TOGIVEL

TEXTBOOK OF
OBSTETRICS AND GYNECOLOGY
INTERNET VIDEO EXPLAINED LECTURES

GYNECOLOGY

Amr Essam, MD

Senior consultant OBGYN
Former Associate Clinical Professor
Obstetrics & Gynecology
Ain-Shams University
Cairo, Egypt

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GYNECOLOGY

CHAPTER 1

PHASES OF LIFE

EMBRYO:

- Normal Sexual Differentiation and development
- Mullerian Development and Anomalies
- **Disorders of sexual development**

PUBERTY

- Normal Puberty
- **Precocious puberty**

REPRODUCTIVE YEARS

- **Steroidogenesis**
- **Hormones and Antihormone Therapy**
- **The Menstrual Cycle**

MENOPAUSE

- **Perimenopause and Menopause**

Chapter 1
PHASES OF LIFE
1.1
EMBYOLOGY: FEMALE SEXUAL DIFFERENTIATION

The sex of an individual is not a singular entity but is dependent on various factors.

• Chromosomal sex (Genetic sex) :	XX	XY
• Gonadal sex	OVARY	TESTIS
• Internal anatomical sex	Tu/Ut/Va	Ep/Va/Sem
• External anatomical sex	VULVA	Penis/Scrotum
• Hormonal sex **at puberty**	*Breast - Fat and hair distribution - Voice*	
• Sex of rearing	GIRL	BOY
• Gender role (Societal role):	WOMAN	MAN

a) Social gender (It includes all behavior with any sexual connotation, such as body gestures and mannerisms, habits of speech, and content of dreams)

b) Sexual orientation (homosexual / heterosexual)

1- Chromosomal Sex:

✓ The first determinant of sex is at fertilization.
✓ Fertilized egg normally will have XX or XY set of sex chromosomes.
✓ Up to 6 weeks intrauterine life the embryo is considered “indifferent embryo regarding gonads, internal and external genitalia.

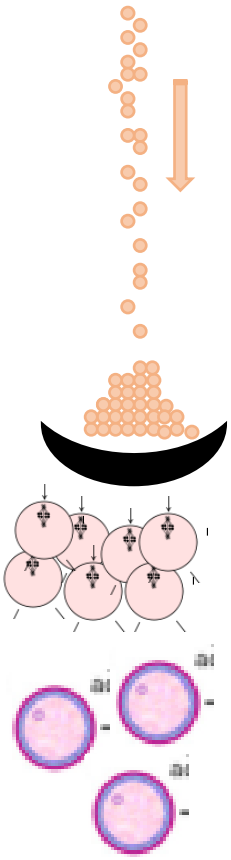
- At 6 weeks of gestation (4 weeks after ovulation) the gonads are indifferent but bipotential, possessing both cortical and medullary areas, and are capable of differentiation into either testes or ovaries. They are composed of:
  - Germ cells,
  - Special epithelia (potential granulosa/Sertoli cells),
  - Mesenchyme (potential theca/Leydig cells),
  - **Wolffian and müllerian ducts exist side by side;**
  - **External genitalia are undifferentiated.**

2- OVARIAN DIFFERENTIATION – Gonadal Sex

A complete 46XX chromosomal complement is necessary for normal ovarian development.
The second X chromosome, therefore, contains elements essential for ovarian development and maintenance.

Germ cells (endoderm) migrate from the yolk sac of the hindgut to reach the genital ridge (mesoderm) which will form the ovary (so the ovary –tissue, granulosa and theca cells- all is mesoderm except for the oocytes which are endodermal in origin)

At 3 weeks germ cells can be seen in the endoderm of yolk sac

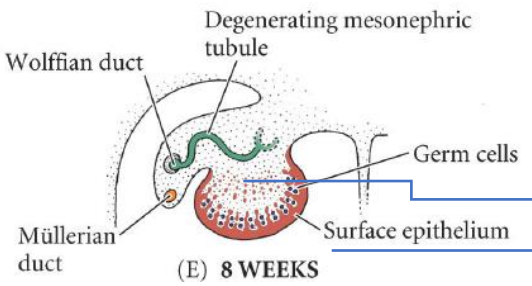


At 5 – 6 weeks germ cells start to migrate from endoderm of yolk sac to the genital ridge (future gonad)

Between 5 and 24 weeks, rapid mitotic expansion of primordial oogonia by mitotic division to reach peak number of 5–6 million at 20 weeks' gestation, followed by first meiotic division and subsequently meiotic arrest as primordial **oocyte** in the prophase of the first meiotic division until the primary oocyte (destined to ovulate) is subjected to the LH surge

The primordial **oocytes become** surrounded by flattened granulosa cells to form primordial **follicles**.

The first primordial follicle usually appears around 6 weeks intrauterine life, and the generation of primordial follicles is complete by about 6 months after birth (Resting pool). Degeneration (atresia) begins even earlier, and by birth, approximately 1–2 million germ cells remain. These have become surrounded by a layer of follicular cells, forming primordial follicles with oocytes that have entered the first meiotic division.



An out-growth from the surface epithelium into the substance of the ovary will form the sex cords, while some cells from the mesenchyme will form the sex stoma

The sex stroma will form the theca cells (as an outer layer)	The sex cords envelop the oocyte to form the granulosa cells

Female Genital Tract Anomalies

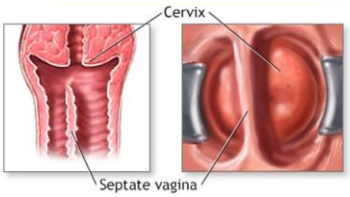
VAGINAL DEVELOPMENT DEFECTS

Failure of SINOVAGINAL BULBS DEVELOPMENT

Vaginal Aplasia

Failure of SINOVAGINAL BULBS FUSION

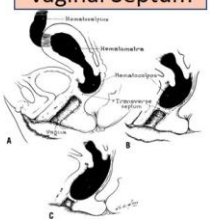
Longitudinal Vaginal Septum



Failure of SINOVAGINAL BULBS CANALISATION

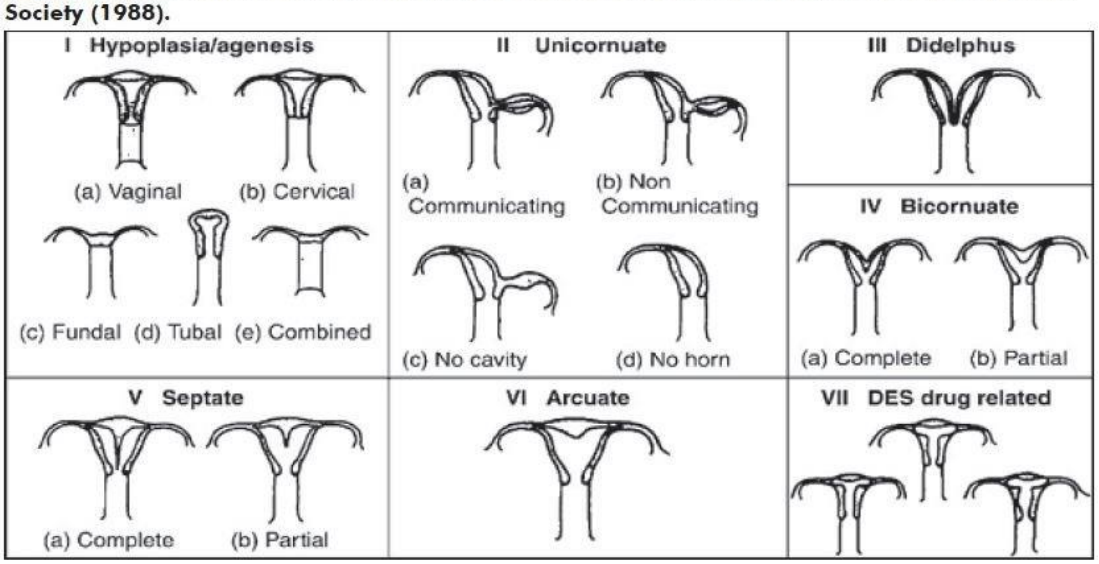
Complete ➔ Vaginal Aplasia

Partial ➔ Transverse Vaginal Septum



American fertility Society Classification of Female Genital Tract Anomalies

Figure 2. Classification of congenital uterine anomalies as described by the American Fertility Society (1988).



