophin deficiency i.e. Kallman's Syndrome**
- **Hypopituitarism**
- **Hyperprolactinemia**
- **Hypothyroidism**
- **Gonadal failure i.e. ovarian dysgenesis/agenesis, premature ovarian failure**

Pure Gonadal Dysgenesis

- **<u>DEFINITION:</u> Gonadal dysgenesis is defined as an incomplete or defective formation of the gonads, resulting from a disturbance in germ cell migration or organization, caused by structural or numerical sex chromosome abnormalities or mutations in the genes involved in formation of the urogenital ridge and sexual differentiation of the bipotential gonad**

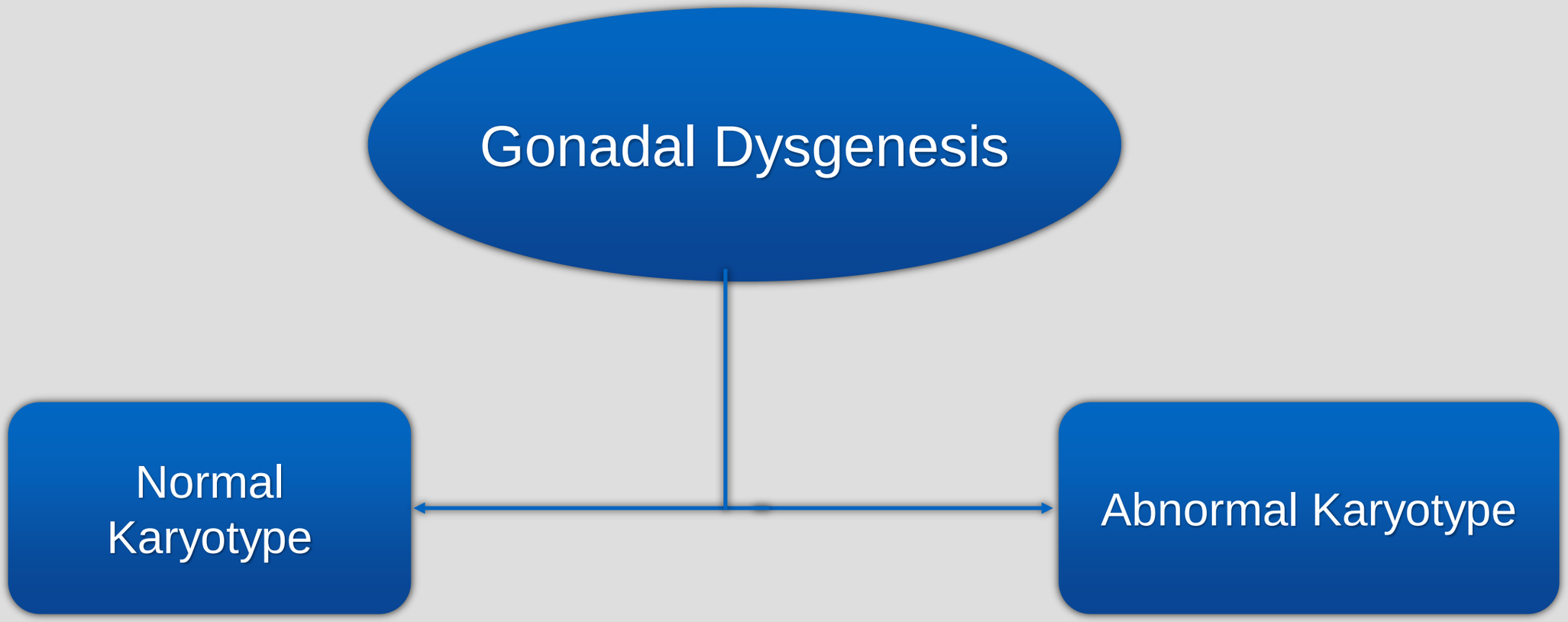
- **Individuals who are phenotypically female with sexual infantilism, primary amenorrhoea, normal stature, and no karyotypic abnormalities (46,XX or 46,XY) have pure gonadal dysgenesis**

- **The gonads are usually streaks, but there may be some development of secondary sexual characteristics, and a few episodes of uterine bleeding**

- **Due to the absence of ovarian follicles or their accelerated depletion the gonads contain only stroma and appear as fibrous streaks**