I. Segmental müllerian hypoplasia or agenesis
- a. Vaginal
- b. Cervical
- c. Uterine fundal
- d. Tubal
- e. Combined anomalies

II. Unicornuate uterus
- a. Communicating rudimentary horn
- b. Noncommunicating horn
- c. No endometrial cavity
- d. No rudimentary horn

III. Uterine didelphys

IV. Bicornuate uterus
- a. Complete—division to internal os
- b. Partial

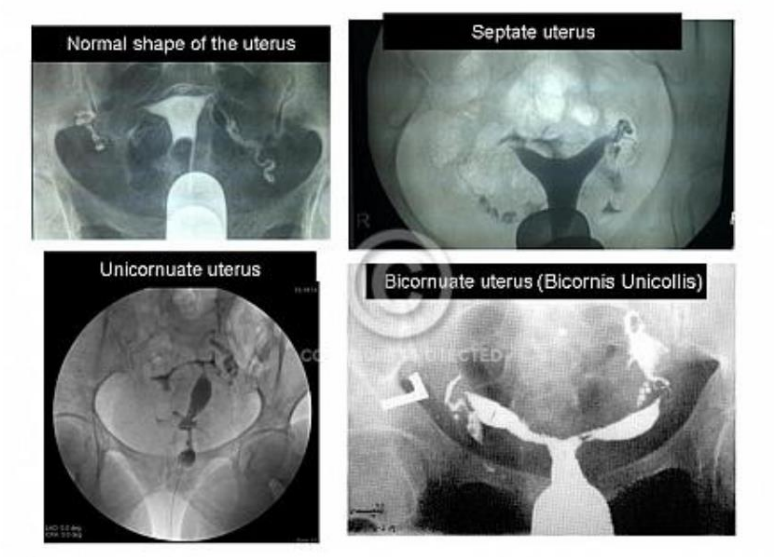
V. Septate uterus
- a. Complete—septum to internal os
- b. Partial

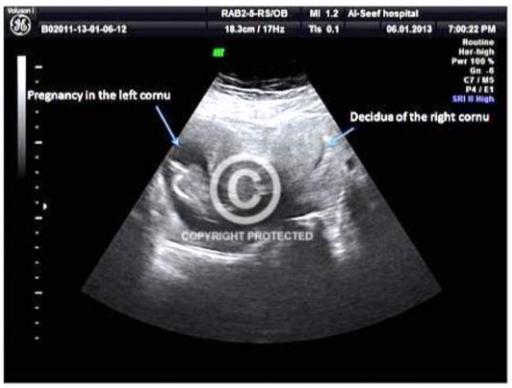
VI. Arcuate

VII. Diethylstilbestrol related

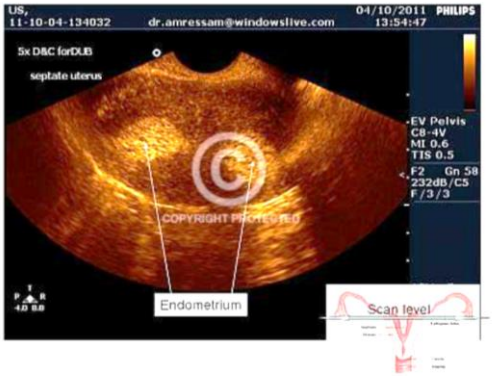
Adapted from the American Fertility Society, 1988.

Images from obgynegy gallery
www.obgynegy.com/gallery



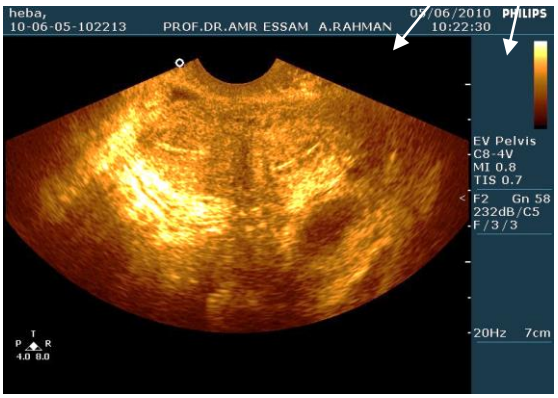


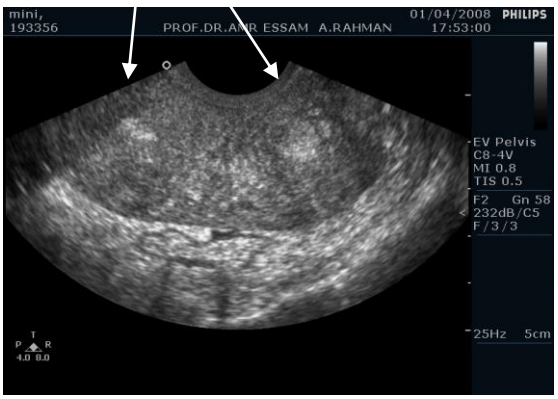
Bicornuate gravid uterus



Septate uterus

SEPTATE UTERUS





Disorders of sexual development:

- **Intersex** is a condition of imperfect sexual differentiation into either male or female.
- *It is a relative term because no human being is completely male or female. Each carries the rudiments of the sexual apparatus of the other; many men are slightly effeminate and many women slightly masculine in bearing and outlook.*
- **Gender identity** is determined by the genetic, gonadal, and phenotypic sex, social mores and environmental upbringing.

- Occasionally, there is discordance between sex and gender, as well as the elements of sex/gender.
- **Classification of DSDs according to Karyotype**

1. **Not 46XX or 46XY - Sex chromosome DSD**
    1. 45 X0 – Turner - 45X0/46XX mosaic Turner
    2. 47 XXY Klinefelter
    3. 45 X, 46 XY – Mixed gonadal dysgenesis, ovitesticular DSD **(True hermaphrodite)**
2. **46 XY DSD**
    1. Disorder of testicular development
        1. Complete gonadal dysgenesis **(XY sex reversal)**
        2. Partial Gonadal dysgenesis
    2. Disorders of Androgen Synthesis/action **(Male pseudohermaphrodite)**
        1. Androgen biosyntheis defect
        2. Androgen action defect
        3. LH receptor defect
        4. Disorders of AMH/AMH receptors
    3. Other
        1. Severe hypospadius
        2. Cloacal-extrophy
3. **46 XX DSD**
    1. Disorders of gonadal development
        1. Ovitesticular DSD **(True hermaphrodite)**
        2. Testicular DSD **(XX Male)**
        3. Gonadal dysgenesis
    2. Androgen excess **(Female pseudohermaphrodite)**
        1. Fetal 21 or 11 hydroxylase deficiency
        2. Fetoplacental aromatase deficiency
        3. Maternal lutoma or exogenous androgen
    3. Others
        1. Cloacalextrophy
        2. Murcs

Disorders of sexual development

Normal Sex Chromosome DSDs - 46 XY DSDs AND 46 XX DSDs

46 XY with Defective OF AMH/TESTOSTERONE

COMPLETE ANDROGEN INSENSITIVITY

- Unlike previous conditions the defect here is not testosterone synthesis, the defect being androgen receptor insensitivity

•Chromosomal sex is XY,

•Gonads are testes.

•AMH => regression of Mullerian

•Testosterone insensitivity => No wollfian

•Testosterone insensitivity => Female external genitalia.

- Hormonal influence is un-opposed oestrogenic female secondary sexual characters• Phenotypic female: Female distribution of fat and female voice• Good breast development• No body hair (hairless female) except scalp• External genitalia female but infantile
- Vagina absent or blind pouch but normal vulva• Internal gonads usually undescended testes - Uterus and tubes absent (due to AMH from testes)

Differential Diagnosis: Mullerian agenesis - NOT a disorder of sexual development

- **Mayer-Rokitansky-Küster-Hauser syndrome**
- Female 46XX, with Mullerian agenesis

•Chromosomal sex is XX,

•Gonads are Ovaries.

• Mullerian fails to develop

•No Testosterone => No wollfian

•No Testosterone => Female external genitalia.

•Hormonal influence: oestrogenic female secondary sexual characters

•This is the DD of Complete Androgen Insensitivity.

- Both present as primary amenorrheic female with absence of internal genitalia.
- MRKH is subdivided into two types:
  - Type 1, in which only the structures developing from the Müllerian duct are affected (the upper vagina, cervix, and uterus).
  - Type 2, where the same structures are affected, but is characterized by the additional malformations of other body systems most often including the renal and skeletal systems. MRKH type 2 includes MURCS (Müllerian Renal Cervical Somite).

Disorders of sexual development

DSD with Birth Assignment Female
Clinical Presentation at puberty

BIRTH ASSIGNEMNT	PROBLEM START	PROBLEMIS	KARYOTYPE	GONAD	INTERNAL GENITALIA	PATHOPHYSIOLOGY
FEMALE	AT PUBERTY	VIRILISM	46XX 46XX/46XY	OVOTETIS	Variable	SEX CHROMOSOME DSD
	AT PUBERTY	VIRILISM	46XY	CRYPTORCHOID TESTIS	WOLFFIAN HYPOPLASTIC	gonadotropin resistant testes Partial androgen insensitivity
	AT PUBERTY	VIRILISM	46XY	CRYPTORCHOID TESTIS	WOLFFIAN	5 alpha reductase deficiency
	AT PUBERTY	VIRILISM	46XY	CRYPTORCHOID TESTIS	FEMALE	DEFECTIVE ANDROGEN SYNTHSIS
	AT PUBERTY	VIRILISM	46XX	OVARY	FEMALE	CAH
FEMALE	AT PUBERTY	PRIMARY AMENORRHEA + Absent secondary sexual ccc	45XO 46XY (Swyer Syndrome) 45XO/46XX 45XO/46XY 46Xxf 46XX/45XO	STREAK	FEMALE	GONDAL AGENESIS
			46XX	OVARY	FEMALE	AROMATASE DEFICIENCY
	AT PUBERTY CBP	oligomenorrhoea, 2RY amenorrhoea, infertility, premature menopause	47XXX	OVARY	FEMALE	SEX CHROMOSOME DSD
	AT PUBERTY	**Primary amenorrhea + Well developed secondary sexual ccc**	46XY	TESTIS (MAY BE PALPABLE)	NON	COMPLETE ANDROGEN INSENSITIVITY
	AT PUBERTY		46XX	OVARY	NON	MULLERIAN AGENESIS

Endocrinology of Puberty
1- Adrenarche:

Adrenal cortex zonation (differentiation of adrenal cells and changes in steroid biosynthesis) and growth of the zona reticularis increases with age => gradual increase in Adrenal androgens production (androstenedione, DHEA, and DHEAS).

The GH – IGF-1 axis and hormones related to body mass, such as insulin and leptin, have been suggested as modulators of this multifactorial event of adrenal growth and adrenarche.

The onset of DHEA and DHEA-S production from the adrenal zone reticularis leads to the phenomenon of **adrenarche which** precedes The onset of puberty.

Appearance of body odour, and pubic and axillary hair.

It is now evident that the adrenache and puberty events are independent processes.

Endocrinology of Puberty
2- GnRH and GnH

Central and peripheral signals regulate GnRH secretion

Peripheral Signals regulating GnRH: Body mass and composition through hormones related to body mass as GH – IGF-1 axis and,insulin and **leptin**

Central Signals regulating GnRH:
- Gene expression regulartors
- Kisspeptide system
- Glial network integration
- Gonadotropin-inhibitory hormone (GnIH)

Normal Sexual Differentiation

Normal body composition

Normal Sleep and stress level

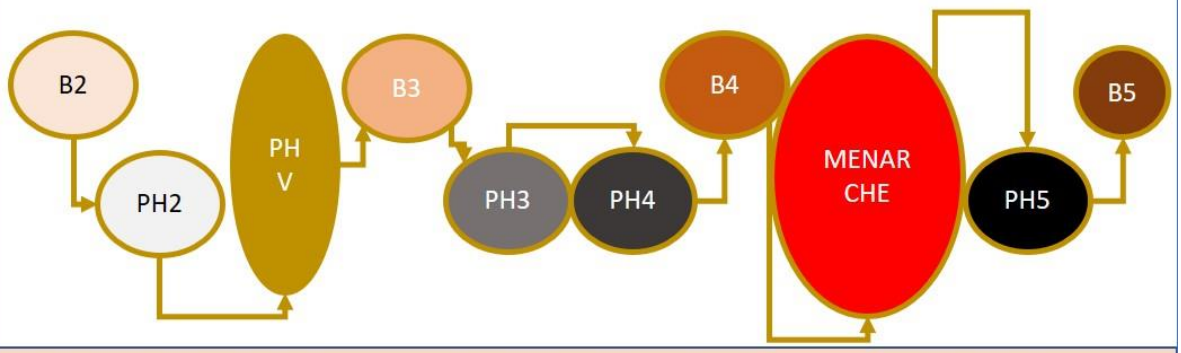
Normal Puberty

Emotional stress can lead to inhibition of the GnRH axis. CRH itself is known to inhibit GnRH

Melatonin is implicated in disorders of the hypothalamic-pituitary-gonadal axis. Specifically, delayed puberty, precocious puberty, and hypothalamic amenorrhea all seem to have a direct link to altered plasma melatonin profiles

NORMAL PUBERTY

The usual sequence of the physiologic events of puberty



Menarche may occur before the appearance of axillary or pubic hair in 10% of normal females.

Normal puberty occurs over a wide range of ages

Breast development – Tanner Staging of Thelarche

Stage 1 (B1)	Preadolescent: elevation of papilla only
Stage 2 (B2)	Breast bud stage: elevation of breast and papilla as small mound enlargement of areolar diameter
Stage 3 (B3)	Further enlargement and elevation of breasts and areola, with no separation of their contours
Stage 4 (B4)	Projection of areola and papilla to form a secondary mound above the level of the breast
Stage 5 (B5)	Mature stage: projection of papilla only, owing to recession of the areola to the general contour of the breast

Asymmetry in breast development is common and best left to observation until complete breast development occurs (usually by 16–18 years of age), however, one must consider the possibility of developmental asymmetry, which may be indicative of breast tissue estrogen insensitivity or prior trauma

PRECOCIOUS PUBERTY
Classification - Etiology

- **GnRH independent Incomplete Precocious Puberty**
  - Isolated
    - Premature thelarche
    - Premature Adrenarche
    - Premature Pubarche
  - No Advanced bone age
- **GnRH Dependent True Precocious Puberty**
  - Premature GnRH axis maturation
    - Idiopathic
    - CNS disease Trauma Infection Tumour
    - Hypo-Thyroidism
    - Syndrome → GnRH
  - Feminization
  - Advanced bone age Except Hypothyroidism
- **GnRH independent Pseudo Precocious Puberty**
  - No Premature GnH axis maturation
    - **Isosexual = Feminization**
      - Estrogen Excess
      - Ovarian cyst / Tumour /
      - Mc Cune Albright Syndrome
      - 
      - Feminization
      - Advanced bone age Except Hypothyroidism
    - **Heterosexual = Virilization**
      - Androgen Excess
      - Adrenal Tumor / CAH
      - Virilizing Ovarian Tumor
      - 
      - Virilization
      - Advanced bone age Except Hypothyroidism