- **Approximately 25% of affected individuals have a normal 46,XX karyotype and may harbour a more subtle abnormality involving one or more specific genes on the X chromosome that are required for normal ovarian function**

CLASSIFICATION



(1/3 of chromosomal abnormality)

Normal Karyotype

1/3 of chromosomal abnormality

46 XX, 46XY female

Rarely single gene mutation - CYP gene mutation

Elevated ACTH

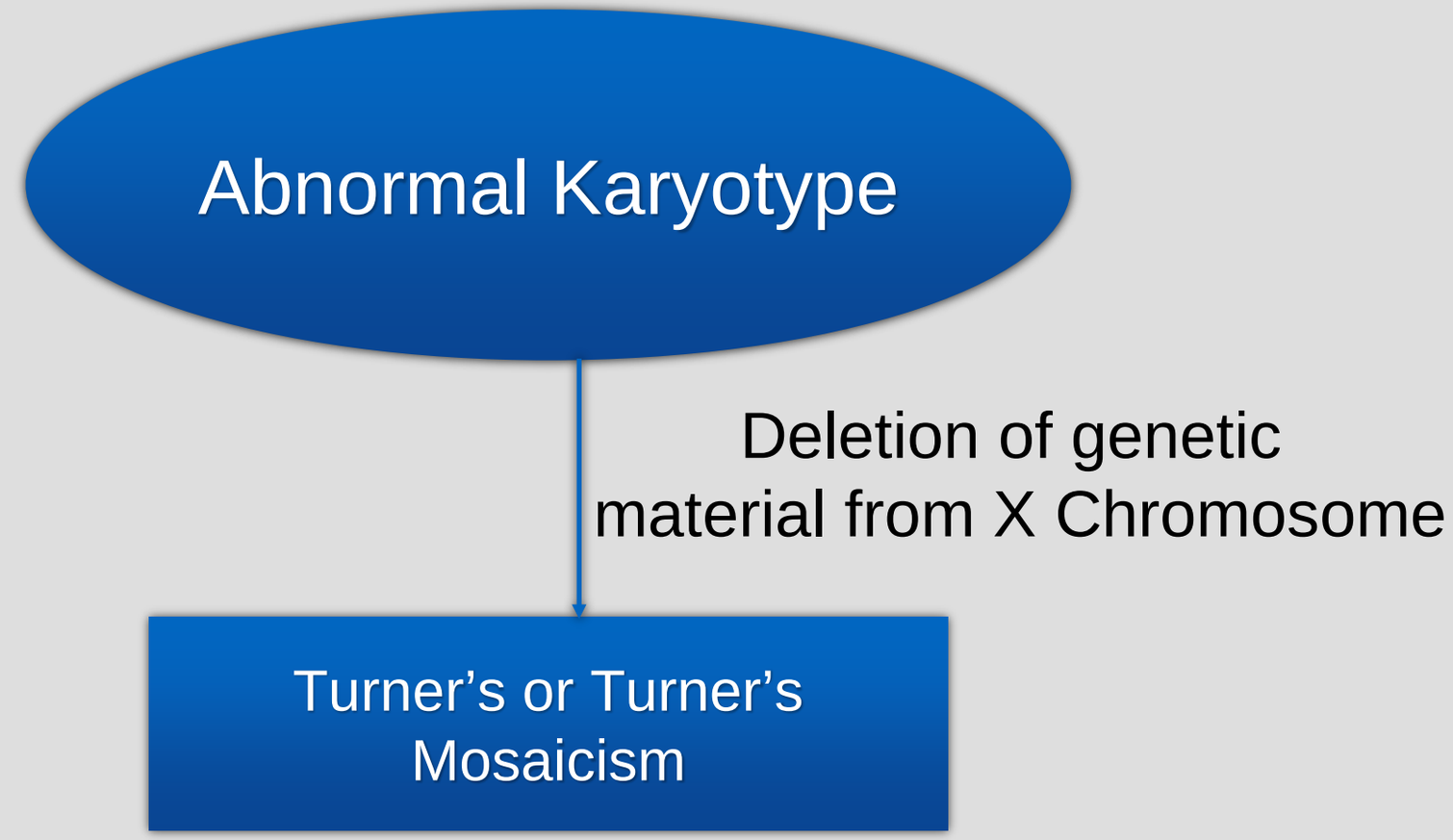
Mineralocorticoid secretion

(Hypokalemia)