PRECOCIOUS PUBERTY

GnRH independent precocious puberty

Incomplete Precocious Puberty

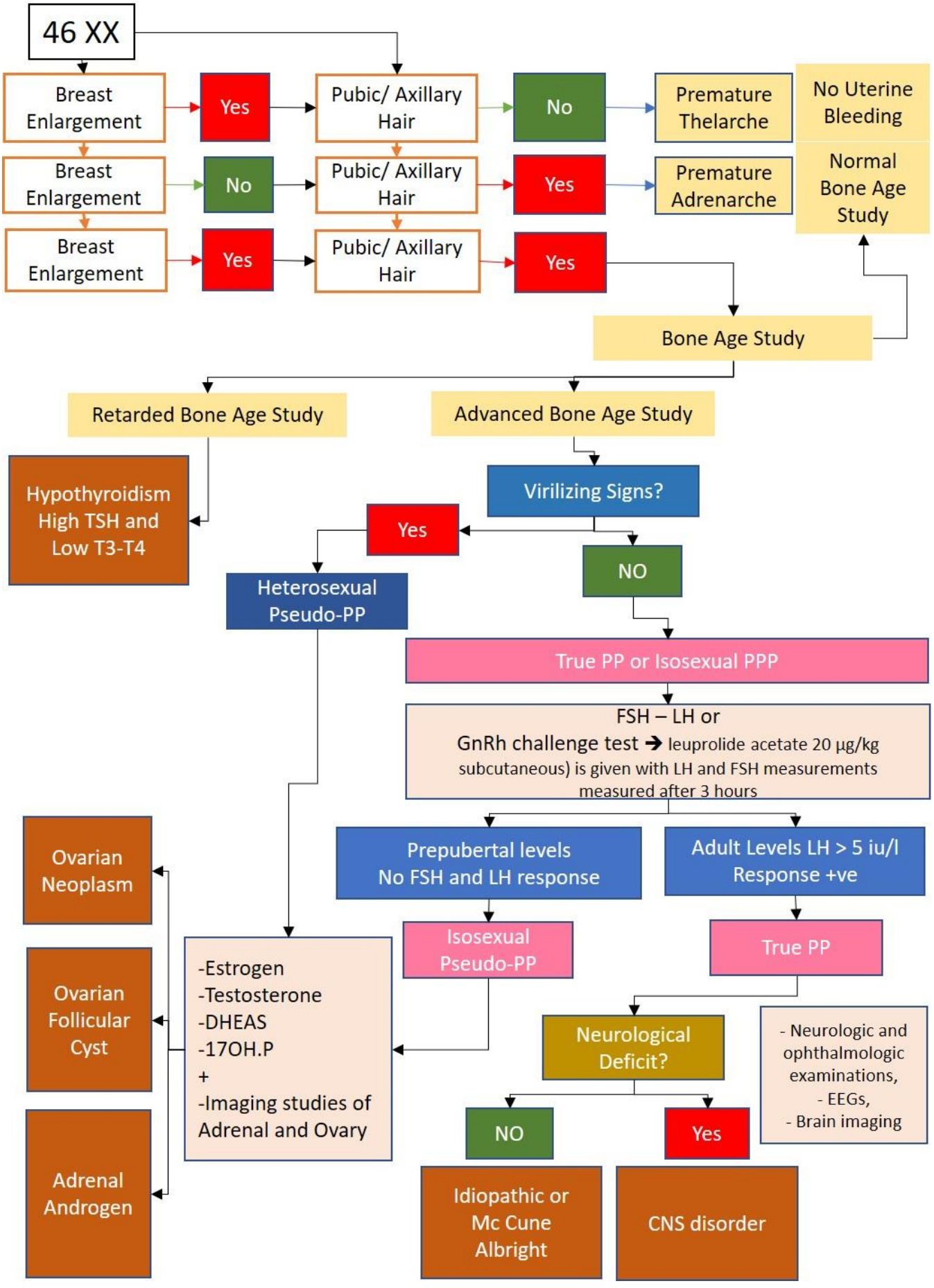
Premature Thelarche

- Isolated unilateral or bilateral breast development as the only sign of secondary sexual maturation.
    - It is not accompanied by other pubertal changes, such as axillary or pubic hair or changes in vaginal epithelium.
    - Estrogen levels are normal prepubertal
    - It is associated with normal linear growth and a normal bone age.
- The cause of premature thelarche is not understood.
- Breast hyperplasia is a normal physiologic phenomenon:
    - Neonatal period up to 6 months of age.
    - Within the first 2 years,
    - Between ages 6 and 8.
- Nipple development is absent.
- Often, the breast enlargement spontaneously regresses.
- It is important to observe these children closely for other signs of precocious puberty.