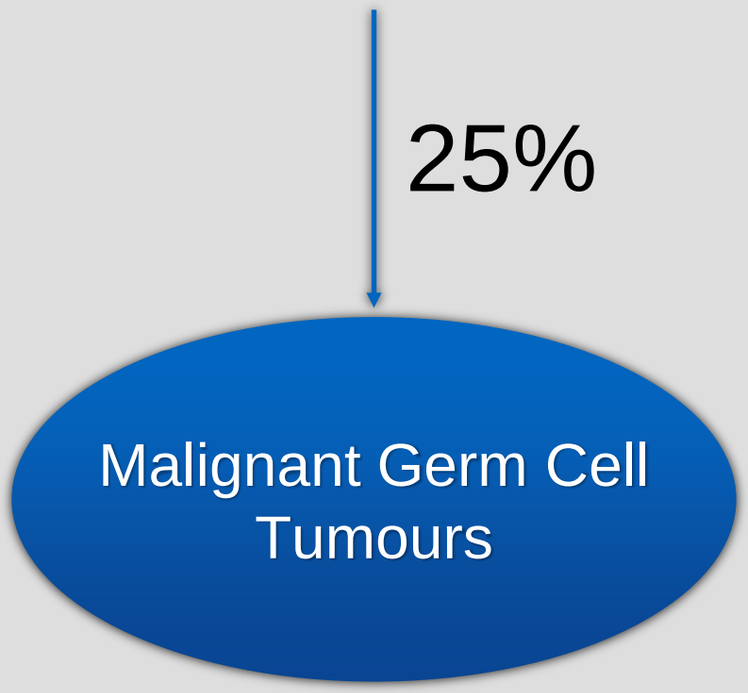
Decreased 17-Alpha Hydroxylase

Decreased production of cortisol, androgen, oestrogen

Mutations in LH & LSH receptors (OVARIAN RESISTANT SYNDROME)



Streak Gonad should be removed if Y chromosomal material is formed



Varieties of abnormal karyotype

	Classic Turner's	Turner Variant	True gonadal Dysgenesis	Mixed Dysgenesis
Phenotype	Female	Female	Female	Ambiguous
Gonad	Streak	Streak	Streak	-Streak -Testes
Height	Short/Normal	Short	Tall	Short
Somatic Stigmata	Classical	+/-	Nil	+/-
Karyotype	XO	XX/XO/Abnormal X	46 XX (Pure) 46 XY (Swyer)	XO/XY

Other Conditions

Constitutional Delay

- **In this condition, there is no anatomical abnormality and endocrine investigations show normal results**