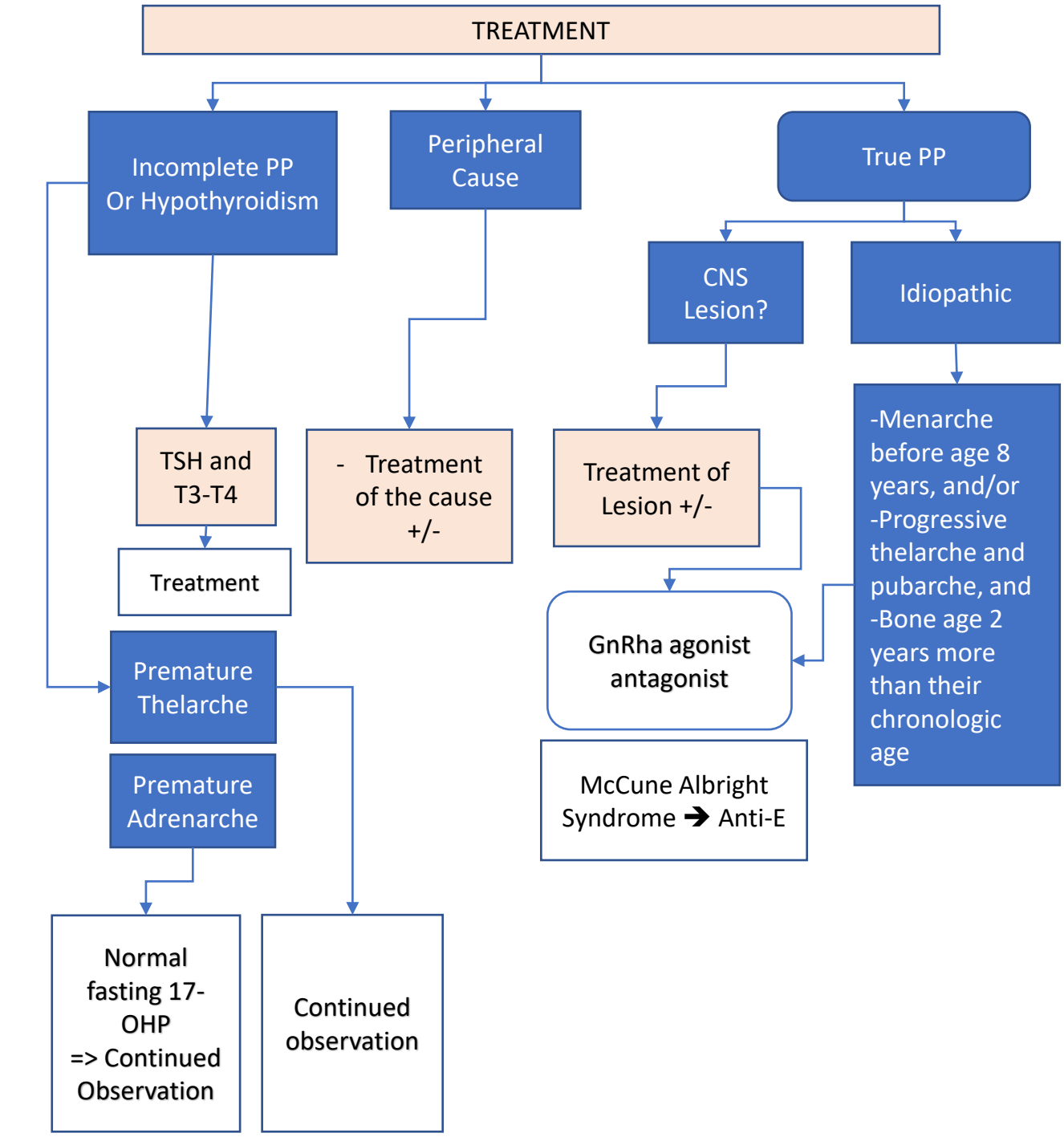
Premature Pubarche or Adrenarche

- Premature pubarche is isolated early development of pubic hair without other signs of secondary sexual maturation. Premature adrenarche is isolated early development of axillary hair.
    - It is associated with normal linear growth and a normal bone age
    - **NOT associated with clitoral hypertrophy.**
- The cause is poorly understood but is believed to be related to increased androgen production by the adrenal glands (DHEA and DHEA-S).
- Many cases of premature adrenarche evolve into PCOS.
- Some cases of premature pubarche have abnormal electroencephalograms (EEGs) without significant neurologic disease.
- It is important to observe these children closely for other signs of precocious puberty

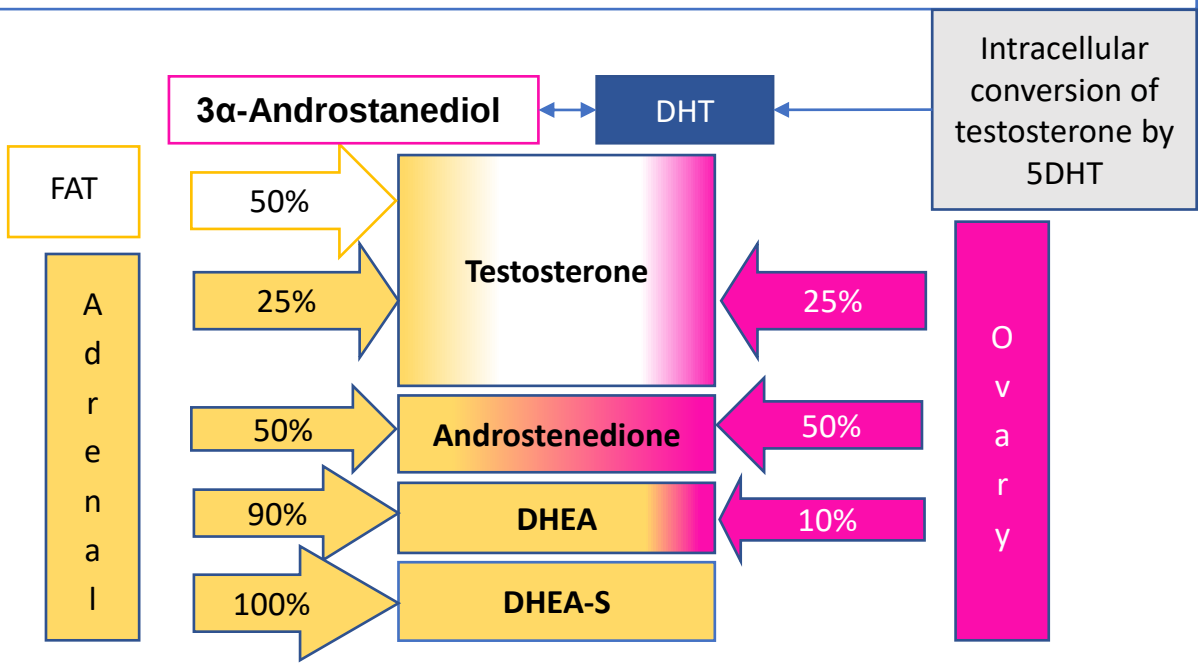
WORKUP PRECOCIOUS PUBERTY



PRECOCIOUS PUBERTY



FEMALE ANDROGENS



	Average Plasma Concentration		
Androgen	**ng/ml**	**nmoles/liter**	Male ng/ml
DHEAS	1700	4630	
DHEA	4.2 (< 10)	14.6	
Androstenedione	1.76	6.1	0.8-1.2
3α-Androstanediol	0.75	2.6	
Testosterone	0.39 (< 1)	1.3	4 - 10
DHT	0.19 (< 0.3)	0.65	

DHEAS, is unable to penetrate cells, it functions as a reserve pool. concentration approximately 8000 to 10,000 times that of T, it has almost no androgenic activity.

DHEA and Androstenedione are much weaker androgens, under normal circumstances they have a very limited androgenic effect

Androstenedione is an important androgen in women because of its peripheral conversion to T or estrone (E)

Testosterone and Androstenedione are metabolized to DHT **intracellularly** (**DHT is a stronger androgen than is T.**) via 5α-reductase activity, this is important for testosterone action in the PSU as well as in the genitalia. It is not necessary for testosterone action in other areas such as in muscle or bone.

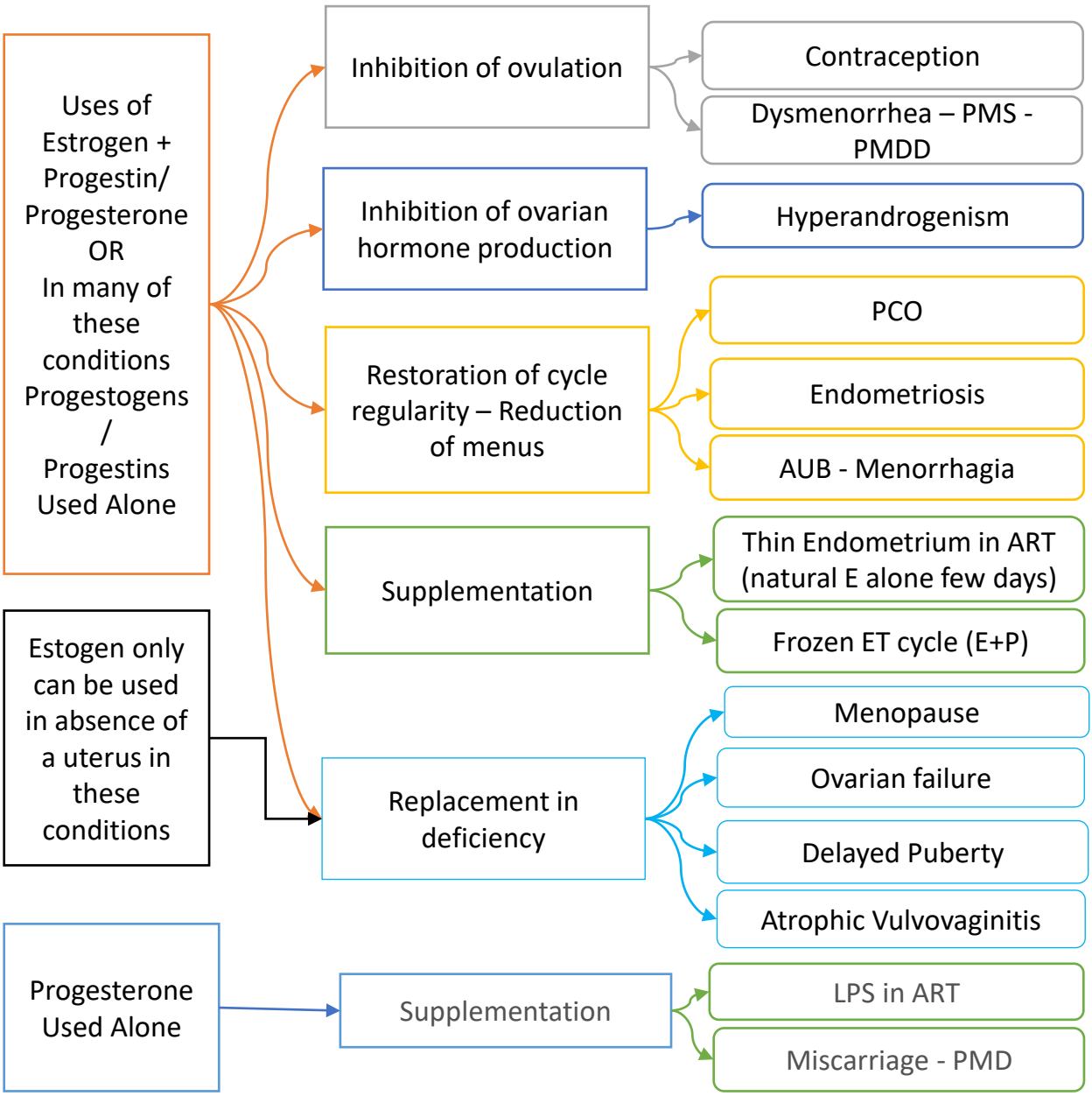
- **Neither the adrenal nor the ovary secretes DHT**,
- Circulating DHT arises from the peripheral conversion of precursor steroids. In women, the major source of DHT is circulating Δ4-A.

3α-Androstanediol has androgenic activity, but because of its ability to bind to the estrogen receptor, it has estrogenic activities as well. However, other than being a precursor of testosterone, its biologic significance is uncertain.

FEMALE HORMONES AND ANTIHORMONE THERAPY

	Agonist	Indirect Antagonist	Direct Antagonist
Estrogen	S: Ethinyl Estradiol N: Estradiol	GnRHa continuous Danazole	SERM • Clomiphene • Tamoxifen • Raloxifen Aromatase inhibitors • Letrozole • Anastrazole Receptor antagonist • Fulvestrant
Androgen	Testosterone	OCP GnRHa continuous	• Cyproterone acetate • Drosperinone • Spironolactone • Flutamide • Finasteride
Progesterone	Progestagens Natural Synthetic		SPRM • Mifepristone • Ulipristal acetate
GnRH	GnRHa pulsatile	GnRHa continuous	GnRH antagonists: • Ganirelix • Citrorelix • Elagolix
Oxytocin	Syntocinone	Tocolytics	• Atosiban
Prolactin			Dopamine agonists Bromocreptine – Lisuride - Cabergoline
FSH	• Purified urinary FSH = Urofollitropin (Fostimon) • Recombinant FSH = Follitropin (Puregon, Follitrope, Gonal F)	• Contraceptive pills • GnRHa continuous • GnRH antagonist	
FSH+LH U = urinary HP = Highly purified	• U.HMG (Menogon) • HP.HMG ➔ Menopur – Merional		
LH	U-HCG➔ Choriomon rHCG➔ Ovidrel - Ovitrelle rLH ➔Lutropin		

Uses of Estrogen and Progesterone

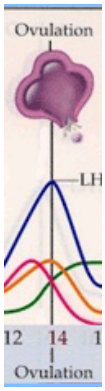


General Contraindications to Estrogen and/or Progesterone

- Active liver disease
- Active or recent arterial thromboembolic disease (angina, myocardial infarction)
- Current, past, or suspected breast cancer
- Known hypersensitivity to the active substance of the therapy or to any of the excipients
- Known or suspected estrogen-sensitive malignant conditions
- Porphyria cutanea tarda (absolute contraindication)
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Untreated hypertension

OVULATION

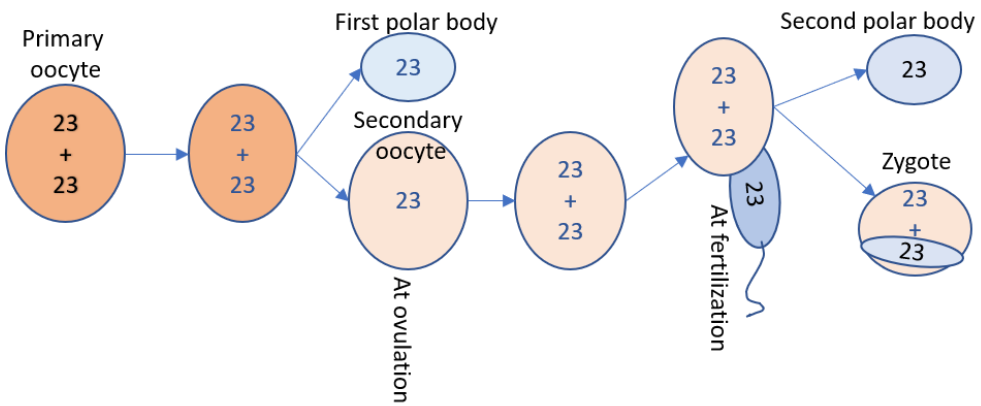
The Graafian follicle continues to produce oestrogen, **independent of FSH stimulation**, and has the highest number of granulosa cells and oestradiol levels with the lowest androgen-to-oestrogen ratio.
This follicle also develops LH receptors in the granulosa cells, which helps with maturation of the oocyte and prepares the follicle for the ovulatory stimulus of the LH surge.
The LH receptors also ensure adequate progesterone production by **the luteinised granulosa cells** from the corpus luteum after ovulation.



- **When the estradiol (E2) levels peak to 200 pg/ml > 20 hours (500–900 pmol/L)** *(which usually coincides with a follicle size of 18–20 mm)*, **the pituitary gland responds by a surge of LH levels to about 15–30 IU/L.**
- This leads to a cascade of changes in the Graafian follicle and leads to ovulation within 36 hours (34–39 hours) of the onset of the LH surge.

The LH surge initiates the following changes in the Graafian follicle and ovary:

- Resumption of meiosis in the oocyte with extrusion of the first polar body (the oocyte becomes haploid) and formations of a secondary oocyte that **becomes arrested into the metaphase of the second meiotic division (which is only completed at fertilization -if it occurs- with extrusion of second polar body)**.
- Induction of angiogenesis and increased vascularity and capillary permeability in the theca cell layers with increased production of follicular fluid and increase in intrafollicular pressure.
- Synthesis and secretion of various prostaglandins that help increase blood flow in the follicular wall and stimulate smooth muscle cells within the ovarian stroma that help expel the oocyte.
- Activation of matrix metalloproteinases and other proteolytic enzymes that digest the follicular wall and ovarian capsule at the site of the follicle to facilitate follicular rupture and oocyte release the i.e. ovulation.
- LH stimulates progesterone synthesis by the granulosa and theca cells



THE UTERINE MENSTRUAL CYCLE

The endometrium consists of two layers:

Basalis layer, which lies against the myometrium,

The basalis layer, does not change significantly across the menstrual cycle, serves as the reserve or endometrium regeneration following menstrual sloughing.

Functionalis layer, which is apposed to the uterine lumen. The functionalis layer is further subdivided into

More superficial *stratum compactum*, a thin layer of gland necks and dense stroma, and

Underlying *stratum spongiosum* containing glands and large amounts of loosely organized stroma and interstitial tissue.