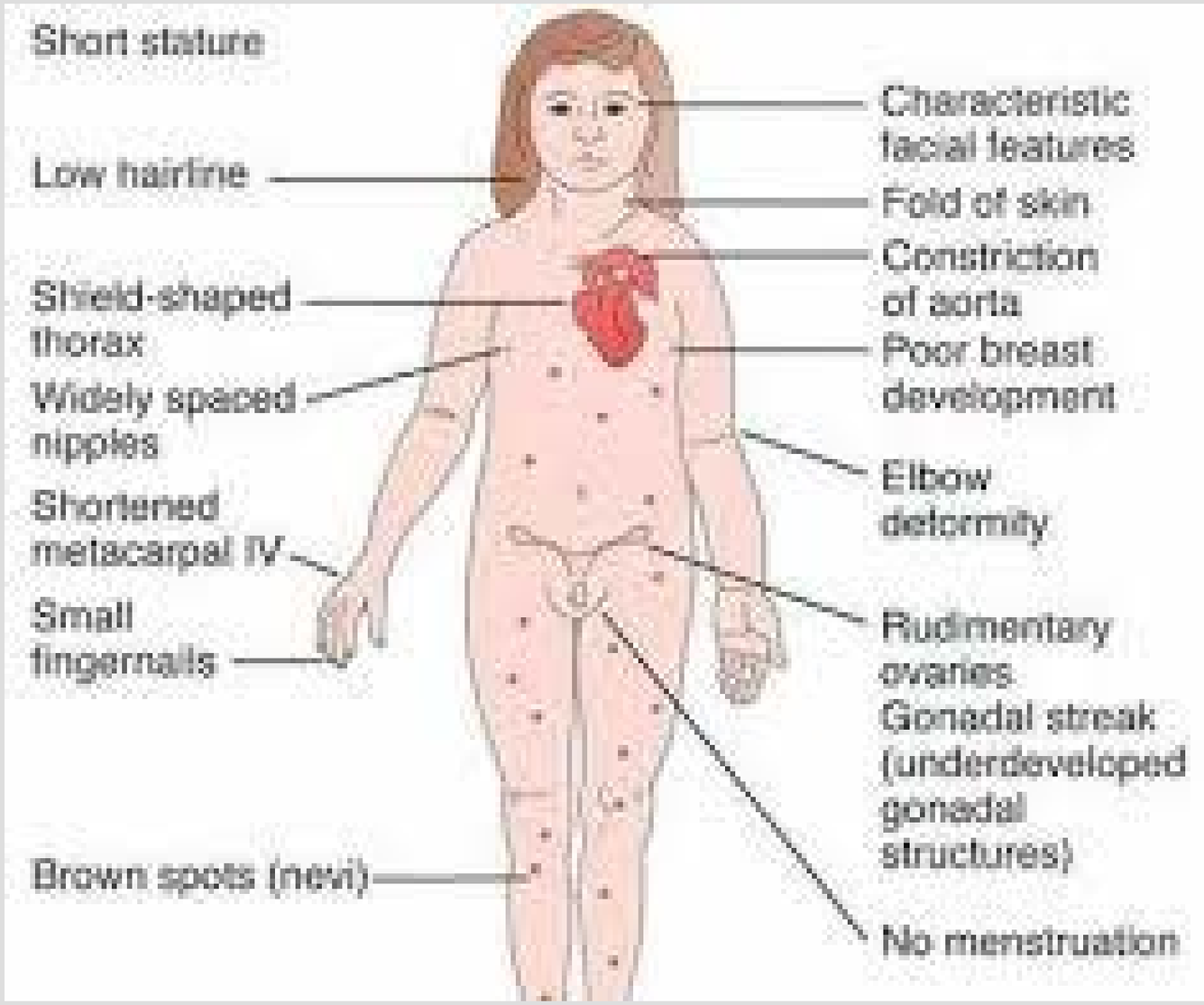
- **It is caused by immature pulsatile release of gonadotrophin-releasing hormone; maturation eventually occurs spontaneously**

Turner’s Syndrome

- **Caused by either a complete absence or partial abnormality of one of the two X chromosomes**