<u>MENSTRUAL PHASE</u> = Shedding coincides with cycle day 1-5 days = early follicular phase of ovarian cycle:

Tissue Degradation and Hemorrhage

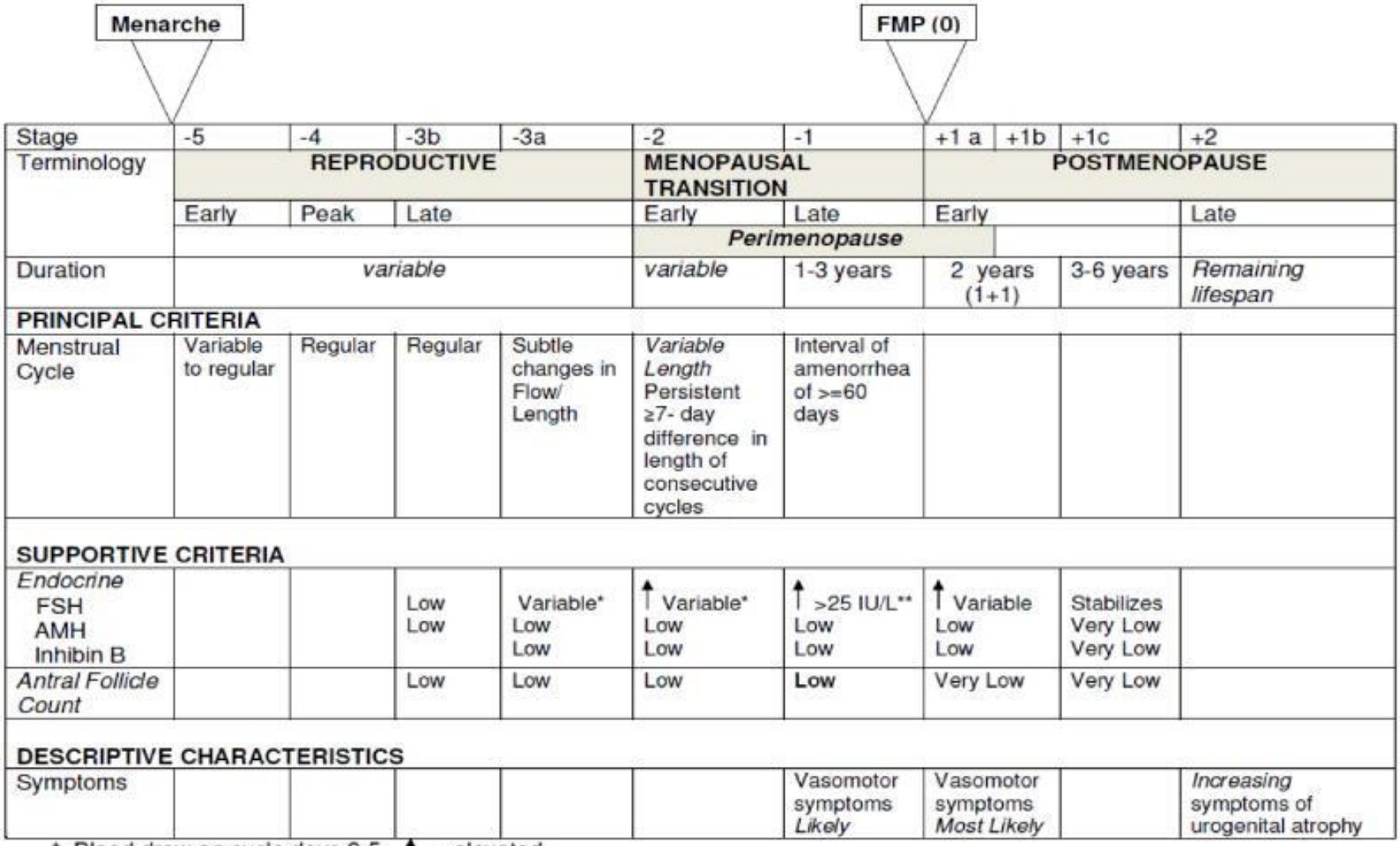
- Tissue factor, activates the coagulation cascade upon contact with blood.
- Urokinase and tissue plasminogen activator (PA) increase the conversion of plasminogen to plasmin to activate tissue breakdown.
- Matrix metalloproteinases (MMPs), during the menstrual cycle. Endogenous MMP inhibitors are increased premenstrually and limit MMP degradative activity.

Vasoconstriction and Myometrial Contractility

- Drop in serum progesterone leads to:
  - Loss of enkephalinase expression ➔ increased endothelin activity ➔ vasoconstriction. ➔ ischemia, endometrial damage, and subsequent menstrual sloughing.
  - Decreases an enzyme that degrades prostaglandins ➔ increases PGF2α activity in the myometrium and triggers myometrial contractions ➔ myometrial contractions ➔
    - Control blood loss by compressing endometrial vasculature and
    - Expelling menstrual discharge.

<u>PROLIFERATIVE PHASE</u> coincides with cycle day 6-14 = Follicular phase of ovarian cycle:

- In the early follicular phase the endometrium is rebuilt from the basalis layer after its superficial layer has been shed in the menses of the previous cycle.
- The prevailing oestradiol secreted from the ovary leads to active mitosis and proliferation of the endometrial glands and stroma.
- This leads to an increase in the thickness of the endometrium from 2–3 mm to about 6–8 mm by the end of this proliferative phase.



Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable*	↑ Variable*	↑ >25 IU/L**	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B			Low	Low	Low	Low	Low		Very Low	
Antral Follicle Count			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67-69]

STRAW; Stages of Reproductive Aging Workshop divided the adult female life into three broad phases (total of 10 stages in the most recent staging) centered on the Final Menstrual Period (Stage 0)

HOT FLUSHES

There are multiple actions of estrogen on the brain, thus some important functions linked to estrogen contribute to well-being in general and, more specifically, to cognition and mood.

Prevalence:

- Usually occur for 2 years after the onset of estrogen deficiency but can persist for 10 or more years-
- In 10% to 15% of women, these symptoms are severe and disabling

Cause of Hot flushes:

Fall in estrogen levels triggers a hypothalamic response (probably mediated by catecholamines).

Presentation:

- Increase in peripheral temperature (fingers, toes); a decrease in skin resistance, associated with diaphoresis; and a reduction in core body temperature
- Irritability, which may affect quality of life.
- Sleep disruption. They may awaken several times during the night and require a change of bedding and clothes because of diaphoresis.
- Sleep efficiency is lower, and the latency to rapid eye movement (REM) sleep
- Embarrasement – fatigue and sense of ill being

The frequency of awakenings and hot flushes is reduced appreciably with estrogen treatment

GENITO-URINARY SYMPTOMS

Estrogen has a positive effect on collagen, which serves as a major support tissue for the structures of the pelvis and urinary system.

Estrogen deficiency results in a thin, paler vaginal mucosa. The moisture content is low, the pH increases (usually greater than 5), and the mucosa may exhibit inflammation and small petechiae

Estrogen has a positive effect on collagen, which serves as a major support tissue for the structures of the pelvis and urinary system.

Nearly 30% of skin collagen is lost within the first 5 years after menopause, and collagen decreases approximately 2% per year for the first 10 years after menopause.

Reductions in collagen support and atrophy of skin, the vaginal and urethral mucosa have been implicated in a variety of symptoms, such as vaginal dryness, vaginal irritation, a frequent need to urinate and urinary tract infections, prolapse and urinary symptoms

RISK OF CARDIOVASCULAR DISEASE

Coronary artery disease is the leading cause of death in women, and the lifetime risk of death is 31% in postmenopausal women

- **Due to:**
  - **Loss of the direct vascular effects of estrogen.**
  - **Changes in lipid and lipoproteins after menopause.**
- Metabolic Changes:
  - Increase in total cholesterol
  - Increases in levels of low-density lipoprotein cholesterol (LDL-C).
  - The oxidation of LDL-C is also enhanced, as are levels of very low density lipoproteins and lipoprotein (a).
  - High density lipoprotein cholesterol (HDL-C) levels trend downward with time, but these changes are small and inconsistent
  - Coagulation balance is not substantially altered
  - Circulating plasma nitrites and nitrates due to reduced nitric oxide synthetase activity.
  - In normal, nonobese postmenopausal women, carbohydrate tolerance also decreases as a result of an increase in insulin resistance.

- ***Coronary artery disease is the leading cause of death in women, and the lifetime risk of death is 31% in postmenopausal women versus a 3% risk of dying of breast cancer.***
- The incidence of cardiovascular disease (CVD) is
  - Three times lower in women before menopause than in men (3.1 per 1000 per year in women ages 45 to 49). Approximately equal in men and women ages 75 to 79 (53 and 50.4 per 1000 per year, respectively).
  - Premature menopause, occurring before age 35, has been shown to increase the risk of myocardial infarction two- to threefold,
  - Oophorectomy before age 35 increases the risk sevenfold .

CANCER RISKS IN POSTMENOPAUSAL WOMEN

- The risk of cancer increases with time after menopause, but this is a function of aging and not as a consequence of menopause per se.
- Leading cause of cancer deaths in post-menopauseal women is lung cancer.
- Leading cause of death in women is ***coronary artery disease (the lifetime risk of death is 31% in postmenopausal women)***
- *Prevention* requires healthy lifestyle measures and screening for early detection.

Clinical Care..

6.Routine screening for cancer of the breast, cervix, and colon is indicated for midlife women. There is considerable controversy regarding the age at which breast cancer screening should begin and end and the frequency of screening. Current guidelines generally include mammograms every 1 to 2 years, starting at age 40 to 50 years until age 70; Pap smears every 3 years or every 5 years with human papillomavirus co-testing until age 65; and colonoscopy every 10 years, starting at age 50 until age 75. (Level II)

8.Testing for sexually transmitted infections should be performed on the basis of history and level of risk.

9.Routine screening for ovarian cancer is not indicated. (Level I)

BONE HEALTH ASSESSMENT

1- Assessment of Bone mass

Radiographic methods:

- Dual-energy x-ray absorptiometry (DEXA) scans have become the standard of care for detection of **osteopenia** and osteoporosis.

T score *is used to reflect the number of standard deviations of bone loss from the peak bone mass of a young adult.*

- Osteopenia is defined by a T score of –1 to –2.5 standard deviations;

- Osteoporosis is defined as greater than 2.5 standard deviations

2- Assessment of Bone Turnover

Biochemical assays:

- Biochemical measurements are useful as markers of the effectiveness of treatment, an increased resorption marker may decrease within months into the normal range with an anti-resorptive therapy, whereas it takes 1 to 2 years to see a change in BMD with DEXA.

3- Assessment of Fracture Risk in women with osteopenia/osteoporosis

The World Health Organization (WHO) has made available an algorithm to predict the 10-year fracture risk of men and women living around the world. This model, called ***FRAX***, can be accessed at www.shef.ac.uk/FRAX and is calculated based on individual patient history data and the results from DEXA.

Pharmacological Treatment is recommended in

1- Women with a T-score of –2.5 or less.

2- women with a 10-year FRAX of at least 20% or a risk of hip fracture of at least 3%.

3- Treatment should also be considered in women who have had a low-trauma fracture, even if DEXA does not indicate osteoporosis.

- Biochemical markers used after initiation of therapy to assess effectiveness.
- DEXA every one or two years can be used to determine the change in BMD.

NON-HORMONAL THERAPIES

- Quit Smoking, alcohol and reduce caffeine, sugar and salt.
- Healthy diet is essential for avoidance of cardiovascular disease
- Exercise has been shown to be beneficial for hot flushes, cardiovascular health and building muscle and bone mass and for reducing falls.

Calcium, vitamin D:

- A woman's total intake of elemental calcium should be 1500 mg daily if no agents are being used to inhibit resorption, and 400 to 800 IU of vitamin D should also be ingested.
- Caution should be exercised in prescribing excessive calcium, particularly in older individuals, as this has been linked to coronary events.
- Blood level of 25 OH vitamin D <30 ng/mL usually warrants supplemental treatment with 25 hydroxy vitamin D.

HOT FLUSHES

- **Antidepressants (SSRIS/SNRIS) (selective serotonin reuptake inhibitors [SSRIS]/ serotonin norepinephrine reuptake inhibitors (SNRIS)**
  - Fluoxetine (20 mg), Venlafaxine (75 mg), Paroxetine (12.5, 25 mg), and Escitalopram (10, 20 mg).
  - Paroxetine, is approved currently by the FDA, at a lower dose of 7.5 mg.
- ***GABAPENTIN:*** Gabapentin in doses ranging from 300 to 900 mg.
- ***ANTIHYPERTENSIVES*** Clonidine 0.1-mg patch is used daily has been the most studied, but methyldopa also has efficacy over placebo in reducing hot flushes..
- ***PHYTOESTROGENS*** It has been suggested that 30% to 60% of women with symptoms at menopause seek "natural" therapies, and the majority are botanicals such as phytoestrogens. Phytoestrogens are a class of plant-derived estrogen-like compounds conjugated to glycoside moieties. There is no evidence for harm if initiated in symptomatic women at the onset of menopause.

FRACTURE and FALL PREVENTION

- House:
  - Rearrange Furniture
  - Keep floors dry all the time
  - Install handrails if possible.
- Corridors:
  - Good light
  - Remove all small mats

Bathroom:

- Install firmly applied grab bars
- Remember to remove mats

The elderly:

- Avoid slippery slippers completely
- Check visual acuity regularly
- Avoid using the stairs and use carefully
- Pay attention to uneven ground.

ESTROGEN DOSE

- For short term treatment of symptoms:
  - Estrogen should be used at the lowest dose that can control hot flushes or can be administered via the vaginal route for symptoms of dryness or dyspareunia.
- For CV protection:
  - There are no data to this point in women regarding ET dose that offer CV protection. Therefore, *lower doses are still recommended, which are sufficient for symptom control.*
- For Osteoporosis:
  - A dose equivalent of 0.625 mg of conjugated equine estrogens(CEEs) **was** once thought to be necessary for the prevention of osteoporosis, but we **now** know that lower doses (0.3 mg of CEE or its equivalent) in combination with progestogens, or even with adequate calcium alone, can prevent bone loss, although there are no long-term fracture data with lower-dose therapy.

- CONJUGATED EQUINE ESTROGEN is a mixture of at least 10 conjugated estrogens derived from equine pregnant urine. Estrone sulfate is the major component.
- Synthetic estrogens, given orally, are more potent than natural E2. Ethinyl estradiol that is used in oral contraceptives, with a dose of 5 µg being equivalent to the standard ET doses used (0.625 mg CEE or 1 mg micronized E2). Standard ET doses are five or six times less than the amount of estrogen used in oral contraceptives.
- 0.625 mg CEE is probably equivalent to 1.5 mg of micronized E2.
- Oral estrogens have a potent hepatic "first-pass" effect that results in the loss of approximately 30% of their activity with a single passage after oral administration. Oral estrogen results in higher levels of estrone (E1) than estradiol(E2); this is true for oral micronized E2 as well as E1 products.
- Estrogen may be administered continuously (daily) or cyclic for 21 to 26 days each month.
- **If the woman has a uterus, a progestogen should be added to the regimen.**
- For women who are totally intolerant of progestogens (regardless of the dose and route of administration) and take unopposed estrogen, even at lower doses, **periodic endometrial sampling is necessary.**
- Progestogens should not be used in women who have had a hysterectomy.