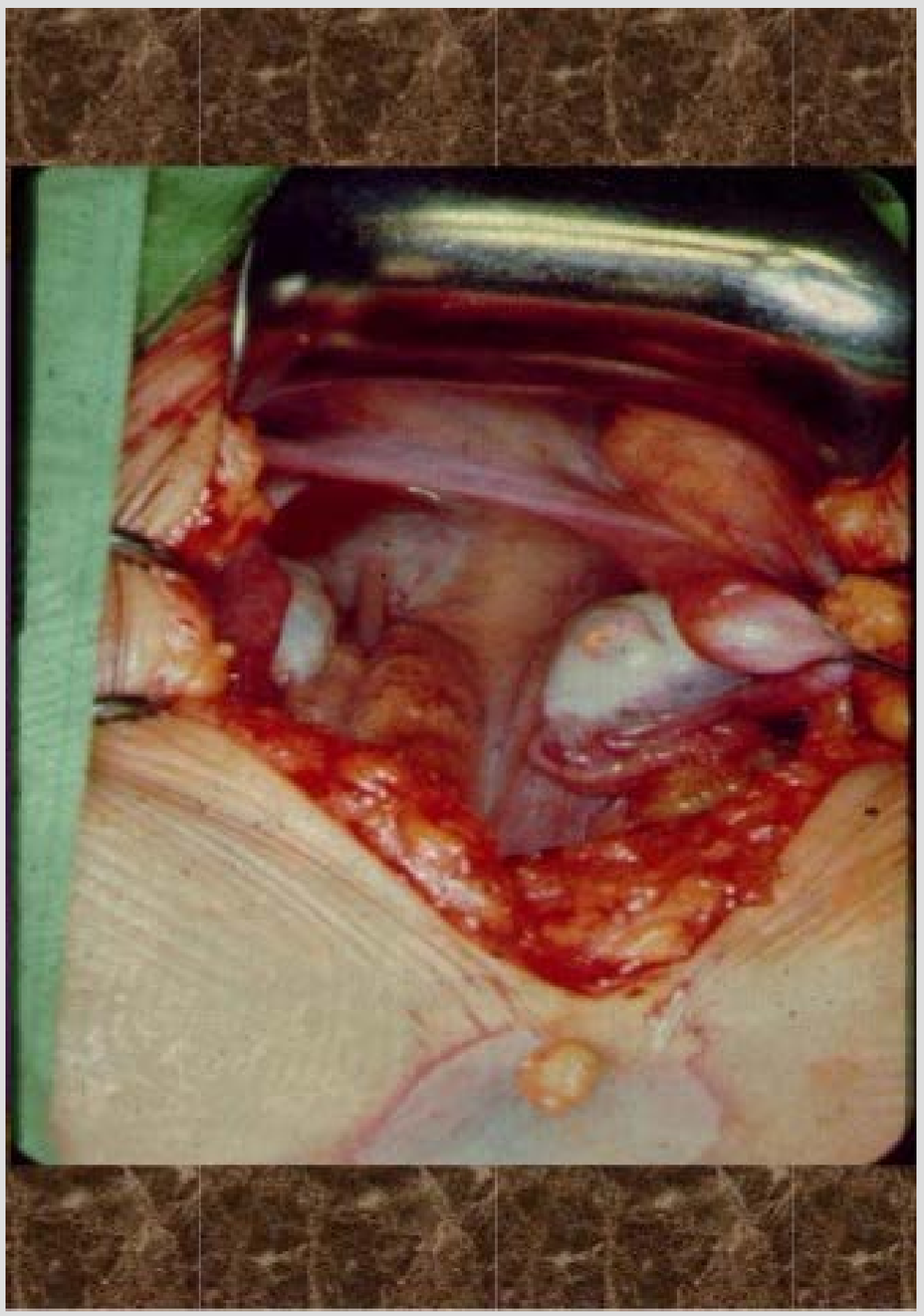
- **About 50% have mosaic forms such as 45X/46XX or 45X/46XY**

- **Features: Short stature, Webbed neck, Lymphedema, Shield chest with widely placed nipples, wide carrying angle, coarctation of the aorta, and Streak Ovaries**



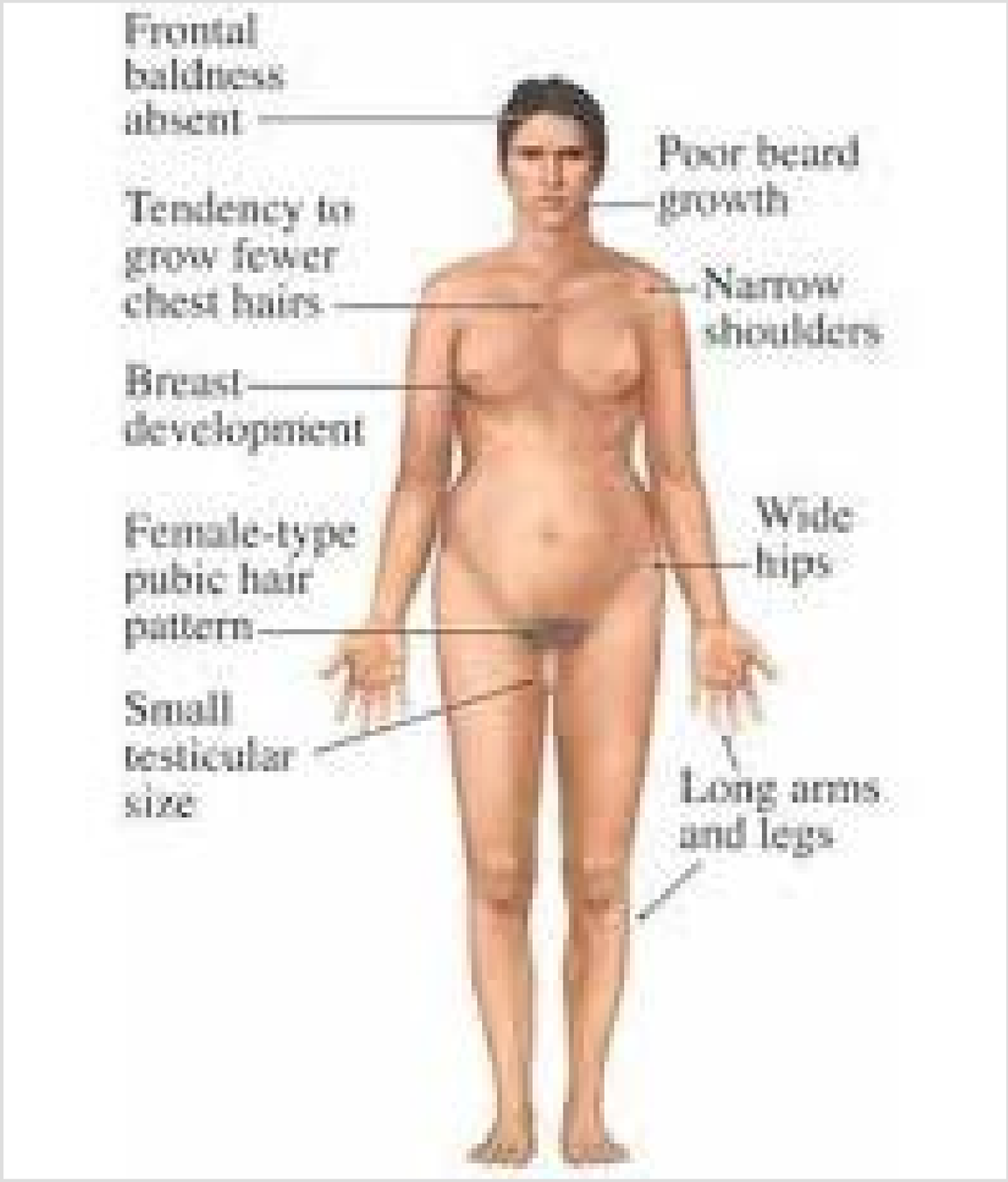
Uterovaginal Agenesis

- **15% of primary amenorrhoea**
- **Normal secondary development & external female genitalia**
- **Normal female range testosterone level**
- **Absent uterus and upper vagina & normal ovaries**
- **Karyotype 46 XX**
- **15-30% associated renal, skeletal, middle ear anomalies**



Androgen Insensitivity Syndrome

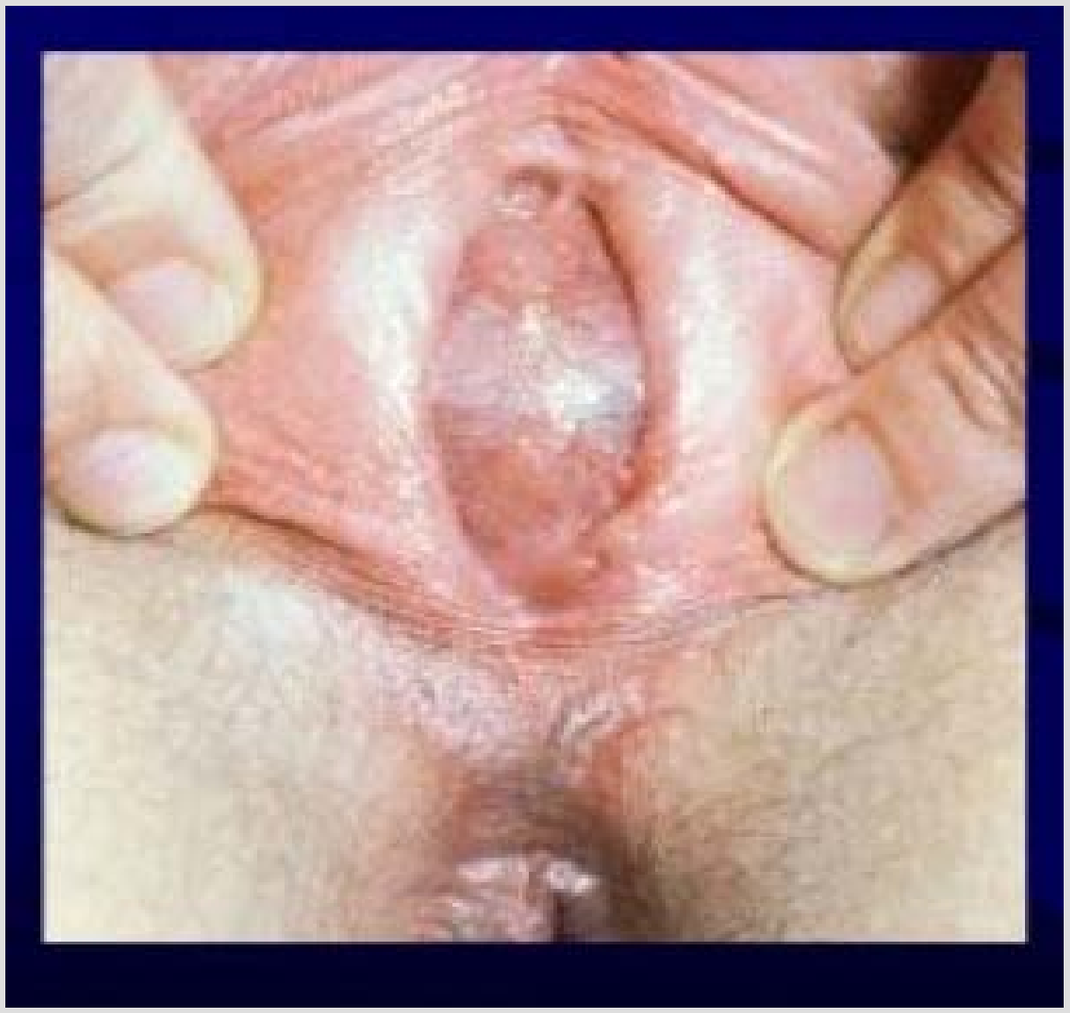
- **Formerly known as testicular feminisation**
- **46XY**
- **Failure of normal masculinisation of the external genitalia in chromosomal male individuals**
- **This failure of virilization can be either complete (CAIS) or partial (PAIS), depending on the amount of residual receptor function**
- **Affected individuals have normal ectopic testes with normal production of testosterone and normal conversion to dihydrotestosterone (DHT), which differentiates this condition from 5-alpha reductase deficiency**



Imperforate Hymen

- **Imperforate hymen represents the most common and most distal form of vaginal outflow obstruction**

- **The differential diagnosis of uterovaginal obstruction includes disorders of vaginal development, such as transverse vaginal septum or complete vaginal agenesis**



Ovarian Failure (Premature Menopause)

Ovarian Failure (Premature Menopause)

(Chromosomal abnormalities)

(Autoimmune Disease)

Age <30y, karyotyping done to rule out mosaicism

Screening for thyroid, parathyroid, and adrenal dysfunction

Autoimmune related Dysfunction

- **The most common association is with thyroid disease, but the parathyroids and adrenals can also be affected**

- **Several studies have shown laboratory evidence of immune problems in about 15-40% of women with premature ovarian failure**

- **In general, ovarian biopsy is not indicated in patients with premature ovarian failure since no clinically useful information will be obtained**

Assessment of Primary amenorrhoea

TSH, Prolactin, Estradiol, FSH, and PCT or ET

High/Low TSH

Thyroid Disorder

Hyperprolactinemia

Low Oestrogen Production

Normal Estrogen Production

Chronic Anovulation

High FSH

Ovarian Failure

Karyotype

FMR1

Anti-CYP21

Low/N FSH

MRI

Pituitary adenoma

Hypothalamic Amennorhoea

Investigations

Site of Disorder	Investigations
Hypothalamus	FSH, LH, estradiol, DHEAS
Pituitary	Prolactin, FSH, LH, estradiol
Ovarian	***FSH, LH, estradiol, Karyotype***
Mullerian Tract	Progesterone Challenge Test, Karyotyping
Genital Tract	FSH, LH, Estradiol, PCT, Examination

Pure Gonadal Dysgenesis

- **Gonads cannot produce oestrogen, preventing development of breasts, growth of uterus and menstruation**
- **Oestrogen may be given transdermally**
- **Likewise, progesterone must be prescribed as gonads cannot produce**
- **Conceiving children naturally does not occur in these patients**
- **Transfer of another woman’s embryo may be given as an option (Embryo transfer)**

Principles of Management of Primary Amenorrhoea

- **HRT (estrogen and progesterone) is given to restore normal menstrual function**
- **Also to prevent osteoporosis: atherogenesis**
- **Periodic progestogen should be taken by eustrogenic amenorrheic women (to avoid endometrial, breast, and ovarian cancer)**
- **If Y chromosome is present gonadectomy is indicated**
- **In case of streak ovaries, embryo transfer is advised**

Thank You